Trends in non-Melanoma Skin Cancer Mortality in Brazil and its Macroregions

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Tendências na Mortalidade por Câncer de Pele não Melanoma no Brasil e suas Macrorregiões

Tendencias de la Mortalidade por Cáncer de Piel no Melanoma em Brasil y sus Macrorregiones

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ABSTRACT

Introduction: Non-melanoma skin cancer (NMSC) is the most common among all malignancies. **Objective:** To describe trends in NMSC mortality rates in Brazil and its macroregions from 2001 to 2018. **Method:** Adjusted mortality rates stratified by sex were estimated and presented per 100,000 person-years. An autoregressive analysis was implemented to assess temporal trends, annual percent change (APC) and 95% Confidence Intervals (95% CI). **Results:** There were 27,550 NMSC deaths in Brazil with higher frequency in males (58.1%) and among individuals aged ≥70 years (64.3%). The overall rates were 2.25 (males) and 1.22 (females) per 100,000 person-years. The trends followed an upward direction in Brazil for males (APC: 2.91%; 95% CI: 1.96%; 3.86%) and females (APC: 3.51%; 95% CI: 2.68%; 4.34%). The same occurred in the North Region, in males (APC: 9.75%; 95% CI: 7.68%; 11.86%) and in females (APC: 10.38; 95% CI: 5.77%; 15.21%), as well as in Northeast Region, in males (APC: 9.98%; 95% CI: 5.59%; 14.57%) and in females (APC: 8.34%; 95% CI: 3.29%; 13.64%). **Conclusion:** NMSC deaths are not rare in Brazil. Upward mortality trends were observed for the whole country and in the North and Northeast regions, which are the closest to the Equator line and also the least developed socioeconomically. A synergism between different types of inequalities and environmental exposure in these macroregions may be promoting an increase in the number of NMSC deaths, a type of cancer which is considered completely preventable.

Key words: skin neoplasms/mortality; time series studies; developing countries.

RESUMO

Introdução: O câncer de pele não melanoma (CPNM) é o mais comum entre todas as malignidades. **Objetivo:** Descrever as tendências da mortalidade por CPNM no Brasil e nas suas Macrorregiões, de 2001 a 2018. **Método:** As taxas de mortalidade ajustadas por idade e estratificadas por sexo foram apresentadas por 100 mil pessoas-ano. Uma análise autorregressiva foi implementada para avaliar tendências, Mudança Percentual Anual (MPA) e intervalos de confiança de 95% (IC 95%). **Resultados:** Houve 27.550 óbitos por CPNM no Brasil com maior frequência em homens (58,1%) e entre pessoas de 70 anos e mais (64,3%). As taxas globais foram de 2,25 (homens) e 1,22 (mulheres) por 100 mil pessoas-ano. As tendências seguiram em elevação no Brasil, em homens (MPA: 2,91%; IC95%: 1,96%; 3,86%) e em mulheres (MPA: 3,51%; IC95%: 2,68%; 4,34%). O mesmo ocorreu na Região Norte, em homens (MPA: 9,75%; IC95%: 7,68%; 11,86%) e em mulheres (MPA: 10,38%; IC95%: 5,77%; 15,21%), bem como na Região Nordeste, em homens (MPA: 9,98%; IC95%: 5,59%; 14,57%) e em mulheres (MPA: 8,34%; IC95%: 3,29%; 13,64%). **Conclusão:** Os óbitos por CPNM não são raridade no Brasil. O país e as Regiões Norte e Nordeste experimentaram taxas com tendência em elevação. Norte e Nordeste são as Regiões mais próximas da Linha do Equador e as menos desenvolvidas socioeconomicamente. Nessas Macrorregiões, um sinergismo entre diferentes tipos de desigualdades e exposições ambientais pode estar promovendo um aumento dos óbitos por esse tipo de câncer considerado totalmente evitável.

Palavras-chave: neoplasias cutâneas/mortalidade; estudos de séries temporais; países em desenvolvimento.

RESUMEN

Introducción: El carcinoma de piel no melanoma (CPNM) es el más común dentre todas las neoplasias malignas. **Objetivo:** Describir las tendencias de la mortalidad por CPNM en Brasil y sus macrorregiones, de 2001 a 2018. **Método:** Las tasas de mortalidad ajustadas por edad y estratificadas según sexo fueron presentadas por 100.000 personas-año. Se implementó una análisis autoregresiva para evaluar las tendencias, el porcentaje estimado de cambio anual (PECA) y sus intervalos de confianza del 95% (IC 95%). **Resultados:** Hubo 27.550 muertes por CPNM en Brasil con mayor frecuencia en hombres (58,1%) y entre personas de edad ≥70 años (64,3%). Las tasas generales fueron 2,25 (hombres) y 1,22 (mujeres) por 100.000 personas-año. Las tendencias continuaron aumentando en Brasil, en hombres (PECA: 2,91%; IC 95%: 1,96%; 3,86%) y en mujeres (PECA: 3,51%; IC 95%: 2,68%; 4,34%). Lo mismo ocurrió en el Norte, en hombres (PECA: 9,75%; IC 95%: 7,68%; 11,86%) y en mujeres (PECA: 10,38%; IC 95%: 5,77%; 15,21%), así como en el Nordeste, en hombres (PECA: 9,98%; IC 95%: 5,59%; 14,57%) y en mujeres (PECA: 8,34%; IC 95%: 3, 29%; 13,64%). **Conclusión:** Las muertes por CPNM no son una rareza en Brasil. El país y las regiones Norte y Nordeste experimentaron tasas con tendencia ascendente. Las regiones Norte y Nordeste son las más cercanas al Ecuador y también las menos desarrolladas socioeconómicamente. En estas regiones, una sinergia dentre diferentes tipos de desigualdades y exposiciones ambientales puede estar promoviendo un aumento de las muertes por este tipo de cáncer considerado totalmente prevenible.

Palabras clave: neoplasias cutáneas/mortalidad; estudios de series temporales; países em desarrollo.

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INTRODUCTION

Non-melanoma skin cancer (NMSC) is a general term used to refer to malignant skin diseases whose origin is diverse and does not involve melanocytes, as occurs with melanoma skin cancer (MSC)[1]. NMSC is the most common cancer type among all the malignancies. According to the current estimates involving 36 cancer types and 185 countries, the global occurrence of NMSC reached more than one million new cases in 2018. The NMSC-related death number worldwide (65,155) was similar to those MSC (60,712) has caused in the same year[2].

The two major histopathological subtypes under the umbrella of NMSC are Basal Cell Carcinoma (BCC) and Squamous Cell Carcinoma (SCC); however, if compared to MSC the epidemiology is understudied[3]. The most substantial risk factor for NMSC that epidemiology describes is the exposure to ultraviolet (UV) radiation[4]. It is part of the spectrum of electromagnetic radiation emitted by the sun, and artificial sources, including light bulbs and welding procedures. UV radiation comprises three wavelength bands (UVA, UVB, and UVC) that provoke different effects in humans. Potentially, UVA and UVB cause skin malignancies[5].

In Brazil, estimates of new cancer cases show that the NMSC will be the most incident in the 2020-2022 triennium, with the annual occurrence of 83,770 (men) and 93,160 (women) new cases, corresponding to an estimated risk of 80.12 and 86.65 per 100,000 person-year, in men and women, respectively[6]. In the rank of all cancer cases in male, in each of the Brazilian macroregions, the NMSC is the most incident in the South (123.67), Midwest (89.68) and Southeast (85.55) macroregions, and the second in rank in the Northeast (65.59) and North (21.28) macroregions. In female, the NMSC occupies the top of rank in all Brazilian macroregions presenting estimated risk of 125.13 (Midwest), 100.85 (Southeast), 98.49 (South), 63.02 (Northeast), and 39.24 (North) per 100,000 person-year[6].

Although NMSC incidence is high worldwide, studies of mortality are scarce. This knowledge gap may be explained by the misleading idea that NMSC causes few deaths, and as a consequence, it is often excluded from large cancer registries as it creates a barrier for more detailed analysis[3]. Therefore, population-based estimates are crucial to scale the true NMSC magnitude and define the best preventive actions targeting the most vulnerable population groups[7].

In Brazil, all deaths are regularly registered in the Mortality Information System managed by the Ministry of Health, specifically, the Department of Informatics of the National Health System (DATASUS)[8]. In this context, analyses of NMSC death data for a continental, tropical country as Brazil can contribute to improve the understanding of this worldwide public health problem. Thus, the present study aimed to describe trends in NMSC mortality rates stratified by sex and age groups in Brazil and its macroregions from the biennium 2001-2002 to 2017-2018.

METHOD

Ecological study conducted in Brazil with the 2001-2018 nationwide death information from DATASUS[8], which is responsible for managing all vital statistics in Brazil. NMSC death occurrence was analyzed in the country as a whole as well in five Brazilian macroregions.

Approximately 92% of the Brazilian territory is located in a tropical zone, where 4 of the 5 Brazilian geographic regions (North, Northeast, Southeast, and Midwest) are found. In Brazil, the UV-radiation level reaches more than 11 points during the summer solstice[9]. The World Health Organization (WHO)[4] created the Ultraviolet Index of exposure category, and values from 8 to 10 are classified as very high, and ≥11, as extreme. It helps to make different interpretations of UV exposure, potentially harmful to health, regardless of the type of skin[9]. The South region, São Paulo state, and part of the Mato Grosso do Sul state extend throughout the subtropical zone, experiencing milder temperatures in part of the year.

Number of deaths and population data

The number of deaths was obtained from the Mortality Information System, a subsystem coordinated by DATASUS[8]. This study only included deaths registered according to code C44 of the International Classification of Diseases – ICD – 10th revision. Annual population estimates stratified by demographic characteristics (sex and age) were obtained from the website of "*Instituto Brasileiro de Geografia e Estatística*" (IBGE)[10].

Mortality rates

Mortality rates were estimated for eight biennium (from 2001-2002 to 2017-2018) stratified by sex (male and female) and age groups (30-39, 40-49, 50-59, 60-69, and 70 or more years). Age-standardized mortality rates (ASMRs) were calculated using the 1960-world population reference[11]. ASMRs were presented per 100,000 person-year considering Brazil as a whole and its five macroregions.

Trend analysis

At first, the trend analysis of NMSC mortality in Brazil and in each macroregion was performed, investigating

the ASMR behavior over time displayed in charts. The dependent variable (ASMR) was plotted in the y-axis and correlated with the independent variable (biennium) plotted in the x-axis.

Next, a generalized linear regression was conducted using Prais-Winsten method as Antunes & Cardoso[12] recommend. In this step, Annual Percent Changes (APC) and respective 95% Confidence Intervals (95% CI) were calculated, and trends were interpreted as increasing, decreasing, or stable.

Ethical statement

This study followed the international recommendations and the Brazilian Resolutions of the National Health Council (CNS) of the Ministry of Health – Resolution number 466/2012[13] and Resolution number 510/2016[14] – for scientific research involving human subjects and as it was developed with de-identified secondary dataset publicly available on DATASUS website, no IRB (Institutional Review Board) ethical approval was required.

RESULTS

From 2001 to 2018, 27,550 NMSC deaths were registered for 30 years-old or older individuals in Brazil. The frequency of deaths was higher in males (58.1%), among individuals aged ≥70 years (64.3%), and with low (≤4 years) formal education (62.3%). The majority of deaths occurred with white individuals, both in Brazil and in its macroregions, except in the North Region where 55.6% of the fatal cases occurred with Brown individuals (Table 1).

The overall ASMRs were 2.25 per 100,000 and 1.22 per 100,000 in males and females, respectively. ASMRs displayed in charts suggested that NMSC deaths in males and females followed upward trends over time in Brazil. The highest rates were observed in the male strata, both in Brazil and its macroregions, except in the Midwest region where adjusted rates remained higher in females from the biennium 2001-2002 to 2011-2012 (Figure 1).

Comparing the 2001-2002 and the 2017-2018 biennium, a positive rate variation occurred in Brazil as

Table 1. Distribution of deaths due to non-melanoma skin cancer according to sociodemographic characteristics, in Brazil and in its macroregions, from the biennium 2001-2002 to 2017-2018

Variables	Brazil	Macroregions				
		North	Northeast	Southeast	South	Midwest
	n=27,550	n=1,313	n=8,178	n=10,991	n=5,277	n=1,791
Age‡						
30-39	644 (2.3)	41 (3.1)	219 (2.7)	232 (2.1)	94 (1.8)	58 (3.2)
40-49	1,637 (5.9)	99 (7.5)	487 (6.0)	679 (6.2)	282 (5.3)	90 (5.0)
50-59	3,149 (11.4)	154 (11.7)	843 (10.3)	1,289 (11.7)	648 (12.3)	215 (12.0)
60-69	4,417 (16.0)	227 (17.3)	1,197 (14.6)	1,797 (16.3)	911 (17.3)	285 (15.9)
≥70	17,703 (64.3)	792 (60.3)	5,432 (66.4)	6,994 (63.6)	3,342 (63.3)	1,143 (63.8)
Sex						
Male	16,015 (58.1)	826 (62.9)	4,682 (57.3)	6,365 (57.9)	3,142 (59.5)	1,000 (55.8)
Female	11,535 (41.9)	487 (37.1)	3,496 (42.7)	4,626 (42.1)	2,135 (40.5)	791 (44.2)
Ethnicity*						
White	19,278 (73.7)	502 (39.2)	3,869 (51.0)	8,827 (84.4)	4,908 (95.8)	1,172 (68.1)
Black	813 (3.1)	42 (3.3)	291 (3.8)	370 (3.5)	60 (1.2)	50 (2.9)
Yellow	120 (0.5)	8 (0.6)	39 (0.5)	51 (0.5)	15 (0.3)	7 (0.4)
Brown	5,916 (22.6)	712 (55.6)	3,372 (44.5)	1,205 (11.5)	138 (2.7)	489 (28.4)
Indigenous	34 (0.1)	17 (1.3)	9 (0.1)	2 (0.1)	3 (0.0)	3 (0.2)
Education*‡						
≤4	13,102 (62.3)	740 (66.1)	4,694 (75.4)	4,354 (53.9)	2,455 (57.8)	859 (63.2)
4-7	4,644 (22.1)	219 (19.6)	863 (13.9)	2,038 (25.2)	1,225 (28.9)	299 (22.0)
8-11	2,181 (10.4)	124 (11.1)	480 (7.7)	1,050 (13.0)	388 (9.1)	139 (10.2)
≥12	1,092 (5.2)	36 (3.2)	188 (3.0)	630 (7.8)	176 (4.1)	62 (4.6)

(*) Variables with missing values.
(‡) Variables measured in years.

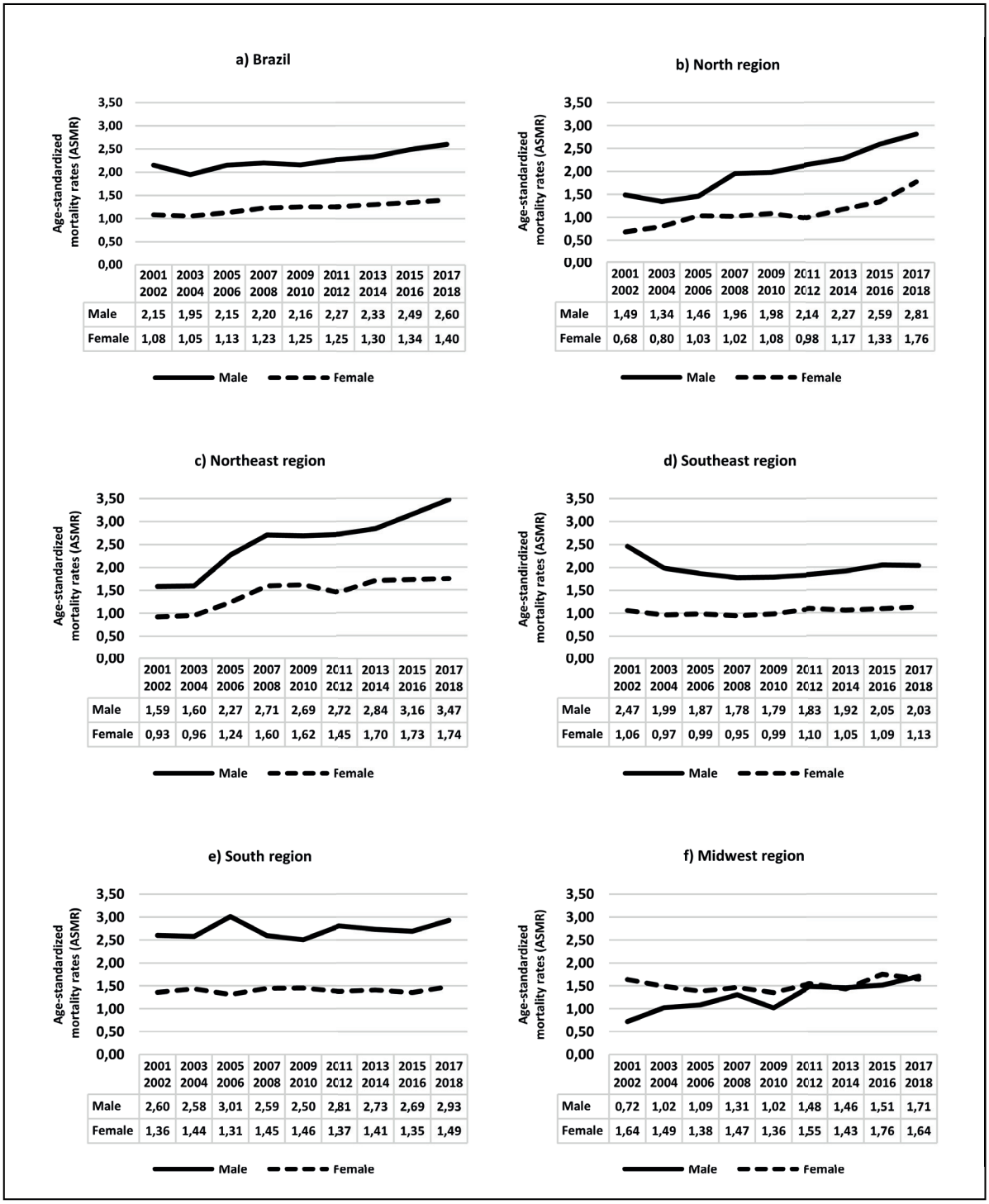

Figure 1. Trends in age standardized mortality rates (ASMR) by 100,000 due to non-melanoma skin cancer according to sex, in Brazil and in its macroregions, from the biennium 2001-2002 to 2017-2018 (a) Brazil, b) North region, c) Northeast region, d) Southeast region, e) South region, and f) Midwest region)

a whole both in males (20.5%) and in females (30.8%), and almost in all macroregions. The rates increased more than two-fold over time, in males of the Midwest Region (139.4%) and in females of the North Region (158.8%). There was a negative rate variation only in the Southeast region among men (-17.5%).

The analysis of ASMR trends indicated a statistically significant upward pattern in Brazil (APC: 2.91% in males; APC: 3.51% in females), as well as in the North (APC: 9.75% in males; APC:10.38% in females), and in the Northeast (APC: 9.98% in males; APC: 8.34% in females) macroregions. The results also showed an increasing trend

in the male stratum of the Midwest region (APC: 8.85%), where both men and women's rates followed a convergent direction reaching similar magnitudes in the 2011-2012 biennium (Table 2).

DISCUSSION

This study focused on deaths attributed to NMSC. It showed that Brazil experienced ASMR higher than 2 per 100,000 person-years in men. Old individuals and men were the most common fatal victims. These results suggested that mortality rates have increased over time in the country as a whole, and in the North and the Northeast regions considering men and women, separately. The most critical variation occurred in males of the Midwest (139.4%) and in females of the North (158.8%) regions. This scenario should encourage the implementation of more initiatives to prevent new deaths and improve the early diagnosis and treatment of NMSC.

Studies suggest that NMSC frequency maintains an inverse correlation with latitude variations[15]. In Brazil, the North and Northeast regions are closer to the Equator Line than the Southeast, South, and Midwest regions. Besides, the North region experiences temperatures higher than 18°C through all months of the year[16]. However, the most essential question suspected to be related to upward NMSC mortality is that the North and Northeast regions are much less developed socioeconomically than the rest of the country. This condition should be thought as a possible determining factor causing the most adverse results, mainly considering that the North's and Northeast's population consists predominantly of Brown and Black individuals, unfortunately having more restrictive access to high-quality healthcare services. However, this is a question that demands future investigations and support from policymakers.

Although in Brazil the lowest incidence rates have been estimated for the North and Northeast regions[6], the current study showed that those two macroregions have experienced a statistically significant upward mortality pattern in both sexes, suggesting that the patients may also be facing barriers to access the health services and to obtain diagnosis and treatment for this type of cancer. In these regions, there is a great concentration of small municipalities with

Table 2. Non-melanoma skin cancer variations: rate values, annual percent changes and trends in age-standardized mortality rates by sex in Brazil and in its macroregions by biennium started in 2001-2002 and ended in 2017-2018

	Age-Standardized Mortality Rates*			Annual Percent Changes		
	2001-2002†	2017-2018†	Variation (%)	(%)	95%CI‡	Interpretation
Brazil						
Male	2.15	2.60	20.46	2.91	1.96; 3.86	Increasing
Female	1.07	1.40	30.84	3.51	2.68; 4.34	Increasing
North						
Male	1.48	2.81	89.86	9.75	7.68; 11.86	Increasing
Female	0.68	1.76	158.82	10.38	5.77; 15.21	Increasing
Northeast						
Male	1.58	3.47	119.62	9.98	5.59; 14.57	Increasing
Female	0.92	1.74	89.13	8.34	3.29; 13.64	Increasing
Southeast						
Male	2.46	2.03	−17.47	−1.81	−6.00; 2.55	Stable
Female	1.06	1.12	5.66	1.45	−0.06; 2.99	Stable
South						
Male	2.60	2.92	12.31	0.67	−0.76; 2.13	Stable
Female	1.35	1.48	9.62	0.23	−0.50; 0.98	Stable
Midwest						
Male	0.71	1.70	139.43	8.85	6.11; 11.66	Increasing
Female	1.63	1.64	0.61	1.07	−1.45; 3.67	Stable

(*) Age-standardized mortality rates by 100,000 person-years.
(†) Initial and Final biennium.
(‡) Confidence Interval 95%.

rural characteristics and with low demographic density experiencing unfavorable influences on the implementation of health actions due to geographical access, precarious living conditions, lack of popular participation and difficulty in allocating and hiring human resources[17]. In this context it is crucial to identify the barriers and propose solutions capable of changing the disappointing scenario drawn from NMSC mortality in Brazil and mainly in the North and Northeast regions.

The protection against skin cancer is highly relevant and recommended for outdoor workers with occupational sun exposure. In this situation, the risk to develop skin cancer estimated in meta-analysis was higher than 70% in individuals with outdoor occupational exposure comparing with workers without sun exposure[18]. The most vulnerable occupations are lifeguards, gardeners, fishermen, construction workers, farmer, rural or agricultural workers[19-21]. Agriculture is one of the strongest segments of the Brazilian economy, and farming workers are particularly important in the North region where livestock and agriculture play a prominent role in the regional, and family economy[22].

Additionally, leisure activities practiced outdoors also confer an increased risk of NMSC. The use of individual protection mechanisms should be encouraged during leisure activities and mainly in the workplace. This involves the use of appropriate clothing, hats, sunglasses, and sun block products[20]. Preventive initiatives should be started in childhood and kept in the daily routine. However, adherence to preventive recommendations is directly influenced by socioeconomic conditions, and preventive products may not be available in the workplace, or people do not have the resources to purchase them or use them irregularly[23]. This is another issue that demand more financial investments and public policy.

Studies about NMSC deaths have highlighted particular issues. At first, the disproportionate NMSC mortality observed among African Americans can be related to the delayed diagnosis and treatment, in part, due to atypical clinical variations, including lesion appearance and anatomical location in non-sun-exposed areas[24]. Another question is that BCC and SCC are malignancies with distinct behaviors and may be markers of other adverse health outcomes as all-cause mortality[25,26]. A Danish cohort study following-up 82,837 patients with BCC and 13,453 with SCC showed excessive death numbers related to some chronic diseases among patients with SCC but not among patients with BCC, comparing with the general population[27].

A study with data of the Russian Federation estimated age-standardized mortality rates of 0.70/100,000 over the 2007-2017 period with a decreasing longitudinal trend[28]. However, the majority of the studies about NMSC mortality are from developed countries. The current results showed age-standardized rates that are between the values estimated for Australia (around 3.0/100,000) and Germany (<1.0/100,000) for males, and on the same level for Australia (around 1.0/100,000), for females[7]. A common fact occurring in those countries is the investment in regular public health UV protective practices campaigns for, and the implementation of body skin cancer screening for insured individuals aged ≥35, only in Germany[7].

Among the risk factors for NMSC, besides excessive sunlight exposure, increased longevity, genetic condition, and immune suppression[29] are also included. NMSC is considered rare in children and youngsters. If it occurs with youngsters, it is suspected to be associated with predisposing heritable and exposure to iatrogenic risk factors such as prolonged immune suppression, radiation therapy, chemotherapy and voriconazole use[30]. Exposed individuals seem to be at risk of developing skin cancer precociously, and health professionals other than dermatologists must be involved in the detection of new skin cancer cases. They will be able to contribute for skin cancer control whether they were conscious of the extent of the problem, and well-trained to identify any suspected skin lesions[31].

An important NMSC mortality-related issue is the population ageing observed worldwide. It is expected that NMSC causes an increasing death number within the next years given the close relation between keratinocyte cancers and older individuals[3]. The effect of UV radiation on the skin is cumulative over time[19]. Additionally, immunosenescence is a condition that encourages the development of opportunistic diseases and malignancies in old age[32]. Risk factor exposure over time, and immunosuppressive drug use[23] aggravates the immunosuppressive status. For example, in a cohort of 165 patients with renal transplantation and at least one year of follow-up at a Brazilian reference center[33], 19 NMSC in eleven of them (6.67%) were found.

This study has advantages and limitations. Firstly, an advantage results from the fact that investigations using NMSC mortality data are still scarce both in Brazil and worldwide. Thus, the study contributed to improve the understanding of this problem in developing countries, since NMSC has been suspected to be increasing in some countries. For example, excluding low risk individuals who are foreigners from Asia, the Pacific Islands, the Middle East, and sub-Saharan Africa, as well as Australian aborigines and Maori from New Zealand, NMSC deaths increased 208% in Australia, between 1981 and 2011, with figures rising 7% a year[34]. Another contribution was estimating age-standardized rates using as reference the

1960-world standardized population designated by Segi et al.[11]. Thus, the standardization procedure may have made the current results more adequate for future international comparisons. However, this routine-data-based study presents some limitations, such as missing values of skin color and education variables. Even though they have been used only to describe the population characteristics briefly, it is a problem that needs to be pointed out. Another question is that the use of aggregated data prevents the result extrapolation for the individual level. However, it is possible that these results have provided useful background that may help to address the decisions against NMSC mortality.

CONCLUSION

In summary, NMSC deaths are not rare in Brazil. The country as a whole, and the North and Northeast regions have experienced upward mortality trends. The North and Northeast regions are the closest to the Equator Line and are also the least developed socioeconomically. In these macroregions, a synergism between different types of inequalities and environmental exposure may be promoting an increase in the number of NMSC deaths, a type of cancer which is considered completely preventable.

CONTRIBUTIONS

Maria Isabel do Nascimento, Jorge Ricardo Furtado Cardoso de Moraes, Esther Rohem Costa Silva, Maria Gabriela Guinancio da Mota contributed equally to conceptualization, study planning, data collecting, formal statistics analysis, interpretation of the results and original drafting. Raphael Mendonça Guimarães participed in the phases of analysis and interpretation of the results and critically reviewed the manuscript. All authors reviewed and approved this version and are responsible for the accuracy and integrity of the work.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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