Epidemiological aspects of melanoma at a university hospital dermatology center over a period of 20 years*

Aspectos epidemiológicos do melanoma em serviço de dermatologia de hospital universitário em um período de 20 anos

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DOI: http://dx.doi.org/10.1590/abd1806-4841.20131855

Abstract: BACKGROUND: The incidence of melanoma has been steadily rising in past decades. Although it accounts for only 3% of all skin cancers, it is responsible for 75% of deaths. OBJECTIVE: to describe the epidemiological aspects of melanoma in a university hospital setting over a period of 20 years. METHODS: A total of 166 patients were analyzed between January 1990 and January 2010 for clinical and histological variables and correlations between them. A 5% level of significance was adopted. RESULTS: The majority of patients were Caucasians (74%), females (61%), with a mean age at diagnosis of 55. The predominant histological type was lentigo maligna/lentigo maligna melanoma (35.7%) and the head and neck was the most affected site (30.7%). Among non-Caucasians, the acral region was the most affected. Most tumors were in situ (41.1%). Growth of the lesion was the most frequent complaint (58.1%) and bleeding was most frequently associated with melanomas with a depth > 4mm. There were seven deaths (4.2%), with a high risk among men, non-Caucasians and those under 20 years of age, with a Breslow's depth > 2mm, with lentiginous acral melanoma and with a history of growth and bleeding. CONCLUSIONS: Our sample differs from most of the studies in the predominant location (head and neck), histological type (lentigo maligna/ lentigo maligna melanoma) and a major risk of death under the age of 20, which could be with a reflex of regional variation. Broader studies are necessary for validation of the results.
Keywords: Epidemiology; Lentigo; Melanoma

Resumo: FUNDAMENTOS: A incidência do melanoma cutâneo aumentou nas últimas décadas. Embora represente 3% dos tumores cutâneos, é responsável por 75% dos óbitos. O diagnóstico precoce constitui a principal chance de cura. OBJETIVO: Descrever os aspectos epidemiológicos do melanoma em hospital universitário em 20 anos. MÉTODOS: Avaliaram-se 166 pacientes no período de janeiro de 1990 a janeiro de 2010, quanto às variáveis epidemiológicas, histológicas e óbitos relacionados ao melanoma e suas correlações. Adotou-se nível de significância de 5%. RESULTADOS: A maioria dos pacientes era brancos (74%), mulheres (61%), com média de idade ao diagnóstico de 55 anos. O tipo histológico predominante foi o lentigo maligno/lentigo maligno melanoma (35,7%) e a localização mais frequente foi a cabeça e o pescoço (30,7%). Entre os não-brancos, a região acral foi a mais acometida. Quanto à espessura tumoral, a maioria dos melanomas era in situ (41,1%). O crescimento da lesão foi a queixa mais frequente (58%) e o sangramento foi mais associado a melanomas espessos. Ocorreram sete óbitos (4,2%), com maior risco de morte em menores de 20 anos e naqueles com história de sangramento, após análise multivariada. CONCLUSÃO: Esta casuística difere da maioria dos estudos em relação à localização (cabeça e pescoço), ao tipo histológico (lentigo maligno/lentigo maligno melanoma) e ao maior risco de óbito em menores de 20 anos, o que pode ser devido à variação regional. Estudos mais amplos são necessários para validação destes resultados.
Palavras-chave: Epidemiologia; Lentigo; Melanoma

Received on 06.05.2012
Approved by the Advisory Board and accepted for publication on 07.08.2012.
* Work performed at the Dermatology Service at Federal University of Minas Gerais Hospital (HC-UFMG) – Belo Horizonte (MG), Brasil.
Financial Support: None.
Conflict of Interest: None.

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INTRODUCTION

The incidence of cutaneous melanoma (CM) has increased continuously in recent decades around the world.[1] The highest rates, 40 to 60 cases per 100,000 inhabitants, are found in Australia and New Zealand.[2,3] In the USA, the incidence of CM rose from 8.7 to 26.5 per 100,000 inhabitants from 1975 to 2007, an increase of 300%.[4] In Brazil, the estimated incidence of CM for 2010, according to the National Cancer Institute (INCA) varies from 3.04 to 3.72 per 100,000 men and 2.92 to 3.04 per 100,000 women, with the highest rates in the Southern region of the country.[5]

In recent years, survival rates have improved, probably due to earlier diagnosis.[3,5] Two thirds of all cases of CM diagnosed in the USA between 1988 and 1999 had a tumor thickness of < 1 mm, while the proportion of CM ≥ 2 mm remained stable.[6]

Various environmental and constitutional risk factors are found to be associated with CM. Among the former, intermittent exposure to sunlight, especially that which results in burns accompanied by blisters during childhood, has been referred to as the most relevant.[7,8] As for constitutional risk factors, of note are lighter phototypes (types I and II on the Fitzpatrick scale), congenital nevus, multiple acquired common or atypical melanocytic nevi, a personal and/or family history of CM, xeroderma pigmentosum, a personal history of other skin cancers and immunosuppression.[9,10]

The more refined knowledge of the epidemiological and histological characteristics of CM may be reflected in the approach taken towards it, especially favoring early diagnosis.

MATERIAL AND METHODS

One hundred and sixty-six patients from the dermatology center at a university hospital were diagnosed with CM from January of 1990 to January of 2010. The sample was defined for convenience.

The following clinical variables were analyzed: sex, age at diagnosis (< 20, 21-40, 41- 60 and > 60), skin color (white and non-white), body location (head and neck, trunk, upper limbs, lower limbs, acral regions and others), atypical nevi (none, < 10 and > 10), non-melanoma skin cancer, non-cutaneous cancer, family history of CM, symptoms and/or signs (bleeding, itching, pain and burning sensation, changes in color or size), metastasis and deaths.

The histological variables analyzed were: histological type (superficial spreading melanoma [SSM], nodular melanoma [NM], acral-lentiginous melanoma [ALM], lentigo maligna / lentigo maligna melanoma [LM/LMM] and others), tumor thickness (in *situ* ≤1 mm, 1.01-2 mm, 2.01–4 mm and >4 mm) and the level of invasion or Clark level (in *situ* or I, II, III, IV and V).

A significance level of 5% was considered. The variables were compared based on the Chi-squared test and Fisher Exact test.

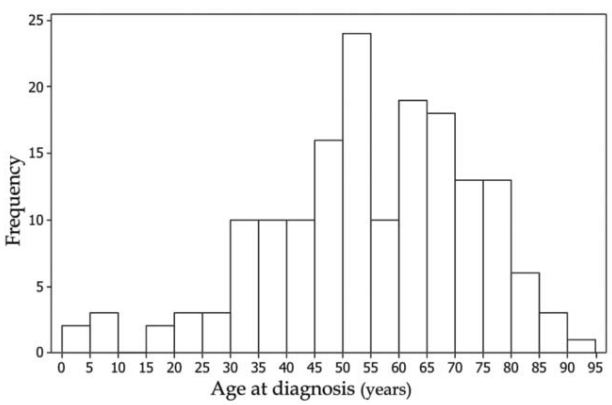
The progression towards death was evaluated based on survival analysis techniques. Only deaths resulting from CM were considered. A univariate analysis was performed utilizing the log-rank test and the multivariate analysis was conducted using the Cox model.

This study was approved by the Research Ethics Committee, and terms of free and informed consent were duly collected.

RESULTS

In the sample assessed, 101 patients (61%) were women and 65 (39%) were men. The mean age at diagnosis was 55, with standard deviation of 18,2 years. The minimum age was one year and the maximum 92 years (Graph 1). The sample consisted of 120 whites (74%) and 42 non-whites (26%).

Regarding body location, 30.7% of the patients presented CM on the head and neck, 21.1% on the trunk, 19.3% in acral regions, 15.1% in the upper limbs and 9.6% on the lower limbs. In a comparison between genders, the men presented a higher proportion of MM on the head and neck (35.3%), followed by the trunk (29.2%). Among the female patients, the extremities (upper and lower limbs) were the most frequent site (34.7%), followed by the head and neck (27.7%). The women presented more affected areas on the lower limbs (13.9%) than the men (3.1%), while among men CM affected the trunk more (29.2%) than among women (15.8%). The white patients had a greater proportion of CM on the head and neck (35.9%), followed by the trunk (25.8%). Among non-



Graph 1: Histogram of age at diagnosis

Table 1: Comparison between location and sex, skin color, age at diagnosis, histological type and signs and symptoms

Characteristics	Location												p-value
	Head and neck		Acral		Trunk		Upper limb		Lower limb		Others		
	N	%	N	%	N	%	N	%	N	%	N	%	
Sex													
Male	23	35.3	13	20.0	19	29.2	4	6.2	2	3.1	4	6.2	0.006[1]
Female	28	27.7	19	18.8	16	15.8	21	20.8	14	13.9	3	3.0	
Skin color													
White	43	35.9	10	8.3	31	25.8	21	17.5	12	10.0	3	2.5	<0.001[1]
Non-white	7	16.7	21	50.0	4	9.5	4	9.5	4	9.5	2	4.8	
Age at diagnosis													
1)<20	1	14.2	1	14.3	2	28.6	2	28.6	0	0.0	1	14.3	...
21-40	8	28.5	5	17.9	7	25.0	4	14.3	1	3.6	3	10.7	
41-60	19	30.1	10	15.9	15	23.8	9	14.3	8	12.7	2	3.2	
>60	23	33.8	16	23.5	11	16.2	10	14.7	7	10.3	1	1.5	
2) ≤40	9	25.7	6	17.1	9	25.7	6	17.1	1	2.9	4	11.5	0.151[1]
>40	42	32.1	26	19.8	26	19.8	19	14.5	15	11.5	3	2.3	
3) ≤60	28	28.6	16	16.3	24	24.5	15	15.3	9	9.2	6	6.1	0.453[1]
>60	23	33.8	16	23.5	11	16.2	10	14.7	7	10.3	1	1.5	
Histological type													
1) LM/LMM	29	53.7	3	5.6	8	14.8	10	18.5	4	7.4	0	0.0	...
SSM	14	26.4	0	0.0	18	34.0	12	22.6	8	15.1	1	1.9	
NM	3	33.4	0	0.0	2	22.2	2	22.0	2	22.2	0	0.0	
ALM	0	0.0	23	88.5	2	7.7	0	0.0	1	3.8	0	0.0	
Others	1	11.1	2	22.2	1	11.1	0	0.0	0	0.0	5	56.6	
2) LM/LMM	29	53.7	3	5.6	8	14.8	10	18.5	4	7.4	0	0.0	<0.001[1]
Others	18	18.6	25	25.8	23	23.7	14	14.4	11	11.3	6	6.2	
Signs and symptoms													
Yes	31	32.3	21	21.8	16	16.7	14	14.6	11	11.5	3	3.1	0.144[1]
No	13	32.5	3	7.5	14	35.0	6	15.0	3	7.5	1	2.5	
Bleeding													
Yes	1	14.3	3	42.8	1	14.3	1	14.3	0	0.0	1	14.3	0.164[1]
No	43	33.3	21	16.3	29	22.5	19	14.7	14	10.9	3	2.3	
Alterations in sensitivity													
Yes	5	25.0	4	20.0	5	25.0	3	15.0	2	10.0	1	5.0	0.908[1]
No	39	33.6	20	17.2	25	21.6	17	14.7	12	10.3	3	2.6	
Darkening													
Yes	10	33.3	4	13.3	5	16.7	7	23.4	4	13.3	0	0.0	0.569[1]
No	34	32.0	20	18.9	25	23.6	13	12.3	10	9.4	4	3.8	
Growth													
Yes	29	36.7	19	24.0	10	12.7	10	12.7	9	11.4	2	2.5	0.013[1]
No	15	26.3	5	8.8	20	35.1	10	17.5	5	8.8	2	3.5	

1: Fisher Exact test, **.... No test**

whites, acral regions corresponded to 50% of the cases (Table 1).

Among histological types, LM/LMM was found in 35.7% of the cases, followed by SSM in 35.1%, ALM in 17.2% and NM in 6%. In a comparison respective to body locations, LM/LMM was the most frequent histological type on the head and neck. ALM was present in 88.5% of the CM cases located in acral regions, while SSM was most common on the trunk (34%).

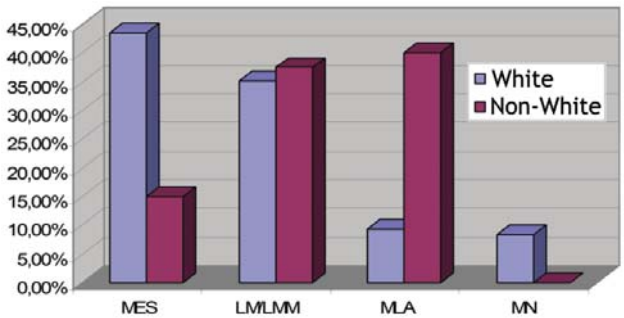
Correlated with skin color, the white patients presented a predominance of SSM (43.5%), followed by LM/LMM (35.2%). Among the non-whites, 40% presented with ALM, followed by LM/LMM (37.5%) (Table 2 and Graph 2).

Roughly 20% of the patients had atypical nevi, with 16.5% presenting less than 10 and 3.4% more than 10 such lesions.

A family history of CM was present in 16 (10%) of the patients.

Regarding tumor thickness, 41.1% were *in situ,* 31.1% presented a tumor thickness < 1 mm, 11.3% were between 1.01 and 2 mm and 9.9% were between 2.01 and 4mm, 6.6% were > 4 mm. In a comparison of histological types, LM/LMM was the most frequent among *in situ* CM or CM with a tumor thickness ≤ 1 mm (92.3%), followed by SSM (73.1%). There was no statistically significant difference in the correlations between tumor thickness and gender, skin color, age and body location (Table 3).

In relation to the Clark level, 42% of the patients presented at level 1 or *in situ,* 13% at level II, 20% at level III, 21% at level IV and 4% at level V. The LM/LMM histological type was the most common at Clark levels I and II (84%). Among cases of level V CM, ALM was the most common histological type (11.5%) (Table 4).



Graph 2: Distribution of histological type by skin color

Symptoms of and/or alterations in the primary lesion were reported by 96 (70.6%) of the patients. Among these, the most frequent report was of growth of the lesion (58.1%), followed by alterations in color by 22%, alterations in sensitivity by 14.7% and bleeding by 5.2%. Darkening was the most common alteration in color, while itching was the most common symptom regarding sensitivity. Reports of bleeding were most common for Clark levels IV and V (83.3%), along with tumor thicknesses > 4 mm (60%). Growth was most commonly reported for level I tumor invasions (50%). Alterations in sensitivity and color were

Table 2: Comparison between histological type and skin color and age at diagnosis

	Histological type										
Characteristics	**LM /LMM**		**SSM**		**NM**		**ALM**		**Others**		**p-value**
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	
Skin color											
White	38	35.2	47	43.5	9	8.3	10	9.3	4	3.7	<0.001[1]
Non-whites	15	37.5	6	15.0	0	0.0	16	40.0	3	7.5	
Age at diagnosis											
1) <20	2	33.3	2	33.3	0	0.0	1	16.7	1	16.7	...
21- 40	5	19.2	11	42.3	2	7.7	5	19.2	3	11.5	
41 -60	19	33.9	20	35.7	5	8.9	8	14.3	4	7.1	
>60	28	44.4	20	31.8	2	3.2	12	19.1	1	1.6	
2) ≤40	7	21.9	13	40.6	2	6.3	6	18.8	4	12.5	0.203[1]
>40	47	39.5	40	33.6	7	5.9	20	16.8	5	4.2	
3) ≤60	26	29.5	33	37.5	7	8.0	14	15.9	8	9.1	0.107[1]
>60	28	44.4	20	31.7	2	3.2	12	19.0	1	1.6	

1: Fisher Exact test, **.... No test**

Table 3: Comparison between tumor thickness and sex, skin color, age at diagnosis, histological type and signs and symptoms

Characteristics	Tumor thickness (mm)										p-value
	In situ		<1.0		1.01-2,0		2.01- 4.0		>4.0		
	N	%	N	%	N	%	N	%	N	%	
Sex											
Male	20	35.7	18	32.1	10	17.9	5	8.9	3	5.4	0.375[1]
Female	42	44.2	29	30.5	7	7.4	10	10.5	7	7.4	
Skin color											
White	40	36.1	39	35.1	14	12.6	10	9.0	8	7.2	0.293[1]
Non-white	21	55.3	8	21.1	3	7.8	4	10.5	2	5.3	
Age at diagnosis											
1) <20	4	66.6	1	16.7	0	0.0	0	0.0	1	16.7	...
21 - 40	11	42.3	9	34.6	2	7.7	4	15.4	0	0.0	
41 - 60	19	34.5	21	38.2	8	14.5	4	7.3	3	5.5	
>60	28	43.8	16	25.0	7	10.9	7	10.9	6	9.4	
2) ≤40	15	46.9	10	31.2	2	6.3	4	12.5	1	3.1	0.752[1]
>40	47	39.5	37	31.1	15	12.6	11	9.2	9	7.6	
3) ≤60	34	39.1	31	35.6	10	11.5	8	9.2	4	4.6	0.563[1]
Histological type											
1) SSM	12	23.1	26	50.0	9	17.3	4	7.7	1	1.9	...
LM/LMM	35	67.3	13	25.0	1	1.9	3	5.8	0	0.0	
NM	0	0.0	1	14.3	1	14.3	3	42.8	2	28.6	
ALM	13	52.0	4	16.0	3	12.0	3	12.0	2	8.0	
2) LM/LMM	35	67.3	13	25.0	1	1.9	3	5.8	0	0.0	<0.001[1]
Others	25	29.1	31	36.0	14	16.3	10	11.6	6	7.0	
Location											
1) Head and neck	24	52.2	11	23.9	5	10.9	5	10.9	1	2.2	...
Acral	13	44.8	5	17.3	3	10.3	3	10.3	5	17.3	
Trunk	12	36.3	11	33.3	5	15.2	3	9.1	2	6.1	
Upper limb	9	36.0	12	48.0	1	4.0	2	8.0	1	4.0	
Lower limb	4	26.7	7	46.6	3	20.0	1	6.7	0	0.0	
Others	0	0.0	1	33.3	0	0.0	1	33.3	1	33.3	
2) Head and neck	24	52.2	11	23.9	5	10.9	5	10.9	1	2.2	0.293[1]
Others	38	36.2	36	34.3	12	11.4	10	9.5	9	8.6	
Signs and symptoms											
Yes	37	41.1	27	30.0	10	11.1	10	11.1	6	6.7	0.287[1]
No	15	40.5	17	46.0	3	8.1	2	5.4	0	0.0	
Bleeding											
Yes	0	0.0	1	20.0	0	0.0	1	20.0	3	60.0	<0.001[1]
No	52	42.6	43	35.2	13	10.7	11	9.0	3	2.5	
Alterations in sensitivity											
Yes	5	27.8	6	33.3	3	16.7	4	22.2	0	0.0	0.183[1]
No	47	43.1	38	34.9	10	9.2	8	7.3	6	5.5	
Darkening											
Yes	10	33.3	9	30.0	5	16.7	3	10.0	3	10.0	0.284[1]
No	42	43.3	35	36.1	8	8.2	9	9.3	3	3.1	
Growth											
Yes	36	48.6	22	29.7	5	6.8	6	8.1	5	6.8	0.099[1]
No	16	30.2	22	41.5	8	15.1	6	11.3	1	1.9	

1: Fisher Exact test, **.... No test**

Table 4: Comparison between Clark's level and sex, skin color, age at diagnosis, histological type, signs and symptoms and location

	Clark's level										
Characteristics	**I**		**II**		**III**		**IV**		**V**		**p-value**
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	
Sex											
Male	20	37.0	8	14.8	12	22.2	11	20.4	3	5.6	0.754[1]
Female	42	45.2	11	11.8	16	17.2	21	22.6	3	3.2	
Skin color											
White	41	38.0	14	13.0	25	23.1	25	23.1	3	2.8	0.097[1]
Non-white	21	53.8	5	12.8	3	7.7	7	18.0	3	7.7	
Age at diagnosis											
1) <20	4	80.0	1	20.0	0	0.0	0	0.0	0	0.0	...
21 - 40	11	44.0	1	4.0	8	32.0	5	20.0	0	0.0	
41 -60	19	34.6	11	20.0	11	20.0	13	23.6	1	1.8	
>60	28	45.1	6	9.7	9	14.5	14	22.6	5	8.1	
2) ≤40	15	50.0	2	6.6	8	26.7	5	16.7	0	0.0	0.384[1]
>40	47	40.2	17	14.5	20	17.1	27	23.1	6	5.1	
3) ≤60	34	40.0	13	15.3	19	22.3	18	21.2	1	1.2	0.186[1]
Histological type											
1) SSM	13	26.0	6	12.0	18	36.0	13	26.0	0	0.0	...
LM/LMM	34	68.0	8	16.0	5	10.0	1	2.0	2	4.0	
NM	0	0.0	0	0.0	1	12.5	7	87.5	0	0.0	
ALM	13	50.0	3	11.5	2	7.8	5	19.2	3	11.5	
2) LM/LMM	34	68.0	8	16.0	5	10.0	1	2.0	2	4.0	<0.001[1]
Others	26	30.6	9	10.6	22	25.9	25	29.4	3	3.5	
Signs and symptoms											
Yes	37	42.5	11	12.6	17	19.6	17	19.6	5	5.7	0.530[1]
No	15	41.6	6	16.7	10	27.8	5	13.9	0	0.0	
Bleeding											
Yes	0	0.0	0	0.0	1	16.7	3	50.0	2	33.3	0.002[1]
No	52	44.5	17	14.5	26	22.2	19	16.2	3	2.6	
Alterations in sensitivity											
Yes	5	29.4	3	17.7	3	17.7	6	35.2	0	0.0	0.309[1]
No	47	44.4	14	13.2	24	22.6	16	15.1	5	4.7	
Darkening											
Yes	10	33.3	5	16.7	7	23.3	6	20.0	2	6.7	0.703[1]
No	42	45.2	12	12.9	20	21.5	16	17.2	3	3.2	
Growth											
Yes	36	50.0	9	12.5	12	16.7	10	13.9	5	6.9	0.039[1]
No	16	31.4	8	15.7	15	29.4	12	23.5	0	0.0	
Location											
1) Head and neck	23	50.0	7	15.2	5	10.9	9	19.5	2	4.4	...
Acral	13	43.4	4	13.3	1	3.3	8	26.7	4	13.3	
Trunk	13	43.3	2	6.7	7	23.3	8	26.7	0	0.0	
Upper limb	9	36.0	5	20.0	7	28.0	4	16.0	0	0.0	
Lower limb	4	26.7	1	6.6	7	46.7	3	20.0	0	0.0	
Others	0	0.0	0	0.0	1	100.0	0	0.0	0	0.0	
2) Head and neck	23	50.0	7	15.2	5	10.9	9	19.5	2	4.4	0.424[1]
Others	39	38.6	12	11.9	23	22.8	23	22.8	4	3.9	

1: Fisher Exact test, **.... No test**

associated with *in situ* and thin CM (Breslow's depth ≤ 1 mm), with 61.1% and 63.3% of cases, respectively, but for the last two characteristics there was no statistical significance (Tables 3 and 4).

Metastasis was detected in 19 (13.4%) patients. Lymph node metastasis was found in 12 (40%) patients, cutaneous in seven (24%), cerebral in five (17%), lung in four (13%), blood in one (3%) and bone, also in one patient (3%).

There were seven deaths resulting from CM. We have included here patients with giant congenital melanocytic nevi (GCMN) and xeroderma pigmentosum (PX). In the univariate analysis, there was a greater chance of death for men, those under the age of 20, non-whites, those with a Breslow's depth > 2 mm, with the ALM histological type and with a history of growth and bleeding. However, following the multivariate analysis, only those under the age of 20 and those with a history of bleeding continued to run a high relative risk of death, approximately 13 and eight times higher, respectively (Table 5).

DISCUSSION

In countries with a lower incidence of CM, such as European countries and Brazil, the majority of cases occur among females and, in contrast, in countries with the high incidence, such as Australia, New Zealand and the USA, there is a predominance of the disease among males or even equality in terms of gender distribution.[2]

In this study, 61% of the patients were female, which is in line with the majority of studies that have been conducted in Brazil.[11-16]

In relation to age, CM is characterized by its incidence among young people. The average age at diagnosis is 52, which is 10 years less than what is reported for more common cancers such as breast, lung and prostate cancer.[17] In this study, a mean age of 55 years was found, which is in consonance with Brazilian and international literature.[11,13, 14, 18-20]

Among risk factors for CM are phenotypical traits such as light or fair skin, hair and eyes, with studies indicating a risk of developing this neoplasm 10 times higher among Caucasians than other ethnicities.[9,10] In the Southern region of Brazil, the majority of studies deal with a population that is almost 100% white.[12,15] In this study, 74% of the patients were white and 26% were non-whites. This ratio of non-whites is higher than that found in the literature studied.[11,16,21,22]

Regarding histological type, the international literature reports that among white individuals, SSM predominates, varying from 37.7% in Chile to 43.6% in Argentina, 60% in Spain, 62% in Switzerland and 73.6% in Australia.[19,23-26] In studies involving non-white individuals, ALM is the most prevalent.[10,27] Forman et al, in the USA, however, found that 56% of the cases were LM/LMM and speculated whether this difference in relation to other studies is due to a change in risk factors or to a regional peculiarity.[28]

In the Brazilian literature, in the Southern region, where there is a prevalence of people with a light skin tone, SSM vary from 35.3 to 68.9%.[12,14,29-35] In other regions in Brazil, where there is a greater proportion of non-whites, the SSM percentage is lower.[16,22] Fernandes *et al* found a predominance of LM/LMM (29.8%), as did the present study.[21] Despite the fact that the difference in proportion between LM/LMM (35.7%) and SSM (35.1%) found in this sample was small, the frequency of LM/LMM is still higher than that reported in the literature (5 to 10%), just as SSM is less frequent when compared with studies in which a white population is predominant (70%).[10] This difference may be due to the frequency of non-whites found in this study (26%) and possibly to sun exposure patterns, although this last variable has not been measured.

In the current sample, SSM was most frequent on the trunk and on the extremities and ALM was responsible for almost 90% of the MM in acral regions. LM/LMM was the most common histological type on the head and neck, which is in concordance with the literature.[1] A higher proportion of ALM was found (17.2%) and, once again, the most plausible explanation is the elevated frequency of non-whites in this sample.

Table 5: Multivariate model - evolution to death

Final model	Coefficient	Standard error	p-value	Relative risk	Confidence interval 95%
Age at diagnosis					
<20	2.6	1.3	0.043	13.1	1.1 a 156.5
21 - 40	0.6	1.4	0.690	1.8	0.1 a 28.7
41 - 60	-0.4	1.4	0.790	0.7	0.04 a 11.1
>60				1.0	
Bleeding					
Yes	2.1	1.0	0.029	8.3	1.2 a 54.9
No				1.0	

The most common body location varies with gender and with the histological type. In the majority of studies, CM occurs with greater frequency on men's dorsal area and on women's legs.[10]

In Brazilian literature, two studies[11,33] found a predominance of CM on the head and neck, as was found in the present study.

The risk of CM is increased in the presence of atypical melanocytic nevi.[10] Gandini and collaborators, in a meta-analysis study, highlighted that finding an atypical nevus increased the risk of CM by 2.4 times, while 10 or more atypical nevi increased the risk by 32 times.[36] In the present study, approximately 20% of the patients presented atypical nevi, which is a rate similar to that described in the literature.[12,37]

The risk of CM is higher in patients that suffer from non-melanoma skin cancer, including basal-cell carcinoma (BCC) and squamous-cell carcinoma (SqCC), since all three neoplasms are related to sun exposure.[38] In the present study, the finding of 27,7% of the patients with a history of non-melanoma skin cancer is higher than that found in the literature.[39,40] One possible explanation would be the chronic exposure to the sun, which may also explain the elevated frequency of CM on the head and neck, even though this feature has not been evaluated by this study.

A family history of CM is an important risk factor. Patients with a history of CM[8] among their relatives face a risk twice as high, while three or more family members with CM may result in a risk that is 35 to 70 times higher.[10] A history of CM in the family was observed in 10% of the cases, which is similar to the rate described by the majority of the authors.[1, 8-10,19,41]

Breslow's tumor thickness is described in various studies as the most important prognostic factor for CM.[2,42]

According to the most recent version of the American Joint Committee on Cancer (AJCC), MMs are classified, based on Breslow's depth, as thin (≤ 1 mm), intermediate (1,01-4 mm) and thick (>4 mm).[42] In recent years some papers, from many areas of the world, have mentioned an increase in the incidence of cases of thin CM, as well as the stabilization of the incidence of thick ones.[2,18,20,43] Regarding the Brazilian literature, some authors have also found a high proportion of cases of thin CM, which is, therefore, in concordance with the findings in the international literature.[14,15,22,44]

In the sampling presented here, 72% of the cases of CM were restricted to the epidermis (in *situ)* or had a tumor thickness of ≤ 1 mm. One possible explanation for the predominance of CM in initial stages results from the diagnosis being made, in the majority of cases, by dermatologists, which contributed to the early identification of the tumor.[45]

The Clark level, or the tumor invasion level, was initially considered an independent prognostic factor. In the 2002 version of the AJCC's staging, this index was computed in order to evaluate the prognosis of lesions with a Breslow's depth of < 1 mm.[42] Now, the Clark level is considered in the staging of thin CMs only when information on ulceration and the mitotic index is not available.[42] In the present study, 55.1% of the patients presented Clark levels I and II, as found in the international literature, which reveals the predominance of lesions with lower invasion levels.[20,46]

Changes in color and size of a previous lesion and the appearance of a new lesion are the earliest characteristics that are noted by patients and that contribute to the diagnosis. Of these, growth has been highlighted as the most frequent clinical sign, followed by alterations in color.[19,24,47] While in some studies growth has been associated with greater tumor thickness, in another this association was not detected.[19,24,47]

Alterations in color have been related to thinner CM and bleeding from thicker lesions.[19,24,47] There is disagreement between authors regarding alterations in sensitivity, especially itching. For some, this is correlated with thin tumors while others associate it with thicker ones.[10,19,24,47] In this study, 70.6% of the patients reported symptoms and/or signs in the lesion. The most common complaint was growth of the lesion, followed by darkening, itching and, less frequently, bleeding. This bleeding was associated with cases of thicker CM and was similar to the findings of the studies mentioned.[19,24,47]

Alterations in color, sensitivity and growth were more frequent in cases of thinner CM, though with no statistical significance.

Metastases denote a poor prognosis, with survival times estimated in months. As a rule, the greater the thickness of the tumor, the greater the chances of metastasis.[46] Cases of CM diagnosed with a Breslow's thickness < 1.5 mm show 10-year survival rates above 90%.[48] The CM disseminates via lymphatic and/or hematogenic routes. The former occurs very early in the evolution of CM. Distant metastases may be either non-visceral (skin, subcutaneous tissue and non-regional lymph node), or visceral, most frequently affecting the lungs (18- 36%), followed by the liver (14-20%), brain (12-20%), bones (11-17%) and gastrointestinal tract (1-7%).[10]

In the sample assessed, metastases were found in 19 (13.4%) patients, with the lymph nodes being the most common (40%). In 80% of the patients suffering from a metastasized disease, the tumor thickness was > 1.5 mm, which is similar to the findings from the literature referred to above.

In addition to tumor thickness, other factors associated with survival rates are: sex, age, primary body

location, histological type, skin color and staging.[10]

The men presented a higher proportion of cases of thick CM than the women, resulting in worse survival rates.[3,15,18,24] Patients over the age of 60 also had poor prognoses with an elevated proportion of cases of thick CM.[3,18,49] Balch *et al* recorded that, even when controlling confusing factors such as gender and tumor thickness, age was an independent prognostic factor in CM.[46] This may be attributed to a decline in the immunological response which occurs with age.[46,49]

Regarding body location, the majority of the authors consider the trunk to be the location with the poorest prognosis.[3,15,18,25,47] In relation to the histological type, some investigations have observed worse survival rates with NM[15,18] while others have recorded that ALM was associated with a poorer prognosis.[47]

As for skin color, Chang *et al* recorded worse survival rates for non-white individuals both in the initial and later stages, though this association did not have an impact on the multivariate analysis.[18]

In this sample a greater chance of death was found among men, those under the age of 20, non-whites, those with the ALM histological type, those with a Breslow's depth > 2 mm and those with a history of growth and bleeding. However, following the multivariate analysis, only the patients under the age of 20 and with a history of bleeding remained at high risk.

Children and adolescents suffer from CM less frequently than adults, which may delay diagnosis, thereby worsening survival rates.[10,41,50] The two cases diagnosed in children occurred in patients bearing GCMN, which is known to carry a poor prognosis, since two thirds of cases of CM in people with GCMN are of a non-epidermic origin, which leads to a late diagnosis and, consequently, reduced survival rates.[41]

Bleeding is most common in cases of thick CM according to the literature and to the results found in this study, which denotes a poor prognosis.[19,24,47]

CONCLUSIONS

In conclusion, in this sample, cases of CM were more common in women, with a mean age of 55 years at diagnosis. Whites represent the majority of patients, but the proportion of non-whites is bigger than other Brazilian states, justifying the higher frequency of ALM than cited in other studies. The most frequent histological type was LM/LMM, that could be because of regional factors and matches with predominant location. Comparing sex and body site, CM was more common in trunk of men and limbs of women. In agree with national and international tendencies, the majority of CM was *in situ* or thin. The number of deaths was small, with more chances of dying in those under 20 years and with a history of bleeding, after a multivariate analysis. In that way, more attention should be taken to children and teenagers, mostly those with predisposing factors such GCMN, PX and atypical nevus, besides CM in these population being rare, the diagnosis of CM with less than 1 mm of growth, is still the best chance of cure for the most lethal type of skin cancer.

This sample analyzed is small and came from a single institution, meaning that these findings cannot be generalized for the entire population of the state. This data may not reflect the reality of CM among the population of this state. Further studies are necessary in order to validate the results obtained. However, this study represents the largest sampling of patients with melanoma in this state, with data collected over the longest period of time. ❑

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How to cite this article: Brandão FV, Pereira AFJR, Gontijo B, Bittencourt FV. Epidemiological aspects of melanoma at a university hospital dermatology center over a period of 20 years. An Bras Dermatol. 2013;88(3):344-53.