Epidemiology of Multiple Myeloma

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Contents

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Abstract Multiple myelomas are a less frequent cancer site among both sexes. On a worldwide scale, it is estimated that about 86 000 incident cases occur annually, accounting for about 0.8% of all new cancer cases. About 63 000 subjects are reported to die from the disease each year, accounting for 0.9% of all cancer deaths. Geographically, the frequency is very unevenly distributed in the world with the highest incidence in the industrialised regions of Australia / New Zealand, Europe and North America. Incidence and mortality seem to be stable in Asian countries and to increase slowly over the decades among whites in the western countries. The etiology is poorly understood. This depends partly upon the fact that the risk factors which play a major role for malignant diseases in general, such as tobacco consumption and diet have not been found strongly involved into multiple myeloma etiology. Nevertheless, some consistency seems to be in the findings about a risk elevation with obesity and a slightly decreased risk with high fruit consumption. Despite some contradicting results, indications to a role of ionising radiation persist. Finally, infections with HIV and hepatitis C virus appear related to an elevated multiple myeloma risk. Currently, large efforts are undertaken to unravel the etiology of malignant lymphoma including those of multiple myeloma.

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2.1 Descriptive Epidemiology

Multiple myelomas are a less frequent cancer site among both sexes. On a worldwide scale, it is estimated that about 86,000 incident cases occur annually (47,000 males and 39,000 females), accounting for about 0.8% of all new cancer cases. About 63,000 subjects are reported to die from the disease each year (33,000 males and 30,000 females), accounting for 0.9% of all cancer deaths (Parkin et al. 2005). In terms of age-standardized rates, the annual incidence rates amount to 1.7 per 100,000 in males and 1.2 in females, and the mortality rates to 1.2 (males) and 0.9 (females). Among the hematological malignancies, the proportion of multiple myelomas ranges in a magnitude of 15–20% (Devesa et al. 1992; Becker et al. 2007).

Geographically, the frequency is very unevenly distributed in the world with the highest incidence in the industrialized regions of Australia/New Zealand, Europe, and North America (Fig. 2.1). The ethnic comparison within the population of the USA shows an almost doubled occurrence of multiple myeloma among the blacks compared to the whites, while people of Asian origin, especially Chinese and Japanese, experience a much lower incidence (Coleman et al. 2008; Parkin et al. 2005).

Incidence and mortality seem to be stable in Asian countries and to increase slowly over the decades among whites in the western countries and blacks in the USA (see Fig. 2.2). The rates and trends for the Asian immigrants into the USA resemble those of the respective countries of origin (Hirabayashi and Katanoda 2008).

The reasons for these differences and the increasing trend among the whites in the western countries are unknown.

The average 5-year survival is about 15–20% with a wide range of survival between some few years to 10 years or more.

2.2 Etiology

The etiology of multiple myeloma is poorly understood. This depends partly upon the low frequency of the disease which makes its investigation difficult; and it partly depends upon the fact that the risk factors which play a major role for malignant diseases in general, such as tobacco consumption and diet (see Wynder and Gori 1977, Doll and Peto 1981 or Harvard Report on Cancer Prevention 1996), have not been found obviously involved in multiple myeloma etiology. However, major efforts are currently undertaken to unravel the etiology of hematological malignancies in general and of multiple myeloma in particular (Boffetta et al. 2007).

2.2.1 Tobacco

In most of the studies which investigated a potential association to multiple myeloma, no risk increase has been found (Alexander et al. 2007). Nevertheless, in a more recent (Nieters et al. 2006a) and a few of the older studies cited in Alexander et al., an elevated risk was observed (RR = 2.4 in males, RR = 2.9 in females for current smoker, respectively) so that the matter appears to still be unresolved. The study of Nieters et al. indicated that the latency between tobacco consumption and occurrence of hematological malignancies might be particularly long, making the confirmation of an association difficult. On the other hand, the recent analysis of the large European Prospective Investigation

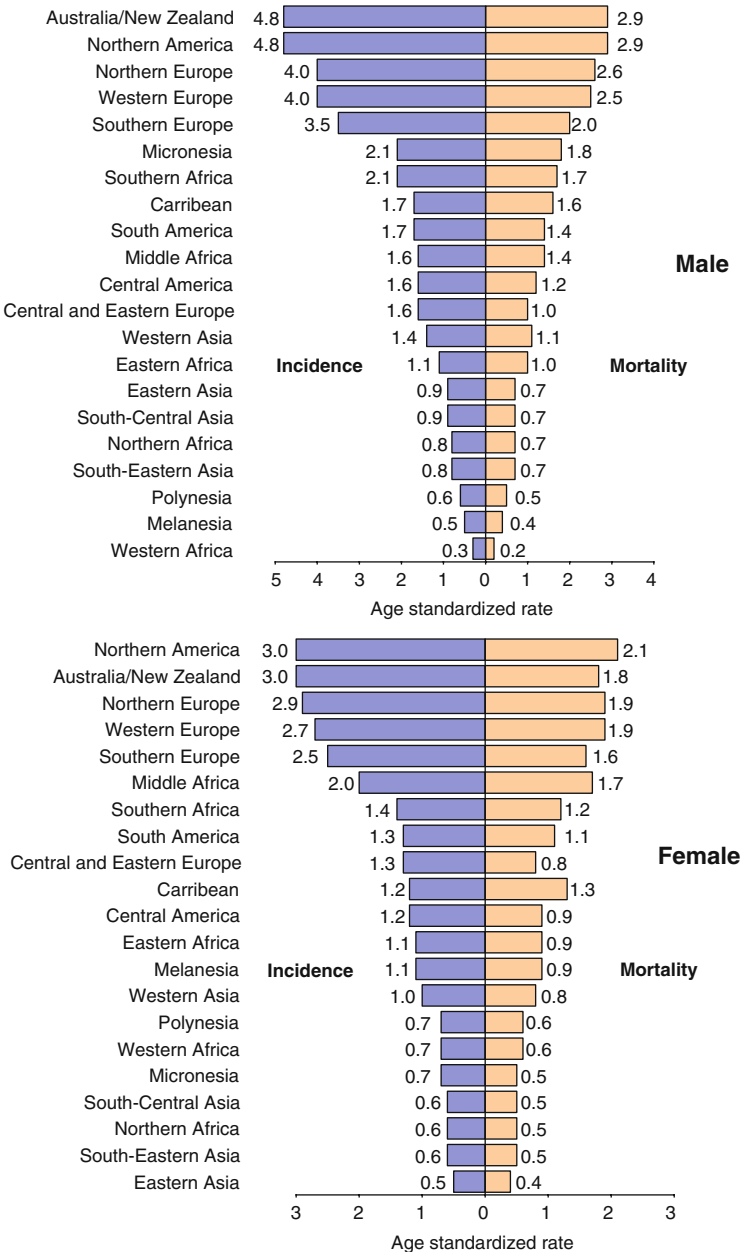

Fig. 2.1 Incidence and mortality rates for multiple myeloma. Rates are age-standardized with world standard as reference and given per 100,000 (Parkin et al. 2005)

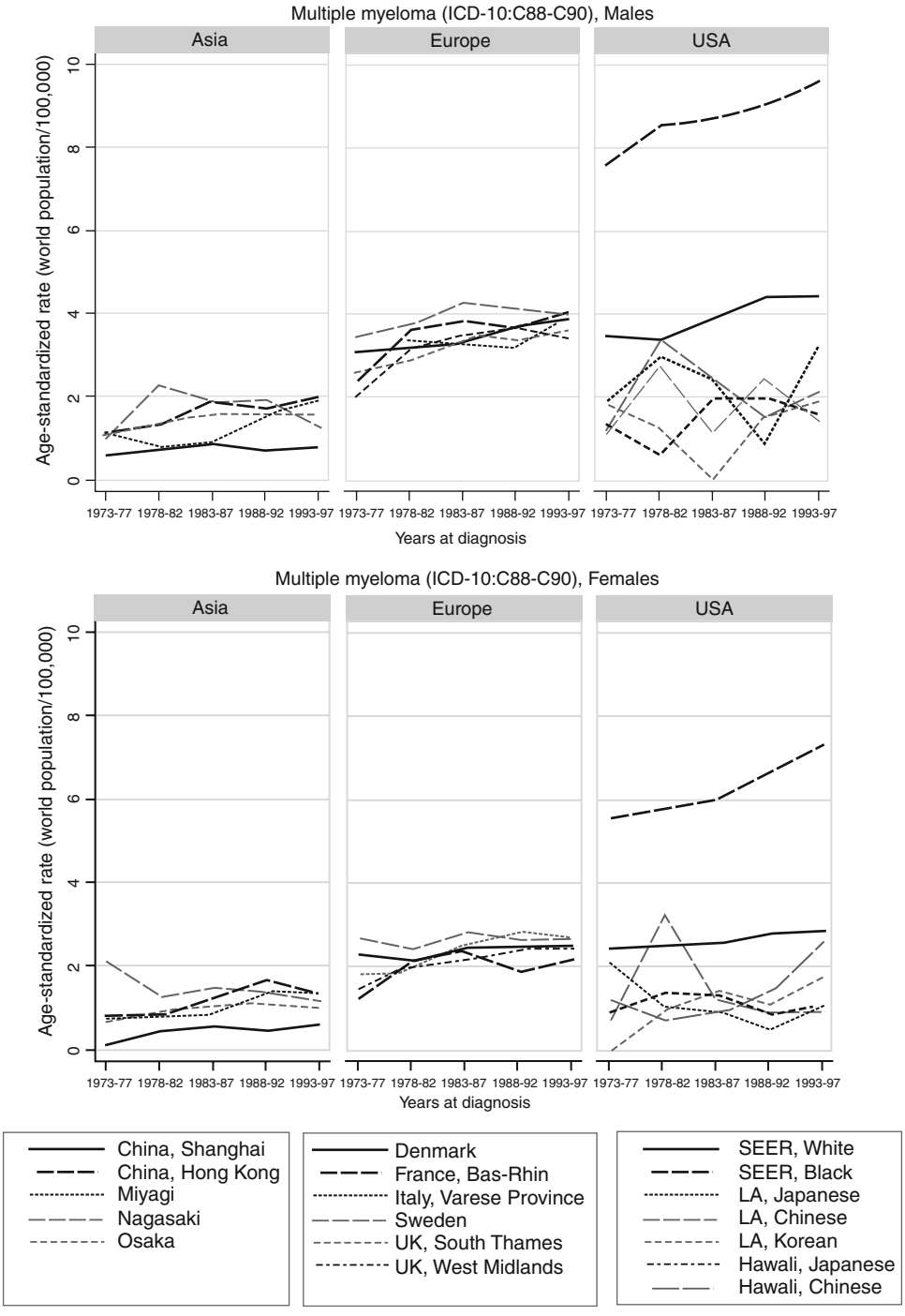

Fig. 2.2 Incidence of multiple myeloma in different parts of the world and different ethnic groups within the USA

into Cancer and Nutrition EPIC could not confirm this notion (Nieters et al. 2008). Thus, the currently available data strongly suggest that smoking is, if at all, at most a marginal risk factor for multiple myeloma.

2.2.2 Alcohol

Similarly, most investigations about the role of alcohol consumption reported a null result, only one an elevated risk in a particular combination of alcoholic beverages and two a decreased risk (Alexander et al. 2007). However, even those recent studies which reported a decreased relative risk with alcohol consumption for lymphoma in general could not observe this effect in multiple myeloma (Nieters et al. 2006a). Thus, also for alcohol consumption, the currently available data do not suggest a relevant contribution to multiple myeloma etiology.

2.2.3 Diet

A multitude of nutritional epidemiologic studies carried out over the past decades suggests divergent effects of different food groups on carcinogenesis. Thus, studies are usually focused on the respective food groups such as fruits and vegetable, meat, fish, etc. whose effects seem to range from potentially protective effects (e.g., high consumption of fruits and vegetable) for some cancer sites to risk elevations (high consumption of specified types of meat).

For multiple myeloma, several studies reported a decreased relative risk with a high consumption of fruits and vegetable (Tavani et al. 1997; Brown et al. 2001; Valjinac et al. 2003) which was confirmed by a recent evaluation of EPIC (Rohrmann et al. 2007). In this evaluation, an effect was seen for fruits, especially citrus fruits, but not for vegetable consumption. On the other hand, previous reports found inverse associations also for high vegetable consumption (see Alexander et al. 2007).

For meat consumption, a current, yet unpublished analysis of EPIC data provided overall a null result which is consistent with previous findings (see Alexander et al. 2007), but some indication to a potentially elevated relative risk for higher intake of chicken meat (S. Rohrmann 2009 personal communication).

Inconsistent results were reported from several studies on fish consumption from which several showed a decreased relative risk while a few also found risk increases (Alexander et al. 2007).

Thus, the current data on effects of diet on multiple myeloma are inconclusive, whereby the results on high intake of fruits and vegetable indicate the highest potential of a true, and potentially protective, effect.

2.2.4 Obesity

Elevated relative risks for obese subjects were reported from several epidemiologic studies, mainly case-control studies (Alexander et al. 2007; Bergström et al. 2001; Larsson and Wolk 2007). Though the recent evaluation of EPIC on body height and weight could not confirm an association to obesity or body fatness (Britton et al. 2008), with other prospective studies, an association could be confirmed (Birmann et al. 2001; Reeves et al. 2007). In the latter cohorts, the relative risk appeared to increase with increasing body weight. Thus, for obesity, the consistency of reports on a risk-increasing effect is relatively high though not yet finally conclusive. Supportive for a true association may be the fact that obese subjects seem to have elevated IL-6 levels and bioavailability of insulin growth factor which appears also related to development of multiple myeloma and survival from the disease (Ge and Rudikoff 2000; Xu et al. 1997), seems also to be affected by obesity (Bianchini et al. 2002; see also Birman et al. 2007).

2.2.5 Physical Activity

Physical activity is considered an established protective factor for several cancer sites (IARC 2002), but has not yet been investigated thoroughly for multiple myeloma. However, Birman et al. (2007) reported from three studies on obesity which also took physical activity into account. They did not observe any deviation of risk from unity (Blair et al. 2005; Oh et al. 2005; Pan et al. 2004). The results of Birman et al. (2007) were consistent to those null results.

2.2.6 Hormonal Factors

One reason for taking hormonal factors into account is that the risk for getting the disease is consistently higher in males than in females. Hormonal factors may affect this gender difference. Another reason is that lifestyle factors, such as obesity, may modulate the hormonal status of subjects (see above kaaks and Lukanova 2002).

Quite a number of studies referenced in Alexander et al. (2007) examined hormone replacement therapy (HRT), age at first birth, and number of pregnancies, the latter factors which have been found in several studies related to other lymphoma entities. None of them showed significant associations to multiple myeloma.

2.2.7 Environment and Occupation

Occupational settings are frequently used in epidemiology to investigate both occupational cancer risks as well as potential environmental hazards. Exposures which occur in the environment as well as in industry can in many instances better be investigated in the industrial environment since the exposures are frequently higher, can better be estimated or measured, and may have a longer and again better assessable duration during lifetime. Obtained results may be extrapolated by quantitative risk modeling to the exposure levels found in environmental settings.

A multitude of occupational-epidemiologic studies provided results for multiple myeloma and have been reviewed in Alexander et al. (2007). Particularly, exposures to pesticides, solvents, especially benzene, other chemicals, and hair dyes have been addressed. Though some studies reported increased relative risks and some other studies reported decreased relative risks, the overall balance appeared inconsistent and did not provide evidence for a major role of these agents on multiple myeloma etiology. The results for radiation will be presented separately below.

On the other hand, it must clearly be stated that many of the studies were based on small numbers which make – as already mentioned above – it difficult to detect moderate or late occurring hazards. Thus, further research will be needed and will move the inconclusive balance in the one or other direction. In this sense, a recent study of Costantini et al. (2008) reported an increased risk of multiple myeloma after benzene exposure and long latency.

2.2.8 Ionizing Radiation

Ionizing radiation was long considered an established risk factor for multiple myeloma based on the data of the atomic-bomb survivor studies (Alexander et al. 2007). However, later evaluations of these data taking a longer follow-up into account could not confirm the previous reports (Preston et al. 1994) so that the matter is open again. Preston et al. drew a parallel to CLL which are known to be unrelated to ionizing radiation and which have the origin from terminally differentiated B lymphocytes in common with multiple myeloma, suggesting biological

plausibility that also multiple myeloma may be unrelated to ionizing radiation.

Other exposures to ionizing radiation may occur in medical applications in the context of diagnostic radiological imaging or radiotherapy for both patients as well as medical staff. None of these circumstances seemed to provide an excess risk for multiple myeloma.

A quite different setting may occur by occupational low-level radiation in nuclear industry since these exposures may be long-lasting in contrast to the shorter and high-dose atomic-bomb exposure. Though the overall balance about the existing studies appears also contradictorily, a recent carefully conducted large study provided indications to a statistically significant overall cancer risk and elevated excess risks for specified cancer sites including multiple myeloma. Nevertheless, the result for multiple myeloma was only marginally statistically significant and needs further confirmation (Cardis et al. 2007).

Finally, the effect of a chronic exposure to alpha-radiation could be investigated in the context of iatrogenically induced cancer death by administration of Thorotrast. Thorotrast was the brand name of a stabilized colloidal solution of thorium dioxide which was used as an X-ray contrast medium between 1930 and 1950. The administration of the medium led to a lifelong chronic α-particle irradiation by thorium decay products in the organs of deposition. Two of the overall four large cohort studies reported an increased myeloma risk among the exposed subjects (Visfeldt et al. 1995; Becker et al. 2008).

2.2.9 Inheritance

More consistent than for other candidate risk factors appear the data on a potential familial aggregation of multiple myeloma. Based on the Swedish family–cancer database, Hemminki et al. (2004) observed an elevated relative risk among offsprings of parents with a diagnosis of multiple myeloma. Several other studies reported more generally an increased risk in first-degree relatives of subjects with a diagnosis of multiple myeloma or hematopoietic malignancies in general (Alexander et al. 2007). The risk elevation was not found in second- or third-degree relatives and not for cancers other than of the hematopoietic system.

2.2.10 Medical History, Viruses, Immunological Conditions

Since lymphomas are malignancies of cells of the immune system, it is suggestive to look for associations with other immunological disorders. Thus, for B-cell lymphoma excluding multiple myeloma, previous studies reported relatively consistently an inverse association to atopic diseases. For multiple myeloma, however, the relationship is much more inconsistent. Alexander et al. (2007) summarized studies which observed an inverse association, but also studies with null results or even elevated relative risks in subjects with allergies. Thus, though more recent studies supported again the notion of an inverse association (Becker et al. 2004, 2007), the matter appears still unresolved.

Correspondingly, the results on associations with autoimmune diseases, childhood, or adult infections are inconclusive with two important exceptions: An elevated relative risk was shown in HIV-infected subjects (Goedert et al. 1998; Grulich et al. 1999) and among hepatitis C virus–infected subjects. The latter association was significant in a Swedish cohort (Duberg et al. 2005), and nonsignificant in a European case-control study (Nieters et al. 2006b).

2.3 Summary

In conclusion, most of the so far examined factors provided either null or inconsistent results (see Table 2.1). Some consistency seems to be in the findings about a risk elevation with obesity

Table 2.1 Summary of associations between established or suspected risk factors and multiple myeloma (Alexander et al. 2007)

Factor	Approximate range of observed associations	Comparison
Accepted risk factors		
Increasing age	12–16	<65 vs. ≥65
Male gender	1.5	Males vs. females
Black race	2–3	Black race vs. white race
Positive family history	1.5–5	Positive family history of MM or LHC in a first-degree relative with MM or LHC
MGUS	25+	MGUS positive vs. MGUS negative
Possible risk factors		
Obesity	1.2–2	Obese (BMI ≥ vs. normal range BMI) (BMI < 25)
Low fish consumption	1.2–1.7	Low vs. high fish consumption
Low green vegetable consumption	1.1–2.5	Low vs. high green vegetable consumption
AIDS	4–12	AIDS diagnosis vs. no AIDS diagnosis
Herpes zoster/shingles	1.2–2.6	History of infection vs. no history of infection
Epidemiologic data inconsistent		
Hair dye use		
Overall exposure	0.8–1.5	Any exposure vs. never exposed
Permanent hair dye	0,6–1.9	Permanent hair dye exposure vs. never exposed
Light hair dye coloring	0.9–1.3	Light hair dye vs. never exposed
Dark hair dye coloring	1.3–3	Dark hair dye exposure vs. never exposed
Farming occupation	1.1–1.2	Farmers vs. nonfarmers[a]
Wood dust or wood exposures	0.7–2.6	Wood dust or wood exposure vs. no exposure
Chronic immune stimulation conditions and/or vaccinations for such conditions[b]	0.7–2	History of chronic immune stimulation condition and/or vaccination vs. no exposure
Autoimmune disease (excluding AIDS		
General category	0.7–2	History of any autoimmune disease vs. no history of autoimmune disease
Rheumatoid arthritis	0.7–2.3	History of rheumatoid arthritis vs. no history of rheumatoid arthritis
Do not appear to be risk factors		
Smoking	0.8–1.3	Current smokers vs. never smokers
Alcohol	0.4–1.5	Alcohol consumption vs. no consumption
Pesticides[c]	0.8–1.4	Pesticide exposure vs. no
Organic solvents		
Overall exposure[d]	0.6–1.5	Any organic solvent exposure vs. no exposure
Benzene	0.7–1.4	Benzene exposure vs. no exposure

(continued)

Table 2.1 (continued)

Factor	Approximate range of observed associations	Comparison
Trichlorethylene	0.8–1.4	Trichlorethylene exposure vs. no exposure
Radiation		Radiation exposure vs. no exposure
Nuclear workers	0.7–1.1	Asbestos exposure vs. no exposure
Occupational therapeutic or diagnostic	0.7–1.4	History of allergic conditions vs. no allergic conditions
Asbestos	0.5–3	
Allergic conditions	0.6–2	

[a]Findings based on meta-analyses of 12–32 studies

[b]Chronic immune stimulation conditions include influenza, polio, smallpox, and tetanus immunizations and a history of tuberculosis, scarlet fever or rheumatic fever

[c]Findings based on general categories of exposure to pesticides or herbicides including applicators and sprayers.

[d]Findings based on studies of petroleum workers, painters, benzene, trichloroethylene, styrene, and general categories of organic solvents

and a decreased risk with high fruit consumption. Some indications to a role of ionizing radiation persist. Finally, infections with HIV and hepatitis C appear related to an elevated multiple myeloma risk. Current worldwide coordinated research activities promise to promote knowledge about the etiology of the disease.

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