

ORIGINAL ARTICLE

Melanoma epidemiology, prognosis and trends in Latvia

K. Azarjana,^{1,*} A. Ozola,² D. Ruklisa,³ I. Cema,^{1,4} A. Rivosh,⁵ A. Azaryan,⁶ D. Pjanova²¹Department of Oral Pathology, Riga Stradins University, Riga, Latvia²Latvian Biomedical Research and Study Centre, Riga, Latvia³Genetics Institute, University College London, London, UK⁴Riga East University Hospital Latvian Oncology Centre, Riga, Latvia⁵Faculty of Computing, University of Latvia, Riga, Latvia⁶Faculty of Life Sciences, University of Vienna, Vienna, Austria

*Correspondence: K. Azarjana. E-mail: kristine.azarjana@gmail.com

Abstract

Background Melanoma incidence and mortality rates are increasing worldwide within the white population. Clinical and histological factors have been usually used for the prognosis and assessment of the risk for melanoma.

Objectives The aim of the study was to describe the clinical and histopathological features of the cutaneous melanoma (CM) in the Latvian population, to test the association between melanoma features and patient survival, and to assess the time trends for melanoma incidence.

Methods We undertook a descriptive, retrospective analysis of archive data of 984 melanoma patients treated at the largest oncological hospital of Latvia, Riga East University Hospital Latvian Oncology Centre (LOC), between 1998 and 2008. Cox proportional hazards model was used to analyse patient survival and autoregressive models were applied to detect trends in melanoma incidence over time for various categories of melanoma.

Results The study showed a significant ascending trend in melanoma incidence in Latvia during the time period from 1998 to 2008 ($\beta = 1.83$, 95% CI = 1.15–2.91, $P = 0.011$). Nodular melanoma was the most common tumour subtype with a frequency of 39.2%. Ulceration was present in 45.2% of melanomas. The mean Breslow thickness was 6.0 mm (6.8 mm) and no significant decline in median Breslow thickness was observed during the study period ($P = 0.609$). A better overall prognosis was detected for females in comparison with males (HR = 1.49; 95% CI = 1.22–1.81; $P < 0.001$).

Conclusions There is a steady increase in melanoma incidence in Latvia with the majority of melanomas diagnosed at late stages with poor prognosis for survival.

Received: 07 April 2012; Accepted: 19 September 2012

Conflict of interest

None declared.

Introduction

Cutaneous melanoma (CM) is the most serious form of skin cancer with a high potential to develop metastases. It comprises only 4% of all skin cancers, but has the highest mortality rate amongst all malignant skin tumours.¹ The incidence of CM has increased substantially within Caucasian population in the last few decades.^{2,3} Moreover, it is one of the most common types of cancer occurring in young adults⁴ making this type of cancer the most serious in terms of the number of years of life lost. Several international studies have shown that the clinical and histological features of CM are very important for assessing the course and prognosis of the disease.^{2,5} No comprehensive study of melanoma epidemiology or histopathological features has been previously conducted

in Latvia except a study of the head and neck melanoma that pointed out the prevalence of late diagnosed melanomas.⁶ The aim of our study was to analyse a considerably broader spectrum of melanoma patients from the Riga East University Hospital Latvian Oncology Center (LOC) to assess the characteristics and trends of the CM in Latvia.

Materials and methods

We analysed the archive data of all CM patients treated at the LOC, the largest oncological hospital in the country with approximately 80% of all melanomas referred, in the period between the January 1st, 1998 and the December 31st, 2008. For each patient information about age, gender, tumour localization and subtype, Breslow thickness of the melanoma, ulceration, presence of pig-

mentation, predominant cell type and clinical stage was recorded. Only patients with confirmed histology of primary CM were included in the study. CM relapse patients and patients with skin metastases with an unknown primary tumour localization were excluded. The total number of patients retained in the study was 984. If a patient had had more than one primary melanoma only the first melanoma was analysed. Each patient was followed up until October 2011, and the overall survival was determined using the Cancer Registry data.

The above mentioned melanoma characteristics were compared amongst male and female patients as well as between two different age groups; younger and older than 63, which was the calculated median age. The difference in characteristics amongst these groups was assessed by a Pearson's chi-squared test. If the number of patients in one of the subgroups was small, Fisher's exact test was used instead of a chi-squared test. If the association with a characteristic was significant and the characteristic studied was a factor with three or more categories, pairwise comparisons between various categories were made to elucidate the major source of the discrepancy. Pairwise analysis was done either by a chi-squared test or a Fisher's exact test if the number of observations in one of the categories was small.

Difference between groups of patients in terms of Breslow thickness and age, both being continuous variables not following the normal distribution, was assessed by the non-parametric Mann-Whitney test.

Gender, age and melanoma characteristics were studied for their impact upon patients survival rate. The overall survival was analysed by the Cox proportional hazards model. When studying a melanoma characteristic with three or more categories, multivariate analysis was performed, otherwise a univariate model was used. The significance of the impact of a factor upon survival was assessed by the logrank test providing the *P*-value for the whole univariate or multivariate model. The hazard ratio for each value of a factor together with its 95% confidence interval was calculated as well. For this purpose, the R function *coxph* from the *survival* package by Terry Therneau⁷ was used. Kaplan-Meier curves were drawn for separate categories of patients. The curves were estimated by the function *survfit* from the *survival* package. Throughout all survival models, the time was measured in months.

The changes in melanoma incidence as well as changes of median Breslow thickness over time were analysed by the autoregressive model of the first order. The model has the form $X_t = \mu + \beta X_{t-1} + \varepsilon_t$ where X_t is the incidence at time t , μ is a constant intercept, β measures the dependence between the incidence rate at neighbouring time units and ε_t is the error term. We are particularly interested in testing whether β is significantly different from 1 and whether incidences form an ascending ($\beta > 1$) or descending ($\beta < 1$) trend. Both the overall time trend and trends within subcategories of patients and melanoma characteristics were studied. The models were fitted by the least squares regression in R using the function *arma* from the *tseries*

package by Adrian Trapletti and Kurt Hornik.⁸ *P*-values measuring the significance of the difference of β from 1 were reported together with an estimation of β and its 95% confidence interval. The incidence of melanoma was measured as the number of new cases per 100 000 inhabitants (crude rate) and adjusted by age using Latvian and European standard populations for each gender separately by direct method. For each stratum of age and gender, an estimate of the Latvian population provided by the Central Bureau of Statistics was used for the normalization. The size of European standard population for each age group was obtained from the data base of the National Cancer Institute. The time was measured in years.

Results

In the studied cohort, the mean standardized incidence of melanoma was 6.5 per 100 000 inhabitants. An ascending trend in the number of diagnoses was observed over time; by 2008, the incidence had increased by 2.69 cases per 100 000 compared with 1998 ($\beta = 1.83$, 95% CI = 1.15–2.91, *P* = 0.011). The increase in melanoma cases was particularly evident for males and changed from 2.52 per 100 000 inhabitants in 1998 to 3.96 in 2008 ($\beta = 1.86$, 95% CI = 1.11–3.12, *P* = 0.019). For females, the increase in melanoma cases was slightly lower and changed from 2.59 per 100 000 in 1998 to 3.85 in 2008 thus remaining insignificant ($\beta = 1.26$, 95% CI = 0.77–2.06; *P* = 0.353) (Fig. 1).

In total, there were 984 melanoma patients included in the study, and only five patients (0.5%) had developed several primary melanomas during the study period. The distribution of melanoma characteristics in association with gender is depicted in Table 1.

There was a correlation between gender of the patient and the localization of melanoma (*P* < 0.001). Female patients were dominating amongst the patients with melanoma localization on either lower or upper limbs, whereas male patients had an excess of melanomas on the trunk (Table 1). *P*-values of all pairwise comparisons with melanoma frequency on trunk were highly significant (Table 2).

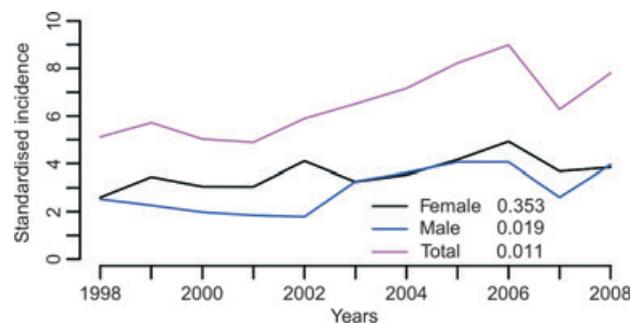


Figure 1 Trends of the melanoma incidence from 1998 to 2008. Separate curves are drawn for the total incidence and the incidence of melanoma for male and female patients. *P*-value showing the significance of a non-constant time trend of a curve is indicated next to the colour definition of the curve.

Table 1 Distribution of melanoma characteristics and patient's age within the analysed cohort: total distribution, distribution for female and male patients

	Total n (%) n = 984	Females n (%)n = 640	Males n (%)n = 344	P-value*
Age (years)				
Median	63.4	64.2	62.6	0.282
Mean (±SD)	61.3 (±15.3)	61.6 (±15.6)	60.7 (±14.7)	
Lesion site				
Lower limbs	320 (32.5)	265 (41.4)	55 (16.0)	<0.001
Upper limbs	158 (16.1)	116 (18.1)	42 (12.2)	
Head and neck	123 (12.5)	84 (13.1)	39 (11.3)	
Trunk	376 (38.2)	172 (26.9)	204 (59.3)	
Genital region	7 (0.7)	3 (0.5)	4 (1.2)	
CM subtype				
Superficial spreading melanoma	40 (4.1)	23 (3.6)	17 (4.9)	0.528#
Nodular melanoma	386 (39.2)	246 (38.4)	140 (40.7)	
Lentigo maligna melanoma	15 (1.5)	12 (1.9)	3 (0.9)	
<i>In situ</i>	7 (0.7)	5 (0.8)	2 (0.6)	
NA	536 (54.5)	354 (55.3)	182 (52.9)	
Breslow thickness, mm				
Median	4.0	4.0	4.0	0.801
Mean (±SD)	6.0 (±6.8)	5.9 (±7.0)	6.2 (±6.5)	
Ulceration				
Present	445 (45.2)	283 (44.2)	162 (47.1)	0.305
Absent	275 (28.0)	186 (29.1)	89 (25.9)	
NA	264 (26.8)	171 (26.7)	93 (27.0)	
Pigment				
Present	797 (80.9)	525 (82.0)	272 (79.1)	0.780
Absent	94 (9.6)	60 (9.4)	34 (9.9)	
NA	93 (9.5)	55 (8.6)	38 (11.0)	
Cell type				
Epitheloid	520 (52.9)	334 (52.2)	186 (54.1)	0.207#
Balloon	24 (2.4)	13 (2.0)	11 (3.2)	
Spindle	144 (14.6)	105 (16.4)	39 (11.3)	
Nevoid	12 (1.2)	9 (1.4)	3 (0.9)	
Mixed	125 (12.7)	80 (12.5)	45 (13.1)	
NA	159 (16.2)	99 (15.5)	60 (17.4)	

*To assess group differences, χ^2 tests were used and data marked by # were obtained using Fisher's exact test, except for age and Breslow thickness where Mann-Whitney test was applied; SD, Standard deviation; NA, Not applicable.

Breslow thickness of melanoma was slightly higher in males (6.2 mm ± 6.5 mm) compared with females (5.9 mm ± 7.0 mm) with distribution of tumour thickness being rather similar in both groups ($P = 0.186$) (Table 1). Likewise, ulcerated melanomas were more widespread amongst males than females; however, these differences were not statistically significant (Table 1). The association of the age with different melanoma characteristics was analysed next. For this purpose, the patients were divided into two age groups according to the median age (≤ 63 and >63 years), and the age distribution across these groups was assessed for each clinical or histopathological feature (Table 3). The characteristic of melanoma that was the most associated with age was localization ($P < 0.001$). In particular, the predominance of the head and neck melanomas amongst the elderly patients (>63 years) was revealed

(Table 3). Pairwise comparisons of head and neck melanoma with all other localizations yielded notable P -values (Table 2). Amelanotic and ulcerated melanomas were also more widespread amongst the elderly ($P = 0.013$ and $P < 0.001$ respectively) and tended to be thicker according to the Breslow thickness ($P < 0.001$) (Table 3).

The analysis of the clinical stage distribution showed that the majority of tumours were stage II melanomas. Clinical stage IIC, IIB and IIA melanomas were found in 20.1% (198), 14.6% (144) and 13.3% (131) of patients respectively. There were no differences in clinical stage distribution neither between genders nor in association with age (data not shown).

The difference in overall survival was assessed for the patients exhibiting different clinical and histopathological features of the

Table 2 Pairwise comparison of melanoma localisations in terms of the correlation with gender and age

Gender	Head and neck	Trunk	Lower limbs	Upper limbs	Genital region
Age					
Head and neck		<0.001	0.001	0.419	0.219 [#]
Trunk	<0.001		<0.001	<0.001	1.000 [#]
Lower limbs	<0.001	0.110		0.023	0.022 [#]
Upper limbs	0.002	0.048	0.540		0.096 [#]
Genital region	0.036 [#]	0.705 [#]	0.453 [#]	0.277 [#]	

*The diagonal of the matrix separates the results of two different analyses. The upper right triangle of the matrix contains *P*-values of the chi-squared test measuring association of a particular localization with gender, whereas the lower left triangle contains the *P*-values of the correlation with age. In cells marked by [#]Fisher's exact test was used.

melanoma. The Kaplan–Meier curves showed a better overall prognosis for females than for males (HR = 1.49; 95% CI = 1.22–1.81; *P* < 0.001) (Fig. 2a). The primary tumour localization did not play a significant role for survival (*P* = 0.197), except for males with melanoma on limbs (HR = 2.29; 95% CI = 1.67–3.14; *P* < 0.001) (Fig. 2b).

The subtype of melanoma plays a significant role in survival (*P* < 0.001). As expected, patients with a superficial spreading melanoma had better prospects than patients with a nodular melanoma (HR = 4.14; 95% CI = 1.83–9.33; *P* < 0.001) (Fig. 2c). As there were many cases with a missing data on melanoma subtype, we included them as a separate category in the model: the overall association with survival remained the same (*P* < 0.001), and the missing cases showed a hazard ratio that was somewhat closer to the nodular melanoma cases (HR = 3.78; 95% CI = 1.68–8.52). Similarly, the correlation between the Breslow thickness of the tumour and the survival rate was significant (HR = 1.04; 95% CI = 1.03–1.05; *P* < 0.001).

The association between the ulceration and survival was also revealed: survival was better for patients without ulceration (HR = 0.39; 95% CI = 0.30–0.51; *P* < 0.001) (Fig. 2d). Inclusion of the tumours with missing ulceration information as a separate category in the model did not change the result (*P* < 0.001), and the hazard ratio of the missing category was approximately average of the remaining ratios (HR = 0.61; 95% CI = 0.48–0.76) indicating no biases in missing information towards any particular category. Pigmented tumours showed brighter prospects than amelanotic melanomas (HR = 1.91; 95% CI = 1.43–2.55; *P* < 0.001) (Fig. 2e). There was no correlation between the predominant cell type of melanoma and a patient's survival (*P* = 0.747) (Fig. 2f). In contrast, the association between the clinical stage and the survival was again clearly evident (*P* < 0.001).

For the analysed study period, a decrease of the median age in males (from 67.2 to 60.3 years) and an increase of the median age in females (from 59.8 to 65.83 years) were observed, although these changes were not statistically significant (*P* = 0.624 and *P* = 0.577 respectively) (Fig. 3a,b). A significant increase in the

Table 3 Distribution of melanoma characteristics and patient's gender for elderly (> 63 years) and younger (≤ 63 years) patients

	≤63 years n (%)n = 506	>63 years n (%)n = 478	<i>P</i> -value*
Gender			
Female	318 (62.8)	322 (67.4)	0.156
Male	188 (37.2)	156 (32.6)	
Lesion site			
Lower limbs	167 (33.0)	153 (32.1)	<0.001
Upper limbs	77 (15.2)	81 (16.9)	
Head and neck	37 (7.3)	86 (18.0)	
Trunk	220 (43.5)	156 (32.6)	
Genital region	5 (1.0)	2 (0.4)	
CM subtype			
Superficial spreading melanoma	26 (5.1)	14 (2.9)	0.161 [#]
Nodular melanoma	185 (36.6)	201 (42.1)	
Lentigo maligna melanoma	9 (1.8)	6 (1.3)	
<i>In situ</i>	3 (0.6)	4 (0.8)	
NA	283 (55.9)	253 (52.9)	
Breslow thickness, mm			
Median	3.8	5.0	<0.001
Mean (±SD)	5.4 (±6.2)	6.6 (±7.4)	
Ulceration			
Present	197 (38.9)	248 (51.9)	<0.001
Absent	165 (32.6)	110 (23.0)	
NA	144 (28.5)	120 (25.1)	
Pigment			
Present	418 (82.6)	379 (79.3)	0.013
Absent	36 (7.1)	58 (12.1)	
NA	52 (10.3)	41 (8.6)	
Cell type			
Epitheloid	270 (53.4)	250 (52.3)	0.087 [#]
Spindle	65 (12.9)	79 (16.5)	
Ballon	17 (3.4)	7 (1.5)	
Nevoid	8 (1.6)	4 (0.8)	
Mixed	58 (11.5)	67 (14.0)	
NA	88 (17.4)	71 (14.9)	

*To assess group differences, χ^2 tests were used and data marked by [#]were obtained using Fisher's exact test, except for Breslow thickness where Mann–Whitney test was applied; SD, Standard deviation; NA, not applicable.

number of melanomas localized on the trunk was discovered (β = 2.21; 95% CI = 1.50–3.23; *P* < 0.001). The number of melanomas with other localizations has been growing as well, although these changes were not significant (Fig. 4a). No significant changes in incidence were observed for various melanoma subtypes, not even for the most common subtype, the nodular melanoma (Fig. 4b). Similarly, the median Breslow thickness did not change significantly over time (β = 0.86; 95% CI = 0.48–1.54; *P* = 0.609) (Fig. 3c).

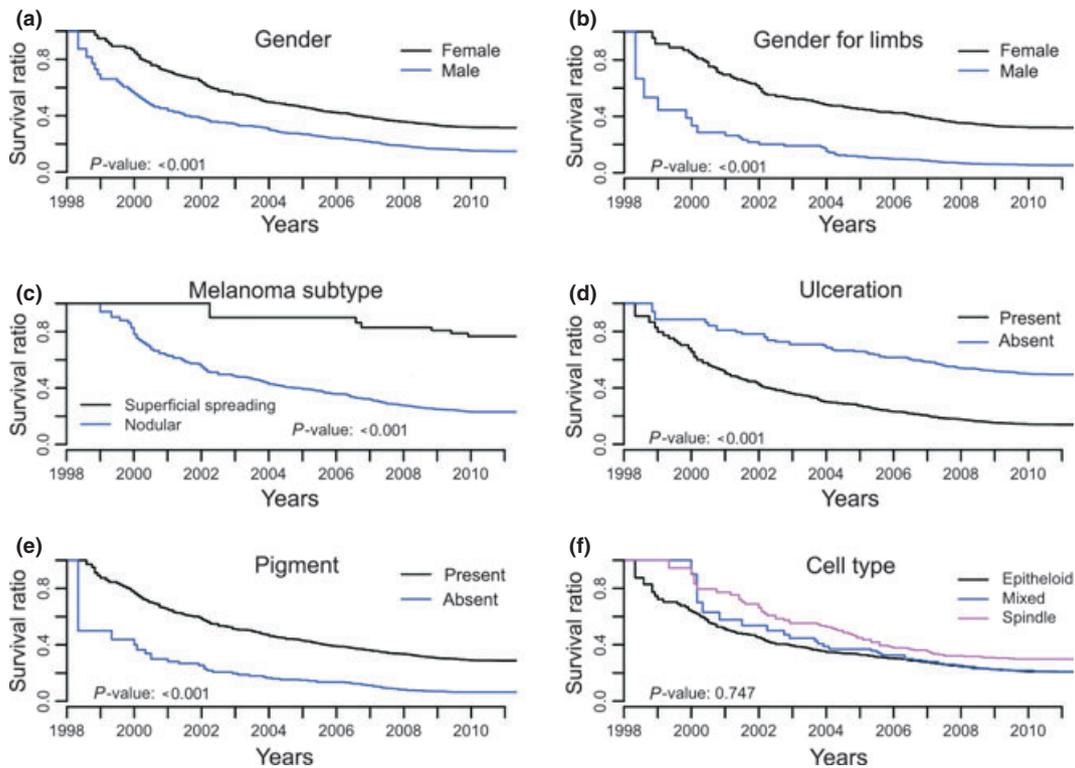


Figure 2 Kaplan–Meier curves for differences in survival: (a) by gender, (b) by gender in case of melanoma localization on the limbs, (c) by melanoma subtype, (d) by presence of ulceration, (e) by presence of pigment and (f) by cell type involved in the formation of melanoma. The *P*-value in each panel shows the difference in survival between all depicted categories and corresponds to the log-rank test applied to the Cox proportional hazards model.

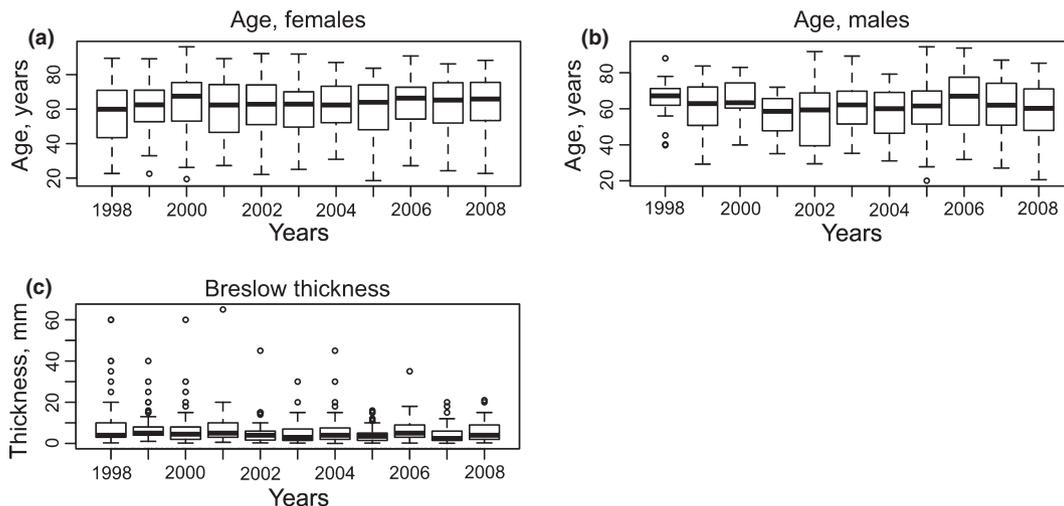


Figure 3 Box plots showing the distribution of age at the time of melanoma diagnosis and Breslow thickness by year: (a) age at diagnosis for females, (b) age at diagnosis for males and (c) Breslow thickness.

A significant increase of non-ulcerated melanomas (Fig. 4c) ($\beta = 2.50$; 95% CI = 1.65–3.80; $P < 0.001$) was revealed. A decrease in amelanotic melanomas, however, insignificant was

detected (Fig. 4d). There were no alterations of clinical stage distribution except for stage IA, where the increase was detected ($\beta = 2.20$; 95% CI = 1.25–3.89; $P = 0.006$ (Fig. 4e).

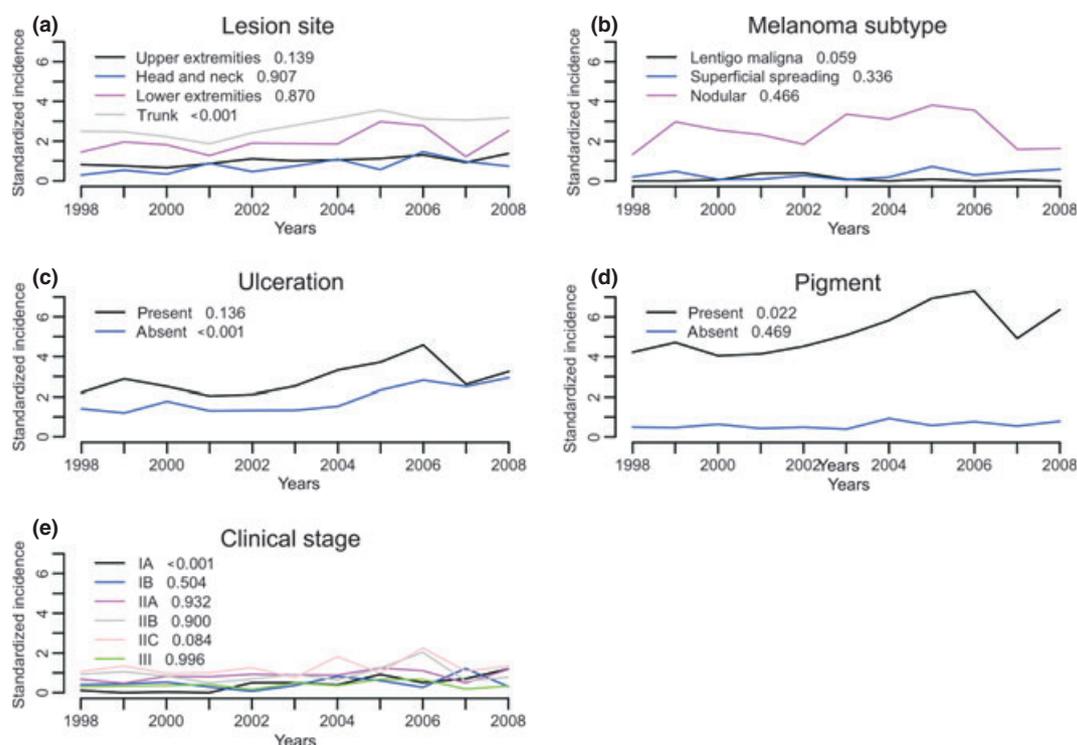


Figure 4 Trends of the melanoma incidence from 1998 to 2008 by various melanoma characteristics: (a) lesion site, (b) melanoma subtype, (c) ulceration, (d) pigment and (e) clinical stage. Time trends for each category of melanoma are depicted as a separate curve. *P*-value measuring the significance of a non-constant time trend of a curve is indicated next to the colour definition of the curve.

Discussion

Our study showed a significant increase in melanoma incidence based on patient data obtained from the largest oncological hospital in the country LOC during the period from 1998 until 2008. The observed increase from 5.1 new cases per 100 000 inhabitants in 1998 to 7.8 new cases in 2008 (Figure 1) is consistent with a similar trend in Latvian Cancer registry as well as in other European countries. The observed predominance of females affected by CM is typical for countries like Latvia with a relatively low incidence of melanoma. In countries with higher melanoma incidence such as Australia, male and female melanoma incidence rates are similar or even higher in males.⁵ Several studies have demonstrated that females have a higher survival rate than males.^{2,9} Our data also indicate a better survival rate for females despite the fact that the mean age at the time of diagnosis is higher in females than in males. We cannot provide a clear explanation for this observation. There might be a correlation with the differences in anatomical sites of the primary CM. According to Freedman *et al.*¹⁰ there is no association with menopausal status, use of hormone replacement therapy, age at first birth or oral contraceptive use.

Several international studies have shown that the mean age at the time of diagnosis lies between 53.7 and 59.0 years.^{11,12} The

mean age at the time of melanoma onset in our study was 61.3 years, thus higher. This could be explained by the fact that melanoma patients in Latvia are generally diagnosed at later stages, which would also explain the comparatively worse survival rates. Furthermore, tanning beds in Latvia became broadly available only in the last two decades. It could mean that patients included in this study had accumulated less of an artificial sun exposure during their life, and therefore have a later onset of melanoma. However, the association between the use of tanning beds and the age of melanoma onset should be still clarified.

It has been previously shown that melanoma patients tend to develop a second primary melanoma;¹³ however, only 0.5% of the patients in our study had developed a second primary melanoma. This number is low compared with other studies,^{13–15} which have reported the incidence rate of multiple primary melanomas to lie between 0.5 and 8.6%. In 29–59% of cases, the next primary melanoma develops during the first year after the initial diagnosis.^{13,15} A part of these melanomas develop later in life, and there is a chance that a second primary melanoma is not diagnosed at all unless regular skin examinations are performed by dermatologists.

In accordance with other studies, we found that the most frequent localization of the tumour was the trunk as well as the head and the neck in males and limbs in females.^{5,9,16} Like Ferrari

et al.,¹¹ we have also shown the predominance of the head and neck melanoma in elderly patients. All localizations in males have been associated with a worse survival rate than for females.¹⁷ We have replicated this finding only for males diagnosed with a melanoma on their limbs.

According to several authors,^{18,19} superficial spreading melanoma is the most frequent tumour subtype. In our study, nodular tumours were the most frequent subtype, showing lower survival rate when compared with superficial spreading melanoma. It has been reported^{16,20} that male patients have a tumour histopathology associated with worse prognosis than females and that nodular tumours occur more frequently in males. We observed more males than females with nodular melanomas, but the numbers had no statistical significance, which could be explained by the predominance of nodular tumours in our cohort. In contrast to the most studies,³ melanomas *in situ* were also very rarely observed in our study indicating delayed melanoma diagnosis in Latvia. Surprisingly, there were no acral lentiginous melanomas in the studied cohort, probably due to the large numbers of cases with unidentified tumour subtype especially for melanomas localized on feet and hands (data not shown).

Our findings underline the importance of Breslow thickness and ulceration for the prognosis of the disease. An increase in tumour depth correlates with a poorer prospect and is one of the most important prognostic factors for melanoma.^{21,22} Although the mean Breslow thickness has declined between 1998 and 2008 (data not shown), the median tumour thickness has not changed over time and remains high (6.00 mm) when compared with other European countries where the mean thickness of melanoma is 0.80–2.24 mm.^{3,5,23} We confirmed significantly higher survival rates for patients without ulcerated melanomas. In our study, we did not analyse the ulceration as a risk factor for metastasis, but according to Balch *et al.*⁹ ulcerated tumours show higher potential to metastasize if compared with those with the same Breslow thickness but without epidermal ulceration. Patients with tumour ulceration, especially males, have worse survival rates than patients of the same gender but without ulceration. Amelanotic melanomas comprised 9.6% of all melanoma cases, which is slightly more than the reported rates which lie between 1.8% and 8.1%.²⁴ Patients with pigmented melanomas had a better survival rate than patients with amelanotic tumours. This could be explained by the difficulties in detecting amelanotic melanomas, which can lead to a delayed diagnosis²⁴ as well as by the fact that the most common presentation of amelanotic melanoma is of nodular variety.²³ Moreover, the growth rate for both nodular and amelanotic melanomas has been shown to be greater in comparison with other melanomas.^{25,26} In concordance with other studies,²⁷ epithelioid cells were the most frequent cells involved in primary melanoma formation in our study. We did not reveal any association between the cell type of CM and a patient's survival.

We observed an increase in stage IA patients, which could imply a recent improvement in the diagnosis of melanoma. However,

the majority of melanoma cases are still diagnosed at late stages in Latvia. This could be due to the melanoma screening not being a mandatory or routine procedure in clinics, especially the full body skin examination. Furthermore, despite various attempts to raise melanoma awareness through informative campaigns, many patients ignore sun protective behaviour²⁸ or suspicious lesions and are afraid to consult medical doctors.

One of the limitations of our study is that the analysed CM patient data were obtained from a large referral centre and cannot be entirely attributed to the whole Latvian population. However, LOC is the largest oncological hospital in the country, where the majority of melanomas are treated. A similar approach to the data collection has been used previously.²⁹ Moreover, the observed increase in melanoma incidence in LOC was similar to the trends in Cancer Registry data. Some of the interpretations were hampered by the large proportion of cases with missing melanoma subtype and ulceration status. The survival rate of melanoma patients with an unknown tumour subtype was quite close to the nodular melanoma cases that form the majority of the cohort thus indicating that many uncharacterised melanomas could actually be nodular. Patients with a missing ulceration status are roughly average of the remaining cases in terms of survival indicating no biases towards any particular category. In concordance with our findings, it was reported by De Vries *et al.*³⁰ that there are fewer superficial spreading melanomas in the Eastern Europe. Eastern and Western Europe Cancer Registries were compared in their study. However, the interpretation of their data was also limited by the large proportion of cases with missing information on melanoma stage and histopathology parameters.

In conclusion, our study showed a steady increase in melanoma incidence in Latvia with a high percentage of delayed tumours. It was also shown that this delay leads to a poor survival and prognosis. To increase the efficiency of melanoma diagnostics as well as to improve the outcome of melanoma in Latvia, more attention has to be paid to the importance of educational campaigns, development of melanoma prevention programs and a better cooperation between general practitioners, dermatologists and oncologists.

Acknowledgements

This work was supported by ERDF project no. 2DP/2.1.1.1.0/10/APIA/VIAA/076, and K. Azarjana is grateful for the support by European Social Fund (ESF) programme Nr.2009/0147/1DP/1.1.2.1.2/09/IPIA/VIAA/009.

References

- 1 Jemal A, Siegel R, Ward E *et al.* Cancer statistics, 2006. *CA Cancer J Clin* 2006; **56**: 106–130.
- 2 Tryggvadottir L, Gislum M, Hakulinen T *et al.* Trends in the survival of patients diagnosed with malignant melanoma of the skin in the Nordic countries 1964–2003 followed up to the end of 2006. *Acta Oncol* 2010; **49**: 665–672.
- 3 Linos E, Swetter SM, Cockburn MG *et al.* Increasing burden of melanoma in the United States. *J Invest Dermatol* 2009; **129**: 1666–1674.

- 4 Reed KB, Brewer JD, Lohse CM *et al.* Increasing incidence of melanoma among young adults: an epidemiological study in olmsted county, Minnesota. *Mayo Clin Proc* 2012; **87**: 328–334.
- 5 Liang JJ, Robinson E, Martin RC. Cutaneous melanoma in New Zealand: 2000–2004. *ANZ J Surg* 2010; **80**: 312–316.
- 6 Berzina A, Azarjana K, Cema I *et al.* Prognostic factors and epidemiological characteristics of cutaneous and mucosal head and neck melanoma. *Stomatologija* 2011; **13**: 49–54.
- 7 Therneau T. (2012). A Package for Survival Analysis in S. R package version 2.36-14.
- 8 Trapletti A, Hornik K. (2012). tseries: Time Series Analysis and Computational Finance. R package version 0.10-29.
- 9 Balch CM, Soong SJ, Gershenwald JE *et al.* Prognostic factors analysis of 17,600 melanoma patients: validation of the American Joint Committee on Cancer melanoma staging system. *J Clin Oncol* 2001; **19**: 3622–3634.
- 10 Freedman DM, Sigurdson A, Doodly MM *et al.* Risk of melanoma in relation to smoking, alcohol intake, and other factors in a large occupational cohort. *Cancer Causes Control* 2003; **14**: 847–857.
- 11 Ferrari Júnior NM, Muller H, Ribeiro M *et al.* Cutaneous melanoma: descriptive epidemiological study. *Sao Paulo Med J* 2008; **126**: 41–47.
- 12 Biau DJ, Latouche A, Porcher R. Competing events influence estimated survival probability: when is Kaplan-Meier analysis appropriate?. *Clin Orthop Relat Res* 2007; **462**: 229–233.
- 13 Bower MR, Scoggins CR, Martin RCG II *et al.* Second primary melanomas: incidence and outcome. *Am Surg* 2010; **76**: 675–681.
- 14 Titus-Ernstof L, Perry AE, Spencer SK *et al.* Multiple primary melanoma: two year results from a population-based study. *Arch Dermatol* 2006; **142**: 433–438.
- 15 Ferrone CR, Ben Porat L, Panageas KS *et al.* Clinicopathological features of and risk factors for multiple primary melanomas. *JAMA* 2005; **294**: 1647–1654.
- 16 Scoggins CR, Ross MI, Reintgen D *et al.* Gender-Related Differences in Outcome for Melanoma Patients. *Ann Surg* 2006; **243**: 693–700.
- 17 Karjalainen S, Hakulinen T. Survival and prognostic factors of patients with skin melanoma. A regression-model analysis based on nationwide cancer registry data. *Cancer* 1988; **62**: 2274–2280.
- 18 Garbe C, Leiter U. Melanoma epidemiology and trends. *Clin Dermatol* 2009; **27**: 3–9.
- 19 Payette MJ, Katz M, Grant-Kels JM. Melanoma prognostic factors found in the dermatopathology report. *Clin Dermatol* 2009; **27**: 53–74.
- 20 Tejera-Vaquerizo A, Mendiola-Fernandez M, Fernandez-Orland A *et al.* Thick melanoma: the problem continues. *J Eur Acad Dermatol Venereol* 2008; **22**: 575–579.
- 21 Staudt M, Lasithiotakis K, Leiter U *et al.* Determinants of survival in patients with brain metastases from cutaneous melanoma. *Br J Cancer* 2010; **102**: 1213–1218.
- 22 Callender GG, McMasters KM. What does ulceration of a melanoma mean for prognosis? *Adv Surg* 2011; **45**: 225–236.
- 23 Barbe C, Hibon E, Vitry F *et al.* Clinical and pathological characteristics of melanoma: a population based study in a French regional population. *J Eur Acad Dermatol Venereol* 2011; **26**: 159–164.
- 24 Gualandri L, Betti R, Crosti C. Clinical features of 36 cases of amelanotic melanomas and considerations about the relationship between histologic subtypes and diagnostic delay. *J Eur Acad Dermatol Venereol* 2009; **23**: 283–287.
- 25 Tejera-Vaquerizo A, Barrera-Vigo MV, López-Navarro N *et al.* Growth rate as a prognostic factor in localized invasive cutaneous melanoma. *J Eur Acad Dermatol Venereol* 2010; **24**: 147–154.
- 26 Liu W, Dowling JP, Murray WK *et al.* Rate of growth in melanomas: characteristics and associations of rapidly growing melanomas. *Arch Dermatol* 2006; **142**: 1551–1558.
- 27 Ascierto PA. Epitheloid cell-type melanoma as a prognostic factor of poor response to immunological treatment. *Ann Oncol* 2000; **11**: 1504.
- 28 Bränström R, Kasparian NA, Chang YM *et al.* Predictors of Sun Protection Behaviors and Severe Sunburn in an International Online Study. *Cancer Epidemiol Biomarkers Prev* 2010; **19**: 2199–2210.
- 29 Buljan M, Rajačić N, Vurnek Živkovic M *et al.* Epidemiological data on melanoma from the referral centre in Croatia (2002–2007). *Coll Antropol* 2008; **2**: 47–51.
- 30 de Vries E, Bray FI, Eggermont AM *et al.* Monitoring stage-specific trends in melanoma incidence across Europe reveals the need for more complete information on diagnostic characteristics. *Eur J Cancer Prev* 2004; **13**: 387–395.