

RESEARCH ARTICLE

Melanoma Incidence Mortality Rates and Clinico-Pathological Types in the Siberian Area of the Russian Federation

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Abstract

Russian rates for melanoma incidence and mortality are relatively low as compared to some other white populations but the tumor is of increasing importance. In this paper, data are based on a retrospective descriptive analysis of melanoma epidemiology and clinicopathological characteristics in Krasnoyarsk Territory belonging to the Siberian Federal District of the Russian Federation. The age-adjusted incidence and mortality rates for the period 1996-2009 were determined with subsequent retrospective analysis of clinicopathological data of 103 primary melanoma cases. Our results showed that incidence and mortality rates in the region under consideration match the Russian national trends and correspond to epidemiological data of the countries of Eastern Europe. Stratification of melanoma cases by age, sex, clinicopathological state and localization revealed a prevalence of lesions on the trunk and lower extremities. Most melanomas diagnosed were of superficial spreading type and the third Clark's level of tumor invasion and stage II according to AJCC. In spite of comparatively low rates of incidence and mortality the trend to increase of melanoma cases in the region under consideration obviously calls for more attention and further investigation.

Keywords: Melanoma - incidence - mortality - Siberia - Russian Federation

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Introduction

Cutaneous melanoma is one of the deadliest cancer types with increasing incidence rates among white population (Mocelin and Nitti, 2001). It has been reported that melanoma incidence rates are known to correlate well with age, gender, socioeconomic status and tumor localization (Jemal et al., 2011), though numerous studies show controversial data on gender influence in melanoma development. In US, melanoma of skin occurs more often in women than in men (Weir et al., 2011). The latest research revealed higher rates of late-stage melanoma incidence in US men whereas women had higher rates of early-stage melanoma incidence (Richards et al., 2011). Singh and co-authors found that cutaneous melanoma incidence prevails in populations with higher education and higher income (Singh et al., 2011). Similar results were obtained in a study carried out in Holland: people of high socioeconomic status had higher incidence rates of cutaneous melanoma (Van der Aa et al., 2011). Moreover, melanoma incidence traditionally rises with age (Pruthi et al., 2009; Youl et al., 2012). Some researchers observed the increase of melanoma incidence in men only over 65, though in women of all ages or in elders of both sexes (Fuglede et al., 2011). Head, neck and trunk are found to be most predominant localization for tumor, with a rising

frequency of its occurrence on a trunk (Bradford et al., 2010). Genome sequencing of melanoma cells revealed that its mutation spectrum associates with ultraviolet light exposure resulting in the most often mutational event with characteristic features of this factor -G>T/G>A transitions (Pleasant et al., 2010). Recent data showed that melanoma mortality rates stabilized or showed increase only in selected groups of melanoma patients (Schubert, 2012). Several reports pointed out melanoma mortality rates stabilization in women (MacKie, 2003).

In the Russian Federation, melanoma is the third tumor type by the annual increase rate-next to renal cancer and brain tumors (Chissov et al., 2011). It should be noted however that comprehensive data accumulated on melanoma incidence and mortality in Russia have not yet been reported abroad. The aim of this study was to evaluate melanoma epidemiology and histopathological features of the tumor in Krasnoyarsk Territory belonging to Siberian Federal District of the Russian Federation. Population of Krasnoyarsk Territory is 2,846,000 inhabitants. Caucasian people compose more than 90% of the Siberian Federal District population mostly inhabiting the middle and southern parts of the region. All patients with melanoma diagnosed must be registered in Krasnoyarsk Territorial Oncological Center, where the doctors are to fill in the obligatory standardized forms with patient's data (full

name, age, gender, social status, ethnicity, diagnosis and method of its confirmation, clinical features, staging and peculiarities of treatment etc.).

Materials and Methods

The incidence and mortality rates were expressed as the number of new cases per 100,000 person-years and adjusted by age using European standard populations with calculating corresponding 95% confidence interval (CI). Cutaneous melanoma epidemiology survey in Krasnoyarsk Territory was based on the data of Krasnoyarsk Territorial Oncological Center and was approved by ethical committee of Krasnoyarsk Territorial Oncological Center. Europe-standardized incidence and mortality rates of cutaneous melanoma were determined by direct standardization using distribution by age categories of population. These rates were estimated for the entire period of our study. The data for each stratum of age and gender, and the estimate of population were obtained from the Territorial State statistics agency of Krasnoyarsk Territory. The annual percentage change was estimated by fitting a least squares regression line to the natural logarithm of the incidence and mortality rates, using the calendar year as a regressor variable ($y=mx+b$, where $y=\ln(\text{rate})$ and $x=\text{calendar year}$, then $APC=100*(e^m-1)$). The tumor cases are encoded by the ICD-10 classification, cutaneous malignant skin melanoma is defined as ICD-10 diagnosis C43.

Besides, retrospectively 103 primary mucosal and cutaneous melanoma cases of patients admitted at Krasnoyarsk Territorial Oncological Center were assessed. Information on patients' characteristics (sex, age, tumor localization, stage and clinico-pathological type) was obtained from medical records of Krasnoyarsk Territorial Oncological Center. Breslow thickness was assessed by using commercial Infinity Capture, Infinity Analyze Software (V.4.6.0), (Lumenera Corporation, Canada). The lymphocytic infiltration was determined in all tumors and classified as brisk, nonbrisk, and absent according to criteria established by Clark et al. (1981). Tumor infiltrating lymphocytes (TILs) were identified as lymphocytes within tumor nodes. Brisk infiltrate was determined in case of diffuse presence of lymphocytes within tumor, non-brisk infiltrate was in focal location of lymphocytes and absent if no lymphocytes were present in a tumor.

Significance was determined by Student's t-test, one-way ANOVA. To analyze the relationship between the individual pairs of qualitative features, the χ^2 test was used, with the construction of contingency tables for all possible pairs of the given attributes. The p values less than 0.05 were considered as significant.

Results

The average standardized incidence of melanoma in 1996-2009 was 3.64 per 100,000 inhabitants (Table 1). For the same time period, the mean melanoma incidence in men was 3.49 and 3.98 in women. We observed increase of melanoma incidence rates more expressed in males with

APC corresponded to 4.53%. Trends in mortality rates showed more considerable elevation in females. APC in female mortality rates was 2.94% (Table 2).

Clinico-pathological analysis of primary melanoma cases revealed the prevalence of superficial spreading melanoma in man and women: the most often clinical type of melanoma incidence was superficial spreading melanoma (56.33%) and nodular melanoma (27.18%), besides 7.76% of melanomas were recorded as lentigo maligna and 5.82% as acral-lentiginous melanomas (Table 3). Superficial spreading type melanoma patients had no gender differences in tumor localization whereas female patients with nodular melanoma had prevalent localization on lower extremities (Table 4). Mean age of patients with superficial spreading melanoma was 59.5 years, nodular melanoma -57.1. Although mean age of mucosal melanoma patients was 76.33 we did not identify significant age differences in accord with clinical type. We also did not find age differences between patients of various melanoma clinical types.

The trends observed in melanoma incidence on body site were as follows: 51.45% melanomas were on extremities, 39.64% on trunk, and 5.94% on face/ears, scalp or neck. Stratification of 103 patients with invasive melanoma in this study by staging and Clark invasion level showed that the major part of patients were diagnosed on

Table 1. Incidence Rates* of Melanoma in Krasnoyarsk Territory of Russian Federation, 1996-2009

Year	General population (95% CI)	Male (95% CI)	Female (95% CI)
1996	2.66 (2.07-3.33)	2.29 (1.38-3.22)	2.91 (2.04-3.76)
1997	3.02 (2.31-3.69)	2.56 (1.58-3.62)	3.47 (2.52-4.48)
1998	3.05 (2.33-3.67)	2.64 (1.66-3.62)	3.42 (2.46-4.34)
1999	2.92 (2.28-3.56)	2.98 (2.03-3.92)	3.10 (2.18-4.01)
2000	3.72 (2.99-4.45)	3.56 (2.53-4.59)	5.06 (3.89-6.23)
2001	4.15 (3.38-4.92)	3.48 (2.45-4.51)	4.80 (3.66-5.94)
2002	3.67 (2.94-4.40)	3.18 (2.19-4.17)	4.17 (3.11-5.23)
2003	3.10 (2.43-3.77)	2.39 (1.53-3.25)	3.61 (2.62-4.60)
2004	4.00 (3.24-4.76)	3.21 (2.21-4.21)	4.20 (3.13-5.27)
2005	4.72 (3.89-5.55)	5.16 (3.88-6.44)	4.47 (3.36-5.58)
2006	3.96 (3.20-4.72)	4.01 (2.88-5.14)	4.40 (3.30-5.50)
2007	4.50 (3.68-5.32)	4.31 (3.14-5.48)	4.68 (3.54-5.82)
2008	3.63 (2.90-4.36)	3.43 (2.39-4.47)	3.85 (2.82-4.88)
2009	4.32 (3.52-5.12)	4.62 (3.41-5.83)	4.93 (3.76-6.10)
APC	3.23 (3.10-3.54)	4.53 (4.21-4.84)	2.70 (2.44-2.96)

*Age-adjusted rates per 100,000 person-year

Table 2. Mortality Rates* of Melanoma in Krasnoyarsk Territory of Russian Federation 1999-2009

Year	General population (95% CI)	Male (95% CI)	Female (95% CI)
1999	1.56 (1.09-2.03)	1.82 (1.08-2.56)	1.30(0.71-1.79)
2000	1.78 (1.28-2.28)	2.31 (1.48-3.14)	1.26(0.68-1.85)
2001	1.73 (1.23-2.23)	1.76 (1.03-2.49)	1.29(0.70-1.88)
2002	1.66 (1.17-2.15)	2.21 (1.39-3.03)	1.38(0.77-1.99)
2003	1.55 (1.08-2.02)	2.28 (1.44-3.12)	1.42(0.80-2.04)
2004	1.85 (1.33-2.37)	1.76 (1.02-2.50)	1.79(1.09-2.49)
2005	1.98 (1.44-2.52)	1.78 (1.03-2.53)	1.40(0.78-2.02)
2006	1.50 (1.03-1.97)	1.21 (0.59-1.83)	1.46(0.82-2.10)
2007	2.02 (1.47-2.57)	2.99 (2.02-3.97)	1.38(0.76-1.00)
2008	1.76 (1.25-2.27)	2.29 (1.44-3.14)	1.55(0.90-2.20)
2009	2.02 (1.47-2.57)	1.88 (1.11-2.65)	1.96(1.22-2.70)
APC	1.61 (1.43-1.79)	0.24 (-0.31-0.79)	2.94(2.70-3.17)

*Age-adjusted rates per 100,000 person-year

Table 3. Descriptive Statistics for Cutaneous and Mucosal Melanoma, Krasnoyarsk Territory

	Men No. (%)	Women No. (%)	Total No. (%)	p
Malignant melanoma				
Total number	33 (32.04)	70 (67.96)	103 (100)	
Mean age in year	58.40±14.43	58.89±14.52	58.86±14.45	
Clinical type (primary tumors only)				
Acral-lentiginous melanoma				
	3 (9.09)	3 (4.28)	6 (5.82)	0.33
Lentigo maligna melanoma				
	4 (12.12)	4 (5.71)	8 (7.76)	0.26
Nodular melanoma				
	9 (27.27)	19 (27.14)	28 (27.18)	0.99
Superficial spreading melanoma				
	17 (51.52)	41 (58.59)	58 (56.33)	0.50
Malignant melanoma, not specified				
	0	0	0	
Mucosal melanoma				
	0	3 (4.28)	3 (2.91)	0.23
Staging (AJCC), excluding mucosal melanoma				
0	1 (3.03)	1 (1.49)	2 (2.00)	0.60
IA	3 (9.09)	2 (2.98)	5 (5.00)	0.19
IB	1 (3.03)	10 (14.92)	11 (11.00)	0.07
IIA	6 (18.19)	24 (35.85)	30 (30.00)	0.07
IIB	10 (30.30)	19 (28.35)	29 (29.00)	0.84
IIC	10 (30.30)	10 (14.92)	20 (20.00)	0.07
IIIA	0	0	0	
IIIB	1 (3.03)	1 (1.49)	2 (2.00)	0.60
IIIC	0	0	0	
IV	1 (3.03)	0	1 (1.00)	0.15
Clark invasion level				
I	2 (6.06)	4 (5.71)	6 (5.94)	0.94
II	4 (12.12)	11 (17.14)	16 (15.50)	0.51
III	10 (30.30)	37 (52.87)	47 (44.90)	0.03
IV	9 (27.28)	10 (14.28)	19 (18.81)	0.11
V	8 (24.24)	7 (10.00)	15 (14.85)	0.03
Localization				
Face, scalp, neck	2 (6.06)	4 (5.71)	6 (5.94)	0.94
Trunk	15 (45.45)	26 (37.14)	41 (39.64)	0.42
Arm and shoulder	7 (21.21)	10 (14.92)	17 (16.50)	0.38
Leg and hip	9 (27.28)	27 (37.95)	36 (34.95)	0.26
Overlapping anatomical sites	0	3 (4.28)	3 (2.97)	0.23
TILs status				
Brisk	24 (72.73)	39 (55.73)	63 (61.18)	0.10
Non-brisk	4 (12.12)	15 (21.42)	19 (18.44)	0.26
Absent	5 (15.15)	16 (22.85)	21 (20.38)	0.37

*p shows differences between male and female cases

Table 4. Gender Differences of Superficial Spreading and Nodular Melanoma Localization

	Men (%)		Women (%)		p
Superficial spreading melanoma					
Face, scalp, neck	1	5.88	4	9.75	0.74
Trunk	8	47.07	15	36.54	0.32
Arm and shoulder	2	11.76	6	14.63	0.68
Leg and hip	6	35.29	16	39.08	0.75
Nodular melanoma					
Face, scalp, neck	0		0		
Trunk	5	55.54	7	36.84	0.06
Arm and shoulder	3	33.34	3	15.78	0.06
Leg and hip	1	11.12	9	47.38	0.03

*p shows differences between male and female cases

IIB-IIC-stage (59% of all cases of primary melanoma) according to AJCC classification and had the third invasion Clark level. TILs status had no gender differences and absent lymphocytic infiltrate was found in 20.1% patients.

Discussion

The average melanoma standardized incidence rates

in Krasnoyarsk Territory were close to the all-Russian indices: 2.92 in 1999 (2.91 in RF) and 4.32 in 2009 (3.75 in RF). These rates show the tendency similar to Eastern European countries: 6.5 per 100.000 inhabitants in Latvia (Azarjana et al., 2012), 2.7 in men and 3.5 in females in Belarus, 4.4 in men and 4.6 in females in Poland (Curado et al., 2007). Being in agreement with a recent research, this observation showed melanoma incidence rates to vary considerably within European countries with the highest rates in Switzerland (19.2/100.000) (Forsea et al., 2012). With regard to genders, the melanoma incidence rates were identical for the analyzed period.

Mortality standardized rates varied in the range of 1.56-2.02 per 100.000 inhabitants. Russian melanoma standardized mortality rate in 2009 was 1.52. Trends observed in females mortality rates could be explained by inefficiency of diagnostics at the early-stages of disease -79.12% of tumors were identified on stage II according AJCC when tumor is at high risk for metastasis development. It could be also related to significant number of female melanoma cases localized on a trunk (37.14%) that considered as unfavorable risk factor. At the same time our study demonstrates the increase of incidence rates that corresponds to the recent observations on the continuing rise of melanoma incidence especially in Southern and Eastern European countries (Erdman et al., 2013). The mean age at diagnosis of melanoma is 58.86 in our study, 59.9 was the mean age of melanoma patients in the Russian Federation (Chissov et al., 2011).

Two of the most often occurred clinical types of melanoma among Caucasians were also found to be such in the present study: superficial spreading and nodular melanoma (Joosse et al., 2011; Micu et al., 2012). For the most part, tumors were diagnosed on III Clark invasion level/stage II by AJCC when tumor cells invade papillary derma.

Site-specific analysis of cutaneous melanoma incidence shows marked differences between men and women. The distribution of favored sites of melanoma is sex-dependent: the most common areas were the trunk for men and extremities for women (Tsai et al., 2005). Such specific site-distributions of skin melanoma are often explained by peculiarities of clothing and sun-bathing behaviors between men and women (Elwood et al., 1998). Moreover, the supposition was made that melanomas from different body sites differ in etiology. Indeed, more recent studies showed melanomas arising from skin without chronic sun damage to harbor BRAF mutations more often than tumors located on body sites exposed to chronic sun damage that has important translational relevance in terms of treatment approaches (Deichmann et al., 2006). According to our study, the tumors of trunk and extremities did not show gender differences.

TILs status is considered to be an important prognostic factor for vertical growth phase of primary melanoma (Busam et al., 2001). It is accepted that patients with brisk lymphocytic infiltrate have better survival rate than those without inflammation features (Rao et al., 2010). The percentage of melanoma patients who had brisk lymphocyte infiltrate did not vary in groups of different age, gender or clinical form and amounted to 61.18%.

This study has several limitations. In Krasnoyarsk Territory Cancer Register is being established since 2012. Because of it, epidemiological and clinical data are based on oncologist's statistical forms and history reports only and depend on the accuracy of filling. Medical records do not include Breslow thickness, TILs status and mitotic indices evaluated as more relevant prognostic factors than Clark invasion level (Balch et al., 2011). This study was performed retrospectively, so there are some apparent drawbacks of this method, such as the mentioned dependence on human factor in data registration which account for incomplete information.

In summary, our study provides evidence of increasing melanoma cases and mortality in Krasnoyarsk Territory of the Russian Federation although incidence levels are still relatively low and comparable to all-Russian rates.

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