ORIGINAL ARTICLE

Analysis of cutaneous melanoma in the province of Vojvodina

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Summary

Purpose: To analyse the incidence and mortality of melanoma in the province of Vojvodina - the north part of Serbia- from the epidemiologic and clinical point of view.

Patients and methods: In this retrospective study, we used databases of the Cancer Registry of Vojvodina, Oncology Institute of Vojvodina in Sremska Kamenica; Clinical Centre of Vojvodina in Novi Sad; Institute of Public Health of Vojvodina in Novi Sad; and Institute of Public Health of Serbia in Belgrade.

Results: The incidence and mortality of melanoma in Vojvodina is permanently increasing over the last three decades. The number of newly diagnosed and deceased patients was higher in men and in women in Vojvodina than in central Serbia. Considering the incidence rate, the region of Vojvodina would be placed in the middle of the European countries. The results are more unfavorable with mortality, especially in male population, similar to the range of higher mortality rates among European countries.

Conclusion: These upsetting facts call for improvement of primary and secondary prevention. Education of the population, continuous efforts to recognize groups of population at high risk for developing melanoma and detection of early phases of the disease increases the chances for cure and significantly reduces treatment costs.

Key words: incidence, melanoma, mortality, Vojvodina

Introduction

Cutaneous melanoma is a malignant tumor that develops from activated or gene mutated epidermal melanocytes. Although it is not as frequent as basal cell and squamous cell carcinomas are, lethal outcome is more probable. Cutaneous melanoma is a malignant disease with increasing incidence throughout the world and in our country during the last few decades. The increase of incidence is more rapid with cutaneous melanoma than with any other malignant tumor, except lung cancer in women [1].

The database of the Cancer Registry for Vojvodina and our own clinical indicators show a continuing trend of increased incidence and mortality from cutaneous melanoma in the province of Vojvodina. The reasons for the increased number of new cases may be related to the reduction of ozone layer, exposure to UV radiation, but also to the frequent diagnosis of the disease [2].

The incidence of melanoma in north Europe is the highest but stagnant during the last decade, while in the countries of east and south Europe the incidence is permanently on the increase. This raising trend is also registered in our country [3,4].

The province of Vojvodina is the north part of Serbia with a population of about 2,000,000 with a specific multicultural environment and where the incidence and mortality from malignant melanoma increases since 1980s.

Patients and methods

The goal of this article was to analyse the incidence and mortality of cutaneous melanoma in Vojvodina from the epidemiologic and clinical point of view.

Epidemiological characteristics of melanoma were analysed on the basis of the official data of Cancer Reg-

istry of Vojvodina (Department of Epidemiology, Oncology Institute of Vojvodina in Sremska Kamenica), Cancer Registry of central Serbia (Institute of Public Health of Serbia) and databases of the Institute of Public Health of Vojvodina in Novi Sad.

The present study considered all the cases in the region of Vojvodina registered under clinical diagnosis code C43 over the period from 01.01.1985 to 31.12.2004. Age- and sex-based distribution of the cases were calculated from the rates on 1/100,000 inhabitants. Age-standardized incidence and mortality rates were calculated according to World Population for comparing data with central Serbia and European countries. Tendency of incidence and mortality rates was analysed by linear trend.

For the purpose of better understanding and explaining the epidemiologic situation of melanoma in Vojvodina we also analysed clinical aspects of melanoma according to data from the Clinical Centre of Vojvodina in a 5-year period (01.01.2003 - 31.12.2007). A total number of 186 patients (female: 53.1%; male: 46.9%) had been operated with mean age 57.0 years (SD=12.3). The average disease duration was between 6 and 12 months.

Results

The rate of melanoma occurrence in the province of Vojvodina is permanently increasing over the last 3 decades. Figures 1 and 2 show an ascending line in a 20-year period for incidence and mortality, the latter of which is a bit higher. Figures 3 and 4 show 10-year indicators of incidence and mortality in women and men based on the data obtained from the Cancer Registry of Vojvodina.

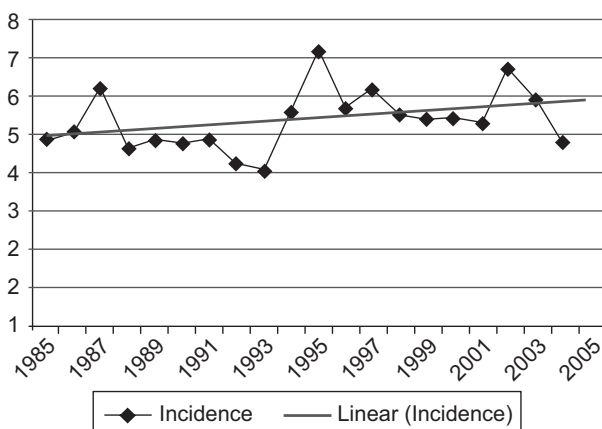The 5-year (1999-2003) average age standardized rate of new cases of malignant melanoma was 5.56/

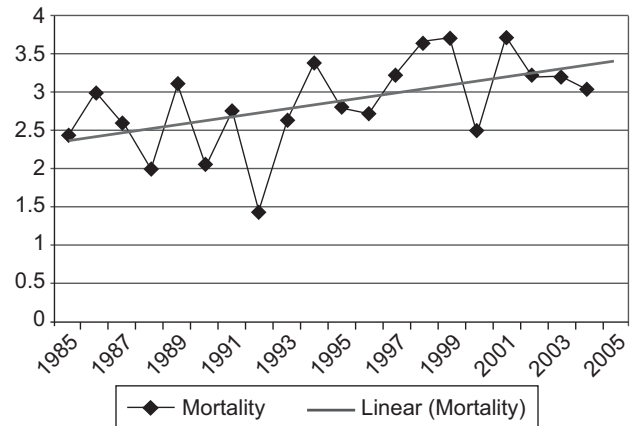**Figure 1.** Trend line of melanoma incidence in Vojvodina from 1985 to 2004.

Figure 2. Trend line of melanoma mortality rate (1/100,000) in Vojvodina from 1985 to 2004.
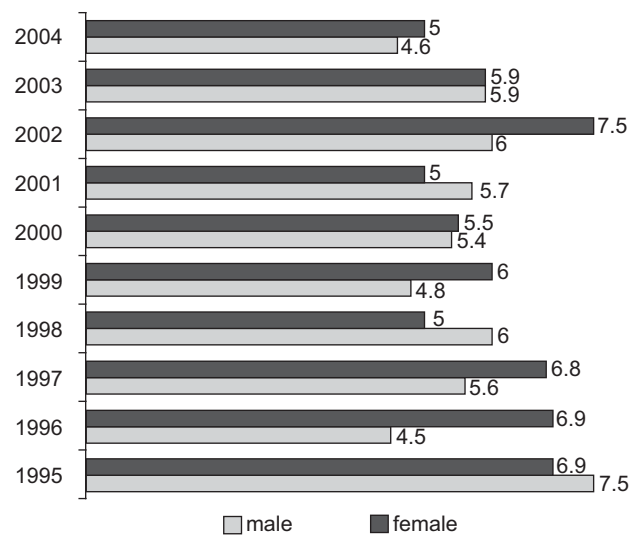

Figure 3. Incidence rate (1/100,000) of melanoma in Vojvodina for 10-year period.
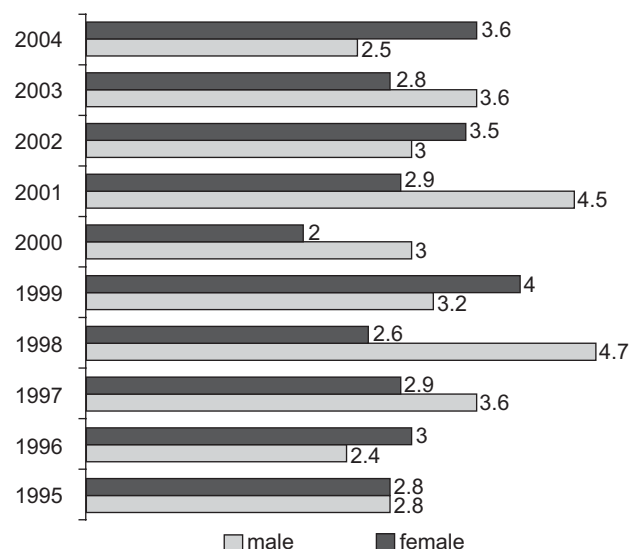

Figure 4. Mortality rate (1/100,000) of melanoma in Vojvodina for 10-year period.

100,000 of male and 5.98/100,000 of female inhabitants; the mortality rate was 3.42 in male and 2.95 in female population.

Comparing data from central Serbia with data from Vojvodina in the same period, a difference emerged in incidence and mortality rates of melanoma (Table 1). The number of newly diagnosed patients as well as mortality rates were higher in both male and female population in Vojvodina than in central Serbia.

Considering the number of newly diagnosed patients among both male and female population, the region of Vojvodina could be placed in the middle of European countries. The results were more unfavorable comparing mortality rates (Figure 5).

Data of the Cancer Registry of Vojvodina (1995-2004) showed a higher percentage of new cases among women (female: 53%; male: 47%) and a slight increase of mortality among men (male: 52%; female: 48%). This sex-based distribution of patients correlates with the relevant data of the majority of European countries.

Comparison of data from 1985 to 1989 and from 2000 to 2004 revealed that melanoma most frequently developed in individuals in the 6th and 7th decades of life, in both examined groups. Concerning the total number in both studied groups of patients, those less than 50 years of age accounted for 30%. The average age of patients was 57.3 years in the first 5-year analysed period and 57.2 years in the second (Table 2). The incidence trend of newly diagnosed patients was equal in all age groups over the years and correlated with European Network of Cancer Registry (ENCR) data for east and south Europe.

Clinical data of operated melanoma patients obtained in a 5-year period conducted at the Clinical Center of Vojvodina are shown in Table 3. The percent of operated patients with thin primary melanoma was 22.6% (T1: ≤1 mm), intermediate melanoma 45.7% (T2,3: 1-4 mm), and thick melanoma 31.7% (T4: >4 mm).

The most prevalent clinical type of melanoma was superficial (59.1%), followed by nodular growth (36.0%). Ulceration accounted for 55.4%.

Tumor was most often localized on the extremities and trunk. Twelve patients (6.5%) had metastases in the regional lymph nodes at diagnosis. Nine of them
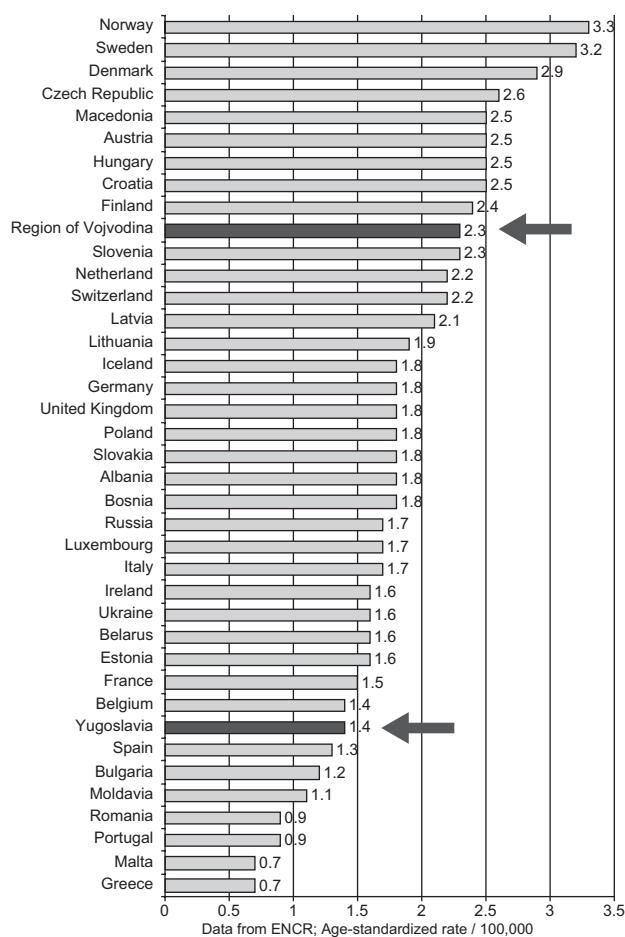

Figure 5. Melanoma mortality in Europe, year 2000 estimates, by country, males. Data from ENCR; age-standardized rate/100,000

Table 2. Age distribution of newly diagnosed melanoma patients from the two different 5-year periods

Age (years)	1985-1989		2000-2004	
	n	(%)	n	(%)
0-19	5	0.96	2	0.33
20-29	19	3.66	16	2.65
30-39	59	11.37	54	8.96
40-49	82	15.80	105	17.41
50-59	128	24.66	42	23.55
60-69	99	17.15	148	24.54
70-79	78	15.03	108	17.91
80+	59	11.37	28	4.65
Total number	519		603	
Mean age	57.3		57.2	

Table 1. Age-standardized incidence and mortality rate/100,000 of melanoma - average value for 5 year period (1999-2003)

	Incidence		Mortality	
	Cancer Registry for central Serbia	Cancer Registry for Vojvodina	Cancer Registry for central Serbia	Cancer Registry for Vojvodina
Men	4.2	4.7	1.8	2.3
Women	3.8	4.8	1.2	1.9

Table 3. Clinical characteristics of operated patients; 5-year period (2003-2007)

Characteristic	n	%
Total number	186	100.0
Breslow's tumor thickness (mm)		
Thin - up to 1	42	22.6
Intermediate 1.1-4	85	45.7
Thick - more than 4.1	59	31.7
Clinical type of melanoma		
Superficial	110	59.1
Nodular	67	36.0
Lentigo	7	3.8
Acral	2	1.1
Presence of ulceration	103	55.4
Tumor regression	20	10.7
Complete regression	1	0.5
Localization of tumor		
Trunk	71	38.2
Head	41	22.0
Extremities	74	39.8
Metastases at diagnosis	12	6.5
Patients' anamnestic data		
Appearance of discomfort	67	36.0
Secretion or bleeding	65	34.9
Inflammation	17	9.1
Previous trauma	45	24.2
Without any symptoms	41	22.0

had primary melanoma localized on the trunk, which favors more rapid disease spread.

The majority of patients came for the first examination only after the appearance of discomfort (36.0%), such as itching, pricking, pins and needles, or after they had noticed secretion or bleeding of the tumor (34.9%). Patients reported tumor growth after an injury in 24.2%. Only every 5th patient came for examination checkup without having any clinical manifestation.

Discussion

According to the evidence of ENCR from 2000, former Yugoslavia (Serbia and Montenegro) was a country with relative low incidence and mortality rates from melanoma in both sexes. However, if we compare ENCR data with data from the Cancer Registry of Vojvodina we get different results.

Considering the number of deaths from melanoma, Vojvodina could be placed together with European countries with higher mortality rates from this disease. This fact seems more alarming when we compare the male population only.

North and central European countries that have high disease incidence also have the highest survival rates; countries with low number of new cases of melanoma have less favorable 5-year survival rates. Explanation may be found in better information of the population regarding the potential risks from the disease, in early detection and diagnosis, and in the use of standardized guidelines for the treatment of melanoma patients [5-7].

Worldwide indicators show that cutaneous melanoma has been more and more associated with young and middle-aged people. On the other hand, data from the Cancer Registry of Vojvodina indicate that the age structure of newly diagnosed patients has not been significantly disturbed over the years.

The higher number of newly diagnosed patients in Vojvodina than in central Serbia could be explained by the heterogeneous structure of the population, i.e. higher percentage of population with skin type I and II according to Fitzpatrick (individuals with fair complexion, blue eyes, and red hair) [8-10].

The high mortality rate in Vojvodina is primarily the result of late disease diagnosis. Thickness of melanoma, presence of ulceration, and anatomic site are the most important variables in the prognosis of patient's survival and treatment outcome of clinically localized disease [11]. Patients with Breslow thickness less than 1 mm and adequate surgical treatment will have a 95% 10-year survival. The percent of patients with early-diagnosed melanoma (T0 and T1) is different in various parts of Europe and ranges from 10 to 70%. Based on this indicator and having in mind that only 22.6% of our patients were surgically treated in T0 and T1 stage of disease, it is evident that our province belongs to the group with low number of patients diagnosed in early stage [12,13].

Melanomas with lateral radial growth (superficial, lentigo, and acral melanomas) are characterized with slower clinical course and better prognosis. Melanomas with predominantly vertical growth (nodular melanomas) have more aggressive clinical course, which results in disease dissemination and higher lethal outcome [14]. Melanomas with lateral spread are characterized with long disease evolution; in time, they evolve into vertical and more invasive growth phase. In developed countries, nodular type with vertical growth is diagnosed in about 15% of melanoma cases among Caucasian population, compared to our clinically diagnosed patients with nodular melanoma accounting for 36%. In about one third of our patients with nodular melanoma, radial growth was recorded first, and in time it evolved into vertical growth, which implies a longer disease course. This unfavorable fact is one of the causes for high mortality [15,16].

Ulceration of melanoma is defined as the lack of epidermis over a smaller or bigger part of the tumor. It

is detected clinically, but verified with a thorough microscopic and histological analysis. According to the most recent TNM classification accepted in 2003 by all relevant world associations for the fight against cancer (WHO, UICC, AJCC, and EORTC), the presence of ulceration in primary melanoma is a poor prognostic factor, which puts the patient into higher disease stage [16,17]. For example, the patient with thin melanoma *in situ* and no ulceration is staged as IA; however, the presence of ulceration classifies the patient into IB stage of the disease, i.e. into the group of patients with 2 mm thick tumors with no ulceration. Our clinical data showed that more than half of the patients had ulcerated melanoma, which is very high compared to European standards [11,18].

According to histopathological parameters, regression of melanoma is a poor prognostic factor. This process was registered in 11% of our group of patients. It is explained as an immune response of the organism to existing diseases (inherent immunogenicity) [19,20]. The frequent regression of melanoma has incited scientists to focus on producing a vaccine that might contribute to the therapy and prevention of melanoma development among risk groups. Although clinical testing of existing vaccines has not produced satisfactory results, it has contributed to the understanding of complex interaction between melanoma and immune system, i.e. regulation of immune response. Multimodal immunotherapy seems to be the direction of the newest researching. This strategy comprises a combination of the ideal vaccine stimulus, with the most potent adjuvant, in the optimal setting (radical surgical resection of tumor, pre-treatment lymphodepleting chemotherapy and immunomodulation with cyclophosphamide) and negative co-stimulatory blockade [21].

Complete regression of melanoma is very rare (2-3% of the cases worldwide). During the 5-year study period, we had only one patient with lymph node metastases and unknown site of the primary tumor (so-called occult melanoma).

Cutaneous melanoma may arise in any part of the body. The most frequent sites are the trunk and back in men and lower extremities, particularly legs, in women. The localization of primary melanoma is important prognostic factor, influencing patient survival [22]. Patients with melanoma of head and neck have poorer prognosis and more rapid disease course than patients with melanoma localized in the extremities, mainly because of the drainage pathways, related to the proximity of the regional lymph nodes. The most frequent localization of melanoma according to our clinical data in male patients was the trunk, primarily on the back, and in female patients the extremities, primarily the legs.

These data suggest that primary melanoma in male patients was, on average, localized on unfavorable sites. As a relevant prognostic factor, it can partially explain the higher mortality rate in men.

Although previous trauma has not been confirmed as etiologic risk factor, 24% of our patients reported tumor growth after an injury [23]. The majority of patients came for the first examination only after the appearance of some kind of symptoms, and just every 5th of them came for examination checkup without having any clinical manifestation. The low percentage of these patients suggests insufficient primary and secondary prevention against this malignant disease [5,6].

Therapeutic dissection of lymph nodes is indicated in case of clinically positive lymph nodes or positive sentinel lymph node (SLN). Out of the total number of patients operated in the Clinical Center of Vojvodina, 12 (6.5%) had already metastases in the regional lymph nodes on presentation. Elective dissection of regional lymph nodes has been rejected because randomized studies showed no improvement in survival. SLN determination in primary melanoma (Breslow ≥1 mm, Clark's level IV and V, presence of ulceration) has been introduced in recent years [24]. This method makes possible elective dissection of regional lymph nodes in patients with normal clinical and ultrasound findings, and detection of micrometastases (< 2 mm), which might remain undetected by standard histology. SLN detection contributes to more precise staging of the disease (TNM classification). It is a valuable prognostic factor and should be used as a routine procedure [15].

Conclusion

The incidence and mortality rate of melanoma in the province of Vojvodina is higher than in central Serbia. Data concerning the number of new cases are comparable with those of the majority of central European countries. Comparing the number of deceased patients, however, especially males, the province of Vojvodina belongs to European countries with higher rates. These upsetting facts should warn us to improve primary and secondary measures of prevention. Permanent education of the population over the harmful effects of UV exposure and protection against it would certainly reduce the risk of the disease. Primary care physicians, i.e. family doctors, should be able to recognize groups of population at high risk for developing melanoma and refer them to routine periodic screenings. Detection of early phases of disease by clinical examination and dermoscopy procedures increases the chances for cure and significantly reduces treatment costs.

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Acknowledgement

We wish to thank Prof. M. Miladinov and colleagues from the Epidemiology department, Oncology Institute of Vojvodina in Sremska Kamenica, for providing the data that was essential for this article.

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