

Case-control study of multiple myeloma with special reference to diet as risk factor

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The case-control study was conducted in Belgrade (Yugoslavia) during the period 1994–1998. The objective of the study was to investigate factors related to the occurrence of multiple myeloma (MM). The study group consisted of 100 newly diagnosed MM patients and the same number of matched hospital controls. In the analysis conditional univariate and multivariate logistic regression were applied. According to multivariate analysis the following factors were significantly related to MM: smoking ≥ 25 cigarettes per day (Odds ratio – OR=6.7, 95% confidence interval – 95% CI=1.3–34.3); having more than two brothers (OR=2.7, 95% CI=1.3–5.3), rheumatoid arthritis in personal history (OR=4.2, 95% CI=1.2–14.8), and frequent (4–7 times per week vs. lower frequency) consumption of yogurt (OR=3.1, 95% CI=1.6–6.0) and vegetables (OR=0.4, 95% CI=0.1–1.0).

Key words: Case-control study, diet, multiple myeloma, risk factors.

Little is known about the etiology of myeloma. Several reports have indicated an increased risk associated with farming and agriculture [5, 15, 18, 23], and food processing. However, evidence relating to the increased risk with the exposure to pesticides or to exposure to some virus or antigen associated with meat is inconsistent. Radiation and various chemicals, besides pesticides, and wood dust have been suggested as risk factors for myeloma [6, 11, 14]. Chronic antigenic stimulation and defective immune response are also postulated to be of importance in development of myeloma. A growing volume of data suggests association of repeated viral infections with multiple myeloma [2, 16].

The objective of the present study was to test the existing hypotheses about factors related to the occurrence of myeloma, as well as to investigate possible relationship between dietary factors and this malignancy.

Material and methods

Investigation was performed in Belgrade (Yugoslavia) during the period 1994–1998.

Case group consisted of 100 consecutive multiple myeloma patients diagnosed and histologically confirmed at the Institute of Hematology, University Clinical Center, Belgrade. Institute of Hematology is reference center for hematocology and the majority of multiple myeloma cases from Serbia without provinces are diagnosed in the Institute. Out of all diagnosed cases only 3 (three) did not accept to participate in the study. The same number of controls was recruited among hospital patients. About 50% of controls had ischialgia, and the other half were patients with light injuries and skin infections. No one among controls refused participation in the investigation. Cases and controls were individually matched by sex, age (± 2 years) and place of residence (rural/urban). Urban and rural population represents population of localities established as such by corresponding legal act or agreement of competent socio-political communities valid at the time of census [19]. All participants were interviewed by two physicians using standard questionnaire including questions about demographic characteristic, habits, personal history, family characteristics, and diet. Dietary information was obtained by using a frequency history approach. Subjects were asked how of-

ten (per week) they usually consumed each one of the 13 main food groups or food items. Engagement in sport activities was classified either as recreation or as sport, depending on whether such activities were for recreational purposes only or they included regular training and taking part in competitions. Various medical conditions present in the personal history of study participants were validated from participants discharge notice except for upper respiratory infections and infectious diseases other than malaria and tuberculosis.

In the analysis of data conditional univariate and multivariate logistic regressions were applied.

Results

Demographic characteristics of cases and controls are presented in Table 1. In both case and control groups, there were 55 men and 45 women. The vast majority of them were ≥ 45 years old. Significantly more cases than controls were married (odds ratio – OR=4.9, 95% confidence interval – 95% CI=1.9–13.2, $p=0.00$). Cases and controls did not differ in their education and occupation. Detailed analysis of participants' occupation showed that among cases and controls there were only a few persons who acted in the capacity of a cook and were in frequent contact with meat. No one among study participants was a butcher and no one worked in forestry, food processing or catering. There were also no differences between cases and controls in professional exposure to radiation and chemicals (Tab. 2). The exposure to a wide variety of chemical agents made it impossible to investigate their separate relevance to multiple myeloma.

Analysis of data concerning birth history, personal history and family characteristics (Tab. 2) showed significant differences between cases and controls for several variables. Allergic diseases (hay fever, allergy to food and pesticides) and tonsillectomy were more frequently reported by controls (OR=0.5, 95% CI=0.2–1.1, $p=0.09$ and OR=0.4, 95% CI=0.2–0.9, $p=0.01$, respectively), and rheumatoid arthritis was more frequently reported by cases (OR=2.6, 95% CI=0.9–7.6, $p=0.08$). Cases and controls did not differ in the number of current smokers, but cases were significantly more frequently heavy smokers, smoking ≥ 25 cigarettes per day (OR=3.8, 95% CI=1.3–11.1, $p=0.01$). Total number of children was greater in families of cases (OR=2.0, 95% CI=1.0–4.1, $p=0.03$). Actually more cases than controls had > 2 brothers (OR=2.6, 95% CI=1.3–5.3, $p=0.00$).

Out of main food groups and food items (Tab. 3), cases more frequently than controls consumed meat (OR=1.9, 95% CI=0.9–3.9, $p=0.05$), yogurt (OR=2.4, 95% CI=1.3–4.7, $p=0.00$) and butter (OR=2.0, 95% CI=1.1–3.6, $p=0.01$). Consumption of fruit and vegetables was more frequently reported by controls (OR=0.6, 95% CI=0.3–

Table 1. Demographic characteristics of cases and their controls

Variable	Cases (No.=100)	Controls (No.=100)	Odds ratio* (95% CI)	p value*
Sex:				
male	55	55		
female	45	45	matched	
Age (years):				
≤ 44	10	7		
45–54	14	15		
55–64	32	37		
65–74	39	36		
75+	5	5	matched	
Education:				
elementary and secondary school	75	81		
high school	25	19	0.7 (0.3–1.4)	ns
Marital status:				
single	2	7		
divorced	2	7	1.0	
widowed	3	13		
married	93	73	4.9 (1.9–13.2)	0.0004
Occupation:				
clerk	43	37	1.0	
farmer	6	9		
worker	35	33	0.8 (0.4–1.4)	ns
housewife	16	21		
Residential area:				
rural	24	25		
urban	76	75	matched	

95% CI – 95% confidence interval, * – according to univariate logistic regression analysis, ns – not significant.

1.1, $p=0.09$ and OR=0.4, 95% CI=0.1–0.9, $p=0.02$, respectively). There were no significant differences between groups in alcohol and coffee consumption.

Cases and controls did not differ in their body mass index (BMI). Preobesity (BMI=25.0–29.9) was present in 38.0% of cases and 35% of controls, and obesity (BMI ≥ 30) in 15% of cases and 14% of controls.

All variables that according to univariate logistic regression analysis were related to multiple myeloma at a significant level of $p \leq 0.10$ were included into the model of multivariate logistic regression analysis (marital status, allergic diseases, rheumatoid arthritis and tonsillectomy in personal history, smoking ≥ 25 cigarettes per day, numbers of brothers > 2 and frequent consumption of meat, yogurt, fruit, vegetables and butter). Total number of children in the family > 2 was not included in the model of multivariate analysis since it was correlated with numbers of brothers > 2 . According to multivariate analysis the following factors were significantly related to multiple myeloma: smoking ≥ 25 cigarettes per day, having more than two brothers,

Table 2. Birth history, personal history and family characteristics of cases and their controls

	Cases (No.=100)	Controls (No.=100)	Odds ratio*	95% CI	p*
<i>Birth history</i>					
Maternal age at participants birth ≥ 29	32	21	1.8	(0.9–3.4)	ns
Paternal age at participant birth ≥ 24	66	63	1.1	(0.6–2.1)	ns
Birth order (3+)	53	42	1.6	(0.9–2.8)	ns
Born as a twin	3	3	1.0	(0.2–6.4)	ns
Congenital malformation	2	1	2.0	(0.1–57.2)	ns
Breast fed	99	99	1.0	(0.1–37.1)	ns
<i>Personal history</i>					
Upper respiratory infections – viral ≥ 2 times per year	16	16	1.0	(0.4–2.3)	ns
Upper respiratory infections – streptococcal ≥ 2 times per year	26	20	1.4	(0.7–2.9)	ns
Malaria	7	11	0.6	(0.2–1.8)	ns
Tuberculosis	6	8	0.7	(0.2–2.4)	ns
Other infectious diseases	14	12	1.5	(0.5–2.9)	ns
Allergic diseases	12	21	0.5	(0.2–1.1)	0.090
Anemia	7	8	0.9	(0.3–2.8)	ns
Rheumatoid arthritis	12	5	2.6	(0.9–7.6)	0.085
Other non-infectious diseases	36	42	0.7	(0.4–1.4)	ns
Tonsillectomy	14	28	0.4	(0.2–0.9)	0.017
Appendectomy	29	31	0.9	(0.5–1.7)	ns
Other operations	37	43	0.8	(0.4–1.4)	ns
Current smokers	29	24	1.3	(0.7–2.5)	ns
Average number of cigarettes smoked per day:					
0	71	76	1.0		
1–24	11	19	0.6	(0.3–1.6)	0.244
≥ 25	18	5	3.8	(1.3–11.1)	0.007
Sport activity	9	5	1.5	(0.5–6.7)	ns
Recreation activity	15	12	1.3	(0.5–3.1)	ns
Possession of pet	18	18	1.0	(0.5–2.2)	ns
Professional radiation exposure	2	2	1.0	(0.1–10.2)	ns
Diagnostic X-ray exposure	2	5	0.4	(0.1–2.3)	ns
Professional chemical exposure**	18	15	1.2	(0.5–2.8)	ns
<i>Family characteristics^x</i>					
Total number of children in the family >2	81	68	2.0	(1.0–4.1)	0.037
Number of sisters >2	29	27	1.1	(0.5–2.1)	ns
Number of brothers >2	40	20	2.6	(1.3–5.3)	0.004

95% CI – 95% confidence interval, * according to univariate logistic regression, ** exposure to benzene, dyes and lacquers, pesticides, fertilizers, solvents, organic acids, plastic resins, glues, ^x leukemia, lymphoma and multiple myeloma were not reported among relatives of either cases or controls.

rheumatoid arthritis in personal history, and frequent consumption of yogurt and vegetables (Tab. 4).

Discussion

In the present study risk factors for multiple myeloma were smoking ≥ 25 cigarettes per day, rheumatoid arthritis in personal history, having more than two brothers, and frequent consumption of yogurt and vegetables.

Since it is known that smoking is a risk factor for many malignant and other diseases the association between number of cigarettes smoked and multiple myeloma does not

come as a surprise. Although, due to small study group, odds ratio estimate for cigarettes smoking is not precise enough (relatively large confidence intervals), this finding is in line with some of previous epidemiological studies that have indicated a link between smoking and the risk of developing hematolymphoproliferative cancers, including multiple myeloma [3]. However, in the large cohort study conducted in Sweden [1] no significant association was found between smoking status, number of cigarettes smoked, or duration of smoking and the risk of developing leukemias, lymphomas, or multiple myeloma.

Concerning rheumatoid arthritis, there were previous reports that stressed the association between autoimmune

Table 3. Consumption frequency of food group and food items of cases and their controls

Food group and food items consumption frequency	Cases (No.=100)	Control (No.= 100)	Odds ratio**	95% CI	p**
* Meat – 7 times per week	31	19	1.9	(0.9–3.9)	0.052
* Milk – 7 times per week	41	30	1.6	(0.9–3.0)	ns
*Yogurt – 4–7 times per week	42	23	2.4	(1.3–4.7)	0.005
*Cheese – 7 times per week	24	20	1.3	(0.6–2.6)	ns
*Eggs – 4–7 times per week	35	43	0.7	(0.4–1.3)	ns
*Fruit – 4–7 times per week	62	73	0.6	(0.3–1.1)	0.098
*Vegetables – 4–7 times per week	81	92	0.4	(0.1–0.9)	0.027
*Juice – >1 times per week	79	70	2.0	(0.8–3.2)	ns
*Butter – >1 times per week	57	40	2.0	(1.1–3.6)	0.017
*Sweets – >1 times per week	75	73	1.1	(0.6–2.2)	ns
*Nitrate treated meat – >1 times per week	63	54	1.4	(0.8–2.7)	ns
*Canned food – >1 times per week	32	29	1.1	(0.6–2.2)	ns
Lard for food preparation	10	10	1.0	(0.4–2.7)	ns
Alcohol consumption	37	30	1.5	(0.7–2.6)	ns
Coffee consumption	84	79	1.8	(0.6–3.0)	ns

95% CI – 95% confidence interval, ns – not significant, * all those whose consumption frequency was lower were taken as a reference group,

** according to univariate logistic regression analysis.

Table 4. Risk factors for multiple myeloma according to multivariate logistic regression analysis

Variable	Odds ratio	95% confidence interval	p
Smoking ≥ 25 cigarettes per day*	6.9	1.3–34.9	0.019
Rheumatoid arthritis in personal history	4.2	1.2–14.8	0.024
Consumption of yogurt 4–7 times per week	3.1	1.6–6.0	0.001
Consumption of vegetables 4–7 times per week	0.4	0.1–1.0	0.022
Number of brothers >2	2.7	1.3–5.3	0.002

* vs non-smokers and light smokers.

disease and lymphoproliferative neoplasm [13]. INOUE et al [12] reported a case of rheumatoid arthritis associated with multiple myeloma, and suggested that prolonged antigenic stimulation manifested by rheumatoid arthritis can be considered as possible pathogenic factor in the development of multiple myeloma. Development of multiple myeloma in patient with rheumatoid arthritis and Bechterev disease is also reported by some other authors [17, 21].

There is no clear explanation why having more than two brothers is a risk factor for multiple myeloma. It is possible that greater number of siblings makes contact with oncogenic agent more likely to occur. We cannot be sure whether the greater number of brothers (but not of sisters) in families of cases is the result of a chance or is in some way related to multiple myeloma risk.

With respect to yogurt as a risk factor for multiple myeloma, the fact that cases in the present study more frequently than controls consumed not only yogurt, but also milk, butter and meat, could point out animal fat as dietary

factor related to multiple myeloma. Elevated risk of non-Hodgkin lymphoma (NHL) was found among men with high milk consumption in Nebraska [22] as well as in the study of TAVANI et al [20]. In the study of TAVANI et al [20] butter intake was also an indicator of the risk of myeloma. An increased energy intake, as a response to changes in fat composition may be considered to be one of the mechanisms by which dietary fat affects development of malignancies [8]. Also, high-fat diet may lead to higher body mass or obesity which is considered as risk factor for some malignant diseases [9]. In recently published large study on risk factors for multiple myeloma in the United States [4] obesity was found to be risk factor for this malignancy with OR=1.9 for whites, and 1.5 for blacks. Besides, the association found between animal fat and some other malignant diseases (cancer of breast, ovary, endometrium, prostate) is most probably effected through changes in the hormonal environment [7]. It is also known that some hormones exercise strong influence on the immune system [10].

Protective effect of fruit and vegetable consumption has been suggested for many malignant diseases. There is only one study suggesting a relationship between multiple myeloma and fruit and vegetable intake. Namely, BROWN et al [4] found that reduced risk for multiple myeloma was related to frequent intake of cruciferous vegetables, and of vitamin C from food and supplements. Vitamin C, carotene, citrus fruit and dark vegetable intake were found to be inversely related with NHL in WARD et al study [22], although only in men. In the investigation of TAVANI et al [20], the highest tercile of intake of beta-carotene was inversely related to lymphoid neoplasms.

Therefore the relationship of multiple myeloma and consumption of yogurt and vegetables found in the present investigation, should be approved on a larger study group.

The absence of relationship between multiple myeloma and some factors such as certain occupations and BMI, found by other investigators [4, 5, 6, 11, 15, 18, 23], could be explained by the fact that our study group was not large enough. For the same reason, that is relatively small number of cases and controls in the present study, because of all drawbacks of investigations based on retrospective data, and since frequency diet history method was used instead of quantitative diet history method, we hold the view that the results obtained should be corroborated by other investigators.

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