RESEARCH COMMUNICATION

Risk Factors for Multiple Myeloma: Evidence from the Japan Collaborative Cohort (JACC) Study

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Abstract

This study assessed the association of multiple myeloma (MM) with age, body mass index (BMI, kg/m$_2$), physical activity, occupational history, and medical history for a Japanese cohort of 46,157 men and 63,541 women aged 40-79 years followed during 1988-2003 years. Cox proportional hazard model was mainly used to estimate the age and sex adjusted hazard ratio (HR) of MM including 95% confidence interval (CI) for both sexes. Same model, adjusted for age, was also used for each sex. In total, 98 MM deaths (men=49 and women=49) was observed for both sexes. Higher age groups (60-69 and 70-79 years) experienced significantly higher unadjusted HR of MM than the age group of 40-49 years. Men revealed significantly higher age-adjusted MM than women (HR=1.5; 95% CI=1.0-2.2). For both sexes, higher BMI of ≥30 kg/m$_2$ (HR=2.8; 95% CI=1.0-7.7), walking ≤30 minutes/day (HR=2.0; 95% CI=1.2-3.4), worried about personal relationship in working place (HR=2.3; 95% CI=1.3-4.2), restricted own pace in working place (HR=1.9; 95% CI=1.0-3.4), and history of peptic ulcer (HR=1.7; 95% CI=1.0-2.7) significantly increased age and sex adjusted MM risk. Some of the above-mentioned significant associations became insignificant for age adjusted sex specific analyses. However, these findings should be validated by further epidemiologic studies in Japan before generalization.

Key Words: Risk factors - multiple myeloma - cohort study - Japan

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Introduction

Multiple myeloma (MM) is a hematologic cancer, more specifically a cancer of the plasma cell. Plasma cells that develop from B cells produce different types of proteins called antibodies or immunoglobulins (Ig), abbreviated as IgA, IgD, IgE, IgG, and IgM. These antibodies are important part of the immune system and work with other parts of the immune system to help protect the body from infections and diseases due to germs and other harmful substances (Multiple Myeloma Research Foundation, 2001; National Cancer Institute, 2004). When B cells are damaged, the resulting plasma cells become malignant (called myeloma cells), meaning they continue to divide unchecked and generating more malignant plasma cells. These cells then travel through the bloodstream and gather in the bone marrow, where they damage tissue. Adhesion molecules found on the surface of malignant plasma cells allow them to attach to the bone marrow structural cells (called stromal cells) and can cause myeloma cells to grow. Cytokines (also called chemical messengers) are produced by both myeloma cells and stromal cells, and some cytokines such as interleukin 6 (IL-6) stimulate the growth of myeloma cells and inhibit natural cell death (called apoptosis) (Multiple Myeloma Research Foundation, 2001).

MM is the third most prevalent blood cancer in Japan, after non-Hodgkin's lymphoma and myeloid leukemia (Health and Welfare Statistics Association, 2004). It constituted 0.8% of all cancers worldwide with 86,000 new cases yearly (Parkin et al., 2005), slightly more than 10% of hematologic cancers (Kyle et al., 2003). According to the data of 2004, it constituted 1.2% of all cancer deaths in Japan (Health and Welfare Statistics Association, 2004). Incidence rate vary from 0.4 to 5 per 100,000, and is very rare in persons under age 40. The incidence is high in North America, Australia, New Zealand, northern and western Europe compared with Asian countries. Recently a slow increase in incidence and mortality from MM is observed in most regions of the world (Kyle et al., 1994; Kyle et al., 2003; Parkin et al., 2005) including Japan (Sonoda et al., 2005).

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The reported increased incidences during the past few decades is probably related more to the aging population, and improve diagnostic techniques than to an actual increase (Kyle et al., 1994; McKean-Cowdin et al., 2000; Kyle et al., 2003; Phekoo et al., 2004; Anagnostopoulos et al., 2005). Unfortunately, the etiology of MM remains largely unknown (Multiple Myeloma Research Foundation, 2001; Zaidi and Vesole, 2001; National Cancer Institute, 2004), although epidemiologic researches have shown that people with certain risk factors are more likely than others to develop MM (National Cancer Institute, 2004). For instance, chronic immune stimulation, autoimmune disorders, exposure to ionizing radiation, exposure to certain chemicals, occupational exposure to pesticides or herbicides, and occupational exposure to dioxin are some of the factors that increase the risk of MM (Herrinton et al., 1993; Zejda et al.; 1993; Multiple Myeloma Research Foundation, 2001; Zaidi and Vesole, 2001; National Cancer Institute, 2004; Parkin et al., 2005; Sonoda et al., 2005). Obesity (Brown et al., 2001; National Cancer Institute, 2004) or greater adiposity may increase the risk of MM (Pan et al., 2004; Samanic et al., 2004; Blair et al., 2005) significantly for both men and women (Calle et al., 2003).

Age, race, and gender may also affect MM (Tsuchiya et al., 1994; Multiple Myeloma Research Foundation, 2001; Zaidi and Vesole, 2001; Garcia-Sanz et al., 2004; National Cancer Institute, 2004; Anagnostopoulos et al., 2005). Some other prognostic factors for survival of MM patients are bone marrow plasma cell, hemoglobin, γ_2Microglobulin (γ_2M), bone lesions, serum calcium, low platelet count, serum albumin, serum creatinine, and C-reactive protein (Tsuchiya et al., 1994; Kaneko et al., 2002; Kyle et al., 2003; Garcia-Sanz et al., 2004; Anagnostopoulos et al., 2005; Greipp et al., 2005).

Although various studies have already been conducted worldwide, most of them focused on MM patients only. To our knowledge, negligible studies analyzed the data of a cohort study to identify risk factors for MM, which is particularly true for Japan. Present study has been originated from this background and aimed to identify some of the risk factors for MM by using the nation-wide data from the Japan Collaborative Cohort (JACC) Study.

Materials and Methods

Study Subjects

Details of the study methods that adopted in the baseline and follow-up surveys are explained elsewhere (Ohno and Tamakoshi, 2001). Briefly, the Japan Collaborative Cohort Study (JACC) Study for Evaluation of Cancer Risk (sponsored by the Ministry of Education, Culture, Sports, Science and Technology of Japan) is a large and nation-wide multicenter prospective cohort study which enrolled 127,477 healthy inhabitants (men=54,032; women=73,445) from 45 municipal areas (6 cities, 34 towns and 5 villages) located in 7 districts (out of 8) of Japan who responded the baseline questionnaire between 1988 and 1990. Number of participants was 12,925 under age 40 years and 3,760 over age 79 years. Most subjects were recruited from the general population or when undergoing routine health checks in the municipalities (Sakauchi et al., 2005). Informed consent for participation was obtained using two strategies either by signing the cover page of the questionnaire (at the individual level which covered majority of the participants) or by explaining the aim of the study and confidentiality of the data (at the group level) to the community leader. For analytical purpose, this study only included the subjects aged between 40 and 79 years at baseline survey. This provided a total of 110,792 subjects (men=46,465; women=64,327), of which 1,904 subjects (men=308; women=786) were again excluded because of past medical history of cancer. Thus, we had a total of 109,698 subjects (men=46,157; women=63,541) for analysis.

At the time of enrollment, the subjects completed a self-administered questionnaire that covered: demographic characteristics such as age, sex, level of education, marital status, place of residence, and occupation; anthropometric measures such as height (cm), weight (kg), and body mass index (BMI, kg/m_2); lifestyle related factors such as smoking, drinking, physical activity (walking, sport activity), dietary habits, sleeping pattern; occupational factors such as kinds of job, sedentary or physical job, shift work, dustiness, noisiness, personal relationship (remain worried or not) in the working place, and restriction about own pace in the working place; and past medical history of several diseases such as history of stroke, hypertension, myocardial infarction, kidney disease, liver disease, gallstone, diabetes mellitus, peptic ulcer, appendectomy and cancer. We analyzed all the above-mentioned factors, but in this paper we reported only the significant variables for both sexes (except the significant factors of dietary habits) namely: age (categories: 40-49, 50-59, 60-69, 70-79), gender (male, female), BMI (<18.5, 18.5-25.0, 25.0-30.0, ≥30.0), walking (≥ 1 hour/day, 30 min to 1 hour/day, <30 minutes/day), worried about personal relationship in the working place (yes, no), restriction about own pace in working place (yes, no), and past medical history of peptic ulcer (yes, no). The same analyses have been done for each sex irrespective of significance level.

Follow-up period and determination of CC death

Follow-up survey was conducted annually until the end of 2003 and 1999 in 42 and 3 areas respectively to determine the vital status of the women using resident registration records available in the respective municipalities. In the most recent data, cause of death was recorded using International Classification of Disease version 10 (ICD-10), where code C90 indicated MM death. All other deaths (except MM deaths) and subjects who alive until the end of follow-up period or who moved out the study areas or lost to follow-up were considered as censored during analysis.

Statistical analysis

Present study analyzed the data (for both sexes, and

separately for each sex) by Statistical Analysis System (SAS) version 9.1 (SAS Institute, Cary, NC). Unadjusted Cox proportional hazard model (PHREG procedure) was used to estimate hazard ratio (HR) of MM mortality including 95% confidence interval (CI) by age groups for both sexes, and specific sex. For both sexes, age adjusted Cox model was applied for estimating the HR of MM mortality by sex and then age and sex adjusted HR for other significant variables. Age adjusted Cox model, for each sex, was also used for all variables. P for trend was reported for the categorical variables of age, BMI, and walking by considering the ordinal values of the categories.

Results

The number of deaths from MM was 98 (49 for each sex) during the follow-up period. For both sexes, the MM mortality rate per 10^5 person-years and the average age at death in years were 6.8 and 72.2 (standard deviation, SD=9.0) respectively. The corresponding figures were 8.3 and 72.4 (SD=8.0) for men, and 5.8 and 72.1 (SD=10.0) for women respectively (not shown).

Distribution of subjects and person-years (only for both sexes), MM deaths, and hazard ratio (HR) for MM including 95% confidence interval (CI) by the selected variables are presented in Table 1. For both sexes, unadjusted HR for MM were about 5 times (HR=5.0; 95% CI=2.4-10.7) and 9 times higher (HR=9.3; 95% CI=4.3-20.3) for the age groups of 60-69 and 70-79 years as compared to the reference age group of 40-49 years. Sex specific analysis also revealed similar results for age. Age adjusted MM was significantly higher for men than women (HR=1.5; 95% CI=1.0-2.2). BMI ≥30 kg/m_2 (HR=2.8; 95% CI=1.0-7.7), walking <30 minutes/day (HR=2.0; 95% CI=1.2-3.4), remaining worried about personal relationship in the working place (HR=2.3; 95% CI=1.3-4.2), restricted own pace in the working place (HR=1.9; 95% CI=1.0-3.4), and having history of peptic ulcer (HR=1.7; 95% CI=1.0-2.7) were significantly associated with age and sex adjusted MM for both sexes. For men, age adjusted HR of MM was significantly higher for those who reported walking <30 minutes/day compared with those group who reported walking ≥1 hour/day. Restricted own pace in the working place was also found to

Table 1. Person-years, Number of Deaths from Multiple Myeloma (MM), Hazard Ratio (HR) of MM including 95% Confidence Intervals (CIs) for Both-sexes, Men and Women by Some Selected Variables of JACC Study, 1988-2003

Variables	Both sexes					Men			Women		
	N§	Person-years	MM Death§	HR	95% CI	MM death§	HR	95% CI	MM death§	HR	95% CI
Age†:											
40-49	27182	384705	8	1.00		4	1.00		4	1.00	
50-59	33680	461014	18	1.90	0.83-4.37	9	2.04	0.63-6.62	9	1.81	0.56-5.87
69-69	33210	420687	42	5.01	2.35-10.67***	23	6.13	2.12-17.74***	19	4.18	1.42-12.29**
70-79	15626	169136	30	9.28	4.25-20.27***	13	9.99	3.24-30.76***	17	9.13	3.07-27.18***
					Trend P<0.0001			Trend P<0.0001			Trend P<0.0001
Sex‡:											
Women	63541	843513	49	1.00							
Men	46157	592028	49	1.51	1.02-2.24*						
BMI‡ (kg/m2) ¶:											
<18.5	6143	73696	5	0.79	0.32-1.98	3	1.02	0.31-3.35	2	0.60	0.14-2.52
18.5-25.0	75398	993125	67	1.00		36	1.00		31	1.00	
25.0-30.0	19824	263996	12	0.72	0.39-1.33	5	0.67	0.26-1.71	7	0.70	0.34-1.75
≥30.0	1752	23041	4	2.79	1.01-7.69*	0	-	-	4	4.11	1.45-11.64**
					Trend P=0.6638			Trend P=0.3515			Trend P=0.1635
Walking/day¶:											
≥1 hr	41868	543504	26	1.00		13	1.00		13	1.00	
30 min-1 hr	16691	211590	12	1.19	0.60-2.36	6	1.23	0.47-3.24	6	1.15	0.44-3.03
<30 min	24600	309040	28	1.99	1.16-3.39*	16	2.25	1.08-4.67	12	1.73	0.79-3.79
					Trend P=0.0130			Trend P=0.0320			Trend P=0.1785
Worried about personal relationship in working place¶:											
No	39134	499567	21	1.00		13	1.00		8	1.00	
Yes	18317	240391	22	2.32	1.27-4.22**	11	1.67	0.75-3.74	11	3.53	1.41-8.79**
Restriction about own pace in working place¶:											
Yes	52117	670727	40	1.00		20	1.00		8	1.00	
No	11539	147181	14	1.87	1.01-3.44*	8	2.15	0.94-4.90	6	1.59	0.64-3.97
Had history of peptic ulcer¶:											
No	79672	1055376	62	1.00		29	1.00		33	1.00	
Yes	15516	198004	22	1.65	1.01-2.71*	12	1.30	0.66-2.55	10	2.20	1.08-4.48*
Total	109698	1435541	98			49			49		

†unadjusted for both sexes, men and women; ‡adjusted for age for both sexes; ¶adjusted for age and sex (for both sexes) and age (for men and women) §total subjects and deaths varied from total due to missing information; ***P<0.001, **P<0.01, *P<0.05

be associated almost significantly with MM (HR=2.2; 95% CI=0.9-4.9; P=0.069). For women, BMI ≥ 30 kg/m_2 (HR=4.1; 95% CI=1.5-11.6), worried about personal relationship in the working place (HR=3.5; 95% CI=1.4-8.8), and having history of peptic ulcer (HR=2.2; 95% CI=1.1-4.5) were significantly associated with age-adjusted MM risk.

Discussion

Present study revealed that the average age at death from MM was around 72 years for each sex and higher age groups (especially 60 years are and above) were associated with significantly higher MM. This means that MM typically occurs in elderly (60+) population, which is also supported by some other studies (Multiple Myeloma Research Foundation, 2001; Zaidi and Vesole, 2001; Kaneko et al., 2002; Kyle et al., 2003; National Cancer Institute, 2004; Phekoo et al., 2004; Shimizu et al., 2004). According to these studies, the average (either mean or median) age of MM patients varied from 65 to 73 years. Several factors such as aging of the population (Kyle et al., 2003), and higher incidence rates in higher age groups for both men and women (Kyle et al., 1994; Kyle et al., 2003; Phekoo et al., 2004) may be associated with higher MM in the elderly population. Combined Japanese data of 2004 indicates that about 83% MM deaths occurred among the people of 65 years and above (Health and Welfare Statistics Association, 2004; Health and Welfare Statistics Association, 2005). Similarly, Phekoo et al. (2004) reported 73% of the MM patients belonged to the age category of 65 years and above in UK. Two percent or less of the MM patients are diagnosed under age 40 (Multiple Myeloma Research Foundation, 2001; Kyle et al., 2003). Phekoo et al (2004) also reported that the incidence rate for both-sexes combined rose steadily with increasing age from 0.14 at age 16 years to 38.4 per 100,000 at age 85+ years. In Japan, death rate from MM per 100,000 population in 2004 was 0.15 for age group 40-44 years, whereas this figure was 15.24 for 75-79 years of age (Health and Welfare Statistics Association, 2004; Health and Welfare Statistics Association, 2005).

Men showed significantly higher MM as compared to women in our study, which may be supported by the higher incidence of MM in men than women (Multiple Myeloma Research Foundation, 2001; Kyle et al., 1994; Kaneko et al., 2002; Kyle et al., 2003; Phekoo et al., 2004). Some studies reported that the incidence rate of MM is significantly higher in men than women (Kyle et al., 1994; Phekoo et al., 2004). Monoclonal gammopathy, a risk factor for hematological malignancies, was also found to be higher in men than women (Ogmundsdottir et al., 2002). The sex differences in MM, particularly the predominance for men at each age cohort, may also be related to a disease-modifying gene on the sex chromosome (Phekoo et al., 2004).

Obese individuals revealed significantly higher HR of MM for both sexes combined. The significant association between obesity and MM is found to be consistent with other studies (Friedman and Herrinton, 1994; Brown et al., 2001; Benjamin et al., 2003; Calle et al., 2003; Pan et al., 2004; Samanic et al., 2004; Blair et al., 2005). The mechanism of linking high BMI to MM is unclear, but some studies suggest that excess caloric intake and obesity may affect immunologic responses (decreased immune response) that are involved in the development of malignancy (Stallone, 1994; Chandra, 1997; Brown et al., 2001). It is reported that the chronic hyperinsulinemic state in obesity reduces the insulin-like growth factor (IGF)-binding protein and increase free IGF-I. Both insulin and IGF-I can stimulate cell proliferation and inhibit apoptosis, thus enhancing tumor development (Gupta et al., 2002; Pan et al., 2004; Samanic et al., 2004). IGF-I also stimulates the proliferation of bone marrow cells (Georgii-Hemming et al., 1996; Ferlin et al., 2000). Another possible mechanism by which excess adiposity may increase the risk of MM is related to the cytokine interleukin 6 (IL-6), which is involved in proliferation and differentiation of both normal and malignant plasma cells. This particular cytokine may increase survival of plasma cells through inhibition of apoptosis (Ferlin et al., 2000; Lauta et al., 2003).

Walking less than 30 minutes per day (an indicator of physical activity) was found to be positively associated with elevated risk of MM for both-sexes, men and women. Unfortunately, the underlying mechanism between physical activity and MM is yet to be known because of scarcity of evidence. However, some speculations could be made in this regard. For example, walking is considered as a common physical activity (Wyatt et al., 2005; Warburton et al., 2006) and less walking may be an indicator of sedentary life style and obesity, which is supported by the other studies (Wyatt et al., 2005; Warburton et al., 2006). Cross-table analysis of our data (not shown) also showed significant association between walking and BMI. Rate of walking <30 minutes/day was highest for the obese subjects and highest for the normal-weight subjects. According to our speculation, reduced weight through physical activity and its associated mechanism mentioned above may partially explain the observed association between MM and walking. However, further studies are recommended to find the answer to: why does walking <30 minutes/day appear as an independent risk factor (HR=1.8; 95% CI=1.0-3.0) even after adjusting for age, sex, and BMI (data not shown)?

MM was found to be significantly higher among the groups of subjects (both-sexes) who reported that "they were worried about personal relationship in working place" and "they were restricted about own pace in working place." Unfortunately, we are unable to report the consistency of the findings as no previous study reported such associations. However, an attempt has been made to explain these associations indirectly. Apparently both groups represent the stressful condition (either psychological or physical) in the working place. Several studies (Zhou et al., 1993; Maes et al., 1998; Cohen et al., 1999; Steptoe et al., 2001; Kiecolt-Glaser and Glaser, 2002; Kiecolt-Glaser et al., 2003) reported that stressors can directly affect the cells of the immune

system and modulate the secretion of pro-inflammatory cytokines. For instance, production of IL-6 and other pro-inflammatory cytokines can be directly stimulated by stressful experiences and negative emotions (Zhou et al., 1993; Maes et al., 1998; Kiecolt-Glaser and Glaser, 2002). Overproduction of IL-6 can be linked to the MM as it is involved in proliferation, activation, and differentiation of immune cells or both normal and malignant plasma cells through inhibition of apoptosis (Willenberg et al., 2002; Lauta et al., 2003). As many studies highlighted the linkage between IL-6 and MM, and as the serum analysis is not suitable for the present study, we recommend further studies such as nested case-control study using the data of stored serum of JACC study. According to the present analysis (data not shown), restriction about own pace lost their significance level when we included it with other variables namely age, sex, BMI, and worried about personal relationship in the working place (remained significant).

Peptic ulcer is identified as a significant risk factor for MM, which seems to be inconsistent as one study reported insignificant association between peptic ulcer and MM in Italy (Vineis et al., 1999) and another study reported insignificant association of IgA and IgG with peptic ulcer in USA (Herrinton et al., 1993). However, peptic ulcer was found as a most common disease among MM patients by one study and the authors concluded that prior inflammatory diseases such as gastrointestinal diseases may be implicated in the pathogenesis of the IgA subset of multiple myeloma (Schafer and Miller, 1979). Rosenstock et al. (2003) reported that patients who increased IgG antibodies to Helicobacter pylori infection (seropositive or borderline) significantly increased the risk of developing an ulcer as compared to seronegative.

The main advantage of the present study lies in its prospective design. Cohort study is generally free from recall bias, which is one of the main limitations for case-control studies. Most importantly, to our knowledge, this is the first cohort study which investigated the association of some important factors with MM and hence reported some leading findings in Japan. However, this study may have some limitations. First, small number of deaths may limit the interpretation of the findings due to limited statistical power. Second, in the Cox model we adjusted only the effect of age and sex for both-sexes and we adjusted only age for specific sex, which may not be sufficient. Last but not least limitation may be related to the missing information of the selected variables.

In short, higher age groups (especially after age 60 years) showed significantly risk of MM for both-sexes, men and women. Men experienced significantly higher MM than women. BMI ≥30 kg/m_2, walking <30 minutes/day, worried about personal relationship in the working place, restriction about own pace in the working place, and history of peptic ulcer are also appeared as the significant risk factors for MM for both sexes. Finally, all the significant findings of the present study should be validated by further epidemiologic studies in Japan before generalization.

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