RESEARCH COMMUNICATION

A Case-control Study of Multiple Myeloma in Japan: Association with Occupational Factors

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Abstract

Recently the incidence rate of multiple myeloma (MM) has increased in Japan. Epidemiologic efforts have suggested that certain occupational and chemical exposures are likely to increase the risk for MM. We therefore performed a case-control study of MM, examining occupational factors. Data for 57 cases and 57 controls were obtained from Sapporo Medical University Hospital and its affiliated hospitals in Hokkaido. Controls were matched to each case by gender, age (± 5 years) and hospital. Detailed information regarding several factors possibly related to MM was obtained by interviews in hospitals. Odds ratios (ORs) and 95% confidence intervals (95%CIs) were calculated with adjustment for cigarette smoking as confounding factor. The occupational category of agriculture and fishery showed a significant association with increased risk (OR = 5.89, 95%CI = 1.24-28.04). Occupational exposure to chemical products including organic solvents or petroleum showed a significant association with increased risk (OR = 8.05, 95%CI = 1.01-64.45). Medical histories of operation for appendicitis and blood transfusion were associated with decreased risk, but not significantly. Our results suggested that occupational exposure to chemicals might play a role in the risk of MM.

Key Words: multiple myeloma - Japan - occupations - medical history - occupational exposure

Asian Pacific J Cancer Prev, **6**, 33-36

Introduction

Multiple myeloma (MM) is a malignant proliferation of plasma cells in the bone marrow, characterized by lytic bone lesions, plasma cell accumulation in the bone marrow and the appearance of monoclonal proteins in the serum or urine. Although MM is a rare disease in Japan, recently its incidence rate has increased with the aging of the population (age-adjusted incidence rate of approximately 1.0-1.5 per 100,000 in 2002) (Parkin et al, 2002). Survival is reported to be poorer for MM than for other cancers (Ohshima et al., 1998). Although there are no clearly identified risk factors, epidemiologic efforts have suggested that high level of ionizing radiation, certain occupational and chemical exposures are likely to be risk factors for MM. We therefore conducted a case-control study in Japan, to investigate whether occupation, occupational exposure and life style factors may play roles in the risk of MM.

Materials and Methods

Subjects

Cases were obtained from the First Department of Internal Medicine of Sapporo Medical University Hospital and its affiliated hospitals in Hokkaido. Fifty-seven cases with confirmed histological diagnoses of MM between 1996 and 2003 were used for the analysis. The age range was 36-86 years old. Fifty-seven controls were recruited from patients by matching gender, age (within 5 years) and hospital. Patients with diagnoses of malignant tumors and other hemopoietic diseases were excluded from the control group. The diagnoses of controls were as follows: oral diseases, cerebrovascular diseases, diabetes, hypertension, urologic diseases and digestive system diseases.

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Data Collection

After informed consent from subjects was received, detailed information regarding several factors possibly related to MM was obtained by in-hospital interviews. The questionnaire used included items for the following information: cigarette smoking (age at onset of smoking, smoking duration in years and number of cigarettes per day), medical history (fracture, blood transfusion, allergic disease, rheumatism, infectious diseases and life style-related diseases), employment history (industry, occupation and employment periods), occupational exposure and exposure to car fuel when driving. Industry and occupation were classified using the major classification items of the Standard Industrial Classification for Japan (with the tenth revision of 1993) and Standard Occupational Classification for Japan (with the tenth revision of 1997), respectively.

Statistical Analysis

Estimates of odds ratios (ORs) and 95% confidence intervals (95%CIs) for MM were calculated by conditional logistic regression models using the sex, age and hospital matched case-control set. Furthermore ORs were calculated with adjustment for cigarette smoking as a potential confounding factor, because more than half of the controls were selected from patients with oral diseases having a possible relation with smoking (Calsina et al., 2002; Krejci and Bissada, 2000; Tomar and Asma, 2000). For cigarette smoking, the smoking index (number of cigarettes per day× smoking duration in years) was used and categorized as 0, <600 and ≧600. The lowest category, with an OR of 1.00, was the reference category. For each category of medical history, all other categories were used as reference categories. ORs for industry and occupation were calculated by comparing each industrial or occupational category with employment for more than five years with each other industrial or occupational category and no employment. ORs of probable occupational exposure were calculated by comparison with the unexposed group. ORs for exposure to a car fuel in driving were calculated by comparison with the category combined by exposure to other fuels and no driving. Analyses were performed with SPSS version11.5.

Results

ORs for cigarette smoking are shown in Table1. The smoking index did not show any association with increased risk. The index was used as potential confounding factor, but no major differences between ORs adjusted by smoking and ORs not adjusted by smoking were found. ORs for industry are shown in Table 2. Agriculture (OR = 3.50, 95%CI = 0.70-17.45) and fishery (OR = 4.84, 95%CI = 0.55-42.56) were associated with increased risk, but not significantly. ORs for occupation are shown in Table 3. The occupational category of agriculture and fishery showed a significant association with increased risk (OR = 5.89, 95%CI = 1.24-28.04). ORs for occupational exposure and exposure to car fuel are shown in Table 4. The OR for chemical products including organic solvents or petroleum showed a significant association with increased risk (OR = 8.05, 95%CI = 1.01- 64.45). ORs for medical history are shown in Table 5. Operations for appendicitis (OR = 0.50, 95%CI =0.21-1.21) and blood transfusion (OR = 0.24, 95%CI = 0.05-1.13) were associated with decreased risk, but not significantly.

Table 1. ORs and 95%CIs of Multiple Myeloma for Cigarette Smoking

Smoking index[a]	No. of Cases (n=57)	No. of Controls (n=57)	OR[b]	95%CI[b]
0	30	28	1.00	
<600	13	13	0.88	0.32 - 2.42
≥600	14	16	0.77	0.28 - 2.12

[a]number of cigarettes per day × smoking duration in years.
[b]adjusted for gender and age.

Table 2. ORs and 95%CIs of Multiple Myeloma for Industry

Industry[a]	No. Of Cases (n=57)	No. of Controls (n=57)	OR[b]	95%CI[b]
Agriculture	7	2	3.50	0.70 - 17.45
Fishery	5	1	4.84	0.55 - 42.56
Mining	3	2	1.82	0.15 - 21.64
Construction	4	6	0.47	0.09 - 2.38
Manufacturing	6	10	0.59	0.21 - 1.67
Communication and Transportation	8	10	0.77	0.27 - 2.20
Sales and Restaurant	14	16	0.85	0.34 - 2.14
Services	13	16	0.74	0.30 - 1.87
Government affairs	7	7	0.96	0.30 - 3.01

[a]employed more than five years.
[b]adjusted for gender, age and smoking index.

Table 3. ORs and 95%CIs of Multiple Myeloma for Occupation

Occupation[a]	No. Of Cases (n=57)	No. of Controls (n=57)	OR[c]	95%CI[c]
Professional and Technical	5	11	0.34	0.09 - 1.26
Occupation[b]	1	4	0.23	0.03 - 2.11
Management	14	20	0.55	0.22 - 1.34
Office work	7	11	0.56	0.19 - 1.67
Sales	11	5	2.21	0.75 - 6.51
Services	12	3	5.89	1.24 - 28.04
Agriculture and Fishery	7	7	1.04	0.31 - 3.47
Communication and Transportation Manufacturing	11	10	1.13	0.43 - 2.94

[a]employed more than five years.
[b]including engineer, teacher, artist, nurse and social services.
[c]adjusted for gender, age and smoking index.

Table 4. ORs and 95%CIs of Multiple Myeloma for Occupational and Engine Exposures

Exposure	No. Of Cases (n=57)	No. of Controls (n=57)	OR[d]	95%CI[d]
Chemical products[a]	8	1	8.05	1.01 - 64.45
Mine dust[b]	5	6	0.64	0.11 - 3.93
Gasoline[c]	25	22	1.23	0.49 - 3.11
Diesel[c]	5	9	0.56	0.16 - 1.96

[a]probable exposure to organic solvents or petroleum.
[b]probable exposure to coal or asbestos.
[c]exposure to a car fuel when driving.
[d]adjusted for gender, age and smoking index.

Table 5. ORs and 95%CIs of Multiple Myeloma for Medical History

Medical history	No. Of Cases (n=57)	No. of Controls (n=57)	OR[a]	95%CI[a]
Fracture	16	15	1.19	0.48 - 2.94
Blood transfusion	6	12	0.24	0.05 - 1.13
Allergic disease	11	8	1.43	0.54 - 3.77
Rheumatism	3	4	0.76	0.17 - 3.43
Tuberculosis	6	6	1.03	0.26 - 4.17
Herpes	9	7	1.29	0.44 - 3.76
Hypertension	16	8	2.21	0.89 - 5.51
Diabetes	4	7	0.59	0.17 - 2.05
Heart failure	5	6	0.83	0.25 - 2.76
Cancer	4	4	1.02	0.25 - 4.10
Appendicitis (operated)	15	22	0.50	0.21 - 1.21

[a]adjusted for gender, age and smoking index.

Discussion

Epidemiological research has not provided evidence that smoking is a risk factor for MM (Brownson, 1991; Heineman et al., 1992; Brown et al., 1992; Linet et al., 1992; Friedman, 1993; Stagnaro et al., 2001). In this study too, smoking did not show any association with risk for MM.

Many studies have reported associations between industries or occupations and MM. A positive association for agriculture was reported in several case-control studies (Flodin., 1987; Boffetta et al.,1989; Demers et al., 1993; Franceschi et al., 1993; Cantor and Blair, 1984; Pearce., 1986) and cohort studies (Steineck and Wilkund, 1986; Viel and Richardson, 1993). Khunder showed a significant positive association of farming with the risk of MM (relative risk =1.23, 95%CI = 1.14 - 1.32) in his meta-analysis (Khunder, 1997). In the present study, the occupational category of agriculture and fisheries also showed significant increased risk. Farmers may be exposed to several agents, including solvents, viruses and other microbes, dust and agricultural chemicals, which might be associated with risk of MM. The etiology of the risk with fisheries for MM is unknown.

Epidemiologic investigations have suggested that several types of occupational chemical exposure are likely to be risk factors for hemopoietic tumors. It is well known that the bone marrow is damaged by chronic exposure to benzene (Wada, 2000). Benzene is included in petroleum and is discharged into the environment as engine exhaust. The result of our earlier meta-analysis of occupational exposure and MM in case-control studies showed that engine exhaust had a significantly increased risk (OR=1.37, 95%CI=1.15±1.63) (Sonoda et al., 2001). Engine exhaust also includes several other harmful chemical agents such as benzopyrene, ethylene, toluene, xylene, formaldehyde, suspended particulate matter (SPM), and so on. Some of these agents, in addition to benzene, may be associated with the risk of MM, although the carcinogenic effects of these agents on hemopoietic cells are not well established. On the other hand, petroleum, benzene and organic solvents did not show significant increased risk in our meta-analysis (Sonoda et al., 2001). Similar results have been reported in some cohort studies (Paci et al., 1989; Yin., 1996; Wong and Raabe, 1997). In the present study, occupational exposure to organic solvents or petroleum significantly increased the risk for MM, but exposure to car fuel during driving had no association . Generally the assessment of occupational exposure in epidemiological research, in particular in case-control studies, is difficult. Some researchers have used questionnaires containing questions regarding exposure to various substances (Linet et al., 1992; Flodin., 1987; Boffetta et al.,1989; Eriksson and Karlsson, 1992). Danish researchers used the industry/occupational codes, which were distributed among Danish industrial hygienists who assessed exposure to 20 substance categories and 27 specific substances (Heineman et al., 1992; Pottern et al., 1992). In our study, the frequency and quantity of occupational exposure were not sufficiently clear, although we conducted detailed interviews. We calculated the risk for MM simply by the presence or absence of probable exposure to occupational chemical products in the past. The assessment of risk for occupational chemical exposure is clearly a problem in case-control studies.

Associations between medical history and MM, especially chronic antigenic stimulation due to bacterial infections, autoimmune disorders and allergy-related disorders, have been pointed out; however the degree of risk remains to be clarified. Only a few studies have suggested a slight positive association between immune-stimulating conditions and MM (Bourguet and Logue, 1993; Gramenzi et al., 1991). In this study, operations for appendicitis showed a decreased risk, that is to say, the presence of an intact appendix might result in increased risk, and blood transfusion showed a decreased risk, though neither was significant. Either might cause stimulation of the immune system, but the etiology remains unknown.

In conclusion, occupational chemical substances may play roles in the risk of MM. Further investigation in a larger case-control study is needed to focus on detailed information concerning occupational exposure.

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