Section 1 Overview of myeloma

Chapter 1

Epidemiology of myeloma

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Introduction

Epidemiology is the basic quantitative science of public health; and as such is concerned with the distribution, determinants, treatment, management and potential control of disease. Concentrating on the first two of these, this chapter reviews the epidemiology of myeloma, which accounts for around 1%–2% of all newly diagnosed cancers, and 10%–15% of all newly diagnosed hematological malignancies [1,2].

Descriptive epidemiology

The accurate description of underlying disease patterns and trends provides the foundation for etiological research [3], hence before considering the epidemiology of myeloma in any depth issues relating to disease ascertainment and classification are briefly discussed below.

Cancer ascertainment and classification

Whilst cancer registration has a long history in many countries, particularly those in the more affluent regions of the world, nearly 80% of the global population is not covered by such systems [1]. Furthermore, for hematological cancers, information gathering and dissemination has long been acknowledged to be a major problem even in countries that have adequate collations processes. These concerns were summarized in EUROCARE 4 in their 2009 statement that *"the evolving classification and poor standardization of data collection on haematological malignancies vitiate the comparison of disease incidence and survival over time and across regions"* [4]. The main issue here is that, unlike many other cancers, the majority of hematological neoplasms are diagnosed by using multiple parameters, including a combination of histology, cytology, immunophenotyping, cytogenetics, imaging and clinical information. This range and depth of data is difficult for cancer registries and other researchers to access routinely, forming a barrier both to complete ascertainment and to the collection of diagnostic data at the level of detail required to systematically implement the latest disease classifications. Hence although WHO's 2001 consensus classification of hematological malignancies [5,6] and its successor [2] were adopted into clinical practice almost uniformly around the world, their publication had no immediate effect on population-based cancer registration systems, where data on hematological malignancies continue to be largely presented using the four broad ICD-10 [7] groupings of multiple myeloma, leukemia, non-Hodgkin lymphoma and Hodgkin lymphoma [8–10].

Whilst continued use of ICD-10 may not be as challenging for the myelomas as it is for lymphomas and leukemias, the appropriateness of this topographic classification (which includes, for example, historical entities such as plasma cell leukemia) undoubtedly impacts on the accuracy of the cancer registration process. Misdiagnosis and undernumeration are particularly problematic for multiple myeloma since, in contrast to many other non-hematological cancers, diagnosis and need for treatment are based on a combination of laboratory tests and clinical findings [2,11,12]. Patients with symptomatic multiple myeloma often present at older ages (see variations with age and sex below) with intermittent and non-specific symptoms such as bone pain in the back or chest, as well as general fatigue. Such symptoms are relatively common in the general population, particularly in older people, and patients may present late and referral to appropriate specialists may be delayed.

In addition to symptomatic disease, in countries with well-developed health care systems, around one

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in five myelomas are diagnosed in patients who have no obvious symptoms; such asymptomatic "smoldering" myelomas often being detected through routine blood tests taken for other purposes [12,13]. Furthermore, in addition to smoldering myeloma, pre-malignant monoclonal plasma cell proliferation is estimated to occur in around 3%–4% of those over 50 years in populations of European descent, resulting in the asymptomatic disorder Monoclonal Gammopathy of Undetermined Significance (MGUS) [14]. MGUS, which like asymptomatic myeloma is usually diagnosed incidentally, is poorly captured by most cancer registries since it is grouped in ICD-10 with other neoplasms of uncertain or unknown behavior (D47). Accordingly, most information about the epidemiology of MGUS is derived from specialist patient cohorts [14–19]. With respect to pathogenic process, both MGUS and smoldering myeloma are associated with increased risks of multiple myeloma, the estimated progression rates being around 1% and 10% per year respectively [2,13].

Variations in incidence with age and sex

With a median age of diagnosis of around 73 years, and hardly any cases recorded before 40 years of age, myeloma is predominantly a disease of older people [8,18,20,21]. The strong relationship with older age, together with the fact that the disease is around 40%–50% more common in men than women, is clearly evident in Figure 1.1 which shows the average number of cases and age-specific rates recorded in the UK 2006–08. The trends with age and sex are similar to those reported by other population-based registers: the incidence rising steeply with age and the sex-specific curves diverging as age increases. In affluent regions of the world such as the UK, the fact that more diagnoses occur in women in the oldest age group reflects the fact that more women than men survive to reach old age.

Evidence from specialist registers in Sweden, the USA and the UK suggest that the age and sex distributions of patients diagnosed with MGUS are broadly similar to those of patients diagnosed with myeloma [14,19,22]. This is illustrated in Figure 1.2 where data on myeloma (ICD-03, M9731/3-9732/3) and MGUS (ICD-O3, M9765/1) diagnosed over the six years 2004–10 in the UK's specialist population-based Haematological Malignancy Research Network (www.HMRN.org) are shown. This register collects information on all hematological malignancies and pre-malignancies diagnosed within two UK Cancer Networks (population 3.6 million); and for comparability purposes (Figure 1.2), the numbers of cases are scaled-up to the UK as a whole [18,22]. The similarity between the two distributions is striking: the median ages at diagnosis and age-standardized sex-rate ratios respectively being 73.0 years and 1.4 for myeloma and 72.2 years and 1.4 for MGUS.

Changes over time

Monitoring disease trends over time is a fundamental activity of descriptive epidemiology, with such analyses often yielding important etiological clues.

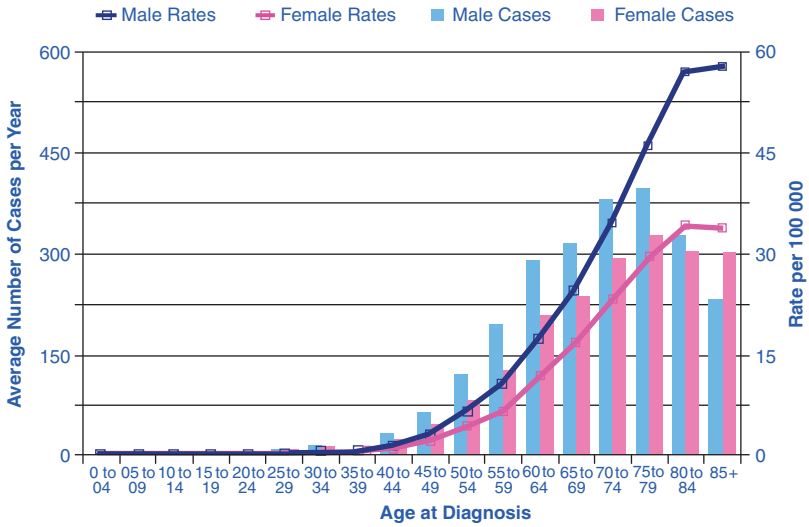

Figure 1.1 Age-specific incidence of myeloma (ICD-10, C90); UK 2006–2008.

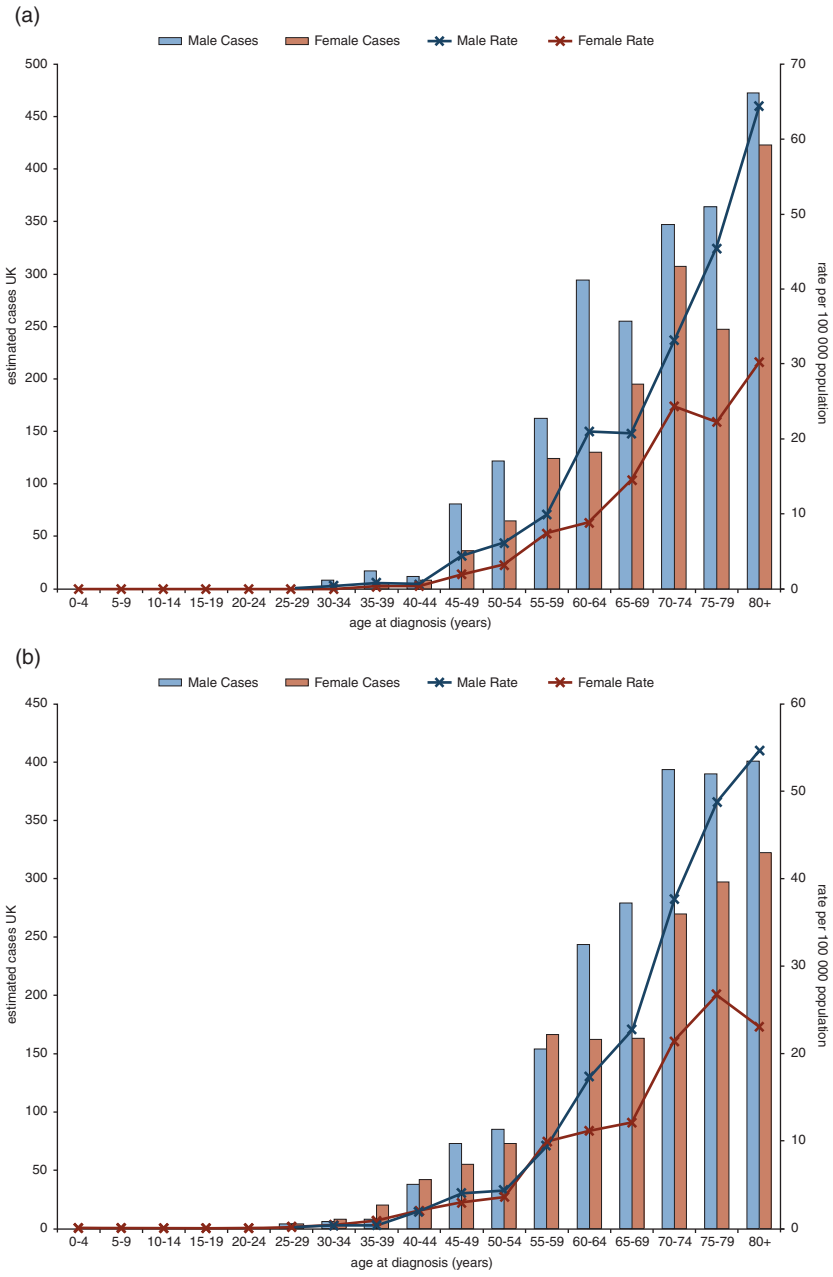

Figure 1.2 Age-specific incidence of (a) myeloma and (b) MGUS (ICD-O3, M9732/3 + 9731/3 and 9765/1 respectively); HMRN 2004–10.

Indeed, there are many examples in the field of cancer epidemiology where this has been the case, particularly in relation to the identification of hazardous occupational and environmental exposures. In this context, the temporal changes reported for myeloma in earlier decades are marked, as can be seen from Figure 1.3, which shows the estimated age-adjusted incidence rates from the Surveillance, Epidemiology and End Results (SEER) Program in the United States (www.seer.cancer.gov).

The increase in the estimated incidence of myeloma seen in the SEER registries in the 1970s and 1980s (Figure 1.3) was mirrored in England and Wales, as well as several other European populations [20,23].

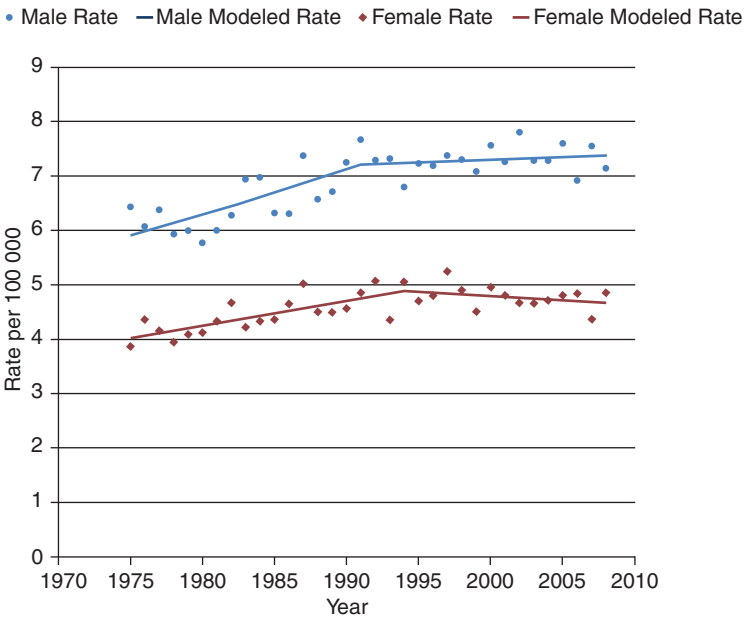

Figure 1.3 Age-adjusted incidence rates by sex; SEER 9 areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah and Atlanta), 1975–2008.

However, in the SEER regions and elsewhere the estimated rates of disease in both males and females have been stable now for more than a decade; and there is evidence from several long-term specialist registries that the age-adjusted incidence may, in fact, have been stable in the 1960s and 1970s in both Europe and America [20,24]. Indeed, it seems likely that the upward trend seen in many national registries in past decades may have been due to an increase in the efficiency of case ascertainment, rather than being reflective of any underlying increase in disease frequency.

Although the incidence of multiple myeloma may be relatively stable, the prevalence of the disease in more affluent populations is increasing markedly as survival improves following the introduction of several novel therapies in recent decades [11,25–29]. With respect to current trends, crude and relative survival curves (the rate of survival of patients compared to that of the general population) of patients newly diagnosed with myeloma (ICD-03, M9731/3 -9732/3; N = 1226) and/or MGUS (ICD-O3, M9765/1; N = 1134) in the UK's HMRN region 2004–9 (followed through to December 2011) are shown in Figure 1.4. The one and five year relative survival estimates for multiple myeloma diagnosed at any age were around 72% (85% $<$ 60 years; 68% $\geq$ 60 years) and 41% (64% $<$ 60 years; 34% $\geq$ 60 years) respectively. These population-based estimates are roughly twice those reported in past decades in Europe and the USA [26,29]. Nonetheless, although survival times are continuing to improve across all ages and in both sexes, multiple myeloma currently remains incurable, with survival times varying by age, stage and performance status [26,29].

As would be expected, the crude and relative survival estimates for patients diagnosed with MGUS (Figure 1.4b) are more divergent than those for myeloma (Figure 1.4a); confirming that many patients with MGUS are likely to die from competing causes. Even so, the one and five year relative survival estimates, which are around 93% and 87% respectively, also confirm that mortality among patients diagnosed with MGUS is marginally increased above that expected on the basis of rates in the general population [19]. Such patterns reflect, at least in part, the fact that some patients subsequently developed multiple myeloma (or another hematological malignancy) and others had MGUS detected as part of routine testing for another more serious disease. The potential contribution that MGUS itself may play is currently unknown.

International incidence variations and ethnicity

Incidence rates from IARC's most recent series of estimates are shown in Figures 1.5 and 1.6. Of the

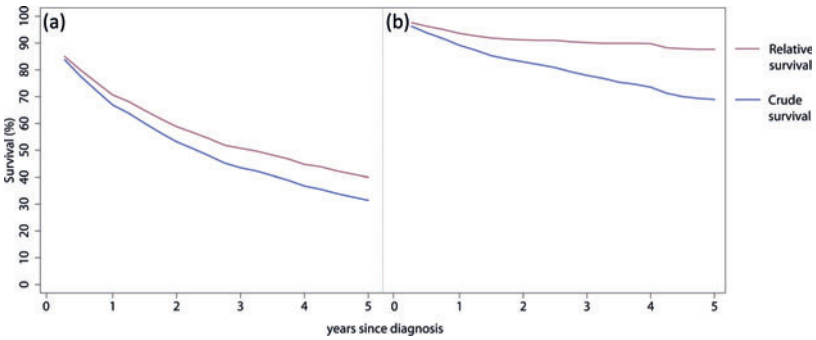

Figure 1.4 Crude and relative survival of (a) myeloma and (b) MGUS (ICD-O3 = M9732/3 + 9731/3 and 9765/1 respectively); HMRN diagnoses 2004–2009, followed-up to end of 2011.

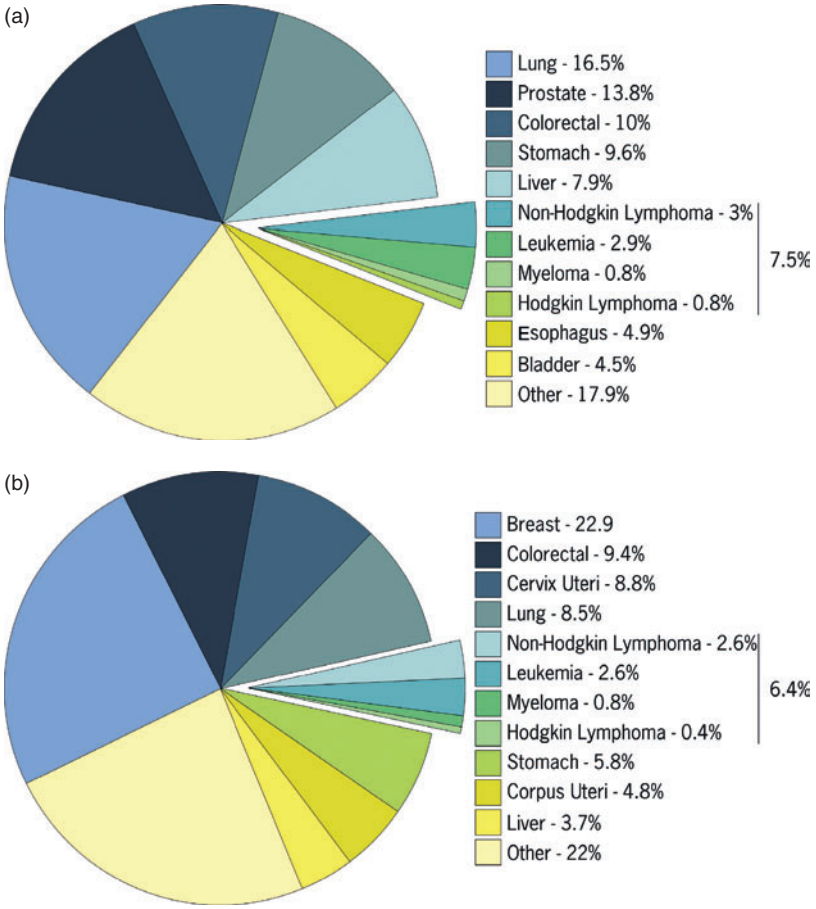

Figure 1.5 Estimated global cancer frequency for (a) males and (b) females; GLOBOCAN.

12.67 million new cancers estimated to have occurred around the world in 2008, 6.62 million were in men and 6.05 million were in women (Figure 1.5). Combined, hematological malignancies were estimated to comprise around 7.5% of cancers in males and 6.4% in females, with myelomas accounting for around 12% of hematological malignancies in both men and women (www.globocan.iarc.fr/).

The age-standardized incidence rates for both sexes combined are globally distributed in Figure 1.6.

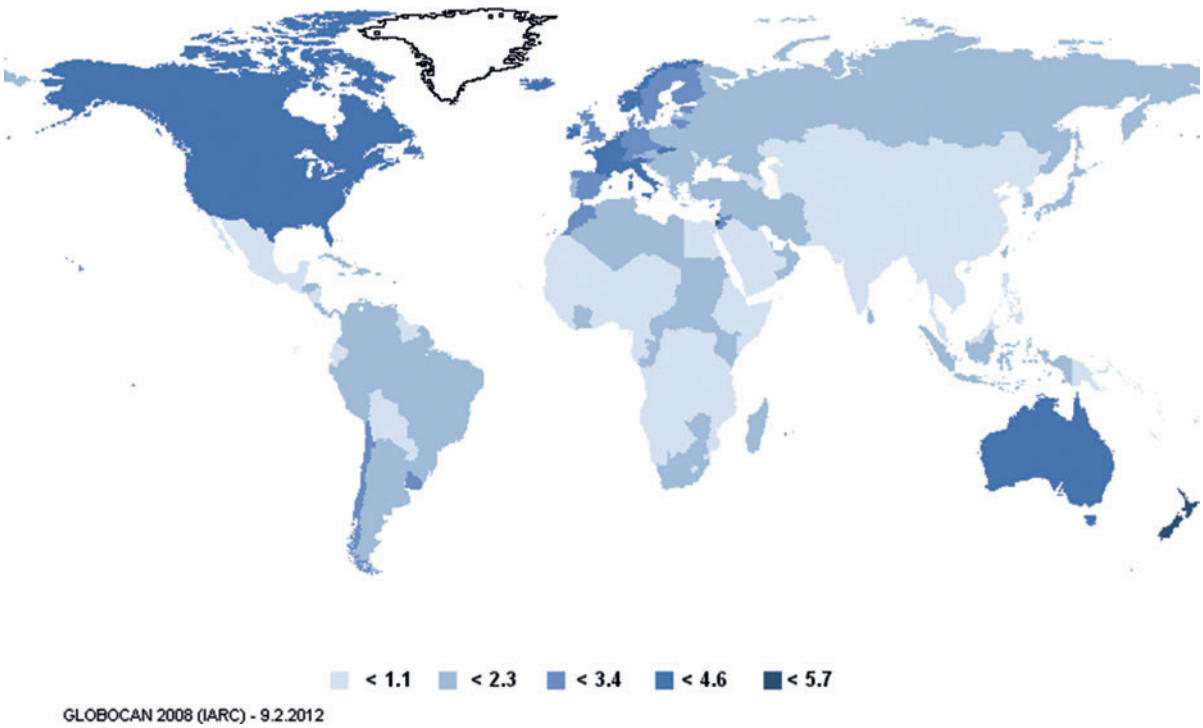

Figure 1.6 Estimated numbers and age-standardized (world population) incidence rates by region for myeloma, both sexes combined; GLOBOCAN.

In general, the geographical pattern is dominated by the high rates in the more economically developed regions of the world: the estimated rates being several fold higher in North America, Europe and Australasia than in large parts of Africa and Asia. However, for the reasons stated in previous sections of this chapter, problems with disease classification and ascertainment make these patterns difficult to interpret with any degree of confidence. Indeed, it seems highly likely that the global estimates shown in Figures 1.3 and 1.4 are conservative, both in terms of the absolute numbers of myelomas occurring and also the proportion of total cancers that they account for. In this regard it is interesting to note that the global patterning of other cancers, including the lymphomas which share many of the same ascertainment problems as myeloma, are broadly similar to that shown in Figure 1.6 [10,30].

Significantly, there is also accumulating evidence that, compared with persons of European descent, both myeloma and MGUS are, in fact, at least twice as common in persons of African descent and lower in those of Asian descent [9,16,17,31–34]. Indeed, the two–three fold increase in myeloma rates observed in men and women of African descent for over 40 years in the USA [34] has recently been confirmed in UK national data for 2003–2006 [9]. Furthermore, a number of US studies have shown similar racial differences for MGUS [14,31]. More importantly perhaps, the prevalence of MGUS has been shown to be comparatively high in Ghanaian men [17,35] and comparatively low in Japanese populations, especially among women [16]. Taken together, these observations suggest that the international variations seen in Figure 1.6 are likely to reflect poor case ascertainment rather than real variations in incidence. Indeed, it is possible that future studies will reveal that the age-specific rates of plasma cell neoplasms are highest in Africa and lowest in Asia.

Etiology

As with most cancers, the causal pathway leading to the development of myeloma is likely to involve the interaction of several individual genetic and environmental components. Examination of descriptive

epidemiological patterns and trends (see above) has revealed associations with increasing age, male sex, and ethnicity; the prevalence of MGUS displaying broadly similar associations [15–18,35], although interestingly no increase in MGUS with age was found in the survey of Ghanaian men [17]. In addition, MGUS itself is a precursor to multiple myeloma, but the frequency of progression is quite low, seemingly occurring at a constant rate of around 1% per year in all populations that have been studied [31].

Genetic variation and family history

Several studies have reported that first-degree relatives (parent, sibling or child) of myeloma or MGUS patients are two to three times more likely to develop myeloma or MGUS themselves, in comparison with people without a close family history of these conditions [36–39). This, coupled with the distributional differences with ethnicity and sex, has resulted in considerable speculation and wide-ranging research in the area of genetic susceptibility [40–42].

Neither myeloma nor MGUS are single disease entities [13,44], and it seems likely that genetic variation in several pathways could contribute to their pathogenesis. Genes of interest obviously include those involved in normal plasma cell development, as well as inflammation and immune response. In addition, genes involved in key metabolic pathways such as DNA repair, the metabolism of folate and the metabolism of various xenobiotics have received much attention [43,45]. Thus far, however, few consistent genetic findings have emerged; although results from a recent genome-wide association study (GWAS) in a European population led investigators to conclude that genetically determined dysregulation of *MYC* could be a common mechanism underlying several mature B-cell malignancies [40].

Infections and immunity

As with other mature B-cell malignancies, associations with infection and factors potentially causing immune dysregulation have been the focus of much of the etiological research on plasma cell malignancies conducted to date. In general, for broad categories of autoimmune, infectious and inflammatory conditions relative risks ranging between 1.1 and 1.5 have been reported for both subsequent myeloma and MGUS development – such risks being similar to, but weaker than, those seen for many of the lymphomas [46,47]. In general, reported relationships have tended to be non-specific, one of the most consistent associations being that seen for pernicious anemia, although the underpinning mechanism remains to be elucidated [46,47]. In addition, as might be expected, the risks of both myeloma and MGUS have been observed to be increased in immunocompromised individuals, such as transplant recipients and those infected with HIV, although again the magnitudes are generally smaller than those seen for many of the non-Hodgkin lymphomas [14,48].

Diet and obesity

As well as infectious agents and comorbidities associated with the immune system, several recent studies have reported on the relationship between anthropometric characteristics and myeloma and/or MGUS [49–52). Increased risks ranging from around 1.1 to 2.0 have been reported for obesity, measured as having a body mass indexes (BMI kg/m^2) of 30 or more; and studies that have used other anthropometric measures, such as waist-to-hip ratio, have found similar results [49–52]. Importantly, as with the associations for autoimmunity these relationships are similar to those reported for other B-cell malignancies – and indeed for several other cancers [49,53]. The important public health message here being that, if such associations are real, then disease could be prevented by maintaining a healthy body weight. However, whilst a wide - range of biological mechanisms have been suggested as possible explanations for the association between excess body weight and plasma cell myeloma, including the effects on growth factor signaling and various inflammatory processes, the underpinning mechanisms remain to be clarified (49–53).

Environmental exposures

A number of studies have examined the relation between myeloma and various physical and chemical exposures, notably ionizing radiation in the case of the former and various organic compounds in the case of the latter. Ionizing radiation is mutagenic, but debate surrounds the potentially hazardous effects of exposure at the low-levels encountered in some workplaces (such as nuclear plants) and certain medical procedures (such as X-rays). With respect to myeloma, the available evidence does not support an

association with levels of exposure [54,55]. Likewise, evidence that myeloma is associated with exposure to organic pesticides and/or solvents is weak and inconsistent [56,57].

Conclusion

Multiple myeloma is currently incurable, accounting for around 10% of all hematological malignancies in Western populations. It is a heterogeneous disease with respect to presentation, biological characteristics and response to treatment; its etiology is poorly understood. Currently, the main identified risk factors are old age, male sex, personal history of MGUS, family history of plasma cell disease, and African ethnicity; and the underpinning reasons for these associations are the subject of current research. Within populations, disease incidence is comparatively stable but, following the introduction of new therapies, disease prevalence is rising markedly.

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