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Comparative analysis of incidence and clinical features of cutaneous malignant melanoma in Crete (Greece) and southern Germany (central Baden-Württemberg)

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Conflicts of interest
None declared.

Summary

Background Comparative analysis of the incidence rates and epidemiological features of cutaneous malignant melanoma (CMM) between different ethnic groups exposed to varying environmental factors is critical for consideration of the causes of CMM but can also be utilized in a public health approach to control of the disease.

Objectives To compare incidence rates and clinical features of CMM in a Greek and a central European population (central Baden-Württemberg, Germany).

Methods Incident cases of CMM were traced in all hospitals of the island of Crete for the period 1999–2002. Age-standardized incidence rates per 100 000 inhabitants per year for the European Standard Population were calculated based on the Cretan population statistics. A comparison was performed between the Cretan findings and those of southern Germany as registered by the hospital-based Central Malignant Melanoma Registry, which likewise documents more clinical features than normally recorded by population-based cancer registries.

Results Mean incidence rates in Crete for 1999–2002 were 4·01 per 100 000 inhabitants per year for males and 4·05 for females as compared with 10·6 for males and 11·1 for females in southern Germany. There were striking differences in the clinical characteristics of CMMs, with significantly higher tumour thickness in Crete (median 1·4 mm vs. 0·7 mm in southern Germany). Correspondingly, significantly more nodular melanomas were observed in Crete (29%) as compared with southern Germany (11%).

Conclusions Incidence of CMM in Crete, with about four cases per 100 000 inhabitants per year, is clearly higher than previously estimated, and there is an urgent necessity for earlier recognition of CMM in Crete. However, the incidence of CMM in southern Germany is much higher.

In recent decades incidence rates of cutaneous malignant melanoma (CMM) have been steadily increasing in many European countries, particularly among white-skinned populations.[1] Rising incidence trends first emerged in Scandinavia, reaching up to 15 cases per 100 000 inhabitants per year, followed by western, eastern and southern Europe.[1,2] Similar trends for the incidence of CMM are reported for Italy, Spain and the former Yugoslavia, reaching up to five to seven cases per 100 000 inhabitants per year even though Mediterranean populations are considered to be at low risk for the development of this tumour.[1–3] Therefore, in Europe there is a gradient in incidence rates with the highest rates in the northern countries and the lowest ones in the southern countries.[4,5] This has been attributed to the more intensely pigmented complexion of the southern European populations offering more protection against ultraviolet radiation but also to the different pattern of sun exposure (chronic rather than intermittent in southern Europe). Better to understand the causes of CMM (genetic, environmental and others) it would be pivotal to analyse the differences in CMM incidence rates between different ethnic populations. Herein, we attempted for the first time a comparative analysis of incidence and clinical characteristics of CMM between a

southern (Crete, Greece) and a central European population [central Baden-Württemberg (CBW), Germany].

Patients and methods

Crete is the most southerly and the largest Greek island, with a stable and homogeneous indigenous Greek population of 560 707 inhabitants (2001 census). Crete is isolated from continental Greece by *c.* 600 km and, accordingly, nearly all of the medical care is delivered by Cretan hospitals and clinics. In Crete, there is no mandatory case reporting to a cancer registry, nor is there a national or local (Greek) health information network. Hence, the data related to CMM are collected by the Melanoma Unit of the Dermatology Department of the University of Crete, from all hospitals, as well as from all surgical departments and pathology laboratories of the island. All pathology reports of the respective years were checked for the diagnosis of CMM and as we had no refusals on behalf of the patients to allow us to use their data for the purposes of our study, we registered all the patients that we traced by their pathology reports and medical records.

CBW is located in southern Germany with an indigenous population of 923 000 inhabitants according to the Statistic Landesamt (2003 census). As only the German population has been included in the analysis there were no racial subdivisions in the study population of CBW; living conditions are primarily industrial with some of them rural. The data presented here for CBW were collected by the Central Malignant Melanoma Registry (CMMR) of the German Dermatological Society, which is a hospital-based melanoma registry. In Germany, most patients with CMM are referred to hospitals for treatment, and cooperative management of the patients between the dermatologist in private practice and the hospital is conducted. Thus, most patients are seen by both the hospital and the specialist in private practice. Therefore, registration of patients with CMM to the CMMR in a given region with a participating hospital centre seems to be almost complete[6] and in CBW more than 90% of patients with CMM are registered by the CMMR.

The present analysis included 529 patients of Cretan and CBW origin. All patients had their first histopathologically confirmed diagnosis of primary invasive CMM (Clark level II or deeper) between 1999 and 2002. The data collected for every case included age, sex, place of birth and residence, tumour thickness, level of invasion, histological subtype and anatomical site of the tumour, stage of CMM according to the latest American Joint Committee on Cancer staging system and the date of diagnosis.[7–9] Tumour thickness was analysed in four subgroups (≤1·0, 1·01–2·0, 2·01–4·0 and > 4·0 mm) and age was classified into seven subgroups (≤30, 31–40, 41–50, 51–60, 61–70, 71–80 and >80 years). Histopathological reports of the responsible dermatopathologists of the respective hospitals were re-evaluated within the present study.

To calculate the CMM age-standardized incidence rate (ASR) for the years 1999–2002, the populations of Crete and CBW were divided into 10-year age spans in accordance with the 2001 Greek census and 2003 CBW census, respectively. The ASR was calculated by direct standardization using the European and World standard populations. Comparisons of variable distributions between groups were performed using the χ^2 test. For continuous variables the independent sample *t*-test was used. All P-values calculated were two-sided and $P < 0{\cdot}05$ was considered to be statistically significant. All calculations were performed with the Statistical Package for Social Sciences version 11.5 (SPSS, Chicago, IL, U.S.A.).

Results

During the study period (January 1999–December 2002), 97 and 432 invasive CMMs were diagnosed in Crete and CBW, respectively. There were 203 and 49 male and 229 and 48 female patients of German and Cretan origin, respectively. The male to female ratio was approximately equal and the age and sex distributions did not differ significantly between the two populations (Table 1). Seventy-three per cent of patients from CBW were at stage I compared with 38% of the patients from Crete ($P < 0{\cdot}0001$). Conversely, 1·7% of the German patients and 18·6% of the Cretan patients were at stage IV at the time of their first diagnosis ($P < 0{\cdot}0001$). The median tumour thickness was 0·7 mm for CBW and 1·4 mm for Crete ($P < 0{\cdot}001$). The vast majority (62·4%) of invasive melanomas in CBW measured ≤1 mm in thickness and only a small percentage (4·5%) of melanomas was > 4 mm in thickness, while in Crete the corresponding percentages were 37·2% and 16·3%, respectively ($P < 0{\cdot}0001$).

Significant differences between the two groups were also found regarding the Clark level of invasion (Table 1). Histological ulceration (40% vs. 12%, respectively, $P < 0{\cdot}0001$) was significantly more common in Cretan patients than in CBW patients. Superficial spreading melanoma was the most common histogenetic type in both populations, but its proportion was significantly higher in the German population than in the Greek one (65·0% vs. 43·3%, respectively, $P < 0{\cdot}0001$). In contrast, the proportion of nodular melanomas (NMs) in Crete was significantly higher compared with CBW (28·9% vs. 11·1%, respectively, $P < 0{\cdot}0001$), whereas the percentage of lentigo maligna melanoma was similar between the two groups (9·3% vs. 8·8% for Cretan and German patients, respectively). Acral lentiginous melanomas were twice as common in Crete as in CBW (6·2% vs. 2·5%, respectively).

The anatomical localization of CMMs was similar between patients from CBW and Crete. Most melanomas occurred on the trunk and the lower limb, accounting for approximately two-thirds of all melanomas in both populations. The incidence of CMM during the study period was almost threefold lower for the Cretan population compared with CBW in both men and women (Table 2).

Discussion

The results of the current study were based on the analyses of two small data sets of incident invasive CMMs diagnosed in

Table 1 Demographics and diagnostic features of melanoma patients from southern Germany (central Baden-Württemberg, CBW) and Crete, Greece

	CBW, n (%)	Crete, n (%)	P-value[a]
Gender			
Male	203 (47)	49 (50·5)	0·53
Female	229 (53)	48 (49·5)	
Age (years)			
≤30	40 (9·3)	8 (8·2)	0·314
31–40	56 (13·0)	16 (16·5)	
41–50	68 (15·7)	6 (6·2)	
51–60	95 (22·0)	22 (22·7)	
61–70	105 (24·3)	27 (27·8)	
71–80	53 (12·3)	13 (13·4)	
>80	15 (3·5)	5 (5·2)	
Median	57·0	56·0	
Histogenetic type			
Superficial spreading	281 (65·0)	42 (43·3)	<0·0001
Nodular	48 (11·1)	28 (28·9)	
Lentigo maligna	38 (8·8)	9 (9·3)	
Acral	11 (2·5)	6 (6·2)	
Other	54 (12·5)	11 (11·3)	
Anatomical site			
Head/neck	72 (16·8)	15 (15·5)	0·8
Trunk	145 (33·8)	38 (39·2)	
Upper limb	64 (14·9)	14 (14·4)	
Lower limb	131 (30·5)	28 (28·9)	
Unknown origin	17 (4·0)	2 (2·1)	
Stage (AJCC[b])			
I	304 (73·1)	37 (38·1)	<0·0001
II	56 (13·5)	26 (26·8)	
III	49 (11·8)	12 (12·4)	
IV	7 (1·7)	18 (18·6)	
Tumour thickness (mm)			
≤1·0	249 (62·4)	32 (37·2)	<0·001
1·01–2·0	84 (21·1)	19 (22·1)	
2·01–4·0	48 (12·0)	21 (24·4)	
>4·0	18 (4·5)	14 (16·3)	
Median	0·70	1·40	
Level of invasion (Clark)			
II	105 (24·3)	28 (28·8)	0·015
III	126 (29·2)	28 (28·8)	
IV	143 (33·1)	22 (22·7)	
V	19 (4·4)	6 (6·2)	
Not evaluable	39 (9·0)	13 (13·4)	
Histological ulceration			
Yes	52 (12·0)	38 (40·0)	<0·0001
No	380 (88·0)	57 (60·0)	

[a]Pearson's χ^2, two-tailed significance. [b]Staging of melanoma according to the latest system of the American Joint Committee on Cancer.[9]

Table 2 Number of cases of melanoma in southern Germany (central Baden-Württemberg, CBW) and Crete for 1999–2002, the incidence of cutaneous melanoma per 100 000 inhabitants per year in CBW and Crete for the same years, standardized according to the European (ESP) and World standard population (WSP), and the overall incidence (ESP and WRP) for the entire period 1999–2002 with the corresponding 95% confidence interval (95% CI)

	Cases				ESP				WSP			
	CBW		Crete		CBW		Crete		CBW		Crete	
Year	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
1999	50	49	11	12	10·54	10·41	3·01	4·11	7·95	8·73	2·08	3·22
2000	60	51	12	12	12·43	9·45	3·65	3·62	9·84	7·75	2·86	2·81
2001	47	59	12	13	9·73	11·25	4·02	4·59	7·84	9·27	2·95	3·44
2002	46	70	14	11	9·70	13·32	5·37	3·86	7·25	11·20	4·14	3·00
Overall (95% CI)	–	–	–	–	10·6 (8·56–12·63)	11·1 (8·48–13·73)	4·01 (2·99–5·13)	4·05 (2·89–5·20)	8·22 (6·43–10·0)	9·23 (6·92–11·54)	3·01 (2·14–3·88)	3·12 (2·21–4·03)

Crete (Greece) and CBW (southern Germany). In this study, we used data derived from a relatively small area of the CMMR to compare two populations of a similar magnitude. In Greece no incidence values have ever been reported, due to the lack of cancer registries.[10–13] There are, however, estimated incidence rates of 2·3 and 2·8 per 100 000 person-years

for males and females, respectively, which are based on the empirical relationship between incidence and mortality.[12,13] The ASR of CMM in Crete, calculated in this study, is almost twofold higher than the estimated one, but is similar to the reported incidence for other Mediterranean countries.[14] On the other hand, the incidence rates calculated in this study for CBW are very similar to those reported for population-based registries such as the Saarland registry which is integrated in the UICC project 'Cancer Incidence in Five Continents'.[11] In Crete, however, the incidence of CMM may be higher than suggested here. An unknown number of resident patients may have had their melanoma diagnosed and treated elsewhere in Greece or in another country without any record in Crete or they might have died without receiving medical attention. Although we believe that this number is very small, this factor would result in an underestimation of the incidence.

This is the first report to compare directly the incidence rates and the clinical characteristics of melanoma between two populations of different latitude in Europe. Our study confirmed the inverse association between melanoma incidence rates and latitude of residence, with significantly higher incidence rates in central than in southern Europe.[1,11] In contrast, in the U.S.A. and Australia the risk of melanoma increases with proximity to the equator.[15–20] People with moderately or highly pigmented skin exhibit a low risk of developing melanoma and among white-skinned Europeans there are important differences with respect to skin colour.[12,21] Furthermore, central European populations may have been subjected to more intermittent exposures due to differences in sun-exposure habits and sunny holidays in southern countries.[22,23] If the latter gave rise to a significant effect in the difference in melanoma incidence rates observed in our study, then we would expect in CBW a higher proportion of melanomas arising in the intermittently sun-exposed body parts (e.g. trunk) than in Crete. However, in the present study no such difference was observed. Moreover, the proportions of lentigo maligna melanoma, known to be associated with chronic sun exposure, were similar between the two populations. This may reflect the fact that also in central Europe, chronic sun exposure occurs either in occupationally exposed individuals or in elderly individuals who spend long periods in more southern countries.

In our study we also found that the proportion of early stage, prognostically more favourable CMMs, was significantly higher in CBW than in Crete. It is likely that this might be due to earlier detection of CMM in this German population. As dermatologists in Greece do not remove pigmented lesions in private practice, the possibility of selection bias, due to a number of early melanomas diagnosed and treated in private practice, is unlikely. Furthermore, histological examinations are performed only in the laboratories of the hospitals of the island which offered their data to the study. Cross-checking the data from surgery with data of the pathology laboratories reinforced the completeness of registration. In CBW, approximately two-thirds of melanomas had Breslow tumour thickness below 1 mm, while in Crete those tumours accounted only for one-third of the total number. Conversely, the proportion of thick tumours (>4 mm) was almost four times lower in CBW than in Crete. Similarly, histological ulceration, which is an important unfavourable prognostic factor for CMM, was more common in Crete.[7]

This difference in the stage of melanomas between the population of CBW and Crete had an impact on the distribution of the different histological variants of CMM. Thus, in CBW the percentage of superficial spreading melanomas was much higher, whereas the percentage of NMs was significantly lower than in the Greek population.[24–26] Notably, the frequency of NM among Cretan patients in our study resembles that reported in melanoma patients from central Europe during 1981–1985.[6] Also, the median melanoma thickness in central Europe during those years was similar to that observed in the present study for Crete. Recent data from the Scottish Melanoma Group reported that the incidence of thick melanomas, which were mainly of the nodular type, was stable during the last two decades, while during the same period the overall melanoma incidence significantly increased. The authors suggested that these tumours might be behaviourally different from other types of melanoma.[27] After all, high numbers of NMs are related to low *BRAF* point mutations and *N-ras* proto-oncogenes mutated at codon 61 in some regions of Europe, among which Crete is a candidate.[28,29] This notion should be supported by basic molecular biology studies, which are a goal of our future investigations.

In the Cretan sample, the possibility of misclassification of the histogenetic types of melanoma is unlikely, because most melanomas in Crete were re-evaluated by the same two experienced dermatopathologists, who used the same diagnostic criteria. The histological diagnosis of NM was made by the dermatopathologists when the growth pattern was monophasic or purely vertical. This infiltration sometimes coexists with intraepidermal growth extending no more than three rete ridges from the nodule.[30,31]

Current data appear to reflect differences in awareness in the general population that are most pronounced in the proportions of thin and less invasive tumours. In Germany, CMM has been given attention as a public health problem and awareness of the population keeps improving thanks to health promotion activities that educate Germans about suspicious pigmented lesions and sun-safe behaviour.[32] In contrast, in Crete the rates of self-examination and self-detection of suspicious lesions are very low and most of the patients present with symptomatic advanced tumours. In Crete, it is imperative to set up health educational campaigns about sun protection and self-examination for skin cancer.

In conclusion, in this study we calculated a much lower CMM incidence rate for Crete (Greece) than for CBW (southern Germany). However, patients with CMM in CBW are diagnosed at an earlier tumour stage compared with those patients from Crete. It is hoped that this report and follow-up data will emphasize the need for primary prevention of CMM in the form of appropriate education of the public at risk, together with secondary prevention by early diagnosis and treatment of thin, curable melanomas.

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