

Trends in Melanoma Mortality in Brazil: A Registry-Based Study

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PURPOSE A substantial increase in melanoma incidence has been consistently observed worldwide over the past decades. However, melanoma mortality rates have remained stable or declined over the past years in most regions. Given the paucity of melanoma mortality data for different Brazilian regions, we sought to describe melanoma mortality trends in southeastern Brazil and their relationship with demographic variables.

MATERIALS AND METHODS A cross-sectional registry-based analysis was conducted to describe melanoma mortality trends in the state of São Paulo, Brazil, from 1996 to 2016. Demographic information from melanoma-related death records, including sex and age, was collected from the Fundação Sistema Estadual de Análise de Dados database. The annual percentage change (APC) was calculated to identify mortality trends over the period.

RESULTS An increasing melanoma mortality trend was detected among males, regardless of age (APC, 1.72%; $P < .001$), and was more pronounced for men ≥ 60 years old (APC, 2.63%; $P < .001$). Melanoma mortality rates have also increased for patients ≥ 60 years old, regardless of sex (APC, 1.11%; $P < .001$). A non-statistically significant increase in the overall melanoma mortality rate was observed over the 20-year period analyzed (APC, 0.36%; $P = .4$).

CONCLUSION Our data suggest a stable melanoma mortality over the past two decades for the overall population studied; however, a significant increase in melanoma mortality rates has been demonstrated among males and in the population ≥ 60 years old, emphasizing the need to implement prevention strategies and expand access to effective therapies for this population.

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INTRODUCTION

Melanoma is a highly aggressive primary cutaneous malignancy and is responsible for a majority of skin cancer-related deaths. Although the incidence of melanoma varies significantly among different regions, a substantial increase in its incidence has been consistently observed worldwide.¹⁻⁴ In the United States, melanoma currently represents the fifth most incident malignancy in men and sixth in women⁵ after a doubling of its incidence between 1982 and 2011.³ In Europe, data from population-based cancer registries during the period from 1995 to 2012 also demonstrated a statistically significant increase in incidence of invasive melanoma.⁶ This trend of increased incidence is similar in regions with the highest incidence of melanoma, such as Australia.⁷

Interestingly, this increase in incidence does not appear to be directly translating to a proportional increase in mortality.³ In most regions, melanoma

mortality rates have remained stable or declined over the past years. Although melanoma mortality trends may vary between different age groups,⁸ in the United States³ overall mortality from melanoma has remained unchanged, and Australian data also point to a trend toward stability or decrease in melanoma mortality rates.⁷

Brazil is a country of continental dimensions, predominantly located in a region of low latitude and high UV radiation incidence, a known risk factor for melanoma.⁹ Data from the Brazilian National Cancer Institute for the year 2020 indicated melanoma incidence rates of 4.03 new cases per 100,000 for men and 3.94 new cases per 100,000 for women in Brazil.¹⁰ However, mortality data for different Brazilian regions remain scarce and are potentially affected by underreporting. We sought to describe melanoma mortality trends in southeastern Brazil over the past years and their relationship with demographic variables.

ASSOCIATED CONTENT

Data Supplement Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

We sought to describe melanoma mortality trends in southeastern Brazil and their relationship with demographic variables.

Knowledge Generated

An increasing melanoma mortality trend was detected among males, regardless of age, and was more pronounced for men older than age 60 years. Melanoma mortality rates have also increased in patients older than age 60 years, regardless of sex.

Relevance

A significant increase in melanoma mortality rates has been demonstrated among males and in the population older than age 60 years, emphasizing the need to implement prevention strategies and expand access to effective therapies for these populations.

MATERIAL AND METHODS

A cross-sectional registry-based analysis was conducted to describe melanoma mortality trends in the state of São Paulo, Brazil. Melanoma mortality records in the state of São Paulo retrieved from death certificates were surveyed from 1996 through 2016 using the 10th edition of the International Classification of Diseases. Demographic information from melanoma-related death records, including sex and age, was collected from the Sistema Estadual de Análise de Dados (SEADE) database. The SEADE Foundation is an official entity charged with producing statistical data for the state of São Paulo and assembling information from all death certificates issued in the state.¹¹ Additional population data, such as total resident population, sex, and age distribution, were used to calculate indicators and were also collected from the SEADE database (SEADE Population Projections System).¹²

Mortality rates are expressed in units of deaths per 100,000 individuals per year. Annual age-standardized mortality rates were ascertained using the direct method and using 2010 São Paulo State's population as reference. Mortality trends were also analyzed by sex and broad age groups (0-29, 30-59 and ≥ 60 years old) to ascertain age-specific temporal trends.

The annual percentage change (APC) was calculated to identify mortality trends. The APC is one way to characterize trends in cancer rates over time. An increase or decrease in trend is statistically significant when different $P < .05$ and stable when $P > .05$.¹³ Trend analysis was carried out by linear regression using the Joinpoint Regression Program, version 4.7.0.0 from February 2019, from the SEER Program of the National Cancer Institute.¹⁴

RESULTS

Melanoma Mortality Trends From 1996 to 2016

From 1996 to 2016, 8,217 deaths from melanoma were recorded in the state of São Paulo, Brazil. The average annual mortality rate as a result of melanoma was 1.05 per

100,000 inhabitants per year (1.17 per 100,000 inhabitants per year for males and 0.93 per 100,000 inhabitants per year for females) between 1996 and 2016. A non-statistically significant increase in the overall melanoma mortality rate in the general population was observed over the 20-year period analyzed (APC, 0.36%; $P = .4$). Male mortality from melanoma exceeded female rates throughout the period since 1999 (Fig 1).

An increasing mortality time trend was detected among males, regardless of age (APC, 1.72%; $P < .001$), ranging from 1.10 in 1996 to its highest level of 1.36 per 100,000 in 2013. Among females, a non-statistically significant decrease in mortality was observed (APC, -1.07% ; $P = .1$), ranging from 1.22 in 1996 to 0.80 in 2016, with a minimum value of 0.61 in 2000 (Table 1).

Age-Specific Melanoma Mortality Trends

The average annual melanoma mortality rates in the age groups of 0-29, 30-59, and ≥ 60 years old were 0.06, 0.99, and 5.32 per 100,000 inhabitants per year, respectively. Throughout the period, melanoma mortality was concentrated in the age group ≥ 60 years, which accounted for 58.2% ($n = 4,783$) of the deaths, followed by the group age

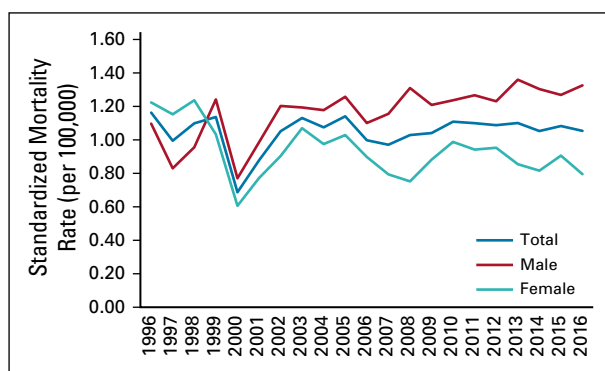


FIG 1. Standardized melanoma mortality rates (per 100,000) by sex in the state of São Paulo (Brazil) from 1996 to 2016.

TABLE 1. Melanoma Mortality Rates (per 100,000) by Sex in the State of São Paulo (Brazil) from 1996 to 2016

Sex and Age Group	APC	95% CI	P
All	0.36	-0.5 to 1.2	.4
Female	-1.07	-2.3 to 0.1	.1
Male	1.72	0.9 to 2.6	< .0001
All			
< 30 years	-0.11	-2.5 to 2.4	.9
30-59 years	-0.73	-1.7 to -1.6	.1
≥ 60 years	1.11	0.1 to 2.1	< .0001
Female			
< 30 years	-3	-6 to 0.1	.1
30-59 years	-1.89	-3.4 to -0.4	< .0001
≥ 60 years	-0.5	-1.7 to 0.7	.4
Male			
< 30 years	2.25	-1.2 to 5.9	.2
30-59 years	0.37	-0.8 to 1.6	.5
≥ 60 years	2.63	1.6 to 3.7	< .0001

Abbreviation: APC, annual percentage change.

30-59 years, with 38.9% ($n = 3,196$) of the deaths (Table 2). Average annual melanoma mortality rates were higher among men age ≥ 60 years (6.57 per 100,000 inhabitants per year for men and 4.36 per 100,000 inhabitants per year for women) and in the population between 30 and 59 years (1.14 per 100,000 inhabitants per year for men and 0.84 per 100,000 inhabitants per year for women); however, there was no significant sex difference in the population younger than age 30 years (0.06 per 100,000 inhabitants per year for both males and females).

Mortality patterns by broad age group were quite distinct (Fig 2). An increasing mortality time trend was detected for the population ≥ 60 years (APC, 1.11%; $P < .001$) regardless of sex. The male population ≥ 60 years old showed the most pronounced increase in mortality (APC, 2.63%; $P < .001$), with mortality rates ranging from 6.18 per 100,000 in 1996 to 8.44 per 100,000 in 2016. Mortality from melanoma remained stable among men and women younger than 60 years, although there was a statistically significant decrease in female mortality rates for the age group between 30 and 59 years (APC, -1.89%; $P < .001$).

DISCUSSION

Based on this cross-sectional analysis of mortality records retrieved from death certificates, an upward trend in mortality rates has been demonstrated during the 20-year period analyzed in the state of São Paulo, Brazil. Male mortality from melanoma exceeded female rates almost throughout the period and during the past decade, and there was a significant increase in cause-specific mortality over the years among male patients. The increase in mortality was more pronounced among men than among

women. Mortality as a result of melanoma was concentrated in the age group ≥ 60 years, whose male population presented the most significant increase in mortality in the period evaluated. A trend toward stabilization of mortality was observed among women and in the population < 60 years.

After a consistent increase in incidence observed in the United States,³ Europe,⁶ and Australia and New Zealand,² in most regions, there seems to be a trend toward stabilization or reduction in melanoma mortality over the past years.^{3,7} In contrast to data from these regions, our data suggest an increase in melanoma mortality in southeastern Brazil, especially among males. Indeed, in line with our data, a registry-based Brazilian study analyzing the period from 1980 to 2005 showed an increase in melanoma mortality in the country, with an annual APC of 0.6% for the whole country, with higher mortality rates found in the South and Southeast regions and marked heterogeneity between different Brazilian regions.¹⁵ According to the Brazilian 2010 census, 47.7% of the Brazilian population is self-declared white, with a heterogeneous ethnic distribution across the country.¹⁶ In the South and Southeast, 78.5% and 56.7% of residents were categorized as White, respectively; whereas in the North region, $> 75\%$ of residents were categorized as Nonwhite.¹⁶ Thus, the heterogeneity of melanoma mortality in different Brazilian regions could be explained to some degree by the different ethnic compositions of each region,¹⁵ although influences of clinicopathologic, social, and health care access issues cannot be ruled out.¹⁷ Although there was an apparent difference in the mortality trend in the first 4 years of our series, we were not able to identify clinical, epidemiologic, or methodologic factors that could explain this possible variation.

Regarding sex- and age-specific trends in melanoma mortality, our findings of higher mortality increases among men, especially in the age group ≥ 60 years, are consistent with data from Brazil,^{15,18} Australia,⁸ and the United States.^{19,20} Although sex differences in melanoma incidence and mortality have been consistently observed, their causes have not been completely elucidated and could be related to behavioral or biologic factors, such as the expression of hormone receptors,²¹ or even to genetically determined differences, such as tumor mutational burden variations.²² Although there are no clinical trials demonstrating that screening decreases the mortality from melanoma, identifying subgroups with increasing mortality trends could prompt the design of additional trials for higher-risk populations or public campaigns encouraging sun protection for skin cancer prevention.

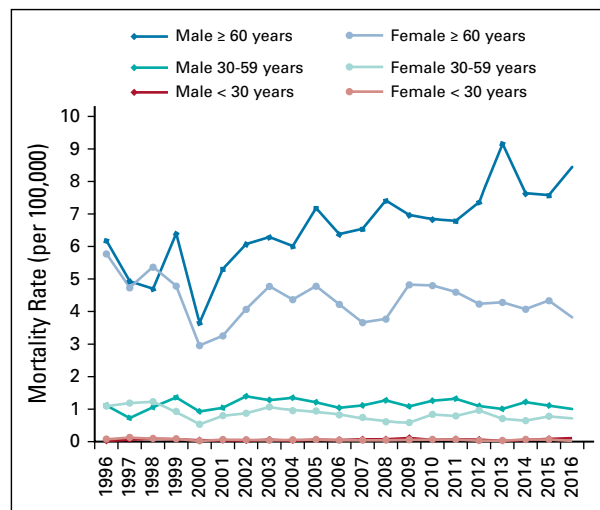
It has been speculated that the disparity between the incidence and mortality trends could be related to increased screening for cutaneous malignancies with consequent higher detection of early-stage cancers, which are associated with more favorable clinical outcomes.²³ However,

TABLE 2. Melanoma Mortality Rates (per 100,000) by Age Groups in the State of São Paulo (Brazil) From 1996 to 2016

Year	No. of Deaths per 100,000 Population								
	< 30 Years			30-59 Years			≥ 60 Years		
	Female	Male	Total	Female	Male	Total	Female	Male	Total
1996	0.07	0.02	0.05	1.09	1.11	1.10	5.78	6.18	5.96
1997	0.12	0.06	0.09	1.18	0.72	0.96	4.74	4.93	4.82
1998	0.09	0.09	0.09	1.23	1.06	1.14	5.37	4.70	5.08
1999	0.08	0.07	0.08	0.93	1.36	1.14	4.79	6.40	5.50
2000	0.02	0.04	0.03	0.53	0.93	0.72	2.96	3.65	3.26
2001	0.06	0.04	0.05	0.79	1.04	0.91	3.25	5.31	4.15
2002	0.05	0.03	0.04	0.87	1.39	1.12	4.07	6.08	4.95
2003	0.04	0.06	0.05	1.06	1.28	1.17	4.78	6.29	5.44
2004	0.05	0.03	0.04	0.95	1.35	1.14	4.37	6.01	5.09
2005	0.06	0.06	0.06	0.94	1.21	1.07	4.79	7.18	5.83
2006	0.04	0.05	0.05	0.82	1.04	0.93	4.23	6.38	5.16
2007	0.04	0.07	0.06	0.74	1.11	0.92	3.66	6.54	4.91
2008	0.04	0.07	0.07	0.61	1.27	0.92	3.77	7.42	5.35
2009	0.05	0.11	0.08	0.58	1.08	0.82	4.83	6.97	5.76
2010	0.06	0.05	0.06	0.83	1.26	1.04	4.80	6.84	5.68
2011	0.06	0.07	0.07	0.78	1.32	1.04	4.60	6.79	5.55
2012	0.03	0.06	0.05	0.96	1.09	1.02	4.24	7.37	5.59
2013	0.03	0.02	0.03	0.71	1.01	0.85	4.29	9.17	6.40
2014	0.06	0.05	0.06	0.64	1.22	0.92	4.08	7.64	5.61
2015	0.06	0.08	0.07	0.78	1.11	0.94	4.34	7.58	5.74
2016	0.02	0.10	0.06	0.72	1.00	0.86	3.82	8.44	5.82

data from the SEER Program found an increasing incidence of melanoma of all thicknesses, indicating that the observed disproportion could not be fully explained by increased detection of early-stage cancers.²⁴

Over the past decade, rapid and significant improvements in efficacy of melanoma therapeutics have been achieved, in both the adjuvant and metastatic settings, especially as a result of the incorporation of immune checkpoint inhibitors and targeted agents directed at the MAP kinase pathway in *BRAF*-mutant melanomas.²⁵ Since 2011, the use of these therapies has more than doubled the expected median overall survival of patients with metastatic melanoma, with a subset of patients having durable response rates and long-term tumor control,²⁵ and this may have affected melanoma mortality trends in some regions. Nevertheless, these revolutionary therapies are only accessible to a minority of the Brazilian population, and chemotherapy remains the standard of care for patients with advanced melanoma treated through Brazil's public health system, which encompasses > 70% of the population.²⁶ Similarly, adjuvant treatments in the form of

**FIG 2.** Melanoma mortality trends (per 100,000) by age groups in the state of São Paulo (Brazil) from 1996 to 2016.

immune checkpoint inhibitors or *BRAF*/*MEK* inhibitors, now considered standard of care options for those with stage III melanoma, are only available through supplemental health care. These inequalities in access to efficacious and potentially curative approaches for patients with melanoma could also explain some of the findings of our study. In addition, challenges such as limited availability of multidisciplinary teams and referral centers, late diagnosis, and suboptimal or delayed initial surgical management could also negatively affect the mortality rates observed.

To our knowledge, this is the first series to report the evolution of melanoma mortality during a 20-year period in southeastern Brazil. Strengths of our study include the fact that the SEADE Foundation receives all death certificates issued in the state of São Paulo, which limits the possibility of registration bias. Our study has limitations, including the fact that the data were obtained from information on death certificates, which could introduce a potential bias considering that some physicians might have not registered melanoma as the basic cause of death in some cases. In addition, reliable data on the evolution of the incidence of melanoma in our population are limited, which may also affect a broader interpretation of our data.

In conclusion, our data suggest a stable melanoma mortality rate over the past two decades for the overall population studied. However, a significant increase in melanoma mortality rates has been demonstrated among males and in the population ≥ 60 years old, emphasizing the need to expand access to effective therapies for this population.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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