



Research Article

Impact of Environmental Factors on the Risk of Multiple Myeloma, a Case-Control Study in Myanmar

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Abstract

Background: Environmental factors, including exposure to chemicals and certain pathogens, may increase the risk of developing Multiple Myeloma (MM), as indicated by studies conducted primarily in industrialized countries. On the other hand, some epidemiological and experimental data also support the hypothesis that exposure to infections may enhance cancer immunosurveillance, particularly against multiple myeloma. **Aim:** To improve our understanding of the association between environmental factors and the risk of multiple myeloma, particularly in developing countries, this research was conducted to ascertain, in a South-East Asian setting, if environmental factors can modulate the risk of developing multiple myeloma. **Methodology:** A hospital-based case-control study was conducted using simple questionnaires in two large public hospitals in Myanmar from July to September 2020, with 40 multiple myeloma cases and a double control population seeking care in the medical and surgical Units of the same hospitals. **Results:** Even if not significant, our results suggest an increased risk of developing multiple myeloma after exposure to chemicals used in farming, and a reduced risk for those with a history of infections such as tuberculosis, hepatitis, measles, or pneumonia. The reduction was significant for malaria at the country level. **Conclusion:** These results support the idea that certain infections can improve cancer immunosurveillance, although they still need to be confirmed in other series of patients.

Keywords: Multiple myeloma; Environmental factors; Chemicals; Infections; Cancer immunosurveillance; Myanmar

Introduction

According to global data, multiple myeloma has been progressively increasing in both industrialized and developing countries since 1990 [1]. Geographically, the incidence is unevenly distributed worldwide, with the highest incidence among Caucasians and African Americans, but increases have also been reported in some Asian nations [2-5]. Although the incidence is lower in Asia than in Western countries, 228 new cases have been identified in Myanmar (0.31% of all cancers) with a cumulative risk of 0.05 per 100,000 in 2020 due to increased awareness of the disease, a faster referral system, and a growing population in the country [6,7].

To date, no specific environmental exposure has been clearly identified as the cause of multiple myeloma. Several factors have been suggested as possible causes of the increased incidence of multiple myeloma and various observational study designs have been used to investigate a variety of possible causal factors [8,9].

Age and male gender have also been associated with an increased risk of multiple myeloma. Genetic polymorphisms explain the risk of multiple myeloma in different studies and offspring of parents diagnosed with multiple myeloma have a higher relative risk [10-16]. Body mass or nutritional status may play a role in the development of multiple myeloma, while high dietary intakes of green vegetables and fish have been associated with a lower risk of the disease [17-20]. It also appears to be predisposed by radiation exposure, and people in certain occupations seem to be at greater risk [21-23]. Employment in agriculture and animal husbandry are other possible etiologic variables for multiple myeloma. The healthier lifestyle of farmers may be attributed to the fact that they have lower mortality rates than the general population for all malignancies. However, the evidence for the link between farming and multiple myeloma is conflicting [24-28].

A few other risk factors have been suggested, such as occupational exposure to asbestos [29,30], petrochemicals, plastics, and rubber [31,32]. Chemicals, such as benzene, toluene, ethylbenzene, and xylene [33], hair dyes [34,35], are also environmental risks for multiple myeloma. Several epidemiologic studies have shown that occupational exposure to pesticides (insecticides, fungicides, and herbicides) increases the risk of developing multiple myeloma [26,28,36-42]. However, the majority of research does not report significant correlations, with point estimates equal to, less than, or greater than unity [15,27,43,44].

In addition, infectious or non-infectious agents alter the host's immune response or otherwise they influence the risk of multiple

myeloma. Several epidemiologic studies have investigated the relationship between chronic immunologic stimulation and the risk of multiple myeloma. Certain infections and inflammatory disorders, as infections have been suggested as a possible factor in translocations, leading to clonal expansion of plasma cells in the bone marrow [33,34,45]. The risk of developing multiple myeloma is positively or negatively correlated with various infections, including influenza, polio, smallpox, tuberculosis, chronic inflammatory disorders (especially bacterial), and malaria [46-49]. Furthermore, infections with HIV and hepatitis C virus appear related to elevated multiple myeloma risk [45-47]. The mechanisms underlying these associations are not well understood. There is more than one way to interpret each study, but none of them clearly explains how an infection can contribute to multiple myeloma [48,49].

Myanmar, as a developing country, faces a double burden of communicable and Non-Communicable Diseases (NCDs). However, data on the possible relationship between environmental factors, including infections, and NCDs are scarce, as epidemiological studies are mainly conducted in industrialized countries. This research, therefore, conducted a case-control study in Myanmar to determine whether environmental factors may play a role in the risk of multiple myeloma.

Methods

Description of the study

All old and newly diagnosed patients with multiple myeloma admitted to the clinical hematology departments of Yangon and Mandalay general hospitals in Myanmar were included in this study. Forty confirmed cases of multiple myeloma diagnosed by hematologists according to the diagnosis criteria (i.e., major and minor criteria as defined by the International Myeloma Working Group [55]) between July 2020 and September 2020 were used for the analysis. Eighty controls were randomly recruited from patients receiving treatment in medical and surgical units of the same hospitals by matching sex, age (within 3 years), and region of residence (10 years previously).

Patients diagnosed with malignancies or other hemopoietic diseases were excluded from the controls. For ethical reasons, and because of very low prevalence of multiple myeloma in Myanmar (0.31% of the total cancer incidence in Myanmar with a cumulative risk of 0.05% per 100,000 population [6]), controls were considered free of multiple myeloma on the basis of the absence of obvious prolonged bone pain with apparently normal blood films.

With the reference: UPH-IRB (2020/ Research/14), the University of Public Health, Yangon, Institutional Review Board approved the study based on the Declaration of Helsinki and the ICH Good Clinical Practice Guidelines.

Data Collection

After receiving informed consent from the subjects, relevant clinical data from each participant were obtained by hospital interviews. To achieve optimal compliance, a short ethics committee-approved questionnaire was used with sociodemographic indicators and a problem-oriented occupational exposure history (supplementary material). For cases, the interview included detailed disease information, such as patient age at diagnosis, clinical presentations at diagnosis, myeloma-related target organ damage, and myeloma stage.

Statistical analysis

Sample size was calculated using PS program 3.1.6 for power and sample size determination. We planned to recruit independent cases and controls, with 4 controls per case. Prior data indicated a prevalence of 0.0134 among controls [57]. To detect an increase in the OR of 10 at the significance level of 0.05, with a power of 80%, a sample size of 45 cases and 180 controls was required. However, the situation in Myanmar did not allow this number to be reached.

Logistic regression analyses were used to estimate multivariate odds ratios (OR) for each variable related to multiple myeloma and their 95% confidence intervals (CIs). Statistical analyses were performed using the SPSS 27.0 statistical software, and a p-value lower than 0.05 was considered as significant.

Results

Forty cases of multiple myeloma were recruited in this study. Individuals of the same age, sex, and residence admitted to the same hospitals for medical or surgical problems were included as controls. (Figure 1A) shows the geographic distribution of cases. The majority of patients were from Mandalay and Yangon, which accounted for 25% and 23% of all cases, respectively, followed by Sagain and Bago, close to the participating hospitals, which accounted for 18% and 15% of cases, respectively. A few patients from northern and southern Myanmar were admitted to the hospitals throughout the study period, but they had to be excluded because there was no corresponding control for these cases.

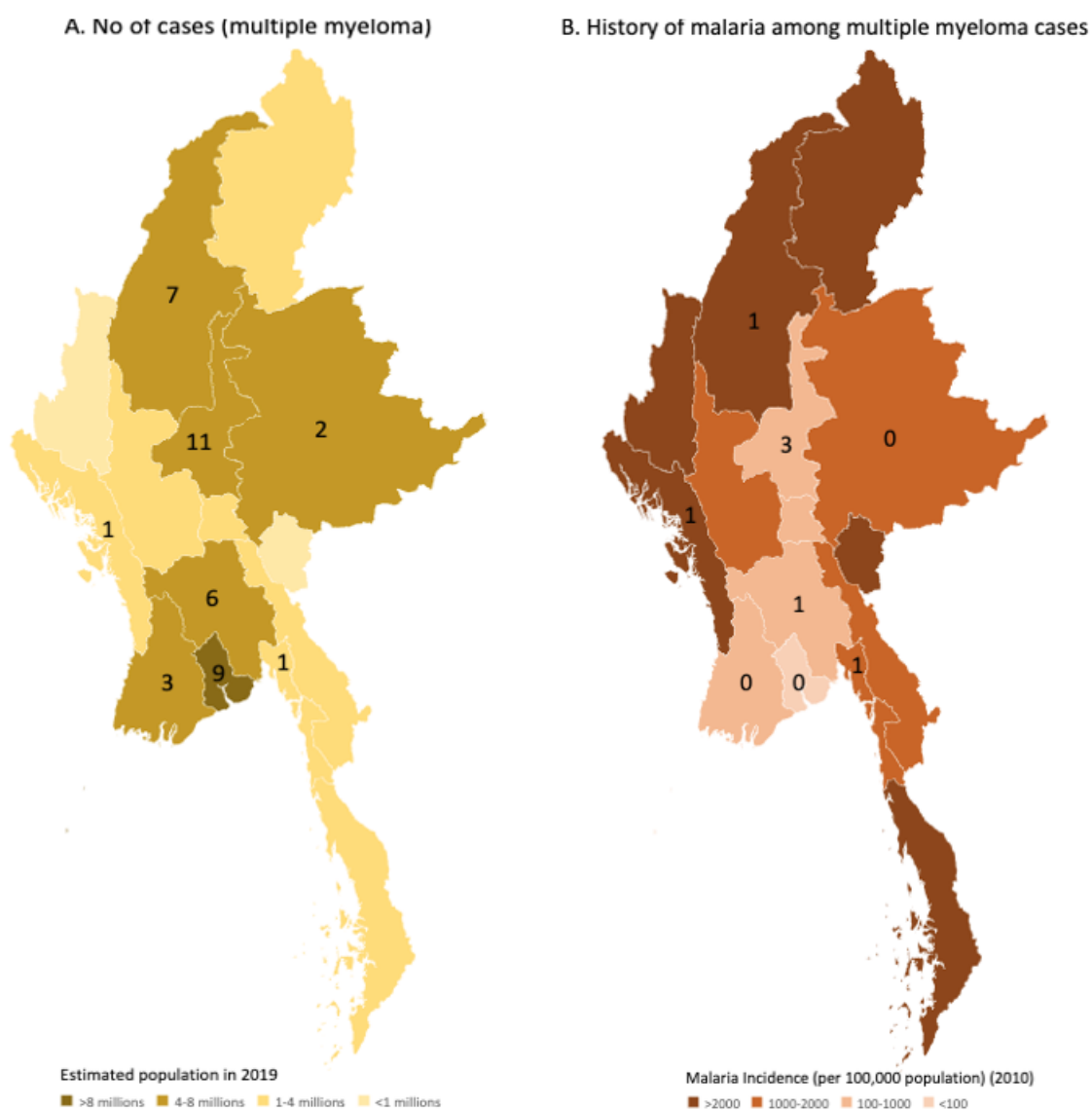


Figure 1: Geographical distribution of the multiple myeloma and of malaria positive case.

Table 1 shows the descriptive characteristics of the multiple myeloma cases and controls in the study. The age distribution ranged from 35 to 81 years, with a median age of 60 years. There were 18 females and 22 males, or 45% and 55%, respectively. Only 4 (10%) of the multiple myeloma cases had a history of chemical exposure, but 11 (27.5%) had a history of infection. Supplementary Table 1 shows a bivariate distribution of age and sex in multiple myeloma cases versus hospital controls. As in many other studies conducted in Asian populations [50], the median age of multiple myeloma was 60 years (range: 35-81). 55% of the cases were male with a 1.2:1 male/female ratio. The distribution of controls by major diagnostic categories is shown in Supplementary Table 2. Most medical patients matched to myeloma cases admitted to the hospitals had neurological diseases (40%) but 63% of patients with gastrointestinal diseases were admitted to the surgical units during the study period.

Variable Cases	Multiple myeloma (n=40) n° (%)	Medical controls (n=40) n° (%)	Surgical controls (n=40) n° (%)	Total controls (n=80) n° (%)	Odds Ratio (95%CI)	p-value
Age -yrs						
Mean (SD)	60.1 ± 10.7	60.1 ± 10.3	59.3 ± 10.9	59.7 ± 10.6		
Median (range)	60 (35-81)	60 (38-83)	59 (32-83)	60 (32-83)	matched	
Sex – n° (%)						
Male	22 (55.0)	*	*	44 (55.0)		
Female	18 (45.0)	*	*	36 (45.0)	matched	
Education level						
Primary or less	16 (40.0)	22 (55.0)	21 (52.5)	43 (53.8)		
Secondary or more	24 (60.0)	18 (45.0)	19 (47.5)	37 (46.2)	2.08 (0.91-4.77)	0.08
Occupational exposure to chemicals						
Yes	4 (10.0)	1 (2.5)	2 (5.0)	3 (3.8)		
No	36 (90.0)	39 (97.5)	38 (95.0)	77 (96.2)	3.66 (0.63-21.17)	0.15
History of infections						
Malaria	7 (17.5)	6 (15.0)	6 (15.0)	12 (15.0)	1.51(0.44-5.18)	0.51
Tuberculosis	1(2.5)	4 (10.0)	4 (10.0)	8 (10.0)	0.15 (0.01-1.76)	0.13
Measles	1(2.5)	1(2.5)	1(2.5)	2 (2.5)	0.74 (0.05-11.50)	0.83
Viral hepatitis	1(2.5)	1(2.5)	5(12.5)	6 (7.5)	0.26 (0.03-2.32)	0.23
Pneumonia	1(2.5)	1(2.5)	1(2.5)	2 (2.5)	0.80 (0.02-36.05)	0.91
*Balance for sex and place with case						

Table 1: Characteristics of the study participants.

	Multiple myeloma (n=40)		Medical controls (n=40)		Surgical controls (n=40)	
	Male	Female	Male	Female	Male	Female
<45	1	1	1	0	1	1
45-54	8	4	8	6	6	6
55-64	3	7	3	6	6	6
65-74	8	5	8	4	7	4
>75	2	1	2	2	2	1

Supplementary Table 1: Age and sex distribution across multiple myeloma cases and matched controls.

	Medical controls (n=40)	Surgical controls (n=40)
Nervous	16 (40.0)	-
Cardiovascular	13 (32.5)	1 (2.5)
Endocrine	5 (12.5)	8 (20.0)
Gastro-intestinal	4 (10.0)	25 (62.5)
Respiratory	1 (2.5)	4 (10.0)
Genito-urinary	1 (2.5)	2 (5.0)
Total	40 (100)	40 (100)

Supplementary Table 2: Clinical sectors of hospital controls.

Because information was collected through interviews, in the absence of original medical records for infection history, responses may depend on the educational level of the participants. We divided the participants into two groups based on their education level. Education of secondary level or more was predominant in multiple myeloma cases (60%) compared with controls (46.2%) (Table 1). However, there was no association between higher education level and history of infection (OR = 1.20; 95% CI 0.52-2.77, p=0.66) and there was a negative association between high education level and history of chemical exposure (OR = 0.14; 95% CI 0.02-1.21, p=0.07).

Myanmar is an agricultural country, and many farmers use herbicides and insecticides. We found a positive association (OR = 3.66; 95% CI 0.63-21.17, p=0.15) between multiple myeloma and chemical exposure but it was not significant. In contrast, although not reaching significant level, a reduced risk of multiple myeloma could be suggested for those who had a history of tuberculosis and viral hepatitis (OR=0.15; 95% CI 0.01-1.76, p=0.13; and OR=0.26; 95% CI 0.03-2.32, p=0.23, respectively), contrasting with those with a history of measles (OR 0.74; 95% CI 0.05-11.5, p=0.83) and pneumonia (OR 0.80; 95% CI 0.02-36.05, p=0.91) (Table 1).

In this study, the data showed a positive association between multiple myeloma and malaria occurring more than 10 years before diagnosis (18% vs 15%, OR=1.51; 95% CI 0.44-5.18, p=0.51). Forty-three percent of our malaria-positive cases originated in central Myanmar, Mandalay. In contrast, Yangon, the city with the highest population density [51], had 23% of myeloma patients but no malaria cases. Interestingly, only one myeloma patient from Rakhine, the third highest malaria-incidence city in Myanmar [59], had a history of malaria (Figure 1). Patients with a history of malaria had a higher multiple myeloma stage (stage 3; 71.4%), compared to the lower stage (stage 1 and 2; 28.6%) (p = 0.21). There was a non-significant negative correlation between multiple myeloma cases and malaria cases (r = -0.15) but a significant negative spatial correlation between multiple myeloma cases and malaria incidence across regions (spatial correlation r = -0.53, p-value = 0.05).

Discussion

Multiple myeloma is a global burden with increasing incidence worldwide. The prevalence of multiple myeloma is also increasing in Asian countries [58], including Myanmar (hospital data from the clinical hematology departments of Yangon and Mandalay general hospitals). The incidence is higher in men than

in women [60]. It usually affects older people, with a median age at diagnosis of 65 years [52], although diagnosis should be considered at any age. Like several other studies in Asian populations, the median age of multiple myeloma was 60 years (range: 35-81), with a male preponderance (55%) in this study.

Although education level is not related to the disease, the majority of cases in this study had a secondary school education or higher. Such an excess of cases in higher education, relative to controls, is consistent with a previous study of white Americans that also reported higher education among hospitalized cases [30]. However, low education level prevailed among the cases in multicenter case-control study of European countries [28]. Even though exposure to environmental chemical contaminants is not exclusively associated with low socio-economic status, education status can influence exposure and interpretation of health information [63-65]. This study also showed a non-significant negative association between the education level of cases and the history of chemical exposure.

According to the working definition in this study, chemical exposure is defined as exposure in agriculture, food, and petrochemical industries, farmers exposed to insecticides, individuals exposed to organic solvents, and those with long-term exposure to hair dyes. Despite the small study group, the odds ratio estimate for chemical exposure is not precise enough with relatively wide confidence intervals. This result is consistent with some previous epidemiological studies that have suggested an association between chemical exposure and the risk of developing hemato-lymphoproliferative cancers, including multiple myeloma [16, 27-29], although limited to some farming jobs [30] and while exposure to pesticides such as glyphosate could not be clearly linked to the development of multiple myeloma [31]. Again, these studies focused on multiple myeloma in industrialized countries. Because of the long latency period for a rare cancer with a broad spectrum of environmental factors that may be linked, it is difficult to obtain large series of multiple myeloma, especially in countries like Myanmar. National-level cancer registry would be relevant for conducting an ecological study but are not available in Myanmar. As in all case-control studies, our results might be explained by other factors such as a more frequent history of occupational exposure in multiple myeloma patients than in controls, or by the small number of participants that could be recruited due to health conditions in Myanmar. Although limited in size, our study does suggest that chemical exposure, including in agriculture may also be a risk factor for multiple myeloma in developing countries.

Many infections, including with *Helicobacter pylori*, human papillomavirus, and hepatitis B and C viruses, have been shown to have a causal role in carcinogenesis. Infection-related cancer cases were estimated at 2.2 million worldwide in 2018 [56]. Conversely, epidemiological evidence has suggested that various

infectious diseases experienced early in life have inhibitory effects on the development of gastrointestinal, genital, skin, and lung cancers [57]. Experimental models have supported this hypothesis, demonstrating that pathogens and their products have the ability to stimulate cancer immunosurveillance [58].

An association between infections and multiple myeloma has been reported in a large Swedish study, although such an association between inflammation and multiple myeloma has not been observed in other studies [59-61]. An increased risk of multiple myeloma was previously associated with tuberculosis and Bacillus Calmette-Guérin (BCG) immunization in a hospital-based case-control study from northern Italy [62]. In contrast, in our study, we found a reduced history of tuberculosis and viral hepatitis in multiple myeloma patients compared with control patients. This is consistent with the protective role of febrile infections, including tuberculosis, against melanoma development reported by others [70]. In our study, the negative association cannot be related to BCG immunization, because Myanmar introduced BCG vaccination under the Expanded Programme on Immunization (EPI) only in 1978 [63]. Because multiple myeloma predominantly affects adults older than 40 years, the vast majority of cases in this study had never been vaccinated.

A major limitation of our study resides in the small number of patients that we were able to recruit. Multiple myeloma is a rare cancer (less than 2% of all cancers in Europe), with an estimated prevalence of about 5 per million people in Asian countries. Therefore, in addition to the health situation, with travel restrictions that prevented patients from reaching major hospitals, this rarity of multiple myeloma explains the small number of cases we could find in Myanmar. This small number of patients and controls only allowed us to observe trends that did not reach significant differences between multiple myeloma patients and controls. Larger studies in non-industrialized countries, particularly in Southeast Asia, are therefore needed to clarify the environmental factors that may influence the incidence of multiple myeloma in this part of the world. Although obtained with a small number of patients in this study, the data nevertheless support the hypothesis that certain infections, in the context of a Southeast Asian population, may enhance immunosurveillance against multiple myeloma, whereas exposure to agricultural hazards increases the risk of developing this cancer.

Conclusion

In conclusion, this small hospital-based preliminary study in Myanmar shows a positive correlation between chemical exposure, including through farming, and multiple myeloma, but a negative correlation between some infections and multiple myeloma. However, the very small number of multiple myeloma patients who reported these infections makes it difficult to draw definitive conclusions. These results, which would need to be confirmed

in a wide range of patients, support the hypothesis that certain infections can enhance cancer immunosurveillance. This could explain a lower rate of multiple myeloma in southern countries. These environmental factors should be taken into account to target early diagnosis campaigns for multiple myeloma.

Ethical Statement

The University of Public Health, Yangon, Institutional Review Board approved the study based on the Declaration of Helsinki and the ICH Good Clinical Practice Guidelines.

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