

Chapter 2

Epidemiology of Multiple Myeloma

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Introduction

Multiple myeloma represents about 0.8% of all cancer cases worldwide, with incidence rates ranging from 0.4 to 5 per 100,000 persons in different parts of the world.¹ The highest rates of myeloma are observed in Australia, New Zealand, North America, northern and western Europe, while the lowest rates are seen in Asia. Modest increases in both incidence and mortality for myeloma have been observed over the last few decades, without an apparent explanation.¹

As with other forms of cancer, there is great interest in the role of environmental, immunologic, and genetic risk factors for myeloma. Unlike some subtypes of leukemia and lymphoma for which environmental and/or infectious risk factors have been clearly defined, there are few generally accepted predisposing insults leading to the development of myeloma. There are anecdotal cases of myeloma occurring in spouses,^{2–6} as well as rare reports of community clusters of myeloma cases.^{7,8} These observations imply the existence of environmental exposures capable of dramatically influencing the risk of myeloma, although the insult(s) remain to be defined. Nevertheless, a number of epidemiologic observations offer clues regarding the etiology and pathogenesis of myeloma. We will review the epidemiology of myeloma and monoclonal gammopathy of unknown significance (MGUS), with particular attention to known associations with race, environmental exposures, genetics, immunologic function, and infection.

General Epidemiology

In 2006, there were an estimated 16,500 new myeloma cases, and 11,310 deaths with myeloma in the United States, translating to an overall age standardized incidence rate of 7 per 100,000 persons.⁹ The median age at diagnosis of myeloma is ~70 years, and the risk increases exponentially with age, with over 75% of cases occurring in individuals over the age of 50, as shown in Fig. 1.⁹ In the United States, the incidence of myeloma varies substantially by

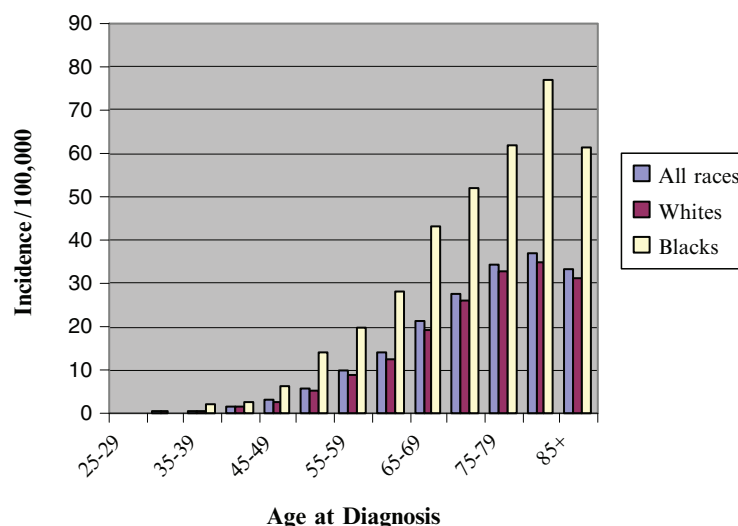


Fig. 1 Incidence of multiple myeloma according to age (SEER Data, 2000–2004). (see Plate 1).

race, where it is greatest among blacks, intermediate for whites, and least in Asians.^{10,11} Incidence rates in the Caribbean and Central America are similar to those of US residents of African decent,¹ lending support to the idea that some of the disparity in incidence by race may be genetic in origin.

Much has been written about the relationship between myeloma and MGUS, and a separate chapter in this volume is devoted to a detailed discussion of MGUS. Risk factors for MGUS parallel those identified for myeloma, with age being the dominant predisposing factor. In a large population-based study of 21,463 older adults in Olmstead County, MN, the prevalence of MGUS was 3.2% among persons age 50 and older, 5.3% for age 70 and older, and 7.5% for age 85 and older.¹² The risk of progression from MGUS to myeloma appears to be constant over time, occurring at a rate of ~1% per year.^{13–15} It is difficult to determine the proportion of myeloma cases that are preceded by MGUS, given that MGUS is typically asymptomatic and is not usually detected on routine blood analyses.

Racial Differences in the Incidence of Multiple Myeloma

The incidence of myeloma among blacks is approximately twice that of their white counterparts, as shown in Table 1. Differences in both genetic susceptibility and environmental factors have been postulated to explain the disparity in incidence according to race.¹⁶ In addition, age-adjusted incidence rates have increased for both blacks and whites over the past three decades, and the explanation for this observation remains unclear.

In a detailed examination of Surveillance Epidemiology and End Results (SEER) data, Francis has shown that both incidence rates and racial disparities vary by geographic location.¹⁷ Over the time period of 1975–2002, Detroit had

Table 1 Incidence, mortality, and survival rates for multiple myeloma over various time periods by race and gender.

	Incidence (1975–2002)			Mortality (1975–2002)			Five-year survival (1974–2001)		
	Total	Males	Females	Total	Males	Females	Total	Males	Females
All races	5.5	6.8	4.5	3.6	4.5	3.0	30.0	31.0	29.0
Whites	5.1	6.4	4.1	3.3	4.1	2.7	29.5	30.6	28.2
Blacks	11.2	13.6	9.7	6.8	8.3	5.8	32.4	33.2	31.7

the highest incidence of myeloma regardless of race, followed by Atlanta, in comparison with seven other geographic regions: San Francisco, Connecticut, Hawaii, Iowa, New Mexico, Seattle, and Utah. In eight of the nine geographic locations, the incidence rate for blacks was approximately twofold that of their white counterparts. In contrast, the corresponding difference was approximately threefold among Iowans. These differences imply the existence of environmental or lifestyle factors that influence the incidence of myeloma; however, there are not yet firm data identifying specific factors that can account for the observed differences.

Several studies also suggest an increased risk of MGUS among blacks.^{18–21} In the largest study to date, Landgren et al.²¹ examined the prevalence of MGUS and subsequent risk of myeloma among 4 million men who were admitted to Veterans Affairs (VA) hospitals. The age-adjusted prevalence ratio of MGUS for African Americans versus whites was 3.0 (2.7–3.3; 95% CI). In that study, the cumulative risk of progression to myeloma during the first 10 years of follow-up was similar between the two groups (17% for African Americans and 15% for whites, $p = 0.37$). These results suggest similar degrees of increased risk for both MGUS and myeloma in blacks, without evidence of racial differences in the risk of progression from MGUS to myeloma.

Socioeconomic Status, Diet, and Tobacco

Baris et al.²² examined the effect of socioeconomic status (SES) on the incidence of myeloma in a population-based case-control study. They observed an inverse correlation between occupation-based SES and myeloma risk for both black and white persons. Risk was significantly increased for individuals in the lowest category of SES (OR = 1.71, 95% CI = 1.16, 2.53). Among blacks, 37% of myeloma occurred in low-SES persons versus 17% of myeloma in whites, largely due to a higher representation of blacks in the lowest SES category. The authors concluded that occupation-based SES may account for about half of the excess occurrence of myeloma in blacks.²² The explanation for an association with SES remains unclear, but differences in diet, occupational or environmental insults, or infectious exposures have been proposed as possibilities.

Nutritional status and diet have also been associated with the risk of myeloma in a number of studies and are undoubtedly linked to differences in SES. Obesity, defined in terms of body mass index, has been associated with

an increased risk of myeloma in a number of studies.^{23,24} In a case-control study, Brown et al.²³ observed an association of obesity with increased risk of myeloma among both blacks and whites of both genders. Friedman et al.²⁴ also observed an association with obesity, but only for white men. There are modest racial differences in the prevalence of obesity, particularly among women; however, this cannot explain the magnitude of difference in the incidence of myeloma among blacks versus whites.

Data on dietary factors and risk of myeloma are mixed, but some studies suggest a protective effect of green vegetable and fish intake. A large Italian study showed an inverse correlation between intake of green vegetables and risk of myeloma.²⁵ More specifically, the study of Brown et al.²³ suggested a protective effect associated with intake of cruciferous (mustard, broccoli, cauliflower, and cabbage family) vegetables, fish, and vitamin C. Several case-control studies suggest an inverse correlation between fish consumption and myeloma.^{23,25–27} In contrast, Svensson et al.²⁸ reported an increased risk of mortality from myeloma among eastcoast Swedish fishermen, who have a high intake of fatty fish.²⁹ The significance of this observation is obscured by the demonstration of high levels of organochlorine compounds in the plasma of fishermen from this region.²⁹

Several large studies have examined the effect of tobacco use on the risk of hematologic malignancies, and there is little evidence of an increased risk of myeloma among current or past smokers. Three large prospective surveillance studies followed a total of over 500,000 persons over periods spanning several decades, and each failed to demonstrate an association between smoking and myeloma, although there was some evidence of a weak association between tobacco use and lymphoma.^{30–32} In a case-control study, Brown et al. also failed to demonstrate an association between smoking and myeloma, although this study again suggested an association with non-Hodgkin's lymphoma.³³ The only large study suggesting an association between tobacco use and myeloma is a German case-control study of smoking and hemato-lymphoid malignancies, which showed an odds ratio for myeloma of 2.4 (95% CI = 0.98–5.74) for current male smokers and an odds ratio of 2.9 (95% CI = 1.1–7.4) for women smokers.³⁴ It should be pointed out, however, that this analysis included only 76 myeloma cases; thus, the confidence intervals are wide.

Ionizing Radiation

Ionizing radiation is a well-established risk factor for acute myelogenous leukemia; however, its role in the pathogenesis of other hemato-lymphoid malignancies is less clear, and the effects less dramatic. The largest body of data regarding acute radiation exposure and the risk of myeloma comes from studies of survivors of the Hiroshima and Nagasaki atomic bomb exposures. Early studies from the Atomic Bomb Casualty Commission observed an increased risk of myeloma, and this was most evident in individuals exposed to an estimated marrow dose of at least 50–100 rad.^{35,36} The magnitude of increased risk correlated with the estimated radiation dose to the marrow, was demonstrable in survivors between ages 20 and 59 years at the time of exposure, and had a latent period between exposure and diagnosis of at least 20 years.^{35,36} Preston et al.³⁷ extended the analysis of cancer incidence through

1987, and, in contrast to earlier studies, did not observe an excess risk of myeloma among bomb survivors. The analysis was limited to first cancers, but beyond this the study was similar in methods and population to the previous studies. Pierce et al.³⁸ examined cancer mortality through 1990 and did observe an increased risk of myeloma-related mortality among exposed individuals. Another recent study suggested a marginally increased incidence of MGUS among bomb survivors, without clear evidence of an accelerated rate of progression of MGUS to multiple myeloma.³⁹

Studies of cancer mortality among individuals receiving radiation therapy for ankylosing spondylitis⁴⁰ and metropathia hemorrhagia⁴¹ indicate an increased incidence of myeloma among exposed individuals. In another case-control study, an increased risk of plasmacytoma was observed among persons exposed to the old contrast agent thorotrast.⁴² Taken together, these studies coupled with those from the Atomic Bomb Casualty Commission suggest a dose-dependent effect of acute radiation exposure on the subsequent risk of both myeloma and MGUS.

The effects of chronic low-level radiation exposure are less clearly defined, both for myeloma and for other cancer types. Several studies examining cancer-related mortality following chronic low-level occupational radiation exposure have identified myeloma as one of the malignancies that occurs in excess in radiation exposed individuals.^{43–47} In one of the early studies, a threefold excess of myeloma-related death was observed among female radium dial workers.⁴³ More recently, a 15-country collaborative study examined cancer risk among over 400,000 nuclear industry workers with individual exposure data and long-term medical follow-up. There was a dose-dependent increase in cancer mortality, and a trend toward a dose-dependent increase in the risk of myeloma-related death among chronically exposed workers.⁴⁷ On the contrary, other large studies of radiation workers have failed to identify an increased risk of myeloma among exposed persons.^{48–51} Overall, the data suggest that if there is an effect of chronic low-level exposure, it is modest compared with the risks associated with more intensive acute radiation exposure. Furthermore, with modern industrial protections and regulations, it is unlikely that occupational radiation exposure remains a major risk factor for myeloma.

Other Occupational and Environmental Risk Factors

Although organic solvents, pesticides, and other chemicals have all been investigated as potential risk factors for myeloma, studies have generally failed to show consistent and compelling associations with the risk of myeloma. Lack of accuracy in defining the types of exposures for a given workforce, challenges in quantifying an individual's exposure, and the relatively low-baseline incidence of myeloma all contribute to difficulties in designing appropriately powered studies and interpreting results.

Farmers and other agricultural workers have been extensively studied because of their exposure to chemicals and pesticides, as well as peculiarities in diet and lifestyle associated with rural living. Three meta-analyses have compiled data from available epidemiologic studies of farmers,^{52–54} and taken together their results suggest that the age-adjusted risk of myeloma among farmers is similar to that of the general population.

Pesticide exposure has also been specifically studied, and results have been inconsistent, with some studies suggesting positive and others negative associations with myeloma. These data have been reviewed in detail by Alexander et al.⁵⁵ In the large US Agricultural Health Study, exposures to atrazine, alachlor, chlorpyrifos, and glyphosate, a total of over 160,000 persons were evaluated, and no association with myeloma could be identified for any cohort of applicators.^{56–59} Herbicides such as dioxin and TCDD have received public attention as possible carcinogens, and a few studies suggest modest increases in the risk of myeloma associated with occupational or accidental exposure.^{60–62}

Exposure to organic solvents does not appear to be a major risk factor for myeloma. In a recent meta-analysis of multiple myeloma mortality among solvent-exposed workers, the summary relative risk estimate was 1.14 (95% CI, 0.83–1.15).⁶³ An early study of California petroleum workers suggested an excess of myeloma-related mortality,⁶⁴ but the excess was limited to workers enrolled before 1949. Studies of more recent cohorts of workers do not suggest significant increases in myeloma among exposed individuals in the petroleum industry.^{65–70}

Immunology, Infection, and Myeloma Risk

Although myeloma is not considered an AIDS-defining malignancy, several large surveys have shown a significantly increased risk of myeloma among persons living with AIDS.^{71–75} In a case-control study of elderly persons with AIDS, the increased risk became apparent at about 2 years after the onset of AIDS.⁷⁵ Similarly, in a cohort study of AIDS patients in New South Wales, the risk of myeloma and other malignancies increased over time after the original AIDS-defining illness.⁷³

Following the discovery of human herpesvirus-8 (HHV-8) DNA sequences in Kaposi's sarcoma tissue from patients with AIDS,^{76–78} several studies suggested a possible relationship between HHV-8 and several hemato-lymphoid malignancies including primary effusion lymphoma, plasmacytic lymphoma, multicentric Castleman's disease, and myeloma. More rigorous epidemiologic studies suggest a role for the virus in a subset of cases of primary effusion lymphoma, plasmacytic lymphoma, and multicentric Castleman's disease, but do not support a relationship between HHV-8 and myeloma.^{79–83} Thus, it is difficult to invoke HHV-8 as the explanation for an increased risk of myeloma among AIDS patients. It is more likely that failure of immune surveillance mechanisms plays a role in enabling the emergence of overt myeloma in some patients.

Historically, there has been great interest in the hypothesis that chronic or recurrent antigenic stimulation might serve as a possible predisposing factor for development of multiple myeloma. Results of epidemiologic studies offer only weak support for this hypothesis. Most case-control studies examining medical history in relation to myeloma have failed to identify strong and consistent associations with prior infections, autoimmunity, or inflammatory conditions.^{11,84–87} On the contrary, in one case-control study from four geographic areas of the United States, risk of myeloma was inversely related to the number of diseases for which the person reported having been immunized.⁸⁶ It is unclear whether this observation relates to an immunologic effect, or to

differences in SES. One of the largest studies examining infection as a risk factor included all myeloma patients diagnosed in Denmark over a 20-year period (more than 4,000 cases and 16,000 matched controls). A history of pneumonia was associated with a 1.6-fold (95% CI 1.3–2.0) increased risk of myeloma, with the increased risk limited to pneumonia episodes occurring within 5 years of the diagnosis of myeloma.⁸⁸ Although the observed association in this study is statistically robust, it may simply be a reflection of the humoral immune compromise associated with myeloma, rather than a causative factor in its development.

Inherited Predisposition to Myeloma

Available data from both case-control and cohort studies suggest a two- to fourfold increased risk of myeloma among persons with affected family members.^{89–93} Some studies also suggest a more modest increased risk of myeloma in association with a family history that includes other hemato-lymphoid malignancies.^{90,91,94,95} Reports of the occurrence of myeloma in monozygotic twins add additional evidence of a genetic contribution in some cases.^{96–98}

The possibility of an association between HLA antigens or haplotypes and myeloma has been widely studied, based on the general hypothesis that immune recognition mechanisms might somehow be involved in the pathogenesis of the disease. Early studies were hampered by limited understanding of the HLA genes and by primitive testing reagents.^{99–103} In a case-control study from Louisiana, Leech et al.¹⁰⁴ observed an increased frequency of HLA-CW5 among black men with myeloma. More recently, a larger study from the NCI observed an increased risk of myeloma among both blacks and whites associated with the HLA-CW2 antigen.¹⁰⁵ The relative risk associated with the CW2 antigen was 5.7 (95% CI, 1.5–26.6) for blacks and 2.6 (95% CI, 1.0–7.2) for whites. The antigen frequencies among black and white controls were similar, but the data raise the possibility of a stronger risk modifying effect associated with CW2 in blacks. Taken together, studies of HLA associations with myeloma support the hypothesis that the incidence of myeloma may be affected by “genetic background,” leaving open the question of whether the effect is immunologic or a result of linkage disequilibrium with particular alleles of other genes in the same region.

The most compelling evidence for the existence of inherited predisposition to myeloma comes from reports of rare families with numerous members affected with myeloma and/or MGUS. Some of these families display patterns of occurrence consistent with autosomal dominant inheritance of a weakly penetrant phenotype.^{95,106–108} Several reports suggest the possibility of genetic anticipation, which refers to the earlier onset of disease with successive generations.^{95,108–110} The latter possibility is particularly interesting in light of the association of inherited disorders showing anticipation with mutations involving instability of trinucleotide repeats.

In the largest series of 39 multiple myeloma families, Lynch et al.¹⁰⁸ described 10 families in which myeloma occurred in the context of clustering of other tumor types. The most common other cancer types were lymphoma, leukemia, breast, colon, and pancreatic carcinomas. A significant increase in the incidence of myeloma has been described in a survey of cancers among

Ashkenazi Jewish BRCA1 and BRCA2 mutation carriers.¹¹¹ In addition, Sobol et al.¹¹⁰ identified a likely mutation in BRCA2 in the proband of a family with multiple cases of both breast cancer and myeloma. Finally, Dilworth et al.¹¹² described a germline mutation in CDKN2A with loss of the normal allele in the bone marrow of a myeloma patient from an otherwise typical family with multiple cases of melanoma. Thus, it is likely that a modest increase in the risk of myeloma may be part of the spectrum of several familial cancer syndromes, the specifics of which will require much larger genetic epidemiological studies.

Conclusions

The most undisputed risk factor for myeloma is increasing age, which is undoubtedly a surrogate marker for genetic insults that contribute directly to the pathogenesis of the disease. Acute high-level radiation exposure (>50–100 cGy) is a predisposing factor, but accounts for few cases of myeloma today. The role of other environmental pathogens in the pathogenesis of the disease is unclear, although there is a suggestion that herbicides may play a role.

The observation of a twofold difference in incidence between blacks and whites is intriguing, and available data suggest that both genetic and environmental or lifestyle factors likely play a role in the higher incidence of both myeloma and MGUS among blacks. Obesity, diet, and occupational risk factors have all been identified as potential contributors to the observed differences in incidence, but these are likely surrogate markers for as yet unidentified specific factors.

An increased risk of myeloma among AIDS patients has been a consistent observation in cohorts from around the world. It remains to be shown whether this observation reflects immunologic or infectious mechanisms, or a failure in immune surveillance mechanisms. In any event, with the aging of the AIDS population as a result of better antiviral and supportive therapies, we will undoubtedly see more multiple myeloma in the context of AIDS.

Inherited predisposition to myeloma remains poorly understood, although several distinct mechanisms are likely in play. It appears that there may be a rare gene (or genes) predisposing to a relatively “pure” myeloma phenotype; inheritance is autosomal dominant, penetrance is incomplete, and there is some suggestion of genetic anticipation in successive generations. In addition, myeloma may be part of the spectrum of several of the cancer family syndromes such as BRCA1, BRCA2, and familial melanoma. Finally, there may be additional more common, but less penetrant genes that predispose to a variety of hemato-lymphoid malignancies including myeloma, non-Hodgkin’s and Hodgkin’s lymphomas, and leukemias.

With the aging of the population upon us, we can expect that the prevalence of myeloma will continue to increase over the next few decades. Enormous progress has been made over the last decade in the development of novel strategies for treatment of myeloma, as discussed elsewhere in this volume. As we move forward, the challenge will be to continue to translate knowledge gained from the Human Genome Project and other basic science research into a greater understanding of the pathogenesis of myeloma, with development of effective strategies for prevention, prognostication, and more effective management of the disease and its complications.

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