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Epidemiological differences for cutaneous melanoma in a relatively dark-skinned caucasian population with chronic sun exposure

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Abstract

The aim of this study was to reveal differences in the epidemiology and to identify significant risk factors for cutaneous melanoma (CM) in a relatively dark-skinned, chronically sun-exposed Caucasian population. This group is considered to have a low risk for this tumour. One hundred and ten newly diagnosed patients with primary CM and 110 age- and gender-matched controls, all of Cretan origin, were interviewed and underwent a complete skin examination. Solar keratoses odds ratio (OR) 6.2 and lentigines (OR 2.2), common and atypical naevi (OR 5.4 and 3.0, respectively), blonde or red hair colour (OR 3.1), skin phototypes I/II (OR 1.8), as well as total sun exposure (weeks per year) (OR 1.03), were all significantly associated with CM risk in a multivariate logistic regression analysis. In the relatively dark-skinned Cretan population, sun exposure indices represent the most important risk markers for CM which contrasts with data from fair-skinned Caucasian populations where melanocytic naevi are the main risk factors.

Keywords: Cutaneous melanoma; Epidemiology; Risk factors

1. Introduction

Most epidemiological data for cutaneous melanoma (CM) are derived from fair-skinned Caucasian populations with high incidence rates for CM. By contrast, little is known for populations with darker skin phenotypes and chronic sun exposure who are considered to be at low risk of CM development. In Crete, the southeast and largest island of Greece (situated 25°E and 35°N), with one of the lowest estimated annual incidence rates for CM in Europe, significant differences regarding melanoma characteristics have been recently described by us (i.e. advanced age, higher incidence in males, nodular melanoma being the commonest histological type in males) compared with other European countries (Lasithiotakis KG, Melanoma Unit, Dermatology Department, Medical School of Heraklion, University of Crete, Greece) [1]. Additionally, the Cretan population, being highly homogeneous and living in a defined geographical area, is useful for epidemiological research. To study epidemiological characteristics of CM and to assess the role of certain risk factors for CM development on Crete, we conducted a case-control study, including melanoma patients diagnosed in the last 4 years.

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2. Patients and methods

2.1. Study population

Cases eligible for inclusion in the study were all patients of Cretan origin, according to their grandparents' place of birth, admitted to the Melanoma Unit of the University Hospital of Crete, who had their first histopathologically-confirmed diagnosis of CM between January 1999 and November 2003. One hundred and ten age-(± 3 years) and gender-matched controls of Cretan origin were randomly included. Exclusion criteria for controls were: non-Cretan origin, positive family history of CM, positive cancer history, immunosuppressive therapies, or photosensitive diseases. Most of the controls were escorts or visitors of inpatients (91%) and 9% were outpatients of the University Hospital of Crete. CM patients' relatives were not selected as controls. All participants were interviewed using a standardised questionnaire and underwent a complete skin examination by the same two experienced dermatologists.

2.2. Diagnostic criteria and definitions of the variables

Pigmentation traits (hair colour, eye colour, skin phototype) were assessed; natural hair colour at the age of 20 years and eye colour were evaluated from the patients' history and by simple inspection of eyes, respectively. Skin phototype was graded into four levels (I–IV) according to Fitzpatrick's classification [2]. Common melanocytic naevus was classified as any melanocytic lesion of $\geqslant$ 2 mm in diameter fulfilling at least three of the following criteria: well-defined border, regular margins, uniformly light to dark brown colour and macular or papular surface. Clinical diagnosis of atypical melanocytic naevus was listed if at least three of the following characteristics were present: diameter of $\geqslant$ 5 mm, ill-defined border, margins which merge gradually with normal skin, irregular pigmentation within the lesion and papular and/or macular surface. Solar lentigines were defined as light brown to grey brown non-infiltrated pigmented lesions on sun-exposed anatomical sites, with finely irregular outline. Solar keratoses were defined clinically as superficial, rough scaly lesions with erythematous component and ill-defined margins in sun exposed anatomical sites. Sunburns in childhood (up to 18 years of age) were designated as episodes of intense erythema with or without blistering, causing pain and discomfort for more than two days. CM family history was considered positive if there was at least one first-degree relative with a reported diagnosis of CM. Since recreational sun exposure in Crete cannot be clearly distinguished from professional exposure (it is an agricultural, and fishing island with a large tourist industry), intermittent sun exposure is difficult to assess and was therefore not considered separately, but was incorporated in the total sun exposure value. Total sun exposure (professional and recreational) was quantified as the number of reported weeks per year when one was exposed to full daylight. Finally, the educational level (years in education) was also assessed. Hair colour, eye colour and skin phototype were considered as pigmentary traits. Total sun exposure (weeks per year), solar keratoses and solar lentigines were regarded as sun exposure indices.

2.3. Statistics

Comparisons of variable distributions between groups were performed using Chi-square or Fisher's exact test. Relative Risks were estimated using Odds Ratios (ORs) and the corresponding 95% Confidence Intervals (CIs) from cross-tabulation. For continuous variables, the independent samples *t*-test was used. In the univariate analysis, all *P* values calculated were two-sided and the significance level was 0.05. All variables found to be significant in the univariate analysis (at the 0.2 level) were entered into a conditional backward stepwise logistic regression model to determine independent risk factors for CM. All calculations were performed with the Statistical Package for Social Sciences (SPSS) version 11.5.

3. Results

From the 114 CM patients diagnosed between January 1999 and November 2003, 3 patients (3%) refused to participate in the study and 1 (1%) did not fulfill the inclusion criteria. In the control group, one person (1%) refused to participate and five (4%) were omitted due to the exclusion criteria. So, 110 newly diagnosed CM patients and the same number of controls were included in the study. The distribution of CM patients according to gender-age, histopathological characteristics and anatomical site of the tumour is displayed in Table 1.

The male to female ratio was approximately 1:1 and ages ranged from 19 to 88 years for patients and 19 to 85 years for controls (mean ± SD, 56.1 ± 16.9 years for patients and 55.7 ± 16.5 years for controls; $P = 0.853$). The educational level was comparable between cases and controls ($P = 0.175$) (Table 2). Fair hair (red/blonde) and eyes (green/blue/grey) (OR 3.9 and 1.9, respectively, $P < 0.05$) and skin phototypes I and II (OR 2.9, $P < 0.05$) were associated with a significantly increased CM risk. CM risk was significantly related to the number of common melanocytic naevi (OR 8.5 for more than 25 naevi) ($P < 0.001$), with a highly significant trend for increasing numbers of naevi ($P < 0.01$) (Table 3). At least one atypical naevus was found four times more often in melanoma patients than in controls

Table 1
Distribution of 110 melanoma patients according to gender, age, tumour pathological variant, thickness and anatomical site

	Males *n* (%)	Females *n* (%)
Age (years)		
<31	3 (6)	5 (9)
31–60	24 (45)	28 (49)
>60	26 (49)	24 (42)
Histogenetic type		
In situ	2 (4)	6 (11)
Superficial spreading	17 (32)	26 (46)
Nodular	17 (32)	11 (19)
Lentigo maligna	8 (15)	6 (11)
Acral	3 (6)	3 (5)
Other	6 (11)	5 (9)
Tumour thickness (mm)[a]		
0–1	15 (33)	30 (56)
1.1–2	11 (24)	8 (15)
2.1–4	12 (27)	9 (17)
>4.1	7 (16)	7 (13)
Anatomical site		
Head/neck	12 (23)	8 (14)
Trunk	23 (43)	16 (28)
Upper limb	8 (15)	8 (14)
Lower limb	9 (17)	24 (42)
Unknown origin	1 (2)	1 (2)

[a] Some data are missing.

Table 2
Distribution of 110 melanoma patients and 110 controls according to age and educational status

	Patients *n* (%)	Controls *n* (%)	*P*[a] value
Age (years)			
<31	8 (7)	9 (8)	0.853
31–40	16 (15)	15 (14)	
41–50	11 (10)	13 (12)	
51–60	25 (23)	26 (24)	
61–70	31 (28)	23 (21)	
71–80	14 (13)	20 (18)	
>80	5 (5)	4 (4)	
Years in education			
⩽6	63 (57)	51 (46)	0.175
7–16	31 (28)	34 (31)	
>16	16 (15)	25 (23)	

[a] Pearson's χ^2 two-tailed significance.

(OR 4.9, $P < 0.01$). Solar keratoses and solar lentigines were revealed as significant risk factors in the univariate analysis with ORs of 4.0 and 2.8, respectively ($P < 0.05$) (Table 3).

Sunburns during childhood raised the CM risk (OR 1.5), but this trend did not reach statistical significance ($P = 0.173$). In addition, CM patients reported more total sun exposure per year than controls (mean ± SD, 21.5 ± 14.2 *vs* 16.6 ± 14.2, respectively, $P = 0.013$). Finally, a positive CM family history significantly increased the risk for melanoma (OR 23.6, $P < 0.01$), but a very wide confidence interval indicated this OR was probably an inaccurate estimation (Table 3).

The final results of the backward stepwise logistic regression analysis are shown in Table 4. A significant association was demonstrated between melanoma and all variables entered in the first step of analysis, except for eye colour and childhood sunburn history. Solar keratoses (OR 6.2, $P = 0.001$), solar lentigines (OR 2.2, $P = 0.032$) and total sun exposure (weeks per year) (OR 1.03, $P = 0.025$) all independently raised the CM risk. Pigmentary traits, blonde or red hair colour (OR 3.1, $P = 0.045$) and skin phototype I/II (OR 1.8, $P = 0.091$) appeared to increase the risk for the development of CM. The existence of a high number (> 25) of common melanocytic nevi (OR 5.4, $P = 0.001$) and the existence of atypical naevi (OR 3.0, $P = 0.025$) significantly increased the melanoma risk.

4. Discussion

The study of melanoma epidemiology and the identification of risk factors predisposing to CM in Mediterranean countries is increasingly gaining interest [3,4]. Differences in phenotypic traits might in the near future reveal genotypic particularities. In this way, our current knowledge concerning this notorious disease may be supplemented and this data could aid in both prevention and treatment strategies.

Epidemiological studies have shown repeatedly that exposure to sunlight is the major environmental risk factor for the development of melanoma in individuals with a fair-skinned complexion [5]. However, the measurement of sun exposure is extremely complex and there are no accepted definitions of different types of sun exposure, categorisations of level and intensity [6]. Furthermore, the relationship between sun exposure and melanoma is complex, in terms of a lack of a clear dose–response association, latent period, body site distribution of CM, histogenetic melanoma types and many other factors [7]. In the present study, it was shown that sun exposure risk indicators [total sun exposure (weeks per year), solar keratoses, solar lentigines] all independently raised the CM risk in a Cretan population (Table 4). In studies where patients with lentigo maligna melanoma (LMM), that is known to be associated with total amount of sun exposure, have been excluded, chronic sun exposure indices were associated with a decreased risk for CM [8,9]. However, when the LMM ($n = 14$) cases were removed in our study and the CM sample re-analysed (now 96 cases), the independent risk factors and their respective ORs remained approximately the same, except for atypical naevi that showed an increase in the OR from 3.0 to 4.7 (data not shown). There are also studies that have found no

Table 3
Risk factors for cutaneous melanoma (CM) (univariate analysis)

	Patients *n* (%)	Controls *n* (%)	Odds Ratio (OR)	95% CI[a] for OR	*P*[b] value
Hair colour					
Blonde/red	23 (21)	7 (6)	3.9	1.5–10.5	0.002
Black/brown	87 (79)	103 (94)			
Eye colour					
Green/blue/grey	45 (41)	30 (27)	1.9	1.0–3.4	0.033
Black/brown	65 (59)	80 (73)			
Skin phototype					
I/II	63 (57)	35 (32)	2.9	1.6–5.2	0.0001
III/IV	47 (43)	75 (68)			
Solar lentigines					
Yes	82 (75)	56 (51)	2.8	1.5–5.2	0.0001
No	28 (25)	54 (49)			
Solar keratoses					
Yes	29 (26)	9 (8)	4.0	1.7–9.7	0.0001
No	81 (74)	101 (92)			
Common naevus count					
0–11	32 (29)	66 (60)	1.0		0.006[c]
12–25	37 (34)	34 (31)	2.2	1.1–4.4[d]	
>25	41 (37)	10 (9)	8.5	3.5–20.7[e]	
Atypical naevus					
Yes	39 (35)	10 (9)			
No	71 (65)	100 (91)	4.9	2.3–11.2	0.0001
CM family history					
Yes	10 (9)	0 (0)	23.6	1.3–399	0.002[f]
No	100 (91)	110 (100)			
Sunburns in childhood					
Yes	68 (62)	58 (53)	1.5	0.8–2.6	0.173
No	42 (38)	52 (47)			
Total sun exposure (weeks per year) (mean ± SD)	21.5 ± 14.2	16.6 ± 14.2	–	–	0.013[g]

SD, standard deviation.
[a] 95% Confidence Interval.
[b] Pearson's χ^2 two-tailed significance.
[c] χ^2 test for trend.
[d] $P = 0.024$.
[e] $P < 0.001$.
[f] Fisher's exact test.
[g] Independent samples *t*-test.

association between long-term occupational sun exposure and melanoma risk, even though all histological types of melanoma were included [10,11]. A major limitation of all of the epidemiological studies performed is that the dosages of sun exposure have been assessed at the skin surface, while the biologically relevant dose is presumably the one reaching the basal cell layer of the epidermis [6,12].

It has been hypothesised that the risk of CM is related to episodes of intermittent and intense sun exposure of usually unexposed skin. This hypothesis aimed to explain epidemiological results regarding the anatomical distribution of CM [11]. However, even in our study, where we have found that total sun exposure predisposes to CM, the localisation of melanomas on the trunk is frequent both in males and females (Table 1). This might be explained by the theory of melanocytic instability proposed by Green which claims that the trunk has less stable melanocytes so mutagenesis and tumour promotion could occur more easily at these sites [13]. In any case, many previous studies have claimed that in areas with a high natural sun irradiation, where

Table 4
Independent risk factors for melanoma on Crete provided by the logistic regression analysis

	OR[a]	95% CI[b] for OR	*P* value
Hair colour			
Black/brown	1.0	–	
Blonde/red	3.1	1.02–9.3	0.045
Skin phototype			
III/IV	1.0	–	
I/II	1.8	0.9–3.7	0.091
Solar lentigines			
No	1.0	–	
Yes	2.2	1.1–4.6	0.032
Solar keratoses			
No	1.0	–	
Yes	6.2	2.2–17.4	0.001
Common naevus count			
0–11	1.0	–	0.001
12–25	1.7	0.6–4.7	0.280
>25	5.4	1.9–14.9	0.001
Atypical naevus			
No	1.0	–	
Yes	3.0	1.1–7.7	0.025
Total sun exposure (weeks per year)	1.03	1.004–1.06	0.025

[a] Odds ratio. Adjusted for presence of solar lentigines, solar keratoses, skin phototypes, eye colour, hair colour, the presence of atypical naevi, number of common melanocytic naevi, total sun exposure (weeks per year), sunburns in childhood and educational level.
[b] 95% Confidence Interval for the Odds ratio.

no clear distinction exists between chronic and intermittent exposure, the results are difficult to interpret [6,14,15].

In our study, we found a positive association between sunburns before 18 years of age and CM even though it did not reach statistical significance (Table 3). Our findings are comparable with those reported in a recent multicentre study from Italy [3].

Solar keratoses are more frequent in men and in sun-sensitive subjects exposed to sun [16]. They are associated with both chronic sun exposure and a history of painful sunburns before adulthood and are significant risk indicators for both melanoma and squamous cell carcinoma [17]. The association between solar keratoses and melanoma remains even when superficial spreading and nodular melanoma are considered separately from LMM which is mostly related with chronic sun exposure [18]. In our study, solar keratoses proved to be the most significant independent risk factor for CM.

Solar lentigines frequently follow a history of prolonged sun exposure and tend to persist indefinitely, being more prevalent in older patients. Data similar to ours, regarding the presence of solar lentigines, have been reported in case-control studies from Central and Southern Europe [3,19,20].

Hair colour, eye colour and skin phototype were evaluated in this study as indicators of the pigmentary status (pigmentary traits) and indirect measures of skin susceptibility to sunlight. Amongst these, hair colour and skin phototype were found to be independent risk markers for CM. Our findings are in line with those reported in a recent systematic review of 10 case-control studies on a total of 3000 cases and 4000 controls, as well as with data from the latest prospective study from Northern Europe, analysis a population of more than 100,000 women [21,22].

The total number of melanocytic naevi on the body is a major risk factor for CM in Caucasian populations [3,19,23]. Additionally, histological remnants of melanocytic naevi are present in up to 20–60% of all CMs, so that they are considered to be precursor lesions of a substantial proportion of CMs [20,24]. In our study, we found a strong relationship between common naevi and CM that is qualitatively comparable with the results reported elsewhere [3,20]. However, the magnitude of this relationship is difficult to assess due to the different techniques that have been utilised for counting naevi and the different sampling schemes for cases and controls. Lower odds ratios were calculated generally in our study for the common naevi–melanoma relationship than those that have been reported from studies of Northern European populations [20].

Similar to common melanocytic naevi, the number, and even the presence of atypical naevi represents a significant independent risk marker for CM [20]. In melanoma–prone families, prospectively diagnosed melanomas have arisen in association with a histopathologically-confirmed dysplastic naevus in more than 80% of cases [25]. Outside of the context of familial CM, several studies in 'white' populations have found atypical naevi to be associated with CM with a corresponding Relative Risk ranging from 2.4 for at least one atypical naevus to 32 for 10 or more atypical naevi [21,26]. In our study, the presence of at least one atypical naevus was independently associated with CM (OR 3.0, $P = 0.025$) (Table 4). For the same reasons mentioned above for common naevus count, it was very difficult to compare our results with those of others, even with those reported for Mediterranean populations. For example, in the study of Landi and colleagues [4] a much lower OR for the development of CM was estimated for the presence of atypical naevi. In that study, the frequency of atypical naevi among controls was approximately two times greater than ours and the mean age of patients and controls approximately 10 years younger.

In conclusion, in the relatively dark-skinned Cretan population, indices of chronic sun exposure (solar keratoses, solar lentigines, and total sun exposure measured

in weeks per year) appeared to be the most important risk markers for CM, whereas in studies reported for the fair-skinned populations of Europe, America and Australia, melanocytic naevi and intermittent sun exposure are the main risk factors for CM.

Conflict of interest statement

The author have no conflict of interest to disclose.

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