

# CLINICAL AND PATHOLOGICAL MELANOMA DIFFERENCES IN YOUNG AND OLD PEOPLE

## Diferenças clínicas e patológicas do melanoma em jovens e idosos

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### ABSTRACT

**BACKGROUND:** Melanoma is often misdiagnosed in older people. Some clinical and histopathological features seem to differ according to age. **OBJECTIVES:** This case series aimed to identify clinicopathological differences of melanoma between older and younger patients. **METHODS:** We identified all incident melanomas diagnosed in a dermatology outpatients unit from January/2007 to December/2014. Data were collected from medical records and pathology registries. **RESULTS:** We included 62 patients (mean age of  $62.1 \pm 4.2$  years), with a median Breslow thickness of 4 mm (1.2 – 6.5). While men were majority in the older group, women prevailed between younger counterparts ( $p = 0.02$ ). Multivariate analysis identified history of chronic sun exposure, multiple naevi, skin phototypes 1 and 2, *in situ* melanoma and the presence of another skin tumour to be correlated with age. In a logistic regression model, the presence of chronic sun exposure and nodular subtype were found to influence age. Major limitations include those inherent to cross-sectional design, including selection and information biases, the lack of confounding factors analysis (including survival and prognosis), and the sample size. **CONCLUSIONS:** On this case series, melanoma seems to be more frequent in older men and in elders with chronic sun exposure; age was found to be significantly related to nodular subtype and chronic sun exposure.

**KEYWORDS:** melanoma; aged; epidemiology.

### RESUMO

**INTRODUÇÃO:** O melanoma é frequentemente diagnosticado de modo tardio em pessoas idosas. Algumas características clínicas e histopatológicas parecem diferir de acordo com a idade. **OBJETIVOS:** Este estudo de série de casos tem por objetivo identificar as diferenças clínico-patológicas do melanoma entre pacientes idosos e jovens. **MÉTODOS:** Identificaram-se todos os casos incidentes de melanoma diagnosticados em uma unidade ambulatorial de dermatologia de janeiro de 2007 a dezembro de 2014. Os dados foram coletados a partir da revisão dos prontuários médicos e registros do laboratório de patologia. **RESULTADOS:** Foram incluídos 62 pacientes, com uma média etária de  $62,1 \pm 4,2$  anos, e tumores com mediana de espessura de Breslow de 4 mm (1,2 – 6,5). Enquanto os homens foram maioria no grupo idoso, as mulheres prevaleceram entre os pacientes jovens ( $p = 0,02$ ). Análise multivariada identificou que a exposição crônica ao sol, presença de múltiplos nevos, fototipos baixos, melanoma *in situ* e antecedentes de neoplasias cutâneas correlacionaram-se com a idade. Modelo de regressão múltipla confirmou que a exposição ao sol e o tipo nodular influenciam a idade. **CONCLUSÕES:** O melanoma foi mais frequente nesta amostra em homens idosos com exposição crônica ao sol; a idade correlacionou-se significativamente com o tipo nodular e exposição ao sol.

**PALAVRAS-CHAVE:** melanoma; idoso; epidemiologia.

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## INTRODUCTION

Malignant Melanoma (MM) is a cancer from melanocytic cells that primarily involves the skin; it accounts for almost 90% of all mortality from skin tumors.<sup>1</sup> Despite recent evidence of reduction on the incidence of MM in some younger European populations, global annual incidence and mortality rates have increased, especially in older and fair-skinned populations, particularly in older men.<sup>2,3</sup>

Melanoma is often misdiagnosed in older people, including delayed diagnosis, inadequate staging, and suboptimal surgical/adjuvant therapies.<sup>4-6</sup> Some melanoma features seem to differ according to age, including prognosis markers and risk factors.<sup>3,5-7</sup> This case series aimed to identify clinicopathological differences of MM between older and younger patients.

## METHODS

All incident melanomas diagnosed from January/2007 to December/2014 in a dermatology outpatient unit located in Bauru (the most populous city in the center-west of São Paulo state, Brazil) were identified using the pathology records. Data were extracted through review of medical records and the respective pathology registries. Only the first diagnosed lesion was included in patients with more than one melanoma. The local ethics committee dispensed informed consent form; this study was conducted in accordance with the Declaration of Helsinki.

The following data were extracted: age, sex, skin phototype, recall of chronic sun exposure (and sunburns, when available), family and personal history of skin tumors, multiple naevi, circumstances of diagnosis, anatomic location (divided into 4 locations: head and neck, lower extremity, trunk, and upper extremity), histologic subtype (including superficial spreading melanoma, nodular melanoma, lentigo malignant melanoma, acral lentiginous melanoma, and other or unclassified subtypes), stage (in situ or not), Breslow thickness, Clark level, presence of ulceration, regression, and number of mitoses/mm<sup>2</sup>. Once diagnosed, MM patients were referred to an oncology secondary healthcare unit, thus data on staging, lymph node status and survival were not available.

All patients aged 65 years old or older were defined as older patients. Chronic sun exposure was dichotomized and defined as frequent unprotected exposure to sunlight during five or more days per week (occupational or leisure). Recall of sunburn was categorized as none, sunburn without blisters and sunburns with blisters. We considered multiple naevi when the patient has more than 50 naevi at the time of melanoma diagnosis. Fitzpatrick skin phototype (I–VI) was

extracted according to the subjective identification registered in the medical records.

Numeric variables were described as mean (standard deviation) or median (25<sup>th</sup>–75<sup>th</sup>) according to their distribution, and categorical data were described as frequency/percentage. Comparisons between groups were performed using a 2-tailed unpaired *t*-test, Mann-Whitney (MW) test,  $\chi^2$  test or Fisher exact test, as appropriate. We applied a bivariate analysis to evaluate the correlation of age with risk factors and prognosis variables, and a multiple linear regression to confirm the relation of age and predictor variables, considering significant when  $p < 0.05$ .

## RESULTS

We included 62 patients, of whom 36 (58.1%) were female. Age ranged from 27 to 95 years (mean age,  $62.1 \pm 4.2$  years), with a median Breslow thickness of 4 mm (1.2 – 6.5) and a median mitoses/mm<sup>2</sup> of 9 (2.5 – 26.5). Thirty-three (53.2%) were younger than 65 years old: male gender prevailed among older patients, while female were dominant among younger counterparts ( $\chi^2$ ,  $p = 0.02$ ).

Nearly 70% (43) of the sample did not have previous cutaneous tumors, most of them from the younger group ( $\chi^2$ ,  $p = 0.03$ ); nine patients were admitted due to other cutaneous complaints. Location of MM on head/neck was higher in the older group (62.5% *versus* 37.5%) and increases with age: average age in patients with MM of head/neck location was  $67.5 \pm 10.8$  years ( $n = 16$ , 31 – 95), while on lower extremity melanoma was  $56.1 \pm 14.7$  years ( $n = 14$ , 37 – 91). Significant differences between age groups were observed for chronic sun exposure ( $\chi^2$ ,  $p < 0.001$ ) and multiple naevi ( $\chi^2$ ,  $p = 0.03$ ), as shown in Table 1. Information regarding lifetime sunburn occurrence were available only for 54.8% (34) cases: 18 elderly and 16 younger patients, most of them (16) without history of sunburns.

**Table 1** Multiple regression analysis of factors influencing age in participants with malignant melanoma ( $n = 62$ ), Bauru 2007–2014.

	B	SE	p-value	95%CI
Constant	51.73	3.58	< 0.001	44.54 – 58.92
Chronic sun exposure	17.40	3.99	< 0.001	9.32 – 25.4
Nodular histologic subtype	14.45	5.09	0.007	4.16 – 24.74

Enter;  $R^2$ : 0.51; DW 2.47; F: 10.54;  $p < 0.001$ .

Multiple naevi was not found to be associated with prognostic factors (Breslow thickness, mitoses/mm<sup>2</sup>, regression or ulceration, for instance) in the older group; however, the distribution of Breslow thickness was different between younger patients with and without multiple naevi (MW,  $p = 0.02$ ). While the median Breslow thickness in younger patients with less than 50 naevi was 1.95 mm, it was 0.74 mm in patients with multiple naevi.

The nodular subtype (NM) was more common in the older group (75% *versus* 25%); the average age on NM patients was  $76.5 \pm 16.0$ . In thirteen cases (20.9%) melanoma was diagnosed as *in situ*, without differences between age groups. The supplementary material includes a table with all relevant variables distribution.

In non-parametric correlation analysis, age was found to be significantly correlated to chronic sun exposure ( $r = 0.514$ ,  $p < 0.001$ ), multiple naevi ( $r = -0.317$ ,  $p = 0.02$ ), low phototypes (types I/II) ( $r = 0.250$ ,  $p = 0.05$ ), presence of other cutaneous tumours ( $r = 0.268$ ,  $p = 0.03$ ) and *in situ* melanoma ( $r = 0.286$ ,  $p = 0.02$ ).

After excluding non-significant variables from the model, age was found to be significantly related to chronic sun exposure ( $p < 0.001$ ) and nodular subtype ( $p = 0.007$ ). When chronic sun exposure was present, age increased 17.4 times (95%CI 9.32 – 24.48); if a nodular histologic subtype was diagnosed, age was 14.4 times higher (95%CI 4.16 – 24.74).

## DISCUSSION

Melanomas in older patients appear to have a different natural history, relation with prognosis factors and survival outcomes when compared to younger counterparts.<sup>3,8</sup> Although numerous risk factors have been associated to the development of MM (including light eyes and low skin phototypes, presence of dysplastic naevi, tendency to freckle and family history of melanoma), the significance of some associations remains unclear, particularly in aged subgroups.<sup>3–5</sup> The risk associated with sun exposure and multiple naevi, for example, are controversial.<sup>8,9</sup>

Traditional prognostic factors for cutaneous MM include thickness, ulceration, mitoses/mm<sup>2</sup>, clinical stage, anatomic location, sex and age,<sup>10</sup> and although some pathologic features were previously linked to lower disease specific survival rates,<sup>4,5,7,10</sup> some associations remain uncertain in older patients.<sup>10</sup>

In accordance to our findings, several studies suggested that melanoma is more common in older men;<sup>3,4,6–8,10</sup> they have focused on histologic features and/or survival, and few evaluated risk factors for melanoma.<sup>3,5,7,8</sup>

MacDonald et al.<sup>7</sup> found that melanoma was less likely to arise from a pre-existing naevi in patients older than 70 years. Although multiple naevi is a powerful predictive phenotypic marker for melanoma development, nevi usually involute after the 40<sup>th</sup> decade; therefore, they are much less numerous in older patients,<sup>9</sup> thus explaining why we found significantly less elderly with more than 50 naevi. As a matter of fact, high nevus count have been recently associated with better disease specific survival, even within positive sentinel lymph node patients.<sup>9</sup> Immunosenescence, telomere unit, tumour suppressor genes (such as CDKN2A) and oncogenes (BRAF) may play a role in nevus senescence, but their specific relationship with melanoma remains unclear.<sup>9</sup>

We found higher frequencies of chronic sun exposure in older patients with melanoma, what may be linked to the higher proportions of lesion on sun exposed locations in this age group. Testori et al.<sup>5</sup> highlighted a consistent association between solar keratosis and nodular melanoma in older patients, probably as result from cumulative sun damage. However, chronic sun exposure seems to be less important than sunburns and intermittent sun exposure as a risk factor.<sup>1,4</sup> Unfortunately, records of occurrence of sunburn were available only for 34 patients.

As age increases, associations with Breslow thickness, ulceration, regression, and mitotic figures seem to worsen prognosis.<sup>4</sup>

Some studies<sup>3,7</sup> found that older patients had thicker melanomas and greater number of mitotic figures. The relationship of aging with the presence of regression and ulcerations remains unclear.<sup>6</sup> We found no differences in pathological patterns between age groups. However, the small sample and lack of data on mortality, survival and lymph node status in this study makes it difficult to identify whether the pathological features are associated with age or prognosis.

There may be several possible reasons for late diagnosis of melanoma in older people. They may be less attentive to perform self-examination and engage on skin-cancer screening programs. Deteriorating vision and development of cutaneous tumors in hard-to-see locations, the presence of seborrheic keratoses, loss of a partner and immunosenescence may also delay medical attention for melanoma.<sup>4–6</sup>

Although the reliability of age as a prognostic factor has been questioned,<sup>10</sup> several authors suggest a more serious evolution and lower survival rates in aged cohorts.<sup>3,5,6</sup> Chang et al.<sup>10</sup> found that lymph node status was the most important prognostic factor in older patients with intermediate-thickness melanoma (1–4 mm).

This study has major limitations, including those inherent to cross-sectional design, as selection and information biases and the lack of confounding factors analysis (including survival and prognosis). This was a small retrospective analysis, from a tertiary single institution, and important factors such as time from first symptoms to diagnosis, lymph node status, coexistence of immunosuppressant risk factors/other malignancy, and mortality and survival were not available. Beyond that, we have to consider the recall bias regarding sun exposure and sunburn occurrence, the dichotomization of multiple naevi diagnosis and the absence of information regarding the presence of atypical naevi.

Finally, interesting gaps may serve as inspiration for new studies: the influence of immunosenescence markers in prognosis and in pathological features of MM in older people

remains unclear, as well as the relationship between prognostic markers and risk factors and their impact on survival curves and mortality.

## CONCLUSIONS

In this small sample of outpatients with cutaneous MM, men were majority among the elderly, while women were more frequent among the younger patients. Age was found to be significantly correlated to chronic sun exposure, presence of multiple naevi, nodular histologic subtype, low phototypes and previous skin tumours.

## CONFLICT OF INTERESTS

The authors report no conflict of interests.

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