Changing presentation of cutaneous malignant melanoma

Anders Klit[1], Cecilie Brandt Lassen[1], Caroline Holkmann Olsen[2] & Jørgen Lock-Andersen[1]

ABSTRACT

INTRODUCTION: The incidence of cutaneous malignant melanoma is rapidly increasing in Denmark like in other Northern and Western European countries. Our objective was to investigate the characteristics of current patients suffering from cutaneous malignant melanoma.

METHODS: We evaluated patient and tumour characteristics in a cross-sectional study based on data from the Danish Melanoma Register. We included all patients diagnosed with cutaneous malignant melanoma in Health-care Region Zealand in 2012 and 2013.

RESULTS: We identified 520 patients with invasive cutaneous malignant melanoma. More females than males suffered from cutaneous malignant melanoma. Furthermore, females were younger than males, and the anatomical distribution of malignant melanoma varied between the genders. Outcome of sentinel lymph node biopsy was associated with tumour thickness.

CONCLUSIONS: When comparing findings in our study with earlier Danish studies, we see a trend towards an increase in age at diagnosis. Furthermore, tumour thickness is decreasing and the topical distribution of cutaneous malignant melanoma in females changes towards a male pattern.

FUNDING: none.

TRIAL REGISTRATION: The study has been approved by the Danish National Data Protection Agency.

The incidence rate of cutaneous malignant melanoma (CMM) has been increasing rapidly during the past two decades throughout Europe [1]. CMM is now the third most common cancer in Australia and New Zealand and one of the ten most common cancers in various European countries [2]. The highest incidence rates in Europe are found in Northern and Western countries (the Scandinavian countries, the Netherlands, UK and Ireland), and the lowest incidence rates are observed in Spain and Portugal [1]. WHO Globocan reports that Danish females have the third highest risk of melanoma in the world (first New Zealand, second Australia); and in 2011, Danish females aged 15-39 years had the highest incidence of CMM in the world [2]. Studies have suggested a continuous annual increase in incidence rate of more than 3% up to 2007 [3, 4]. A recent study reports an annual increase in incidence rate of 7% for women and 8.3% for men in the period from 2008 to 2011 [5].

Whereas CMM only represents approximately 4% of all skin cancers, the disease is responsible for approximately 80% of all skin cancer-related deaths [6]. Since the 1950s, the sun behaviour has changed radically from a sun-avoiding culture to a sun-seeking culture with frequent vacations at lower latitudes. Furthermore, the artificial sun devices were introduced in Denmark in the 1960s and a cross-sectional study by Køster et al in 2009 showed that 29% of all Danes aged 15-59 had used sunbeds within the past 12 months. Among female children and adolescents aged 15-19 years, 59% had used sunbeds within the past 12 months [7].

As a consequence of the altered sun exposure pattern, we hypothesise that patient and tumour characteristics may also have changed during the past decades. The objective of this study was to describe patient characteristics and tumour characteristics in a cohort of Danish CMM patients residing in Health-care Region Zealand (approximately 800,000 inhabitants corresponding to 14% of the entire Danish population [8]).

METHODS

Study design and setting

The study is a cross sectional study based on the entire population living in Health-care Region Zealand, Denmark.

Participants

Data were obtained on 1 March 2014 from the national Danish Melanoma Registry (DMR), which holds prospectively collected information on patients diagnosed with CMM in Denmark [9]. The DMR was initiated in 1984; and since 2011, registration of CMM in DMR has been mandatory for all departments involved in CMM treatment. The data include specific information on patient and disease characteristics, treatment and follow-up. Patients diagnosed with CMM are registered in the DMR after histological confirmation of CMM. Patients were included in the study if diagnosed with primary CMM between 1 January 2012 and 31 December 2013 in Health-care Region Zealand. The exclusion criteria were CMM in situ (Clark level 1), melanocytic tumour of uncertain malignant potential (MELTUMP), unknown if primary CMM or metastasis, unknown thickness and Clark level due to limitations in biopsy material and patients

ORIGINAL ARTICLE

1) Department of Plastic Surgery, Roskilde Hospital
2) Department of Pathology, Roskilde Hospital, Denmark

Dan Med J 2015;62(10):A5142

with otherwise incomplete set of data that could not be supplemented from the patient records. The histological examination was conducted at the Department of Pathology, Roskilde Hospital, which is a highly specialised facility examining all melanocytic biopsies from Region Zealand. All patients were treated at the Department of Plastic Surgery, Roskilde Hospital, which is also a centralised and highly specialised facility providing surgical treatment for all patients in the Region Zealand suspected of or diagnosed with CMM.

Variables

We obtained data on the patients' gender, age (grouped < 21, 21-40, 41-60, 61-80, > 80 years), tumour thickness (grouped ≤ 1 mm, 1.01-2.00 mm, 2.01-4.00 mm, ≥ 4.01 mm), CMM subtype (acral lentiginous melanoma (ALM), desmoplastic malignant melanoma (DMM), lentigo maligna melanoma (LMM), nodular malignant melanoma (NMM) and superficial spread melanoma (SMM)), Clark level (level 2-5), ulceration (yes/no) and sentinel lymph node biopsy (SLNB) outcome. All variables concerning tumour characteristics and SNLB outcome were based on histological examination. SLNB was conducted according to treatment guidelines from the Danish Melanoma Group [8] – which in the study period comprised patients with a tumour thickness exceeding 1 mm, and/or microscopic ulceration and/or a Clark level of 4 or higher [8]. This resulted in a limited number of patients with a tumour thickness < 1 mm requiring SLNB.

Approval

The study was approved by the Danish Data Protection Agency, reference number 2008-58-0020/12-000179.

Statistics

Numbers and proportions were used to describe patient and tumour characteristics. In variables not normally distributed, we used median values with minimum and maximum values. The non-parametric statistical test for difference was used to test for difference in these cases. Differences in overall age and tumour thickness were tested using the Mann-Whitney test. Differences in age groups, tumour site, ulceration and Clark level were tested using the chi-squared test. The level of significance was set at 0.05. All statistical methods were computed using the dedicated statistical software InStat (version 3) and Prism (version 5), GraphPad, USA.

Trial registration: The study was approved by the Danish National Data Protection Agency.

RESULTS

Patients

A total of 848 cases (tumours) of CMM were identified in the DMR according to the inclusion criteria. After reviewing the extracted data, 76 cases were excluded due to incomplete registration (12 patients), incorrect year of diagnosis (42 patients), unknown biopsy date (eight patients), duplicates (13 patients) or not melanocytic tumour (one patient). A total of 29 patients were diagnosed with more than one CMM during the observation period from 2012 and 2013 (29 patients had 63 CMM tumours in total). Only the first CMM was used in the following comparative analysis. A total of 520 patients with invasive CMM (Clark level 2-5) were identified and are described further in this study (**Table 1**). Patients with MELTUMP (18 patients), unknown if primary CMM or metastasis (11 patients), unknown thickness and Clark level due to limitations in biopsy material (50 patients) are presented in **Table 2** only with descriptive data

TABLE 1

Patient and tumour characteristics in 520 patients diagnosed with invasive cutaneous malignant melanoma from 2012 and 2013.

	Female	Male	p-value
Total, N (%)	278 (53.5)	242 (46.5)	
Age, yrs, median (range)	56 (5-96)	65 (21-89)	< 0.01
Age group, n (%)			> 0.01
< 21 yrs	4 (1.4)	0 (0)	
21-40 yrs	46 (16.5)	23 (9.5)	
41-60 yrs	113 (40.6)	68 (28.1)	
61-80 yrs	91 (32.7)	126 (52.1)	
> 80 yrs	24 (8.6)	25 (10.3)	
Localization, n (%)			> 0.01
Head and neck	28 (10.1)	41 (16.9)	
Truncus and genitals	106 (38.1)	149 (61.6)	
Upper extremity	47 (16.9)	25 (10.3)	
Lower extremity	94 (33.8)	27 (11.2)	
NA	3 (1.1)	0 (0)	
Tumour thickness, mm, median (range)	0.7 (0.02-13.00)	0.82 (0.08-23.00)	0.07
Clark level, n (%)			0.23
2	119 (42.8)	86 (35.5)	
3	92 (33.1)	99 (40.9)	
4	52 (18.7)	42 (17.4)	
5	7 (2.5)	8 (3.3)	
NA	8 (2.9)	7 (2.9)	
Ulceration, n (%)			0.17
No	243 (87.4)	204 (84.3)	
Yes	26 (9.4)	33 (13.6)	
NA	9 (3.2)	5 (2.1)	
Histological types of melanoma, n (%)			0.88
Lentigo maligna melanoma	11 (4.0)	9 (3.7)	
Superficial spread malignant melanoma	227 (81.7)	198 (81.8)	
Nodular malignant melanoma	22 (7.9)	24 (9.9)	
Acral lentiginous malignant melanoma	4 (1.4)	2 (0.8)	
Desmoplastic malignant melanoma	2 (0.7)	8 (3.3)	
NA	12 (4.3)	1 (0.4)	

NA = not available.

and were excluded without further analysis due to the limited number of patients in each group. Patients with CMM in situ (144 patients) were excluded and are presented elsewhere.

Analysis

Among patients with invasive CMM, there were more females than males (278 (53.4%) versus 242 (46.5%)), respectively ($p < 0.01$) (Table 1). The females were significantly younger (median age 56, 25-75 percentile: 44-68 years) than the males (median age 65 years, 25-75 percentile: 54-73 years), $p < 0.01$. When comparing age groups (age < 21, 21-40, 41-60, 61-80, > 80 years), we found a larger share of females in the younger age groups and a larger share of males in the older age groups ($p < 0.01$) (**Figure 1**A). We found a significant difference in the anatomical distribution of melanomas between males and females. Where males predominantly had their CMM on the trunk (62%) and on the head and neck (17%), females predominantly had their CMM on the trunk (38%) and on the lower extremities (34%), $p < 0.01$ (Figure 1B).

We found no difference between females and males concerning CMM thickness ($p = 0.07$), Clark level ($p = 0.23$), ulceration ($p = 0.17$) or melanoma type ($p = 0.88$).

Finally, we assessed the association between SNLB outcome and gender, tumour thickness and ulceration, respectively (**Table 3**). We found a significant direct relation between tumour thickness divided into four groups (≤ 1.00 mm, 1.01-2.00 mm, 2.01-4.00 mm, > 4.00 mm) and risk of positive SNLB (Figure 1C), $p < 0.02$. We found no association between gender and positive SLNB ($p = 0.88$) or ulceration and positive SNLB ($p = 0.09$).

DISCUSSION

Our study population reflects the Danish population, which is generally well-educated, ethnically homogeneous (Caucasians) and which benefits from a uniform public health-care system covering all citizens. These characteristics limit the generalisability to other populations with different health-care systems, demographics or treatment protocols. Although all treatment and diagnostics are conducted at a single institution (Roskilde Hospital), all clinical procedures and pathological examinations strictly adhere to the national guidelines provided by the Danish Melanoma Group [9]. Information on given treatment was obtained from the DMR database and thereby carries the limitations of register data. We strove to increase the completeness of our data set by validating all data, identifying irregularities and rectifying the data by reviewing the histological examinations and clinical reports. The cross-sectional design of the study precludes conclusions on causality and analysis of changes in variables over time. Nevertheless, comparing our results with the results of two previously published Danish studies from 1990 [10] and 2003 [11] provides an opportunity to discuss the development in patient and tumour characteristics. The study by Drzewiecki et al [10] is a population-based study measuring CMM-related outcomes in a population of approximately one million inhabitants (about 20% of the entire Danish population in 1982 [8]) from 1964 to 1982 in a geographical area corresponding to the current South

TABLE 2

Patient and tumour characteristics in 520 patients diagnosed with invasive cutaneous malignant melanoma from 2012 and 2013, excluded from further analysis.

	MELTUMP	Unknown if primary CMM or metastasis	Unknown tumour thickness and Clark level
n	18	11	50
Gender, %			
Female	44	45	52
Male	56	55	48
Age, yrs, median (range)	48 (20-81)	64 (41-87)	45 (23-75)
Localization, %			
Head and neck	0	18	32
Truncus and genitals	22	45	26
Upper extremity	11	18	20
Lower extremity	11	9	22
NA	0	9	0
SLNB, %	39	45	20
Positive SLNB, %	0	40	0

CMM = cutaneous malignant melanoma; MELTUMP = melanocytic tumour of uncertain malignant potential; NA = not assessed; SLNB = sentinel lymph node biopsy.

TABLE 3

Sentinel lymph node biopsy outcome in 520 patients diagnosed with cutaneous malignant melanoma in 2012 and 2013.

	Total, n	SLNB, n (% of total)	Positive SLNB, n (% of SLNB)	Negative SLNB, n (% of SLNB)	p-value
Gender					0.88
Female	278	112 (40.3)	28 (25.0)	84 (75.0)	
Male	242	110 (45.5)	29 (26.4)	81 (73.6)	
Melanoma thickness, mm					0.01
≤ 1.00	320	40 (12.5)	4 (10.0)	36 (90.0)	
1.01-2.00	112	107 (95.5)	26 (24.3)	81 (75.7)	
2.01-4.00	56	47 (83.9)	15 (31.9)	32 (68.1)	
≥ 4.01	32	28 (87.5)	12 (42.9)	16 (57.1)	
Histologic ulceration					0.09
Yes	59	49 (83.1)	17 (34.7)	32 (65.3)	
No	448	172 (38.4)	39 (22.7)	133 (77.3)	
NA	13	1 (0.8)	1 (100)	0 (0)	

NA = not assessed; SLNB = sentinel lymph node biopsy.

Denmark Health-care Region (714 cases). In a PhD thesis by Hansen, Danish patients diagnosed with CMM who were registered in the DMR from 1985 to 1994 were evaluated (4,984 cases) [11]. In the study by Drzewiecki et al authors reported that females account for approximately 63% of new primary CMM, whereas males account for 37%. Hansen found that females account for approximately 57%, whereas males account for 43%. In our study, females and males account for 53% and 47%, respectively. This indicates a diminishing trend in the observed gender difference observed through the decades.

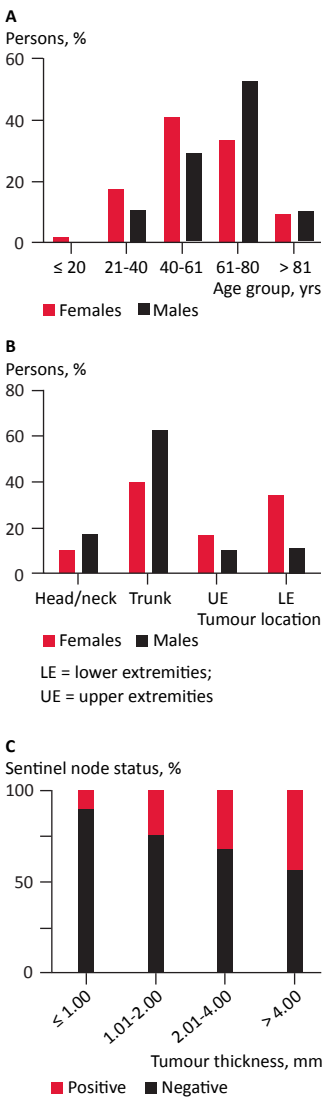
Drzewiecki et al found that mean age (both genders) was 52 years, whereas Hansen found a corresponding mean age of 55 years (male and female mean age 56 years and 54 years, respectively, $p < 0.001$). We found that the current mean age (both genders) is 59 years (male and female mean age 63 years and 56 years, respectively) (mean values calculated for comparison). The age difference between the genders was significant in the present study in analysis based on median values (Table 1). Drzewiecki et al found that in females, CMM was most often located on the lower extremity (35%) followed by the trunk (20%). In males, the most dominant location was the trunk (50%) followed by the head and neck (24%). Hansen found that in females, CMM was almost equally frequent on the lower extremity (31%) and the trunk (29%). In males, CMM was primarily located on the trunk (57%), followed by head and neck (16%). Our study shows that females most often have their melanomas on the trunk (38%) followed by the lower extremity (34%), whereas males had their CMM on the trunk (62%) followed by the head and neck (17%). The change in anatomical distribution shows that females' anatomical localisation has migrated towards a male pattern. Overall, tumour thickness has decreased from a mean tumour thickness of 2.4 mm (Drzewiecki et al, 1964-1982) to a current mean value of 1.5 mm (2012-2013). Data concerning overall tumour thickness are not available from the study by Hansen. Mean tumour thickness between genders as evaluated by Hansen showed a mean tumour thickness on 1.8 mm in females and 2.4 mm in males. The corresponding current (2012-2013) values are 1.3 mm in females and 1.7 mm in males (calculated for comparison). These data show a clear trend towards a decrease in tumour thickness, which is most likely owed to a reduction in patient's delay and doctor's delay as a result of a higher awareness of malignant melanoma.

We found a positive SLNB to be significantly related to tumour thickness, but not – as expected – to histological ulceration ($p = 0.09$) (Table 3). The reason for the non-significant association between histological ulceration and positive SLNB could be limited numbers in the group with histological ulceration, and therefore a limited statistical power in this analysis.

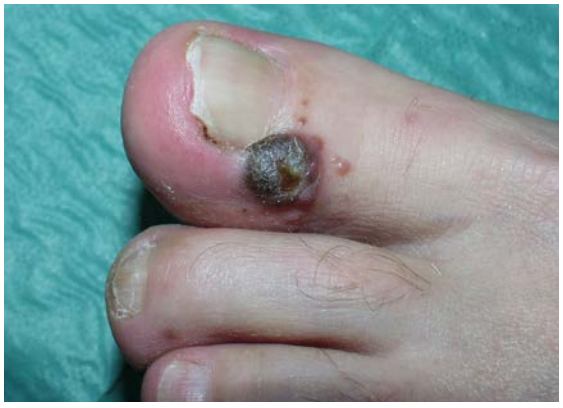
Bradford et al investigated 105,829 cases of CMM from five states in America in the period from 1975 to 2006 [12]. They found that CMM was more frequent in males than in females (54% versus 46%). The overall mean age at the time of CMM diagnosis was 56 years (mean age for males and females was 58 and 53 years, respectively). They found that, in males, CMM was most frequently located on the trunk followed by the head and neck. In females, CMM was most frequently located on the lower extremity followed by the trunk and upper extremity. Trend analysis by Clark et al comparing 397 CMM cases from 1972-1977 with 152 CMM cases from 2004 suggests that differences between genders in the anatomic distribution of CMM are equalizing [13].

Not all patients with a tumour thickness above 1 mm were treated with SLNB (Table 3). SLNB biopsy is a

FIGURE 1



A. Age-distribution between genders among the 520 patients (278 females and 242 males) diagnosed with malignant melanoma in Health-care Region Zealand in 2012 and 2013; $p < 0.01$. **B**. Anatomical distribution of tumours between genders among 517 patients (275 females and 242 males) of the 520 patients diagnosed with malignant melanoma in Health-care Region Zealand in 2012 and 2013 (three patients were excluded due to missing information, all females); $p < 0.01$. **C**. Outcome of the histological examination of sentinel lymph node biopsy in 222 patients with invasive malignant melanoma diagnosed in 2012 and 2013 in Health-care Region Zealand subgrouped according to tumour thickness. Please note that only 12.5% of the patients with a tumour thickness < 1 mm were staged using sentinel lymph node biopsy (Table 3).



54-year-old male with a 12 by 10 mm clinical malignant melanoma with several satellite tumours located at the left first toe close to the nail bed. Histological examination following excision biopsy verified the diagnosis and classified it as a superficially spreading melanoma with a tumour thickness of 3.58 mm, Clark level 4 and without ulceration. Treatment was amputation of the toe and ipsilateral radical groin dissection as the sentinel node biopsy found metastases in all of the removed nodes (three).

staging procedure, and it is not in itself associated with increased survival or decreased recurrence rates. Otherwise, indicated SLNB can be abandoned if the patient rejects, if the clinical setting suggests lymph node dissection without prior SLNB or if distant metastasis is present. Positive SLNB is associated with an elevated recurrence rate and an aggravated prognosis [14]. Lock-Andersen et al [15] and Chakera et al [16] report positive SLNB on 32% and 22% of the patients, respectively. In our study, 26% had positive SLNB, which is in line with the mentioned studies – both of which are comparable on patient characteristics. As expected, our results show a direct relation between tumour thickness and positive SLNB.

We experienced that approximately 9% of the patients identified in the DMR were incorrectly registered. This limits the usability of the data from the clinical database without thorough validation of the data sample. Moreover, it indicates that the use of clinical databases for research purposes is required to improve the future registration.

CORRESPONDENCE: *Anders Klit.* E-mail: akli@regionsjaelland.dk
ACCEPTED: 29 June 2015
CONFLICTS OF INTEREST: none. Disclosure forms provided by the authors are available with the full text of this article at www.danmedj.dk
ACKNOWLEDGEMENTS: The authors would like to express their gratitude to MD *Ann Hærskjold* (Research Unit, The Juliane Marie Centre for Women, Children and Reproduction, Rigshospitalet) for assistance with data management.

LITERATURE

1. Arnold M, Holterhues C, Hollestein LM. Trends in incidence and predictions of cutaneous melanoma across Europe up to 2015. J Eur Acad Dermatol Venereol 2013.
2. International Agency for Research on cancer. Globocan. http://globocan.iarc.fr (29 Oct 2014).
3. Fuglede NB, Brinck-Claussen UO, Deltour I. Incidence of cutaneous malignant melanoma in Denmark, 1978-2007. Br J Dermatol 2011; 165:349-53.
4. Klit A, Drejoe JB, Drzewiecki KT. Trends in the incidence of malignant melanoma in Denmark 1978-2007. Incidence on the island of Bornholm compared with the whole country incidence in Denmark. Dan Med Bull 2011;58(1):A4229.
5. Bay C, Kejs AM, Storm HH et al. Incidence and survival in patients with cutaneous melanoma by morphology, anatomical site and TNM stage: a Danish Population-based Register Study 1989-2011. Cancer Epidemiol 2015;39:1-7.
6. Miller AJ, Mihm MC, Jr. Melanoma. N Engl J Med 2006;355:51-65.
7. Køster B, Thorgaard C, Clemmensen IH et al. Sunbed use in the Danish population in 2007: a cross-sectional study. Prev Med 2009;48:288-90.
8. Statistics Denmark. www.statistikbanken.dk/. FOLK1 and FOLK2 and HISB7 (1 Nov 2014).
9. Danish Melanoma Group. DMG guidelines. www.melanoma.dk (1 Nov 2014).
10. Drzewiecki KT, Frydman H, Andersen K et al. Malignant melanoma. Changing trends in factors influencing metastasis-free survival from 1964 to 1982. Cancer 1990;65:362-6.
11. Hansen LB. Malignant melanoma in Denmark in the period 1985-1994. www.melanoma.dk/download/artikler/MaligntmelanomLBH.pdf (15 Apr 2014).
12. Bradford PT, Anderson WF, Purdue MP et al. Rising melanoma incidence rates of the trunk among younger women in the United States. Cancer Epidemiol Biomarkers Prev 2010;19:2401-6.
13. Clark LN, Shin DB, Troxel AB et al. Association between the anatomic distribution of melanoma and sex. J Am Acad Dermatol 2007;56:768-73.
14. Lock-Andersen J, Horn J, Sjostrand H et al. Sentinel node biopsy in cutaneous melanoma. Scand J Plast Reconstr Surg Hand Surg 2006;40:24-31.
15. Lock-Andersen J, Horn J, Sjøstrand H. Prognosen efter sentinel node-biopsi ved malignt melanom. Ugeskrift Læger 2006;168:2457-62.
16. Chakera AH, Drzewiecki KT, Eigtved A et al. Sentinel node biopsy for melanoma: a study of 241 patients. Melanoma Res 2004;14:521-6.