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Cutaneous melanoma in the Maltese Islands: 2000–2004 ☆

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ARTICLE INFO

Article history:
Received 7 November 2006
Received in revised form 4 April 2007
Accepted 12 April 2007
Available online 25 May 2007

Keywords:
Malignant melanoma
Epidemiology
Classification
Histopathology
Maltese Islands

ABSTRACT

This study aimed to, prospectively, over the 5-year period 2000–2004, accurately determine features of cutaneous melanoma in the Maltese Islands. Data from clinicians were supplemented by histology reports, and where necessary, histology slides were reviewed. Information collected included demographic details including age and gender, anatomical site, Clark's level, Breslow thickness and clinico-pathological melanoma type. During the study period the age-standardised (European Standard Population) rates for invasive melanoma were 8.81 per 100,000 (males) and 7.29 per 100,000 (females) and increased with age. By the end of the study, information on 166 cases of primary invasive cutaneous malignant melanoma were collected. The commonest site affected in males was the trunk (54%) and in females the lower limbs (41%). Overall, 33.8% of invasive melanomas had a Breslow thickness >1.5 mm. The initial melanoma excision was performed by a dermatologist in 68.2% and plastic surgeon in 20.8%. More cases presented in late spring and summer, particularly in females. Melanoma incidence in Malta is lower than that in high-incidence countries and northern Europe and is similar to that in southern Europe. However, incidence appears to be increasing and a relatively high proportion of patients present with thick lesions emphasising the importance of continued efforts to diagnose cases earlier.

1. Introduction

There is a world-wide increase in the incidence of cutaneous melanoma (CM) among white people. The frequency and case distribution according to age, gender and histology shows geographical differences.[1] In most, but not all, white populations, the incidence of melanoma is greater in females than males.[2] Incidence dissimilarities between areas within a country or between different countries, as well as temporary variations of rates, indicate the existence of a diverse array of risk factors in the studied populations and their exposure to these factors throughout different stages of life.[3]

This study aimed to, prospectively, over a 5-year period, accurately determine features of CM in the Maltese Islands, including overall and seasonal incidence, anatomical sites affected and histo-pathological characteristics. The results demonstrate the epidemiological status of this condition in the Maltese resident population between 2000 and 2004.

The Maltese Islands are the southernmost European state and are located 93 km south of Sicily with a population in 2005 of 404,039.[4] The climate is typically Mediterranean with

☆ No specific sources of support were available or utilised in this study. N.B.: The data relating to the first half of the study period, i.e. 1st January 2000 to 30th June 2002 were presented at the Spring Symposium of the European Academy of Dermatology and Venereology, Malta, 27th February–1st March 2003.

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0959-8049/$ - see front matter
doi:10.1016/j.ejca.2007.04.013

hot dry summers and relatively warm winters. The Maltese people are descendents of ancient Carthaginians and Phoenicians, with strong Greco-Roman and Arab influences. European elements, namely Italian, Spanish and French with traces of Anglo-Saxon origins, were assimilated later.[5] In a recent local study,[6] the distribution of Fitzpatrick skin phototypes (SPT) in the Maltese population was as follows: SPT I – 1%, SPT II – 25%, SPT III – 48% and SPT IV – 26%.

2. Materials and methods

A prospective study was conducted from 1st January 2000 to 31st December 2004. Selected clinicians (mainly dermatologists and surgeons) were invited to complete a pre-prepared form for each patient diagnosed with a new CM during the study period. This was supplemented by the histology reports of patients diagnosed with CM over the same period. The latter were accessed via the Malta National Cancer Registry, which collects histology reports from all public and private pathological laboratories in the country. Where necessary, clinicians were also contacted directly for further information about their patients. Great care was taken to ensure completeness of data collection and it is felt that close to 100% of all cases of CM diagnosed in Maltese residents during the study period were included. A case was included if the patient was resident in the Maltese Islands for more than 1 year prior to the diagnosis. This is also the residency criterion for inclusion in the cancer registry.

Information collected included demographic details including age and gender, date of diagnosis, anatomical site, Clark's level, Breslow thickness and clinico-pathological type of melanoma, as well as the medical specialty of the clinician responsible for the initial melanoma excision. The date of submission of the specimen for histological examination was taken as the date of diagnosis. In cases that had subsequent histology reports, e.g. for wider excision or for definitive excision in cases (mainly lentigo maligna/lentigo maligna melanoma), that had an initial incisional biopsy, the date of the first submission was enlisted. Body sites were aggregated into head and neck, trunk, upper limbs, lower limbs and unknown or unspecified body site according to the International Classification of Oncology, second edition (ICD-O-2); the latter was also used to code the clinico-pathological types. Breslow thicknesses were categorised into four groups: less or equal to 0.75 mm, more than 0.75 but less or equal to 1.5 mm, more than 1.5 but less or equal to 4 mm and more than 4 mm.

In those cases where the recorded histological information was ambiguous or incomplete, the slides were reviewed by pathologists with an interest in dermato-pathology (JD and/or PG) SPSS version 13 was used to analyse the data collected. Statistical methods of analysis employed included Fischer's, ANOVA, student-*t* and Poisson Regression. Standardised incidence rates by the direct method were calculated using the European Standard Population.[3] Rates were calculated using both the European and the World Standard Populations.

Each individual primary lesion was counted separately. *In situ* melanomas were counted and analysed separately and not included in the analysis of invasive lesions. Newly diagnosed metastatic melanomas where the primary tumour could not be ascertained were excluded from our study ($n = 8$).

3. Results

During the study period, 235 cases of CM were collected. Of these, 166 cases (86 [52%] in males and 80 [48%] in females) were primary invasive melanoma, while the remaining 69 cases (22 in males and 47 in females) were *in situ* melanomas. Seven patients had two or more primary melanomas diagnosed in this period. Crude and standardised incidence rates for invasive CM over the 5 year period are shown in Tables 1a and 1b (by gender). Using Poisson Regression no significant trend (Males: $p = 0.71$, Females: $p = 0.38$) in incidence rates was identified.

The age-standardised (European Standard Population, ESP) rates for invasive CM were 8.81 per 100,000 for males and 7.29 per 100,000 for females. Correspondingly, the age-standardised (World Standard Population, WSP) rates were 6.46 per 100,000 for males and 5.74 per 100,000 for females. Age-specific rates increased with age (Fig. 1). Below the age of 45 there was a slight preponderance for females. This was reversed over the age of 45 years. The age range of the patients was 15–96 years. The median age at diagnosis was 58 years in males and 56 years in females.

Analysis of data of the Malta National Cancer Registry shows that, for the 5-years preceding this study, i.e. 1995–1999, the age-standardised invasive melanoma incidence rates (using the ESP[d]) were visibly lower namely 4.7 per 100,000 in males and 5.8 per 100,000 in females.

The anatomical distribution by gender and age group is shown in Tables 2 and 3. In males, the trunk was involved in 54% ($n = 46$) of cases, followed by head and neck (17%; $n = 15$), and upper limbs (15%; $n = 13$). In females the commonest sites were the lower limbs (41%; $n = 33$) followed by the trunk (29%; $n = 23$). The difference in distribution between males and females was significant ($p < 0.001$). Overall, the most common site was the trunk accounting for 42% of lesions.

There was also a significant difference ($p = 0.011$) in males in site distribution between different age groups. Lesions on the head and neck and upper limb increased with age while lesions on the trunk were more frequent in the middle and young age group.

In females no statistically significant ($p = 0.53$) difference was detected in site distribution between the different age groups. However, lesions on the head and neck tended to affect more the older age groups while those on the limbs were more frequent in the middle and younger age groups.

Tables 3 and 4 show the distribution of different clinico-pathological types of melanomas according to gender and anatomical site. Overall, superficial spreading melanoma was the most frequent type diagnosed in both sexes account-

[d] The original age-standardised rates used in this paper were calculated using the European Standard Population. However, rates were re-calculated using the World Standard Population when they were being compared with international published rates that were also calculated with the latter population.

Table 1a – Incidence rates (per 100,000) of invasive cutaneous melanoma in males

		Males					
Year	No.	Crude rates/100,000	CI	European Standard Population (ESP) rates/100,000*	CI	World Standard Population (WSP) rates/100,000**	CI
2000	16	8.26	4.21–12.31	8.46	8.04–8.87	5.97	5.67–6.26
2001	16	8.22	4.19–12.25	8.4	7.98–8.82	6.07	5.76–6.38
2002	19	9.68	5.32–14.03	9.95	9.5–10.41	7.19	6.85–7.52
2003	16	8.1	4.13–12.07	8.32	7.90–8.73	6.28	5.97–6.60
2004	19	9.55	5.25–13.84	8.86	8.45–9.26	6.73	6.42–7.05
2000–2004	86	8.76	4.62–12.90	8.81	8.62–9.00	6.46	6.32–6.60

Table 1b – Incidence rates (per 100,000) of invasive cutaneous melanoma in females

		Females					
Year	No.	Crude rates/100,000	CI	ESP*rates/100,000	CI	WSP*rates/100,000	CI
2000	13	6.57	2.99–10.14	6.01	5.68–6.34	4.51	4.26–4.76
2001	18	9.06	4.87–13.25	8.05	7.68–8.43	6.24	5.93–6.55
2002	11	5.5	2.25–8.75	5.03	4.72–5.33	3.73	3.50–3.96
2003	20	9.94	5.58–14.30	8.43	8.05–8.81	6.07	5.78–6.36
2004	18	8.89	4.78–13.00	8.92	8.51–9.34	8.11	7.73–8.50
2000–2004	80	8.00	4.08–11.92	7.29	7.13–7.45	5.74	5.60–5.87

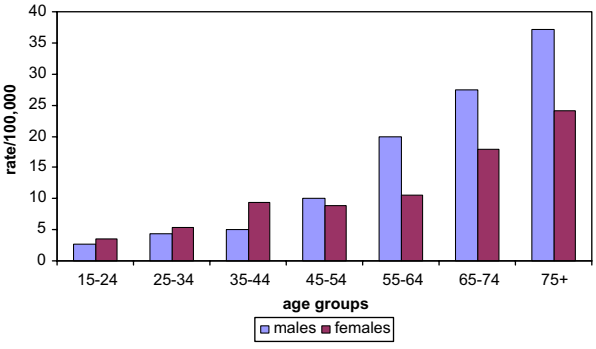

Fig. 1 – Age-specific rates for invasive cutaneous melanoma.

ing for 58% of all cases. Using Fisher's exact test, no significant differences were found between the genders ($p = 0.30$) with respect to histological type. However, whereas superficial spreading melanoma was commoner in males, nodular melanoma was more frequent in females.

The most frequent types of melanomas found on the head and neck were nodular and lentigo maligna melanoma, on the trunk superficial spreading melanoma and on the limbs superficial spreading followed by nodular melanoma.

The distribution of Clark's level in our study for both genders was as follows: Clark's II – 38.6%, Clark's III – 30.7%, Clark's IV – 22.9% and Clark's V – 4.2%. For six (3.6%) of the cases the Clark's level could not be determined. There was no significant difference ($p = 0.57$) in Clark's level between genders. The Breslow thickness by gender, histological type, site and age are shown in Table 5.

In our study, 33.8% of melanomas were more than 1.5 mm and 11.3% were more than 4 mm thick. Overall, the distribution of Breslow thicknesses was as follows: $\leqslant$0.75 mm in 68 cases (42.5%), >0.75 to $\leqslant$1.5 mm in 38 cases (23.8%), >1.5 to

Table 2 – Anatomical distribution for invasive cutaneous melanoma by age group

		Body site					
Age group (years)	Gender	Head and Neck	Trunk	Upper limb	Lower limb	Unknown	Total
0–44	Males	0 (0%)	11 (64.7%)	1 (5.9%)	4 (23.5%)	1 (5.9%)	17 (100%)
	Females	1 (4.0%)	8 (32.0%)	7 (28.0%)	9 (36.0%)	0 (0%)	25 (100%)
45–64	Males	6 (16.7%)	23 (63.9%)	3 (8.3%)	4 (11.1%)	0 (0%)	36 (100%)
	Females	1 (4.0%)	7 (28.0%)	4 (16.0%)	13 (52.0%)	0 (0%)	25 (100%)
65+	Males	9 (27.3%)	12 (36.4%)	9 (27.3%)	3 (9.1%)	0 (0%)	33 (100%)
	Females	5 (16.7%)	8 (26.7%)	4 (13.3%)	11 (36.7%)	2 (6.7%)	30 (100%)
Total	Males	15 (17.4%)	46 (53.5%)	13 (15.1%)	11 (12.8%)	1 (1.2%)	86 (100%)
	Females	7 (8.8%)	23 (28.8%)	15 (18.8%)	33 (41.3%)	2 (2.5%)	80 (100%)

Table 3 – Distribution of melanoma clinico-pathological types by gender; LMM – lentigo maligna melanoma, SSM – superficial spreading melanoma, NM – nodular melanoma, ALM – acral lentiginous melanoma, NOS – not otherwise specified

Morphology	Males		Females		Both genders	
	No	%	No.	%	No.	%
LMM	5	5.8	3	3.8	8	4.8
SSM	56	65.1	41	51.2	97	58.4
NM	16	18.6	24	30.0	40	24.1
ALM	1	1.2	2	2.5	3	1.8
Others & NOS	8	9.3	10	12.5	18	10.8
Total	86	100.0	80	100.0	166	100.0

Table 4 – Distribution of melanoma clinico-pathological types by anatomical site

	Body site					
Morphology	Head and neck	Trunk	Upper limb	Lower limb	Unknown	Total
LMM	7 (31.8%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)	8 (4.8%)
SSM	6 (27.3%)	51 (73.9%)	16 (57.1%)	23 (52.3%)	1 (33.3%)	97 (58.4%)
NM	8 (36.4%)	10 (14.5%)	9 (32.1%)	12 (27.3%)	1 (33.3%)	40 (24.1%)
ALM	0 (0%)	0 (0%)	1 (3.6%)	2 (4.5%)	0 (0%)	3 (1.8%)
NOS and others	1 (4.5%)	7 (10.1%)	2 (7.1%)	7 (15.9%)	1 (33.3%)	18 (10.8%)
Total	22 (100%)	69 (100%)	28 (100%)	44 (100%)	3 (100%)	166 (100%)

Table 5 – Distribution of Breslow thickness by gender, histological type, site and age

Title	Breslow thickness									
	⩽0.75 mm		>0.75 to ⩽1.5 mm		>1.50 to ⩽ 4 mm		>4 mm		Unknown	
	No.	%	No.	%	No.	%	No.	%	No.	%
Gender										
Males	32	37.2	26	30.2	17	19.8	8	9.3	3	3.5
Females	36	45.0	12	15.0	19	23.8	10	12.5	3	3.8
Histology										
NM	3	7.5	4	10	21	52.5	11	27.5	1	2.5
SSM	49	50.5	29	29.9	13	13.4	5	5.2	1	1.0
NOS + others	16	55.2	5	17.2	2	6.9	2	6.9	4	13.8
Site										
Head and neck	7	31.8	8	36.4	5	22.7	0	0	2	9.1
Trunk	34	49.3	16	23.2	14	20.3	5	7.2	0	0
Upper limb	12	42.9	4	14.3	8	28.6	4	14.3	0	0
Lower limb	14	31.8	10	22.7	9	20.5	8	18.2	3	6.8
Unknown	1	33.3	0	0	0	0	1	33.3	1	33.3
Age (years)										
0–44	26	61.9	6	14.3	9	21.4	1	2.4	0	0
45–64	22	36.1	21	34.4	12	19.7	5	8.2	1	1.6
65+	20	31.7	11	17.5	15	23.8	13	20.6	4	6.3

⩽4 mm in 36 cases (22.5%) and >4 mm in 18 cases (11.3%). Females had a larger proportion of the thinnest lesions (⩽0.75 mm). However, females also had more lesions in the thickest category (>4 mm). Student *t*-test analysis showed no significant difference in thickness between the genders ($p = 0.61$). Mean Breslow thickness was 1.93 mm (confidence interval (CI 1.41–2.45) in males and 1.74 mm (CI 1.32–2.16) in females.

ANOVA testing showed a significant difference ($p < 0.001$) in the mean thickness between different histological types. Nodular melanomas had a mean thickness of 3.73 mm (CI 2.78–4.68), superficial spreading melanomas had a mean

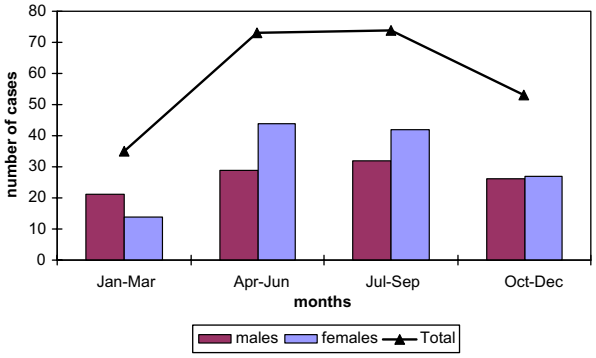

Fig. 2 – Number of cases by months of diagnosis.

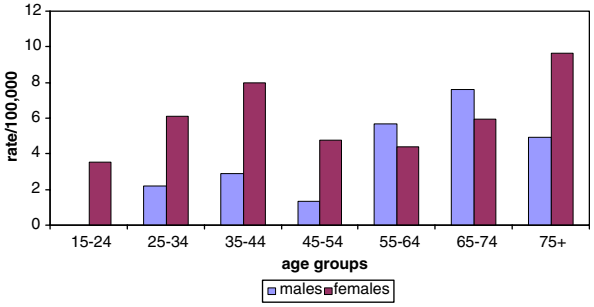

Fig. 3 – Age-specific rates for *in situ* melanoma.

thickness of 1.23 mm (CI 0.97–1.49) and all other melanomas had a mean thickness of 1.19 mm (CI 0.58–1.8).

Lesions on the limbs tended to be thicker than those on the trunk or head and neck, however ANOVA testing showed no significant difference ($p = 0.26$) in lesion thickness according to body site. Pearson correlation showed that thicker lesions were commoner in older patients ($p < 0.009$).

The distribution of all cases of CM (*in situ* and invasive) according to the month of diagnosis is shown in Fig. 2; three-month groupings (January–March, April–June, July–September and October–December) are used to show the time of year when patients were diagnosed. More cases were diagnosed in the summer months, and this variation was more marked in females. Cases diagnosed during the months of May, June and July across the 5-years of the study amounted to almost 40% of the total.

Cases were also assessed by the specialty of the clinician who performed the initial melanoma excision. Most cases of CM (both *in situ* and invasive) were under the care of a dermatologist or plastic surgeon at the time of diagnosis as seen in Table 6.

Table 6 – Specialty of clinician who performed the initial melanoma excision

Clinical specialty	Number of cases	% of cases
Dermatologist	160	68.1
Plastic surgeon	49	20.8
General surgeon	18	7.7
General practitioner	8	3.4
Total	235	100

Table 7 – Distribution of *in situ* melanoma according to anatomical site and gender

	Males		Females		Both genders	
	No.	%	No.	%	No.	%
Head and neck	10	45.5	12	25.5	22	31.9
Trunk	8	36.4	16	34.0	24	34.8
Upper limbs	0	0.0	7	15.0	7	10.1
Lower limbs	3	13.6	11	23.4	14	20.3
Unknown	1	4.5	1	2.1	2	2.9
Total	22	100.0	47	100.0	69	100.0

3.1. *In situ melanoma*

During the study period, 69 cases of *in situ* melanoma were diagnosed (47 (68%) in females and 22 (32%) in males). The median age at diagnosis was 55 years in males and 44 years in females, which is considerably lower than that found for invasive lesions especially in females. Overall, the commonest body site for *in situ* lesions was the trunk (24 cases: 35%). This was also the commonest site for the invasive lesions. However, in males *in situ* lesions were found most commonly on the head and neck (10 cases: 45%), and in females on the trunk (16 cases: 34%). *In situ* melanoma was also found more commonly on the limbs of females than males. The distribution of *in situ* melanoma according to anatomical site and gender is shown in Table 7. Fig. 3 shows the age-specific incidence rate of *in situ* melanoma for the period 2000–2004. The incidence rate for most age-groups shows a higher rate in females.

4. Discussion

World-wide, high incidence of CM is seen in white populations especially in Australia, New Zealand and South Africa. Reported age-standardised incidence rates (using the World Standard Population, WSP) of invasive melanoma in these populations are 42.4,[e] 34.8,[f] and 27.5[1] per 100,000 in males and 31.6,[e] 32.7[f] and 22.2[1] per 100,000 in females, respectively. Within Europe, rates (using WSP) are highest in Northern Europe, e.g Sweden – 13.1 per 100,000 in males and 13.1 per 100,000 in females.[g] In comparison, the age-standardised incidence rates (using WSP) 6.5 per 100,000 in males and 5.7 per 100,000 in females of melanoma for Malta in our study were lower than those in high-incidence countries and northern Europe and appear similar to those in southern Europe.

[e] Rates for all Australia for 2001: http://www.aihw.gov.au/publications/can/ca01/ca01-c03.pdf [March 2006].

[f] Rates for New Zealand for 2001: http://www.nzhis.govt.nz/stats/cancerstats.html [March 2006].

[g] Rates for Sweden for 2003: http://socialstyrelsen.se/NR/ [March 2006].

However, whereas incidence rates in certain parts of northern Europe, e.g. Stockholm appear to be stabilising,[7] this is not the case in Malta which is still seeing an increasing trend in incidence.[8] We are also experiencing changes in the pattern of gender distribution of these tumours. An interesting observation from our study is that while the number of cases of invasive melanomas was greater in males, the number of *in situ* cases was much greater in women. This supports studies which report that in most, but not all white populations, the incidence of melanoma is greater in women than men.[9]

Breslow thickness, body site and histological type of melanoma are important indicators of prognosis and, of these, by far the most important predictor of survival is thickness.[10] Generally, older patients do less well than younger ones with the same tumour thickness even after correcting for age, and females do better than males.[11] Those with thicker lesions tended to be older, the lesions were more commonly found on the legs and were more commonly of the nodular subtype. The proportion of thicker melanomas in our study is higher than in comparable studies from northern Europe[12] emphasising the importance of continued efforts locally to diagnose cases earlier.

In our study, as in many other populations, the trunk was the predominant melanoma site in men and the legs in women. These differences may reflect male/female differences in sun exposure behaviour as well as a cohort effect due to different behavioural tendencies in younger generations to sun exposure in parts of the body that were usually protected against sunlight by older generations.[13] A significant proportion (29%) of melanomas in females in our series occurred on the trunk, which is associated with a less favourable prognosis than other body sites. This relatively high frequency was also noted in the study by de Vries and Coebergh[11], where more than 30% of melanomas in females occurred on the trunk in southern and eastern European cancer registries compared to between 10% and 20% in most other European registry areas.

In our study, nodular melanoma, which is another unfavourable prognostic factor, was also more frequent in females whereas superficial spreading melanoma was commoner in men. However, differences between genders with respect to histological type were not significant. This is in keeping with population-based data for white people showing that the proportions of the different histological types of melanomas are similar in each gender; generally, superficial spreading melanoma accounts for 50–65%, nodular melanoma for 25–35%, lentigo maligna melanoma for about 10% and acral lentiginous melanoma for a small percentage or less.[14] Our study shows similar figures especially for superficial spreading melanoma and nodular melanoma supporting Swerdlow who states that there is 'no evidence of systematic differences in the proportions of different histologies by latitude'.

CM may have an *in situ* horizontal pre-invasive growth phase before the development of invasive tumour. The *in situ* phase is longest in lentigo maligna, short in superficial spreading melanoma and absent in nodular melanoma.[15] As expected, compared to invasive lesions, *in situ* melanomas in our series tended to occur in younger patients. The anatomical distribution of *in situ* melanomas mirrored that for invasive lesions with some differences. The commonest site affected was the trunk, as for invasive melanomas, however relatively more *in situ* lesions occurred on the head and neck, especially in males. This is not surprising considering the known predilection of the *in situ* melanoma lentigo maligna to occur on the head and neck.

For the study period 2000–2004 the standardised mortality rate (using the European Standard Population, ESP) from CM for Maltese males was 1.48 and for females 1.14 per 100,000 (Malta National Mortality Registry).[h] In comparison, the estimated standardised (with ESP) mortality rate for the EU 15 for 1998 was 2.33 in males and 1.63 per 100,000 in females.[16] As described in previous studies mortality rates in Northern European populations with higher melanoma incidence are not much higher than in those with relatively low incidence.[7] One possible reason for this is a difference in the features of melanoma across European cancer registry areas in terms of stage and histology. These two prognostic factors have been found to be slightly more favourable in Northern and Western European populations relative to those in Southern and Eastern Europe.[12]

In our study diagnosis of new cases peaked in the early summer months, especially in females. Seasonal variation in melanoma incidence has been reported previously in other populations[17] and may reflect increased awareness and attention of the population to exposed skin during this period. De Vries et al. demonstrated a direct link between seasonality of melanoma diagnosis and latitude of residence.[12] The amplitude of seasonality in melanoma diagnosis was greater with increasing latitude. The seasonal variation in melanoma incidence in our study is likely also the result of annual melanoma and sun awareness campaigns that, particularly since the 1990s, have been held regularly in Malta in late spring/early summer.

Most patients in our series were under the care of a dermatologist or plastic surgeon at the time of diagnosis. This corresponds with the local tendency to seek advice from a specialist in these fields in the first instance. Nevertheless, in a significant proportion of cases, the initial melanoma excision was performed either by a general surgeon or by a general practitioner, demonstrating the need for melanoma awareness across medical specialties.

The effects of melanoma and sun awareness educational campaigns in Malta are probably still evolving. Although, compared to other populations, the incidence of CM is low, the trend in incidence is currently still on the rise. The higher proportion of thicker lesions and the unfavourable mortality experience compared to regions in Northern Europe emphasise the importance of further efforts to diagnose cases early as well as photo-preventive measures to try to reduce the risks for melanoma incidence over the longer term.

Conflict of interest statement

None.

[h] The Malta National Mortality Registry is the official source of the national mortality information and statistics for the Maltese Islands.

Acknowledgements

We gratefully acknowledge the collaboration of all the clinicians who notified their cases to this study, the invaluable work and support of Dr. Neville Calleja, medical statistician, in the preparation of the results, and Dr. Julian Mamo, epidemiologist, for reviewing this manuscript.

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