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Risk factors for developing cutaneous melanoma in Santa Catarina, Brazil: a case-control observational study

Abstract

Background: Cutaneous melanoma (CM) is a highly metastatic neoplasia with a rapidly increasing incidence worldwide. The incidence rate is particularly high in western Santa Catarina, Brazil. Studies identifying risk factors for CM in Brazil remain limited. The aim this study was to identify risk factors for the development of CM in this region.

Methods: Case-control observational study of 518 people in western Santa Catarina, including 259 patients diagnosed with CM between 2002 and 2012, and 259 age-, sex-, and residence-matched controls. Pigmentation characteristics, presence and size of nevi and history of cutaneous neoplasia, sun exposure, and sunburn were evaluated. Data were subjected to univariate and multiple logistic regression (MLR) analyses.

Results: Significant independent risk factors for CM included: atypical melanocytic nevi (odds ratio [OR]:16.02;(95%CI4.48-57.32)p<0.001), multiple melanocytic nevi (OR:4.82;(95%CI2.91-7.98)p<0.001), personal history of non-melanoma skin cancer(OR:2.40;(95%CI1.10-5.23)p=0.0028), family history of CM (OR:2.19;(95%CI1.11-4.30),p=0.024), and occupational sun exposure(OR:2.76;(95%CI1.80-4.25)p<0.001).When analyzed in an associated way, sunburn in both childhood/adolescence and adulthood was a risk factor.

Conclusion: Atypical or multiple melanocytic nevi, personal history of non-melanoma skin cancer, family history of cutaneous melanoma, and occupational sun exposure were significant independent risk factors for CM in western Santa Catarina, Brazil.

Keywords: melanoma, epidemiology, risk factors, skin neoplasms, environmental exposure, Brazil

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Abbreviations: CM, cutaneous melanoma; UV, ultraviolet; NMSC, non-melanoma skin cancer; Ors, odds ratios; CIs, confidence interval; MLR, multiple logistic regression SD, standard deviation

Introduction

As with most types of malignant neoplasia, cutaneous melanoma (CM) has a multi factorial etiology, with a genetic-environmental interaction.[1] Exposure to ultraviolet (UV) radiation is a risk factor for CM in people with light skin. Age at first sun exposure and history of sunburn in childhood/adolescence appear to have a large influence.[2] Recognized clinical findings associated with neoplasia development include pigmentation characteristics, such as light skin, eyes, and hair, and the presence of ephelides.[3–9] Melanocytic nevi, especially atypical, multiple, or congenital nevi, are also important risk factors.[10,11]

The incidence of CM has been rapidly increasing in the last few decades. Annual increases of 4% to 8% have been recorded in Caucasians, representing relatively high rates among all cancer types.[2,12] Rates vary in different countries and regions. According to the National Cancer Institute in Brazil, estimates of CM incidence for the year 2012 were 6,230 new cases (3,170 men and 3,060 women), with the highest incidence found in southern Brazil.[13] In the western area of Santa Catarina, the incidence and prevalence of CM are greater than the national rates. Between 2002 and 2009, the prevalence was 71.5 cases per 100,000 inhabitants. In 2008, the incidence was 12.2 cases per 100,000 inhabitants.[14] Brazil has also experienced an increase in CM-related mortality, especially in certain areas of the country.[12,13]

It is important to understand the epidemiology of CM for each area of Brazil. However, few case-control studies have addressed this issue, and there is considerable variation in the published results.[15] An absence of compulsory notification/registration and negligence in areas of low cutaneous tumor incidence has led to a paucity of epidemiological information.[16] Therefore, in this study, we sought to identify risk factors for the development of CM in western Santa Catarina, Brazil.

Materials and methods

We performed a case-control study of the population base to identify various risk factors related to the etiology of CM. We compared 259 patients with primary CM living in the western area of Santa Catarina, Brazil, to 259 controls that were paired by age, sex, and residence of origin. All CM cases were initially diagnosed with CM between 2002 and June 2012. CM diagnoses were confirmed by his to pathological exam. Controls were randomly selected from among patients attending a general medical consultation in the public health system, without any dermatological complaints. Four professionals with experience in dermatological exams evaluated the clinical characteristics of the patients.

Photo type was defined using the Boston Classification, following Fitzpatrick,[17] through the question: "What reaction does your skin have when exposed to sun in the middle of the day without sunscreen?". Only photo types I and II were encountered among the cases; therefore, only these photo types were included in the study. For eye and hair color, we considered the natural color. Presence of ephelides in the past or present was considered positive. A typical melanocytic nevi were included only when his to logically confirmed. Congenital nevi were defined as brown-to-black melanocytic maculae or papillae, which were reasonably well-defined and present at birth. We classified them according to size, as small (<3cm²) and large (>3cm²). Multiple nevi were considered as common melanocytic nevi and divided into two groups based on their number: <50 and ≥50 melanocytic nevi. We researched the personal history of non-melanoma skin cancer (NMSC) and family history of CM with the patient and/or family members.

An episode of sunburn was defined by the presence of intense, painful erythema, with or without blisters. When present, it was classified according to the phase of life when it occurred: childhood/adolescence (≤20 years), adulthood, or both. We considered occupational sun exposure to be significant when the person spent most of their working time exposed to the sun over the previous 5 years.

Data were analyzed using odds ratios (ORs) and95% confidence interval (CIs). Initially, we performed a univariate analysis by calculating the raw ORs for all variables as estimates of the relative risk for developing CM. Then, we inserted all of the variables that were statistically significant by univariate analysis into a multiple logistic regression (MLR) model, to control for confounding factors and to determine the independent risk factors for developing CM. Findings were considered statistically significant for $P \leq 0.05$.We used the SPSS v19.0 software for all calculations. The Research Ethics Committee at the Community University of the Chapecó Area (Community University of the Region of Chapeco, Unochapeco) evaluated and approved the research as case number 068/07.

Results

More men were present in both groups, in a proportion of 3:2(108 women and 151 men for cases;106 women and 153 men for controls). Age at initial CM diagnosis ranged from 17 to 89 years (mean±standard deviation [SD], 49.8±14.4 years for cases and 49.8±14.7 years for paired controls; P=0.995). Table 1 shows the results for the univariate analysis of pigmentation characteristics, presence and size of nevi, and history of cutaneous neoplasia, sun exposure, and sunburn in the two groups. Light eyes and hair and the presence of ephelides were less prevalent in cases, but these results were not significant.

Atypical and multiple melanocytic nevi were significantly more prevalent in cases compared to controls. Most subjects had <50 nevi over their whole body. Instances of ≥50 nevi were more prevalent in cases compared to controls. Congenital nevi were significantly more prevalent in cases compared to controls, with a prevalence of small congenital nevi in both groups. A positive family history for CM and significant occupational sun exposure were more prevalent in the case group. History of sunburn was heterogeneous between groups, with most individuals in both groups reporting at least one episode of sunburn in their lives. Cases had a predominance of sunburn in both childhood and adulthood. For controls, the predominant phase for sunburn was adulthood.

Table 2 shows the results of MLR analysis of the significant findings from the univariate analysis. Several risk factors were identified as independent for development of CM, including atypical melanocytic nevi, multiple melanocytic nevi, personal history of non-melanoma skin cancer (NMSC), family history of CM, and significant occupational sun exposure.

Table 1 Univariate analysis of pigmentation characteristics, presence/size of nevi, and history of cutaneous neoplasia, sun exposure, and sunburnin cases (n = 259) and controls (n = 259)

Characteristic	Cases	Controls	OR (95% CI)1	p-value[1]
Eye color[a]				
Dark	120(46.3)	102(39.4)	1*	0.11
Light	139(53.7)	157(60.6)	0.75(0.53-1.07)	
Hair color[b]				
Dark	129(49.8)	117(45.2)	1*	0.291
Light	130(50.2)	142(54.8)	0.83(0.59-1.17)	
Ephelides				
Not present	160(61.8)	174(67.2)	1*	0.199
Present	99(38.2)	85(32.8)	1.27(0.88-1.82)	
Atypical melanocytic nevi				
Not present	223(86.1)	256(98.8)	1*	<0.001
Present	36(13.9)	3(1.2)	13.78(4.18-45.35)	
Multiple melanocytic nevi				
Not present	157(60.6)	226(87.3)	1*	<0.001
Present	102(39.4)	33 12.7)	4.45(2.86-6.92)	
<50	65(25.1)	26(10.0)	3.59(2.19-5.92)	
>50	37(14.3)	7(2.7)	7.61(3.31-17.50)	
Congenital melanocytic nevi				
Not present	194(74.9)	221(85.3)	1*	0.003
Present	65(25.1)	38(14.7)	1.95(1.25-3.04)	
Small	44(17.0)	33(12.7)	1.52(0.93-2.48)	
Large	21(8.1)	5(1.9)	4.79(1.77-12.93)	
Personal history of NMSC				
No	226(87.3)	247(95.4)	1*	0.001
Yes	33(12.7)	12(4.6)	3.01(1.52-5.96)	
Family history of CM				
No	222(85.7)	240(92.7)	1*	0.011
Yes	37(14.3)	19(7.3)	2.11(1.18-3.77)	
Occupational sun exposure				
Small	83(32.0)	139(53.7)	1*	<0.001
Great	176(68.0)	120(46.3)	2.46(1.72 - 3.51)	
History of sunburn				
None	58(22.4)	67(25.9)	1*	<0.001
Childhood/ adolescence	23(8.9)	22(8.5)	1.21(0.61-2.39)	
Adult	57(22.0)	125(48.3)	0.53(0.33-0.84)	
Both	121(46.7)	45(17.4)	3.11(1.90-5.07)	

Data for cases and controls are number (%). aDark (black or brown), light (blue or green); bDark (black or brown), light (blond or red). I Calculated by chi-squared test; *Reference category.

OR, odds ratio; CI, confidence interval; NMSC, non-melanoma skin cancer; CM, cutaneous melanoma

Table 2 Multiple logistic regressions with the OR adjusted for CM

Characteristic	OR (95% CI)	*p*-value
Atypical melanocytic nevi		
Not present	1*	
Present	1 6.02(4.48-57.32)	<0.001
Multiple melanocytic nevi		
Not present	1*	
Present	4.82(2.91-7.98)	<0.001
Personal history of NMSC		
No	1*	
Yes	2.40(1.10-5.23)	0.028
Family history of CM		
No	1*	
Yes	2.19(1.11, 4.30)	0.024
Occupational sun exposure		
Small	1*	
Great	2.76(1.80-4.25)	<0.001

History of sun exposure during a person's lifetime was controlled in the logistic regression model. *Reference category.

OR, odds ratio; CI, confidence interval; NMSC, non-melanoma skin cancer; CM, cutaneous melanoma

Discussion

People with light iris color (OR:1.62), light hair color (OR:1.78),[18] or ephelides (OR:1.99)[19] have been shown to be at greater risk of developing CM than people with dark phenotypes. However, the distribution of pigmentation characteristics can vary within different populations, affecting risk estimates. Moreover, the ORs are lower after adjusting for phenotype, suggesting a significant correlation between these factors.[3,18,20] Similar to our findings, a previous study of 244 cases and 276 controls in an Australian Caucasian population showed that light hair and eye colors and the presence of ephelides in childhood did not have a relationship with CM.[21]

Pigmentation and photo type are both related to the quantity and type of cutaneous melanin. Their interrelationship can make it difficult to evaluate their individual contributions to CM risk, and either can be a confounding factor.[18] Hair and eye color and the presence of ephelides cannot be in a direct causal relationship with CM.[3,18] People with lighter skin predominate in western Santa Catarina because of a high concentration of descendants of Western and Central European immigrants and low levels of miscegenation.[22–25] This phenotypic homogeneity (predominance of photo types I and II) for the population might explain the non significance of the findings.

The presence of atypical, large or multiple melanocytic nevi has been associated with a significant risk of developing CM.[10,26–29] Previous meta-analyses have reported ORs ranging from 3.63 to 6.52 for the presence of one or more atypical nevi.[10,27,29] We obtained high ORs and CIs for the presence of atypical nevi, due to the inclusion of only Histologically proven nevi. We might have overlooked atypical nevi in the control group, given that these people did not have a diagnosis of CM, did not seek dermatological care, and had smaller cutaneous lesions on biopsy. In addition, because we did not include clinically diagnosed atypical nevi, the number of these nevi in the case group might have been lower, resulting in a higher CI. A previous case-control study showed that the presence of multiple nevi influenced the risk of developing CM in direct proportion to the number of lesions, with ORs 2.8 and 4.2 for <50 and ≥50 nevi, respectively.[26] A meta-analysis found similar results.[10] The presence of large melanocytic nevi has been identified as an important risk factor, with ORs of 2.9 and 7.1 for 1 to 2 nevi and ≥3 nevi, respectively.[27] However, these variables were only analyzed by univariate analysis in the present study.

Nevus lesions may be evaluated by various clinical evaluation methods. In a hospital environment, nevus counting is performed. Nevus counting is an easy exam and, therefore, is more reliable than methods used in studies with a population base, resulting in lower ORs. Categorization also influences the results, with higher ORs being obtained in studies that use only dichotomous variables (i.e., that consider only the presence or absence of a lesion and not the number of lesions).[10] This observation might explain the higher OR found for atypical melanocytic nevi.

A personal history of NMSC is considered a strong risk factor for CM, with a previous meta-analysis demonstrating an OR of 3.92.[18] A family history of CM is one of the most important risk factors for developing the disease.[30] We found that the effect of family history on the risk of CM was independent of pigmentation characteristics and nevi count. Similarly, a previous meta-analysis found an OR of 1.74(95% CI:1.41, 2.14) for individuals with a family history of CM in one or more first-degree relatives,[18] a cohort study reported an OR of 2.19(95% CI:1.60-2.99) for individuals with a family history of CM[8], and a combined analysis of eight case-control studies in white populations reported an OR of 2.24(95% CI:1.76-2.86) in people who reported at least one first-degree relative with CM compared to individuals without such a history.[31]

Many studies in the northern hemisphere evaluating the association between CM and sun exposure have demonstrated a higher risk of developing CM when the skin has intermittent UV exposure. These studies have generally found that occupational exposure is not a risk factor. In other studies, the reverse was described: the greater the intensity and duration of sun exposure, the lower the risk of developing CM.[1,32–33] However, it is unlikely that this association means that exposure confers protection against CM.[33]

In this study, occupational sun exposure was an independent risk factor for CM development. One explanation for this finding might be the predominantly rural nature of the area under study (in some cities, >70% of the population lives in rural areas).[24,34] The main economic activity of this area is agricultural. Many subjects reported professions involving chronic sun exposure, such as agriculture and livestock. Another possible contributing factor might be the geographical location of western Santa Catarina, which is situated between parallels 26º and 27ºS. This location is similar to Australia (Queensland is between 26º and 29ºS), which has the highest rates and prevalence of CM in the world.[35–37]

We verified an increased risk for CM when sunburn episodes occurred both in a person's adulthood and childhood/adolescence. This result is in contrast to other studies, which found a higher risk for CM when sunburn episodes were just in childhood/adolescence.[27,38] In the present study, sunburn episodes were subjected to an indirect

quantitative analysis, which may explain the discrepancy between the findings. A person who reported sunburn both in childhood and adulthood ostensibly had more sunburn episodes and, therefore, a higher risk of developing CM.

That a history of sunburn in adulthood was not a risk factor can be explained by the low latitude of the area, with a predominance of photo types I and II and agro industrial economic activity. More than two-thirds of subjects, in both groups, reported having been sunburned at some point in their lives. However, in the case group, sunburn in both childhood and adulthood was predominant. These findings suggest that the risk of developing CM is more related to the total number of sunburns than to the period in which they occur. Similarly, a recent meta-analysis of 51 studies concluded that a greater number of sunburns were associated with a greater risk of CM, independent of when they occurred.[39]

Sun exposure and sunburn are variables that are difficult to evaluate and open to bias, leading to different results in different studies. During the interview, many people could not remember whether, when, or how often they had experienced sunburn episode(s) in their lives. Patients with CM were generally more attentive to factors related to the sun, because they were aware of the risks of the disease. The place where the study was performed is also important, as data from the control group collected in a hospital environment could be to data obtained from individuals who have a dermatological complaint. Finally, the widely differing method used by different studies makes it difficult to compare results from different populations.[1,33,39]

Conclusion

Atypical or multiple melanocytic nevi, a personal history of NMSC, a family history of CM, and extensive occupational sun exposure were identified as independent risk factors for developing CM in the western area of Santa Catarina, Brazil. When analyzed in an associated way, the presence of sunburn episodes in both childhood/adolescence and in adulthood was also a risk factor. However, pigmentation characteristics, such as eye and hair color, and the presence of ephelides did not present a significant risk, as photo types I and II were predominant in both groups.

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Conflict of interest

The author declares no conflict of interest.

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