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# **Epidemiology of Multiple Myeloma**

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## **Abstract**

Multiple myeloma is a heterogeneous hematological malignancy in which epidemiology plays an increasingly important role. In recent years, an unprecedented intensive research, including both clinical and molecular epidemiology, has deepened the knowledge about its pathogenesis, risk factors, and prognostic factors, leading also to the approval of new drugs. Although the etiology remains largely unknown, among the confirmed risk factors, only obesity and the exposure to certain carcinogens are potentially preventable. Familial myeloma and occupational myeloma are topics of great interest. Most population-based cancer registries show a stable incidence or only a slight trend to increase. The diagnostic delay should be avoided as much as possible. Mortality rates, including early mortality, are progressively decreasing, although infection remains the leading cause of mortality. The outcome in terms of overall survival and health-related quality of life has remarkably improved, joining the group of potentially curable malignancies. Nowadays the clinical scenario is challenging. Clinical and epidemiological variables of interest should be standardized in clinical records. Patients should be included in a population-based registry network. The clinical coordination of a multidisciplinary team in a specialized unit is needed in order to maximize the outcome of every patient.

**Keywords:** multiple myeloma, epidemiology, population-based registry, incidence, risk factors, survival

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## **1. Introduction**

Multiple myeloma (MM) is a complex and heterogeneous disease [1–3], with variable survival. MM is a malignancy of terminally differentiated clonal plasma cells (PC) which are primarily

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localized in the bone marrow. In most cases, these PC are able to secrete a monoclonal immunoglobulin (Ig) protein (M protein) in the serum and/or urine. About 15–20% of MM patients secrete monoclonal light chains (LC) only, without expression of the normal Ig heavy chain, which constitutes LCMM [4], a subtype of MM-associated to poor outcome [5, 6]. True non-secretory MM represents only about 3% [7, 8].

The current definition of MM is based on the demonstration of 10% or more clonal bone marrow PC (or a biopsy-proven plasmacytoma) and one or more of the so-called myeloma defining events (MDE), including those events that evidence end-organ damage such as hypercalcemia, renal insufficiency, anemia, or osteolytic bone lesions (CRAB), or the presence of a biomarker of malignancy such as 60% or more clonal PC, 100 or more involved/uninvolved serum free light chain ratio (i/u FLCr), or more than one focal lesion on MRI.

Most patients with newly-diagnosed MM (NDMM) are preceded by a precursor disease (PD) [9, 10]. The most frequent PD is the monoclonal gammopathy of undetermined significance (MGUS), which is defined by a low M protein level (<30 g/L in serum or <500 mg/24-hour in urine), <10% of clonal bone marrow PC, and absence of CRAB or amyloidosis. Smoldering MM (SMM) is an asymptomatic plasma cell disorder. It is an intermediate entity between MGUS and MM, characterized by both the absence of MDE or amyloidosis, and a certain level of M protein (Ig G or A  $\geq$  30 g/L in serum or  $\geq$ 500 mg in 24-hour urine) and/or 10–60% clonal bone marrow PC. The risk of progression to MM of MGUS and SMM is about 1 and 10% per year, respectively [11, 12].

The outcome of patients with NDMM in terms of overall survival (OS) is highly variable according to the type of study, selection criteria and calendar period. The real improvement in OS over time can be shown using population-based registries in which all incident cases are included with standardized rules and thorough follow-up [13–15]. Several well-established or emergent prognostic factors in relation to the disease, the host, the stage and the response to therapy are involved. However, the current risk stratification systems [16–20] cannot accurately predict the outcome in a particular patient.

Multilevel heterogeneity is a common denominator of MM. The epidemiological background [21, 22], the clinical presentation [23, 24], the genetic instability [25, 26] as well as clonal evolution [27, 28], and finally, the response to therapy [29, 30], are the most relevant levels of heterogeneity. All of them have a well-known impact on the outcome. Epidemiology is probably the first level of heterogeneity and its knowledge is key to understand MM outcome. Herein, an updated perspective on the epidemiology of MM will be highlighted.

## 2. Epidemiology of multiple myeloma

### 2.1. Incidence of multiple myeloma

MM incidence within a geographically determined population can be established by means of population-based cancer registries. The main goal of these registries is the identification of all incident cases of NDMM diagnosed among the residents of a defined geographical area [31]. The International Agency for Research on Cancer and the International Association of Cancer Registries provides high-quality statistics on the incidence of cancer from population-based registries around the world [32].

The incidence of MM is generally higher in more-developed countries. The estimated NDMM incident cases in the United States throughout 2017 is 30,280 (17,490 men and 12,790 women), representing 1.8% of all new cancer, with an incidence rate (per 100,000 inhabitants and age-standardized to the 2000 United States standard population) of 8 and 5.2 respectively, and a male/female ratio of 1.5 [33]. Similar or slightly lower age-standardized incidence rates can be found in European countries [31, 34–38]. Conversely, in Asian countries, the incidence is particularly low [39, 40]. There is a marked racial disparity in the incidence of MGUS and MM, with a two to threefold increased risk in blacks compared with whites, after adjusting for socioeconomic and other risk factors, suggesting a genetic predisposition [41].

Most population-based cancer registries show a stable or slightly increasing MM incidence over the last decades. In some registries, an improvement in case ascertainment may be the reason for the slight increase trend in the incidence. Based on data from the Surveillance, Epidemiology, and End Results Program [42] approximately 0.8% of the population will be diagnosed with MM at some point during their lifetime. On the other hand, as expected, the prevalence of MM has increased due to progressive improvement in OS.

## 2.2. Risk factors

MM is a multifactorial disease with a wide variety of risk factors including both environmental and genetic. Despite the growing interest in the field, the etiology of MM is poorly understood. However, many risk factors have been implicated, with variable levels of evidence [43, 44]. Herein, the main risk factors will be reviewed. Interestingly, some of these variables such as age, sex, race, and others, have a double behavior, as risk and prognostic factors. Remarkably, only two risk factors are potentially preventable. On the one hand, obesity is an increasingly common comorbidity. On the other hand, the exposition to certain chemical products, such as some herbicides, has been also demonstrated to be associated with the risk of developing MM.

### 2.2.1. Precursor disease

MM has a multistep pathogenesis [2, 45]. All MM patients are virtually preceded by a PD. Several PD can progress to MM, such as MGUS [46], SMM [12] or solitary plasmacytoma [47]. Despite the fact that MGUS is considered the main risk factor for MM, only few MM patients have a prior knowledge of MGUS at the time of the diagnosis of MM. Remarkably, in a Swedish nationwide study of 14,798 patients with MM, only 2.7% had previously diagnosed as having MGUS, but this subgroup showed significantly better OS [48]. Moreover, in the Granada (south of Spain) population-based cancer registry, all MM with any type of previously documented PD had a better outcome and this trend was maintained over the past three decades and it was not associated to diagnostic delay [49].

### 2.2.2. Age

The incidence of cancer in general and hematologic malignancies increases with age. The median age of MM at diagnosis is about 70 years [14, 38]. 72% of patients included in the Swedish Multiple Myeloma Registry were 65 years or older [38]. The median relative survival was 7.7 years for patients 65 years or younger, in comparison with 3.4 years for those with 66 years or older.

Several studies [50–54] have demonstrated that the advanced age is predictive of shorter OS. Aging is associated with a decrease in the tolerability to treatment, a higher rate of drug discontinuation due to adverse events and lower cumulative delivered-dose. All these circumstances may have an impact on the outcome. Survival in older adults with MM is also improving, but to a lesser extent than in young patients [14, 55].

Age, along with renal failure and certain comorbidities, is associated with early mortality [56, 57]. The number of comorbidities increases with aging, and this may be one of the reasons why elderly people with MM have a poor outcome.

### 2.2.3. *Sex*

Most but not all registries show a higher incidence of MM in men. Moreover, in several studies, men have a trend to poorer survival in relation to women [14, 54, 58, 59] although in most cases this is not statistically significant.

### 2.2.4. *Race*

The prognostic impact of race in OS is controversial. Racial disparities in outcomes may be related with biologic factors, individual factors, health behaviors, and structural barriers [60]. In a large study from the Surveillance, Epidemiology, and End Results (SEER), with more than 40,000 patients, the differences in OS between patients in the white and black race did not reach statistically significant differences [61]. A recent study from the Mayo Clinic did not find any survival difference by race but it showed considerable variability in MM therapeutics utilization with seeming inequity for racial-ethnic minorities [62]. A comprehensive study analyzing ethnically defined NDMM has shown molecular differences between African and European descent cases [63]. If this fact could have a clinical impact remains to be determined. Overall, the current evidence seems to confirm the conclusion of old studies pointing out that race is not a significant prognostic factor in MM, whereas the socioeconomic status may influence survival [64].

### 2.2.5. *Socioeconomic status*

In recent years, the socioeconomic status has been suggested to be a confusing variable in order to analyze more deeply the association between race and survival. However, there was not strong evidence until recently. Fiala et al. [65] showed that low socioeconomic status was independently associated with poorer OS in 562 patients at the Washington University School of Medicine, and this was confirmed in a large cohort of 45,505 patients from the SEER. The most likely hypothesis for this is that this subgroup of patients delay seeking medical attention and thus are farther advanced at presentation. Costa et al. [66] also studied a cohort of 10,161 patients from SEER highlighting the strong impact of social determinants of health, such as marital status (other than married), insurance status, and income. In this study, income and education were reported at the county level, not at the individual level. An important limitation of both studies is that comorbidities are not registered in the SEER database and therefore, its influence could not be explored.

Accordingly, all variables affecting outcomes, including sociodemographic factors, should be taken into account in order to make rigorous comparisons between different therapeutic



approaches. A widening gap among socioeconomic status groups have been shown in the last two decades [67]. In this increasingly complex therapeutic scenario, it is imperative to focus on subgroups that may remain disadvantaged [68].

#### 2.2.6. *Familial MM*

Family history is a well-defined risk factor for cancer. The demonstration of MM in two or more members of the same family is a rare occurrence. However, several reports during the past three decades [69–73] have analyzed the pattern of aggregation and pointed out a putative autosomal dominant mode of genetic transmission, reporting an excess familial risk for MM of about 2- to 4-fold and supporting a role for germline susceptibility genes, shared environmental influences, or an interaction of both. A variation in the presence of defining clinical features in MM patients according to family history of hematologic malignancy has been described [74, 75]. MM showed an association with breast and prostate cancer, and colorectal cancer families, suggesting that MM shares genetic susceptibility with many cancers [76].

#### 2.2.7. *Occupational MM*

To facilitate international comparisons of occupational statistics, the definitions of all groups of occupations should be standardized [77]. The risk of MM has been associated with several manufacturing occupations and industries [78], such as machine operators and tenders, textile, food and beverage preparation, bakers and pastry cooks [79], printing and cleaning [80], hairdressers [81], and others. A meta-analysis including 5 cohort studies and 13 case-control studies on occupational exposure to dichloromethane, a widespread used solvent, showed an excess risk of MM [82].

Agriculture plays an important economic role in both developed and developing countries. There is a growing body of evidence about the association between farming and the risk of MM [83–85]. Despite methodological issues in some studies, the exposure to potential or confirmed carcinogens such as herbicides and pesticides commonly used by agricultural workers have been pointed out as key determinants of the cancer risk observed in agricultural populations. Some studies found a different pattern of risk according to sex [86] or even in female spouses of pesticide applicators [87]. Glyphosate is the most commonly used herbicide in the world and recent meta-analysis points out a marginally significant positive association with MM [88].

#### 2.2.8. *Obesity*

Obesity is one of the biggest problems in public health throughout the world. According to the WHO definition, obese individuals have a body mass index of 30 Kg/m<sup>2</sup> or higher [89]. A causal link between obesity and cancer has been shown. About 20% of cancers are obesity-related, even 40% including overweight [90].

About 32% of NDMM patients are obese [14]. Four meta-analysis have shown a positive association between obesity and MM risk [91–94]. The impact of obesity on the number of obesity-attributable NDMM cases was estimated to be 1.3 as relative risk and about 10% as population attributable risk [95]. On the other hand, the association of obesity with higher

all-cause mortality is consistent [96], although the role of obesity as prognostic factor in MM is controversial. However, evidence suggests that obesity could have a negative impact on MM outcome [97].

#### 2.2.9. *Type 2 diabetes*

Obesity and type 2 diabetes share close ties [98]. Approximately one fifth of NDMM have type 2 diabetes. The association between type 2 diabetes and MM has been evaluated in one meta-analysis [99] showing a trend toward significantly increased odds of MM in patients with type 2 diabetes. Moreover, some genetic variants may influence the risk of developing MM [100]. There is increasing evidence regarding the role of type 2 diabetes as an independent prognostic factor in MM at both clinical and genomic level [101, 102].

#### 2.2.10. *Alcohol*

Alcohol consumption is a major cause of disease and death worldwide. More than 5% of the total number of cancer cases are alcohol-attributable [103]. However, the role of alcohol intake in the MM risk is unclear. Interestingly several studies, including two meta-analyses, have shown a protective effect in terms of MM risk [104–107].

#### 2.2.11. *Smoking*

Smoking is not considered a risk factor for MM [108, 109]. Surprisingly, a recent study shows a potential interaction between certain single nucleotide polymorphisms and smoking associated with increase MM risk [110].

#### 2.2.12. *Diet*

The current evidence about this topic is not strong due to the inherent difficulties and characteristics of the studies. Notwithstanding, some issues can be highlighted. A high consumption of fish is inversely associated with MM risk [111]. The consumption of green tea seems to have a protective effect in some [43] but not all studies [112]. Combined fruit and vegetable consumption has been associated with decreased non-Hodgkin lymphoma risk but it did not reach statistical significance for MM [113]. Remarkably, a diet-induced obesity promotes an MM-like condition [114]. Despite the potentially important role of diet and nutrition in cancer prevention, the current evidence is inconsistent [115].

#### 2.2.13. *Physical activity*

The literature surrounding MM and physical activity are very limited [116]. Leisure-time physical activity was associated with lower risks of many cancer types, including MM [117, 118]. The effectiveness of participation in exercise programs remains unclear for patients with MM [119].

#### 2.2.14. *Other risk factors*

Little evidence supports the infection with hepatitis B and C viruses [120, 121], environmental factors [122], or the use of drugs [123], as risk factors for MM.

Besides obesity and type 2 diabetes, other conditions such as autoimmune diseases [124], thyroid disease [125], or inflammatory disorders [126], may increase the MM risk.

Autoimmune diseases constitute a heterogeneous group of disorders, which jointly affect 5–10% of the population. In relation to the potential association of autoimmune diseases and MM, an individualized approach must be implemented. A significant increase in MM incidence after ankylosing spondylitis and systemic sclerosis was showed [124]. A few cases of immune thrombocytopenia purpura associated with MM at the time of MM diagnosis have been reported [127]. In a Swedish cohort study, a significant increase of MM was demonstrated in women previously diagnosed with pernicious anemia [128]. A history of the autoimmune disease has been recently associated with impaired OS in MM and MGUS [129].

Host-related immunodeficiency is known to play a role in the development of MM [130]. More than 8% of NDMM have a prior or synchronous malignancy [14]. MM is associated with many other malignancies, including colorectal, breast and prostate cancers, non-thyroid endocrine tumors, leukemia and cancer of unknown primary [76]. The prognosis of patients with a second or third cancer is inferior [131]. Sometimes, NDMM and other hematological neoplasm such as myelodysplastic syndrome are diagnosed at the same time in the same patient [132]. Increased life expectancy has led to renewed concerns about the long-term risk of second primary malignancies [133].

### 2.3. **Survival**

OS remains the key end-point in both clinical trials and real-life patients. Survival in MM is highly variable and depends on prognostic factors, which can be categorized into four groups: host-related, disease-related, staging and therapy. Among host-related factors, comorbidity plays an important role. However, the analysis of prognostic factors is beyond the aim of this chapter. Notwithstanding, it must be emphasized that many of the above-mentioned risk factors can also behave as prognostic factors, as is the case of age. In this regard, less than 3% of patients with MM are younger than 40 years, showing similar clinical features to the whole MM population, except for a higher proportion of LCMM [134]. On the other hand, renal impairment is a common presenting complication of MM with a negative impact on the outcome; despite this, there has been a major improvement in OS in these patients, although the risk of early death remains high [135]. Moreover, the size and type of institution where the patients are treated may have an impact on the outcome in some studies [38, 136, 137]. OS has continuously improved over the past decades due to better supportive care and advances in therapy. Population-based studies are needed to accurately estimate OS in real-life patients [14, 35, 38]. An important gap exists between the outcome of these patients and those included in clinical trials, which have to fulfill specific selection criteria. Although some patients can achieve deep



responses and become long-term survivors, being some of them cured, the goal of curing MM in a significant proportion of patients is still far away. In the current scenario, getting and maintaining a minimal residual disease has become the primary objective of therapy before cure [29]. In the meantime, the importance of improving quality of life should be pointed out [138].

## 2.4. Mortality

Based on data from the SEER Program [42], MM is the fourteenth leading cause of cancer death in the United States. The number of deaths was 3.3 per 100,000 men and women per year (age-adjusted rates), based on 2010–2014 deaths.

Comorbidity has also an impact on mortality, in particular, early mortality [57]. Infection remains as the first cause of death in most studies, frequently associated with aging, renal failure, and relapse. Therefore, every effort to avoid serious infection should be taken into account. In this regard, prophylactic antibiotics [139] and vaccines are key measures.

## 2.5. Prevention

Little is known about effective measures to avoid the development of MM. Early treatment of asymptomatic patients with high-risk SMM or even high-risk MGUS, now only in the context of clinical trials, may prevent the appearance of MM, increasing the probability of cure [140].

Currently, the potentially preventable risk factors for MM are obesity and the exposure to MM-related carcinogens, particularly in the context of farming. Efforts should be made to fight globally and effectively against these risk factors.

On the other hand, the prevention of treatment-related adverse events is a matter of concern [141].

## 3. Conclusions

- MM is a very complex and heterogeneous disease. Heterogeneity is largely responsible for the great variability in the outcome of patients and can be stratified in several levels. Epidemiology should be considered the first level of heterogeneity. Therefore, the knowledge of the epidemiological background should be taken into account in both real-life and clinical trials settings to accurately assess the outcome, allowing a precise comparison between studies.
- MM epidemiology is an exciting research topic. In the era of precision and personalized medicine, both clinical and molecular epidemiology should be integrated as a mandatory step in the optimized workup of every patient.
- MM is a multistep malignancy. Virtually all patients with NDMM had a previous precursor disease. However, the proportion of NDMM patients with a previously known precursor disease is remarkably small. Both MGUS and SMM have also a heterogeneous pattern of risk progression. Early treatment in high-risk SMM is expected to increase the rate of cure.

- MM is a multifactorial condition. Many risk factors are involved with variable levels of evidence. The meta-analysis is located at the top of the pyramid of evidence, having largely contributed to highlight the role of potential or plausible risk factors.
- MM is a rapidly changing field. In the last decade, the pathogenesis, diagnosis, prognosis, and treatment of MM have dramatically changed. The knowledge of the epidemiological perspective can help to better understand current and future challenges, leading to an optimized MM care.

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