# Melanoma signature in Brazil: epidemiology, incidence, mortality, and trend lessons from a continental mixed population country in the past 15 years

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The current research aimed to understand melanoma epidemiology in Brazil and to evaluate temporal trends in incidence and mortality. The data came from Brazilian Hospital Cancer Registries, Population Based Cancer Registries, and the National Mortality Information System from 2000 to 2014. Descriptive statistics were used for epidemiological and clinical characteristics. To describe trends in change in incidence and mortality rates, the Average Annual Percentage Change (AAPC) was calculated. Between 2000 and 2013, in men, the median incidence rate rose from 2.52 to 4.84, with an AAPC of $+21.5\%$ [95% confidence interval (CI): 15.4–28] and in women from 1.93 to 3.22 per 100 000, with an AAPC of $+13.9\%$ (95% CI: 8.1–20). Regarding mortality, between 2000 and 2014, the rates went from 0.85 to 0.9 per 100 000 for men (AAPC $= +0.8$, 95% CI: 0.4–1.1) and from 0.56 for 0.53 per 100 000 for women (AAPC $= -0.1$, 95% CI: $-0.2$ to 0). From the database, a total of 28 624 patients with melanoma were included. Most of the patients were females (51.9%), White (75%) and with stage I or II (53.2%). Sex, ethnicity, education level, geographical area of the cancer center, topography, histology, time between diagnosis and treatment, and early death were significantly associated with distant metastases. Brazil is a large country with a very young population and a low rate of melanoma incidence and prevalence that should increase over the years. Understanding the trends attributed to melanoma is important for behavioral counseling interventions that focus on promoting skin cancer prevention. *Melanoma Res* 28:629–636 Copyright © 2018 Wolters Kluwer Health, Inc. All rights reserved.

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## Introduction

Cutaneous melanoma is the most aggressive skin cancer [1] and has shown an increasing incidence worldwide in the past decades, with 232 000 new cases (1.6% of all new cancers) in 2012 (*http://globocan.iarc.fr/*). The regions affected are largely those with White population, and by far the highest incidence in both males and females is in Australia and New Zealand. There was an estimated 55 000 deaths in 2012 worldwide (0.7% of all cancer deaths), with almost two out of three melanoma deaths occurring in more developed regions (*http://globocan.iarc.fr/*) [2].

According to the Brazilian National Cancer Institute – INCA – the projection for 2018 is to have 6260 cases of melanoma, accounting for 3.6% of all skin cancers, with 1547 related deaths (*http://www.inca.gov.br/estimativa/2018/*). Brazil is a large country with deep regional contrasts, including socioeconomical, demographic, and ethnic differences. The Brazilian population was formed by an admixture from three different ancestral roots – Amerindians, Europeans and Africans – resulting in a great variability of skin pigmentation [3]. Melanoma epidemiology, incidence, and mortality in this heterogeneous population are poorly described in the literature regarding data of this continental country that covers from the Equator line to lower latitudes [4–13].

The main objectives of this paper were to understand melanoma epidemiology in Brazil using hospital-based data and to evaluate temporal trends in incidence and mortality employing the Brazilian population-based cancer data and the mortality information system, respectively.

## Materials and methods

This study was approved by the Ethics in Human Research Committee of the INCA, Rio de Janeiro, Brazil (reference number 128/11 CAAE – 0104.0.007.000-11) and is in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines.

For incidence, data from the Brazilian Population Based Cancer Registries (23 registries covering around a quarter of the Brazilian population) between 2000 and 2013, with

at least 5 years of consolidated information, were obtained on 2 April 2017. Crude incidence rates of cutaneous melanoma per 100 000 men or women by age and year of diagnosis were calculated by dividing the number of new cases by the male or female population, respectively, and rates were then adjusted for the world population. The median incidence rates allowed the estimation of an annual incidence rate for the country as a whole. To adjust for short-term variability of incidence rates between the years, a triennial weighted moving average technique was employed.

Mortality data (number of deaths due to cutaneous melanoma) in Brazil between 2000 and 2014 were collected from the National Mortality Information System, disaggregated by sex and age. Crude annual mortality rates were calculated by dividing the number of new cases by the male or female population, respectively, per 100 000 men or women by age group and year of diagnosis for the country as a whole. Rates were adjusted for the world population.

To describe trends in change in incidence and mortality rates, the Average Annual Percentage Change (AAPC) was calculated. The population used as a denominator for incidence and mortality rates was estimated by the Interagency Network of Information for Health (RIPSA) for the period between 2000 and 2013, and by the Secretariat of Health Surveillance (SVS) for 2014, taken from the website of the Department of Informatics of the Ministry of Health from Brazil (*http://www.datasus.gov.br*).

The data of patients diagnosed and treated with cutaneous melanoma between 2000 and 2014 in 315 hospital units from the 25 states and the Federal District of Brazil came from the Brazilian Hospital Based Cancer Registries System and the Oncocenter Foundation of São Paulo, both available on the internet (*www.inca.gov.br*, *www.fosp.saude.sp.gov.br*).

According to the International Classification of Diseases for Oncology, third ed., the following primary sites of cutaneous melanoma were included: head and neck (codes C44.0–C44.4), trunk (code C44.5), upper limbs/shoulders (code C44.6), lower limbs/hips (code C44.7), or other, including overlapping areas of skin and not otherwise specified (NOS) (codes C44.8–C44.9). The histologic subtypes were classified as superficial spreading (International Classification of Diseases for Oncology, 3rd ed., histologic code 8743), nodular (code 8721), lentigo maligna (code 8742), acral lentiginous (code 8744), malignant NOS (code 8720), or other (codes 8722, 8723, 8730, 8740, 8741, 8745, 8761, 8770–8774, and 8780). Patients with in-situ melanomas were excluded, except those classified as lentigo maligna. There was no central pathology review.

Patients were followed up until the end of the first course of all melanoma-directed treatment. All modalities of therapy (surgery, chemotherapy and radiotherapy) were included regardless of the sequence or the degree of treatment completion. The following variables were collected: age at diagnosis, sex, ethnicity/skin color (according to the Brazilian Institute of Geography and Statistics – IBGE), education level, geographical area of the cancer center, origin of referral to the cancer center (public system or private facility), time between the diagnosis and first treatment, tumor stage (according to TNM), and first course of therapy. Early death was considered when it occurred before the end of the first treatment.

Descriptive statistics [mean and SD or median and interquartile range (IQR) for continuous variables and frequency for categorical variables] were used for demographic, epidemiological, and clinical characteristics. The results were based on valid data; missing data was excluded. Pearson's $\chi^2$, analysis of variance, and the median test for independent sample tests were used to determine the differences between the groups, according to variable characteristics. Data were analyzed using Microsoft Excel (2007; Microsoft, Redmond, Washington, USA) and SPSS version 21.0 (IBM, São Paulo, Brazil).

## Results

Between 2000 and 2013, in men, the median incidence rate adjusted for the world population rose from 2.52 to 4.84 per 100 000, with an AAPC of + 21.5% [95% confidence interval (CI): 15.4–28], whereas among women, in the same period, the increase was from 1.93 to 3.22 per 100 000, with an AAPC of + 13.9% (95% CI: 8.1–20; Fig. 1a). Regarding mortality, between 2000 and 2014, the rates went from 0.85 to 0.9 per 100 000 for men (AAPC = + 0.8, 95% CI: 0.4–1.1) and from 0.56 for 0.53 per 100 000 for women (AAPC = − 0.1, 95% CI: − 0.2 to 0; Fig. 1b).

From the database, a total of 28 624 patients with melanoma were included – patient and tumor characteristics are listed in Table 1. Most of the patients were females (51.9%), 40–69 years old (59.4%), and from the Southeast part of the county (47.3%). The ethnicity/skin color distribution of melanoma cases was composed of 75% White, 21.9% Brown, 2.4% Black, and 0.7% Yellow/Indigenous. Most patients (53.2%) were diagnosed with stage I or II (localized melanoma), 20.6% at stage III, and 26.1% at stage IV. Regarding the topography, the primary melanoma was diagnosed on the trunk (27.1%) followed by lower limbs/hips (26.2%), head and neck (19%), and upper limbs/shoulders (14%). Most cases of melanoma were classified as malignant melanoma NOS (78.1%). More than 50% of cases represented patients with incomplete elementary school, and 77.1% of the entire group was referred by the public health system facilities to tertiary care centers.

Male patients with melanoma were older at diagnosis compared with their female counterparts (mean age at diagnosis: male 58 ± 16 vs. female 56.5 ± 17; *P* < 0.01; Fig. 2

Fig. 1
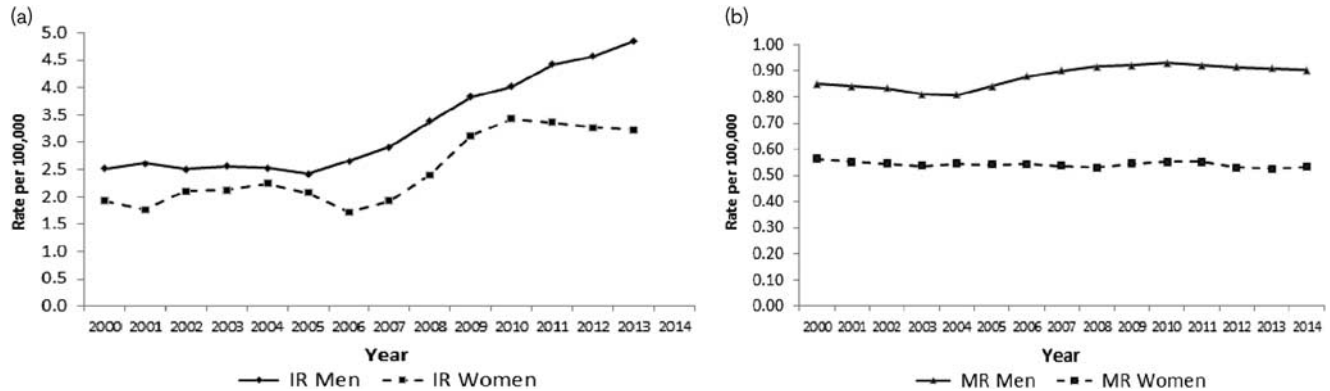


(a) Adjusted incidence rate per 100 000 of melanoma in Brazil (2000–2013). (b) Adjusted mortality rate per 100 000 of melanoma in Brazil (2000–2014). IR, incidence rate; MR, mortality rate.

and Table 2). Furthermore, older patients at diagnosis were often Black ($P < 0.001$), with lower education level ($P < 0.001$), were more often diagnosed at stage II ($P < 0.001$), in the head and neck topography ($P < 0.001$) and exhibited lentigo maligna subtype ($P < 0.001$; Table 2).

Acral melanoma was diagnosed in 812 patients (Table 1). The proportion of acral melanoma among all melanoma subtypes was bigger in Brown/Black people and in patients 60 years and older. The differences in the frequency of acral melanoma between men and women were not statistically significant (Table 3). Lentigo maligna was detected in 549 patients (Table 1), most commonly in elderly people and women (Table 3).

The median time between diagnosis and the first treatment was 43 days (IQR = 21–85): 41 days (IQR = 21–81) between patients referred by public health system facilities and 31 days (IQR = 14–63) between patients referred by private centers to tertiary care centers ($P < 0.001$). More than 37% of patients faced long waiting times for the first treatment, with a considerable proportion of patients (23.6%) waiting 90 days and more (Table 4).

Surgery was the first treatment in 82.4% of the cases, as patients were more often diagnosed with localized melanoma or regional metastases; 11% of patients with melanoma in this cohort died before the end of the first scheduled therapy (Table 4).

The variables associated with distant metastases at diagnosis are shown in Table 5. Sex, ethnicity/skin color, education level, geographical area of the cancer center, topography, histology, time between diagnosis and treatment, and early death were found to be significantly associated ($P = 0.001$) with distant metastases.

## Discussion

This is the largest study conducted in Brazil evaluating patient demographics with cutaneous melanoma; however, some limitations must be addressed. As part of this is a hospital-based study, the cohort does not represent the entire Brazilian population; hospital-based studies should be more susceptible to selection bias than studies based on population registries, which were used here only for the incidence data. The retrospective design using data collected over a long period of time (15 years) from 315 cancer hospitals may justify the lack of information in most of the collected variables. Moreover, during this long period, many changes in melanoma classification and staging have taken place. In addition, associations may have been statistically significant owing to the large sample size, and exploratory analyses may have found associations not clinically meaningful.

The incidence rate of cutaneous melanoma is rising globally with some countries counting more than a sevenfold increase during the past 50 years [14,15]. In the USA, at current rates, one in 74 Americans will develop melanoma during a lifetime [16]. In Brazil, after 2000, both incidences in men and women started to climb and an additional doubling of incidence rates happened moving from 2.52 to 4.84 in men and from 1.93 to 3.22 per 100 000 inhabitants in women. This is not only a local trend as melanoma represents a significant public health problem, with its incidences rising faster than that of any other cancer in the USA. Brazil is far from Australia and New Zealand, where incidence rates have been reported from 40 to 60 cases per 100 000 inhabitants.

The number of new melanoma cases will rise around the world because of aging populations and high specific melanoma rates in the elderly. It is happening in Brazil, which has one of the youngest populations in the world, with an average age of 29 years [17], predicting that most of the melanoma cases are to come. In White Americans, annual new cases are expected to rise from around 70 000 in 2007–2011 to 116 000 in 2026–2031, with 79% of the increase attributable to rising age-specific rates and 21% to population growth and aging [18]. These global trends with

**Table 1   Patient and tumor characteristics**

| Variables | $N^a$ (%) |
|---|---|
| **Sex** | |
| Male | 13767 (48.1) |
| Female | 14857 (51.9) |
| **Age (years)** | |
| <20 | 305 (1.0) |
| 20–29 | 1223 (4.3) |
| 30–39 | 2857 (10.0) |
| 40–49 | 4888 (17.1) |
| 50–59 | 6095 (21.3) |
| 60–69 | 6007 (21.0) |
| 70–79 | 4817 (16.8) |
| ≥80 | 2432 (8.5) |
| **Ethnicity/skin color** | |
| White | 14849 (75.0) |
| Brown | 4346 (21.9) |
| Black | 478 (2.4) |
| Yellow/Indigenous | 138 (0.7) |
| **Education level (years)** | |
| <8 | 10700 (50.4) |
| ≥8 | 10535 (49.6) |
| **Geographical area of the cancer center** | |
| Southeast | 13544 (47.3) |
| South | 9646 (33.7) |
| Northeast | 4405 (15.4) |
| North/Middle-West | 1029 (3.6) |
| **Origin of referral to the cancer center** | |
| Public system | 13570 (77.1) |
| Private facility | 4030 (22.9) |
| **Period of diagnosis** | |
| 2000–2003 | 4204 (14.7) |
| 2004–2007 | 7151 (25.0) |
| 2008–2011 | 9636 (33.7) |
| 2012–2016 | 7633 (26.7) |
| **Clinical stage (TNM)** | |
| I | 4558 (32.0) |
| II | 3024 (21.2) |
| III | 2941 (20.6) |
| IV | 3726 (26.1) |
| **Primary site** | |
| Head and neck | 5444 (19.0) |
| Trunk | 7757 (27.1) |
| Upper limbs, including shoulders | 3998 (14.0) |
| Lower limbs, including hips | 7499 (26.2) |
| Other | 3926 (13.7) |
| **Histology** | |
| Malignant melanoma, not otherwise specified | 22350 (78.1) |
| Nodular melanoma | 2923 (10.2) |
| Superficial spreading melanoma | 1188 (4.1) |
| Acral lentiginous melanoma | 812 (2.8) |
| Lentigo maligna | 549 (1.9) |
| Amelanotic melanoma | 260 (0.9) |
| Spindle cell melanoma, not otherwise specified | 146 (0.5) |
| Other | 396 (1.4) |
| Total | 28624 (100.0) |

[a]Differences are due to missing information.

continued increases in melanoma numbers will challenge melanoma control in the very young Brazilian population.

In the past decades, the incidence of melanoma increased in epidemic proportions. The main reason for that pseudoepidemic is the improved criteria and techniques for diagnosis that allow melanomas to be recognized more accurately and at earlier stages. Some countries have registered an increase in the skin biopsy rate of ~6% per year despite an increase in the overall melanoma incidence rate of 1% per year over the same period of time [19,20].

**Fig. 2**
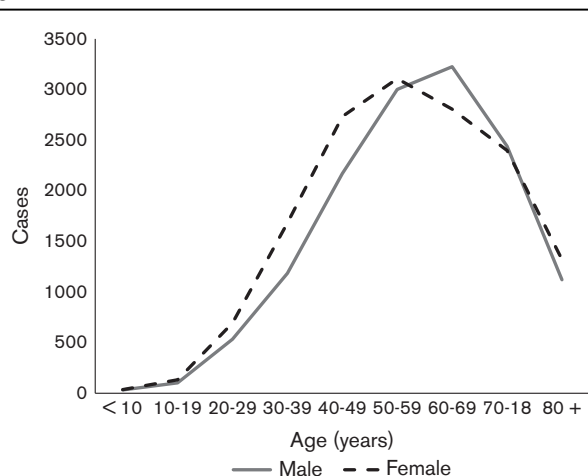


Age at diagnosis of melanoma by sex in Brazil (2000–2014).

**Table 2   Mean age at the diagnosis**

| Variables | Mean ± SD | $P$-value |
|---|---|---|
| **Sex** | | <0.01* |
| Male | 58±16 | |
| Female | 56.5±17 | |
| **Ethnicity/skin color** | | <0.001* |
| White | 55.9±16.4 | |
| Brown | 59.2±16.8 | |
| Black | 61.6±15.4 | |
| Yellow/Indigenous | 54.7±16.8 | |
| **Education level (years)** | | <0.001* |
| <8 | 62±15.6 | |
| ≥8 | 52±15.8 | |
| **Geographical area of the cancer center** | | <0.001* |
| Southeast | 58.3±16.6 | |
| South | 55±15.8 | |
| Northeast | 58.7±17.3 | |
| North/Middle-West | 56.6±16.9 | |
| **Period of diagnosis** | | <0.001* |
| 2000–2003 | 55.7±16.8 | |
| 2004–2007 | 56.2±16.5 | |
| 2008–2011 | 57.5±16.5 | |
| 2012–2016 | 58.6±16.2 | |
| **Clinical stage (TNM)** | | <0.001* |
| I | 55.8±16.1 | |
| II | 59.7±16.1 | |
| III | 58.2±15.8 | |
| IV | 57.5±15.4 | |
| **Primary site** | | <0.001* |
| Head and neck | 60.6±17.2 | |
| Trunk | 53.7±15.6 | |
| Upper limbs, including shoulders | 56.3±16.2 | |
| Lower limbs, including hips | 59.3±16.5 | |
| Other | 56.3±16 | |
| **Histology** | | <0.001* |
| Malignant melanoma, not otherwise specified | 56.7±16.5 | |
| Nodular melanoma | 58.9±16.6 | |
| Superficial spreading melanoma | 54.9±15.5 | |
| Acral lentiginous melanoma | 64.4±14.3 | |
| Lentigo maligna | 65.5±14.4 | |
| Amelanotic melanoma | 56.7±16.4 | |
| Spindle cell melanoma, not otherwise specified | 61.4±17.5 | |
| Other | 56±17.9 | |
| Total | 57.2±16.5 | – |

*Statistically significant.

**Table 3** Sex, age, and skin color/ethnicity according to topography and histology

| Variables | %Male | %Age (≥60 years) | %Black[a] |
|---|---|---|---|
| Primary site | | | |
| Head and neck | 52.4* | 56.5* | 23.5 |
| Trunk | 55.8* | 36.5* | 16.7* |
| Upper limbs, including shoulders | 38.7* | 43.2* | 19.1* |
| Lower limbs, including hips | 40.0* | 52.2* | 38.0* |
| Other | 52.0* | 43.5* | 21.6* |
| Histology | | | |
| Malignant melanoma, not otherwise specified | 47.7* | 44.8* | 24.5 |
| Nodular melanoma | 52.3* | 50.6* | 21.6* |
| Superficial spreading melanoma | 45.0* | 38.9* | 8.3* |
| Acral lentiginous melanoma | 47.0 | 64.4* | 51.8* |
| Lentigo maligna | 43.4* | 71.0* | 19.9 |
| Amelanotic melanoma | 53.1 | 44.2 | 34.2* |
| Spindle cell melanoma, not otherwise specified | 61.6* | 58.9* | 44.6* |
| Other | 50.3 | 48.5 | 29.2 |
| Total | 48.1 | 46.3 | 24.5 |

*Statistically significant.
[a]Brown or Black.

**Table 4** Treatment characteristics

| Variables | N[a] (%) |
|---|---|
| Time between diagnosis and treatment (days) | |
| <30 | 5187 (35.2) |
| 30–59 | 4027 (27.3) |
| 60–89 | 2054 (13.9) |
| ≥90 | 3475 (23.6) |
| First treatment[b] | |
| Surgery | 20211 (82.4) |
| Chemotherapy | 4518 (18.4) |
| Radiotherapy | 2936 (12.0) |
| Immunotherapy | 618 (2.2) |
| Hormonal therapy | 116 (0.4) |
| No treatment | 4120 (14.3) |
| Early death[c] | |
| Yes | 1867 (11.0) |
| No | 15125 (89.0) |
| Total | 28624 (100.0) |

[a]Differences are owing to missing information.
[b]Some patients received more than one treatment modality.
[c]Death before the end of the first treatment.

Data from Private Health Management Organizations have shown that 41.7% of melanomas were self-discovered by patients; healthcare providers detected 29.9% and others detected 27% and that the main component in melanoma diagnosis delay was patient-related, as only a small part of the patients knew that melanoma was a serious skin cancer, and most thought that the pigmented lesion was not important, causing a delay in seeking medical assistance [21], not to mention the disparities depending on the medical system [22]. This database with high proportion of advanced cases can be related to a deficient knowledge of the population regarding melanoma, physicians' misdiagnoses of suspicious lesions contributing to delays in diagnosis and long waiting times for medical assistance. It must be also considered that in Brazil, it is recommended but not mandatory to register all cancer cases, but the

**Table 5** Variables associated with distant metastases at diagnosis

| Variables | Distant metastases [N (%)] | Localized/ regional [N (%)] | P-value |
|---|---|---|---|
| Sex | | | **<0.001** |
| Male | 2190 (58.8) | 4852 (46.1) | |
| Female | 1536 (41.2) | 5671 (53.9) | |
| Age (mean±SD) (years) | 57.5±15.4 | 57.6±16.1 | 0.6 |
| Age (years) | | | 1 |
| <60 | 1980 (53.1) | 5588 (53.1) | |
| ≥60 | 1746 (46.9) | 4935 (46.9) | |
| Ethnicity/skin color | | | **<0.001** |
| White | 1832 (72) | 3431 (76.6) | |
| Brown | 629 (24.7) | 909 (20.3) | |
| Black | 64 (2.5) | 94 (2.1) | |
| Yellow/Indigenous | 19 (0.7) | 43 (1.0) | |
| Education level (years) | | | **<0.001** |
| <8 | 1520 (54.5) | 3623 (47.8) | |
| ≥8 | 1267 (45.5) | 3956 (52.2) | |
| Geographical area of the cancer center | | | **<0.001** |
| Southeast | 1701 (45.7) | 6925 (65.8) | |
| South | 1304 (35.0) | 2489 (23.7) | |
| Northeast | 564 (15.1) | 922 (8.8) | |
| North/Middle-West | 157 (4.2) | 187 (1.8) | |
| Origin of referral to the cancer center | | | 0.9 |
| Public system | 1786 (78.3) | 3085 (78.3) | |
| Private facility | 494 (21.7) | 857 (21.7) | |
| Topography | | | **<0.001** |
| Head and neck | 629 (16.9) | 2091 (19.9) | |
| Trunk | 934 (25.1) | 2866 (27.2) | |
| Upper limbs, including shoulders | 326 (8.7) | 1688 (16.0) | |
| Lower limbs, including hips | 885 (23.8) | 2808 (26.7) | |
| Other | 952 (25.6) | 1070 (10.2) | |
| Histology | | | **<0.001** |
| Malignant melanoma, not otherwise specified | 3068 (82.3) | 8038 (76.4) | |
| Nodular melanoma | 389 (10.4) | 1039 (9.9) | |
| Superficial spreading melanoma | 31 (0.8) | 592 (5.6) | |
| Acral lentiginous melanoma | 66 (1.8) | 361 (3.4) | |
| Lentigo maligna | 15 (0.4) | 257 (2.4) | |
| Amelanotic melanoma | 65 (1.7) | 64 (0.6) | |
| Spindle cell melanoma, not otherwise specified | 33 (0.9) | 37 (0.4) | |
| Other | 59 (1.6) | 135 (1.3) | |
| Time between diagnosis and treatment (days) | | | **<0.001** |
| <30 | 732 (36.9) | 1605 (29.4) | |
| 30–59 | 469 (23.6) | 1578 (28.9) | |
| 60–89 | 256 (12.9) | 902 (16.5) | |
| ≥90 | 528 (26.6) | 1371 (25.1) | |
| Early death[a] | | | **<0.001** |
| Yes | 1279 (60.0) | 6631 (95.2) | |
| No | 851 (40.0) | 332 (4.8) | |

[a]Death before the end of the first treatment.
Statistically significant differences are in bold.

majority of, if not all, cases at public health system that require surgery or systemic treatment are registered, leading to a significantly higher proportion of late-stage disease.

There is no global consensus regarding survival over time. In Europe from 2000 to 2014 there was a tiny increase in mortality in men and a decrease in women.

Part of the improvement in survival may be attributed to early diagnosis [23]. Regarding mortality in Brazil, the results presented here were quite similar at the same time interval with mortality in men ranging from 0.85 to 0.90 per 100 000 and in women decreasing from 0.56 to 0.53 per 100 000. Although the incidence rates have continued to increase in recent birth cohorts, mortality rates have stabilized in many countries [24].

Certain populations, such as men older than 60 years and lower socioeconomic status groups, face a greater disease burden. For any given stage and across all ages, men have shown worse melanoma survival than women, and low socioeconomic status groups have increased levels of mortality [25,26]. Almost 50% of patients in this cohort were older than 60 years. It is a very high rate in older men considering that less than 20% of Brazilian population is older than 60 years [17]. This is completely in accordance with most of global data that point age as the highest risk of presenting with or dying owing to melanoma [27]. Of the majority of patients who had less than 8 years of schooling and 2/3 who were referred by the public health system facilities to tertiary care centers, they may represent a group that works at a job that includes plenty of physical labor, with most of them working outdoors.

As a continental country, Brazil has a large area at the Equator line from north to under the Tropic of Capricorn at the south. An opposite relationship in Brazil was observed with highest melanoma incidences at areas of low rate of ultraviolet radiation, where the influence of European ancestry is robust [28]. In many White populations, including that of the USA, melanoma incidences and mortality rates increase according to proximity of residence to the Equator [29–31]. In UK, melanoma incidence was high in young people in the north, reversing the expected north–south incidence gradients. Prevalent sunbed use in northern UK and holiday sun exposure abroad may explain these emerging trends [32]. This argument is not valid in Brazil because sunbeds were forbidden by law since 2009, but even before, they were not popular among Brazilians. Although there are reports proposing that melanoma incidence is associated with increase UV index and lower latitude only in non-Hispanic Whites, it was not confirmed in this Brazilian cohort where a high interracial combination results in a complex heterogeneous genetic population and also where race is self-defined by patient [28–30].

A direct correlation between sunburn and melanoma prevalence among men and women was not established in this cohort as previously described in the literature [31]. Trunk melanoma was more prevalent in men (55.8%) but we had no data to support its relation with sunburn, recreation or occupational sunburn. Trunk melanoma could be an indicator of recreational sun exposure in women and could represent occupational exposure in men, although occupational sun exposure is not related to increased risk of melanoma [33,34].

There is an algorithm to predict the risk of melanoma in White population according to individual case–control characteristics. These could be practical but must need validation in different cohorts to estimate the absolute risk of developing melanoma combined with population-specific data [35].

Although there is a spectrum of ultraviolet radiation with a different geographic distribution, this study was not powered to establish any relation between melanoma induction and ultraviolet A or ultraviolet B radiation. Polymorphisms in the *MC1R* gene are a major source of normal variation in human hair color, skin pigmentation, response to ultraviolet radiation, and skin cancer susceptibility; however, there is no study evaluating polymorphisms in the *MC1R* gene in the Brazilian population [36]. Epidemiology of melanoma is complex, and individual risk depends on sun exposure, host and genetic factors, as well as in their interactions. Sun exposure can be classified as intermittent, chronic, or cumulative overall exposure, and each appears to have a different effect on each type of melanoma.

Recent data support some anthropometric characteristics as risk factors for melanoma, but this study did not compare body size, weight, height and birth weight and neither reported a relation with weight loss and decreasing melanoma risk as reported in the literature [37,38]. Vitamin D and its receptor, vitamin D reposition, smoking, alcohol consumption, and dietary habits have been related to melanoma development playing many different roles in the carcinogenesis process [39–43], but this study was not designed to establish any correlation with these habits and melanoma in Brazil.

Nearly five million immigrants were attracted to Brazil between 1870 and 1953; most of the immigrants were from Italy or Portugal, but also significant numbers of Germans, Spaniards, Japanese and Syrian-Lebanese. They chose to inhabit the south and southeast part of Brazil, far from Equator, with lower ultraviolet radiation. These two regions concentrate 56.6% of Brazilian population and 80% of Brazilian melanoma (*http://www.inca.gov.br/estimativa/ 2018/*) [17]. Data of genetic studies concluded that European ancestry accounts for 67 and 77% of the heritage of southeast and south Brazilian population, respectively [44]. At areas close to Equator with high ultraviolet radiation exposure but low melanoma incidence like northeast, Brazilians have 27% of African ancestry and 15% of native American and in the north, 16% African and 32% of native American ancestry [44]. It appears that melanoma incidence is more related to genetic background than the geographical and ultraviolet radiation exposition as confirmed in other studies [45]. In the current study, the ethnicity/skin color distribution of melanoma cases was composed of 75.0% White, 21.9% Brown, 2.4% Black, and

0.7% Yellow/Indigenous, whereas in the country, 50.2% are White, 42.5% Brown, 6.6% Black, and 0.7% Yellow/Indigenous [17].

In this cohort, there was no difference in the number of patients diagnosed with melanoma regarding education level. However, patients with 8 or more years of study had a lower mean age at diagnosis comparing with patients with less than 8 years of study. Furthermore, patients with higher education levels had less distant metastasis than understudied ones. It may represent underprivileged minorities that had poor access to medical assistance, including diagnosis and treatment [46]. Similar findings are observed with the Hispanic population in the USA [47,48].

Brazil has more than 200 million inhabitants, and the main health provider is a public system called Sistema Único de Saúde. By law, the Brazilian government is obliged to provide, at no cost, all healthcare for the citizens, including preventive and primary to tertiary healthcare. Up to 76% of population have only public healthcare assistance, which is very limited regarding access to dermatologists and many other facilities that help on early melanoma diagnosis.

There has been a significant survival benefit in patients with metastatic melanoma since the introduction of immune checkpoint blocking and molecular targeted agents [49]. This study was not able to measure it, as the data were collected until 2014, when neither immunotherapies nor targeted therapies were available in Brazil for patients treated on public healthcare, which represent 77.1% of the study patients and ∼76% of the entire Brazilian population. Until now, the only treatment offered by public healthcare system for metastatic melanoma is dacarbazine as first line and palliative care as second line.

## Conclusion
Understanding the epidemiology, mortality trends, and productivity losses attributed to melanoma is important for evaluating the feasibility and trade-offs of public health and behavioral counseling interventions that focus on promoting skin cancer prevention. Brazil is a large country with a very young population and a low rate of melanoma incidence and prevalence, which should increase over the years. Therefore, further studies are clearly warranted.

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