Article

Hospitalization and mortality rates of malignant prostatic neoplasms in Brazil: A cross-sectional study from 2008 to 2018

Alberto Fernando Oliveira Justo[1], Rita de Cássia Collaço[2], Anna Ligia Oenning Soares[3], Caroline Marques Caloi[4], Camila Stefani Estancial[5], Guilherme Lemos[6], Fabio Henrique da Silva[7], Eduardo Costa Alexandre[2], Fabiano Beraldi Calmasini[6*]

[1]*Department of Internal Medicine, University of São Paulo Medical School (FMUSP), São Paulo, Brazil,* [2]*Department of Pharmacology, Faculty of Medicinal Sciences, State University of Campinas (UNICAMP), Campinas, São Paulo, Brazil,* [3]*Department of Mathematics, University of Mato Grosso (UFMT), Cuiabá, Mato Grosso, Brazil,* [4]*Cuiabá Institute of Education and Culture (ICEC), Cuiabá, Mato Grosso, Brazil,* [5]*Department of Collective Health, Faculty of Medicinal Sciences, State University of Campinas, Campinas, Sao Paulo, Brazil,* [6]*Department of Pharmacology, Escola Paulista de Medicina, Universidade Federal de São Paulo, São Paulo, SP, Brazil,* [7]*Laboratory of Multidisciplinary Research, São Francisco University (USF), Brazil*

Prostate cancer (PCa) is a highly prevalent condition among men worldwide, resulting in reduced quality of life and increased costs to health systems due to hospitalization and death. This study aimed to explore and understand the evolution of PCa in Brazil from 2008 to 2018. Data were obtained from the National Health System Department of Informatics (DATASUS) using code C61 for malignant prostatic neoplasms. We presented the hospitalization and mortality rates in a temporal-, regional- and age-dependent manner. From 2008 to 2018, a year-dependent increase in hospital admissions due to PCa was reported in Brazil, in which the Southeast region showed the highest prevalence. Men aged ≥80 and those 70-79 years old had similar hospitalization rates, followed by men aged 60-69, 50-59, 40-49 and 30-39 years old. Similarly, an increase in deaths due to PCa was reported during this period, with the highest rates seen in the Southeast. Men aged ≥80 years had higher mortality rates, followed by those aged 70-79, 60-69, 50-59, 40-49 and 30-39 years old. The results obtained indicate an age- and region-dependent increase in PCa morbidity and mortality in Brazil overtime and may contribute to the ongoing discussion on the role and future perspective of the health care system in Brazil.

Keywords: Prostate cancer. Brazilian epidemiology. Hospitalization rate. Mortality rate. Public health care.

INTRODUCTION

Aging has emerged as a global public health concern. Its association with prolonged exposure to environmentally harmful factors and unhealthy lifestyle is considered an important risk factor for the development of chronic diseases, such as urological disease (Calmasini *et al.*, 2016; Lopes *et al.*, 2022; Oliveira *et al.*, 2019),

cardiovascular disease (Brandes, Fleming, Busse, 2005; Parreira *et al.*, 2018), Alzheimer's (Xia *et al.*, 2018) and cancer (Schneider *et al.*, 2019).Studies in the literature have addressed several pathways in order to understand the link between aging and cancer, such as protein degradation, decreased enzyme activity, increased redox signalling and cellular proliferation (Ghatak, Ho, 1996; Lakkur *et al.*, 2014; Vaz*et al.*, 2015). However, due to the multifactorial pathophysiology of cancer, the link between aging and cancer is still unclear.

Prostate cancer (PCa) is one of the most prevalent conditions affecting men, and lead to high hospitalization

*Correspondence: F. B. Calmasini. Department of Pharmacology. Escola Paulista de Medicina. Universidade Federal de São Paulo. Rua 3 de Maio, 100, São Paulo, SP, Brasil. CEP.: 04044-020. Phone: +55-19-3521-6125. E-mail: fabiano.calmasini@unifesp.com. ORCID:https://orcid.org/0000-0002-7790-2550

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and mortality rates worldwide (Bergengren *et al.*, 2023). It is a silent disease, and a lack of symptoms may decrease the odds of early diagnosis and successful treatment, negatively affecting patient outcomes (Castro *et al.*, 2011; Guo *et al.*, 2018). Although newer drugs approved for PCa therapy exhibit fewer side effects and better efficacy, aggressive treatment may elicit several unwanted detrimental effects in the patient. Moreover, the cost of cancer treatment is very high, which negatively impacts the public health care system (Imber *et al.*, 2019).

In this regard, epidemiological studies are valuable tools for better understanding the trends related to a specific disease in a determinate region, population and sex. Such studies may help health systems and governments plan, execute and evaluate strategic interventions to prevent, control and treat specific diseases or conditions. Several epidemiological studies addressing PCa prevalence have been conducted across Europe and the United States (Duncan, Goldacre, 2010; Li, Siegel, King, 2018; McMahon *et al.*, 2019); however, in developing countries such as Brazil, epidemiological reports are still scarce. This study aimed to understand the PCa profile in Brazil from 2008 to 2018. Specifically, we aimed to identify the PCa-associated hospitalization and mortality rates according to patient age and geographical region

MATERIAL AND METHODS

This cross-sectional study was conducted between November and December 2019 and included hospital admission and deaths associated with malignant prostate neoplasia in male individuals over 30 years of age. The inclusion criterion was defined as subjects within the above-mentioned age who were living in Brazil between January 1st, 2008 and December31st,2018.

The data were retrieved from the National Health System Department of Informatics (DATASUS), which comprises registers collected through Municipal Health Secretaries and is freely available for consultation. DATASUS provides hospitalization and mortality data through the hospital and mortality information systems, respectively (Ministry of Health, 2019). The methodology of data collection did not change during the study period.

Information regarding the male population residing in Brazil and its geographic regions was collected from the Brazilian Institute of Geography and Statistics (IBGE) website (Candiago, Abreu, 2007). Demographic data on the population and cartographic bases of the Brazilian Federal Units and regions were obtained from the last census conducted in 2010.

In the present study, we used the International Classification of Diseases (ICD) version 10 (ICD-10) code C61 for malignant prostate neoplasia on DATASUS. Thus, the individuals for who information was extracted were not individually identified. This study did not require approval from the ethics committee.

For the proportional rates of hospitalization and deaths, we used the male population by age, region or calendar year as the denominators and the total number of hospitalizations and deaths as numerators. To understand the pattern of prostatic neoplasia, single linear regression was applied to evaluate trends in hospitalization and mortality rates by age and calendar year. The groups were compared using the Student's t-test (parametric data). Data were analyzed using Prism version 6.0 (GraphPad Software, San Diego, CA, U.S.A) and a value of $P<0.05$ was considered statistically significant.

RESULTS

According to the last census from the IBGE, the total Brazilian population was 190,732,694, of which 44.28 million were men over 30 years old. Men aged 30-39 years old are the main age-related group included in this study, consisting of approximately 14.4 million people, followed by men aged 40-49 (12.02million), 50-59 (8.72 million), 60-69 (5.26 million), 70-79 (2.75 million) and 80 years old or older (1.13 million) (Figure1A). In terms of population density, the Southeast region is the most populous geographic region in Brazil with 19.80 million male individuals over 30 years old, followed by the Northeast, South, Midwest and North with 11.31, 6.85, 3.27 and 3.14 million, respectively (Figure1B).

Considering men aged ≥30 years old, a total of 283,083 hospitalizations due to PCa have been reported in Brazil between 2008 and 2018 (Table I). To obtain a better understanding of the PCa profile in Brazil, we

evaluated hospitalizations according to the geographic regions where they were registered. The total number of hospitalizations was analyzed before and after correction for the respective regional populations, as follows. We found 149,612 hospitalizations registered in the Southeast, 62,290 in the Northeast, 46,266 in the South, 7,599 in the North and 17,316 in the Midwest (Table I). Correcting these numbers by the proportional population per million inhabitants, the Southeast region still had the highest number of hospitalization (7,556 individuals), followed by the South (6,754), Northeast (5,508), Midwest (5,295) and North (2,420) (Figure2A). It is important to note that the number of hospitalizations registered from 2008 to 2018 in Brazil increased over time, as indicated in Figure 2B.
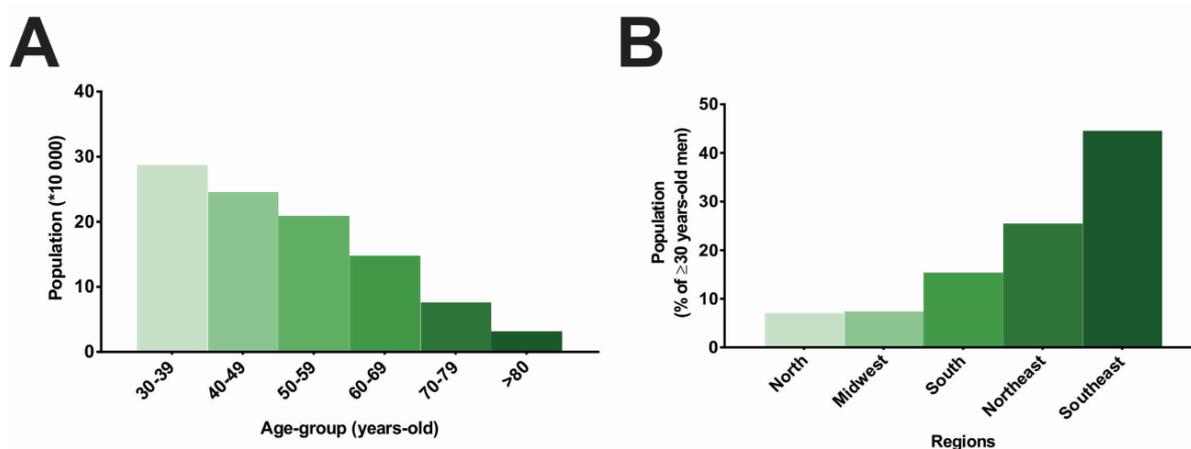

FIGURE 1 - Distribution of Brazilian population by regions and age.

TABLE I - Frequency of hospitalization and deaths from malignant prostate neoplasia per age and regions. 95% confidence interval (CI:95%)

	Hospitalization		Deaths	
	n	**% (95% CI)**	**n**	**% (95% CI)**
Age (Years old)				
30-39	343	0.12 (0.123;0.10)	25	0.09(0.14;0.06)
40-49	4866	1.71(1.76;1.67)	194	0.77(0.89;0.67)
50-59	41190	14.55(14.68;14.42)	1764	7.05(7.37;6.73)
60-69	108377	38.28(38.46;38.10)	5996	23.96(24.50;23.43)
70-79	90325	31.90(32.07;31.73)	9545	38.15(38.75;37;55)
≥80	37982	13.41(13.54;13.29)	7493	29.95(30.52;29.38)
Years				
2008	17580	6.21(6.29;6.12)	1284	5.13(5.41;4.86)
2009	20084	7.09(7.19;7.00)	1593	6.36(6.67;6.08)
2010	22338	7.89(7.99;7.79)	1782	7.12(7.44;6.90)
2011	23443	8.28(8.38;8;17)	1980	7.91(8.25;7.58)
2012	25256	8.92(9.02;8.81)	2081	8.31(8.66;7.97)

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TABLE I - Frequency of hospitalization and deaths from malignant prostate neoplasia per age and regions. 95% confidence interval (CI:95%)

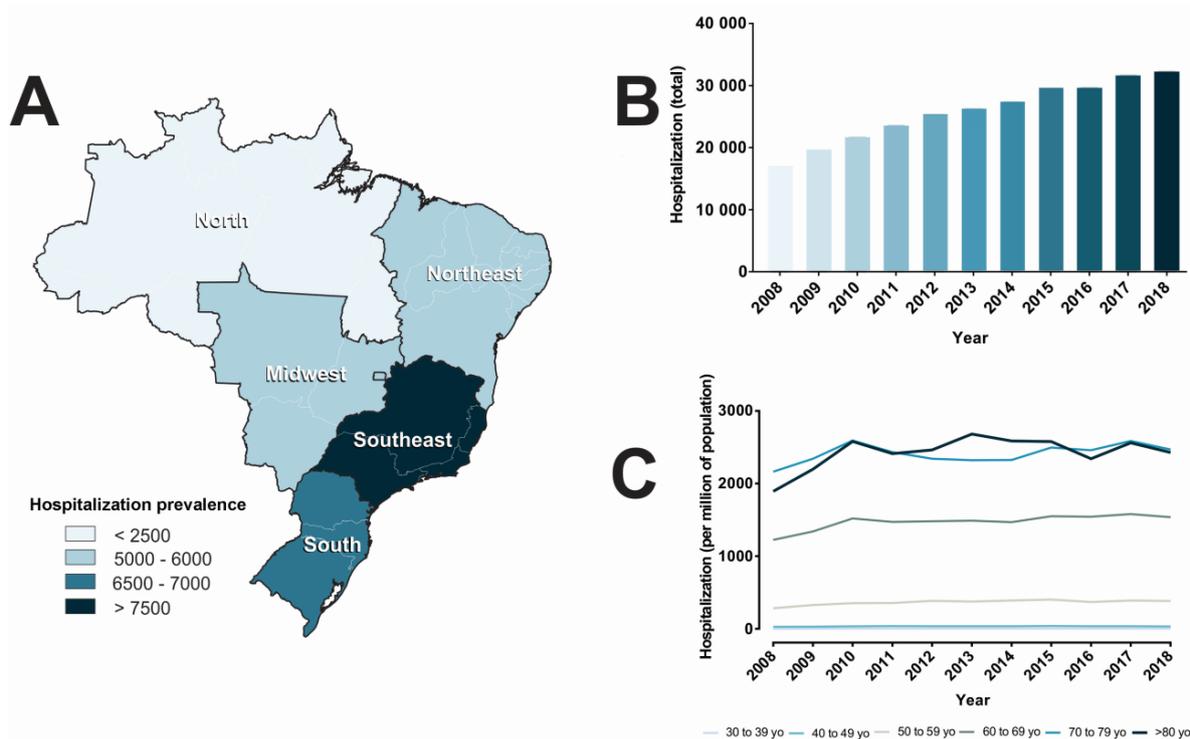|	Hospitalization		Deaths	
	n	% (95% CI)	n	% (95% CI)
2013	26186	9.25(9.35;9.14)	2318	9.26(9.63;8.90)
2014	27291	9.64(9.75;9.53)	2477	9.90(10.27;9.53)
2015	29286	10.34(10.45;10.23)	2665	10.65(11.04;10.27)
2016	29117	10.28(10.39;10.17)	2770	11.07(11.46;10.68)
2017	30993	10.94(11.06;10.83)	3013	12.04(12.45;11.64)
2018	31509	11.13(11.24;11.01)	3054	12.20(12.61;11.80)
Regions				
North	7599	2.68(2.74;2.62)	62	10.35(13.07;8.02)
Northeast	62290	22.00(22.15;21.85)	92	15.35(18.49;12.56)
Southeast	149612	52.85(53.03;52.66)	162	27.04(30.79;23.52)
South	46266	16.34(16.48;16.20)	161	26.87(30.62;23.36)
Midwest	17316	6.11(6.20;6.02)	122	20.36(23.81;17.21)
Total	283083	100	25017	100

FIGURE 2 - Proportional hospitalization by prostate cancer (ICD-10: C61) according to region (A), calendar year (B) and hospitalization rates according to their respectively population (C). Note the increased hospitalization rates over time, the higher rates in the Southeast region and the similar rates between men aged 70-79 and 80 or older. Rates per million inhabitants; yo = years old.

The total number of hospitalizations was stratified by age and the highest number of hospitalization was seen in men aged 60-69 years, followed by men aged 70-79, 80 or older, 50-59, 40-49 and 30-39 years (Table I). However, if the total number of hospitalizations was corrected by the number of the respective age group, a similar rise in the hospitalization rate was seen between men aged 80 years or older (P<0.001, R2=0.901) and men aged 70-79 years (P<0.0001, R2=0.981), followed by a steady rise in men aged 60-69 (P<0.0001, R2=0.989), 50-59 (P<0.0001, R2=0.918) and 40-49 years (P=0.006, R2=0.584)(Figure 2C). In contrast, no increase was observed in men aged 30-39 years overtime (P=0.45, R2=0.062; Figure 2C).

During the period analyzed, 25,017 deaths from PCa were reported in Brazilian men aged >30 years old (Table I). Similar to the hospitalization rates, the Southeast region had the highest number of deaths (13,002), followed by the Northeast (4,898 deaths), South (4,419 deaths), Midwest (1,719 deaths) and North (979 deaths) (Table I). However, when the mortality numbers were divided by the proportional population per million inhabitants, a different profile was obtained. The Southwest region had the highest mortality rate (657 deaths), followed by the South (645), Midwest (526), Northeast (433) and North (312) regions (Figure 3A). Importantly, total mortality increased drastically from 2008 to 2018 (Figure 3B).

Considering the age groups, the highest mortality rate was found in men aged 70-79 years, followed by those aged 80 or older, 60-69, 50-59, 40-49 and 30-39 years old (Table I).When the mortality data were corrected for the number of patients in each age group, we found a steady increase in deaths due to prostatic neoplasia, especially in older subjects (Figure3C). The above-mentioned increase was greater in men aged 80 or older (P<0.0001, R2=0.967), followed by men aged 70-79 (P<0.0001, R2=0.977), 60-69 (P<0.0001, R2=0.931) and 50-59 years (P<0.0001, R2= 0.815) (Table I). No statistically significant differences were observed in men aged 40-49 years (P=0.38, R2=0.0833) and no deaths were reported in subjects aged 30-39 years (Figure 3C).
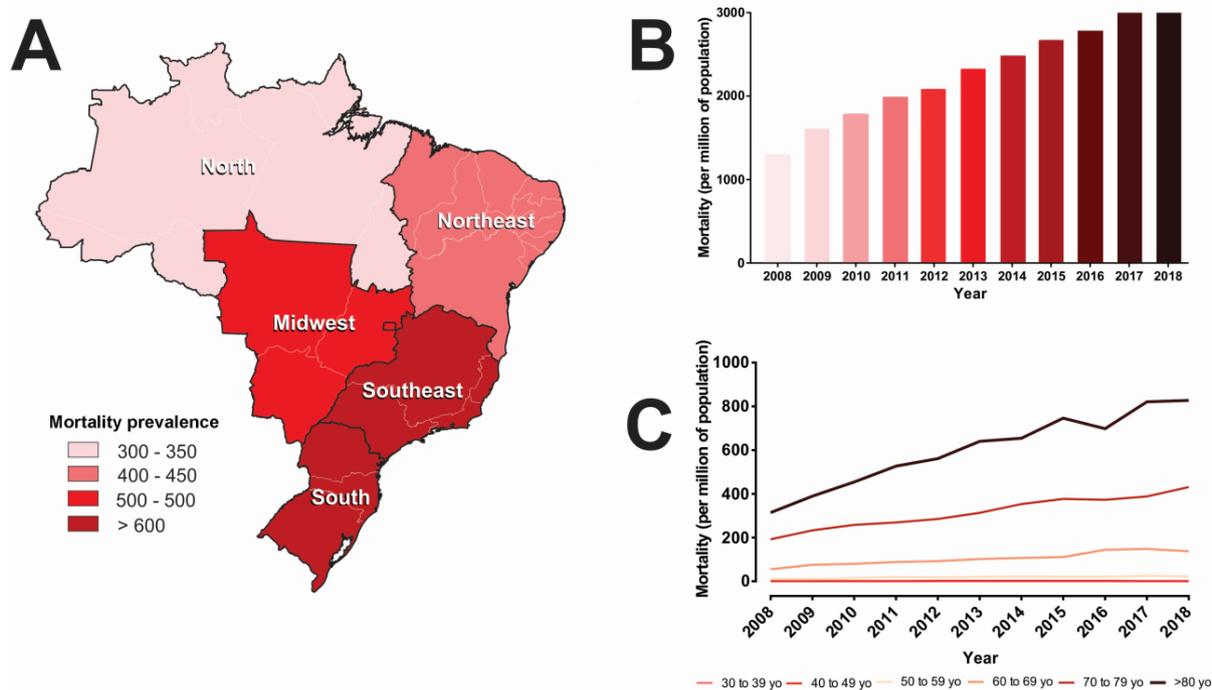

FIGURE 3 - Proportional of deaths by prostate cancer (ICD-10: C61) according to region (A), calendar year (B) and mortality rates according to their respectively population (C). Note the increased mortality rates over time, especially in men aged 80 or older and 70-79, and the higher rates in the South and Southeast regions. Rates per million inhabitants; yo = years old.

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DISCUSSION

In the present epidemiological study, we have demonstrated an increase in hospitalization and mortality rates by PCa in Brazilian men over 30 years old between 2008 and 2018. Specifically, the results obtained here indicate higher absolute and relative numbers of hospitalizations and deaths due to PCa in the Southeast region of Brazil. In contrast, the Northern region exhibited the lowest rates of hospitalization and deaths due to PCa. We also found age-dependent rates of hospitalization and mortality in Brazilian men, which is in accordance with epidemiological data from other countries.

Over the analysis period, an increased number of overall hospitalizations were observed among Brazilian men. The prevalence was highest in men aged 80 years or older and those aged 70-79 years, followed by 60-69, 50-59 and 40-49 years old, indicating an age-dependent tendency. The results presented here are in accordance with previous clinical reports, indicating a well-described relationship between aging and PCa (Bergengren, *et al.*, 2023). Similarly, mortality rates were higher in aged men than in young men, further corroborating this age-dependent phenomenon. A possible explanation for both conditions could be the increase in life expectancy in the Brazilian population, which could account for the increased PCa prevalence and mortality in older men. However, considering that 1) life expectancy has increased worldwide and 2) developed countries have decreased mortality due to PCa in recent decades (Duncan, Goldacre, 2010; Rawla, 2019), such an explanation is not accurate. Therefore, we suggest that the increased mortality in Brazil, which is in contrast to that in some developed countries, may be considered an indication that 1) the National Health Service is not resolving the demand for this type of cancer and/or 2) there is a lack or inefficient implementation of awareness programs for prostate cancer screening.

One of the most clinically employed examinations used as an indicator of prostate health is the digital rectal examination. Despite some limitations, such as invasiveness and nonpalpable prostatic areas, this examination is a cheap, simple and reliable method for evaluating prostate anatomy (Castro *et al.*, 2011). This anatomical evaluation may be further associated with biochemical measurements such as prostate-specific antigen (PSA) levels, thereby increasing the accuracy of prostate screening (Castro *et al.*, 2011). Although digital rectal examination and PSA test are currently the standard protocols for the initial prostatic cancer diagnosis (Nogueira, Corradi, Eastham, 2009), there is no medical consensus regarding the PSA periodicity especially for older patients (Chen *et al.*, 2018; Steffen *et al.*, 2018). Nonetheless, after the implementation of PSA testing in clinical practice, the incidence of undiagnosed PCa has decreased worldwide. For instance, studies addressing the British population showed a steady increase in mortality due to PCa until the early 80s, which stabilized around 1992 and declined thereafter, suggesting that PSA examination implementation in the clinic led to early PCa diagnosis and higher efficacy of PCa treatments (Duncan, Goldacre, 2010; Hussain *et al.*, 2009). Therefore, increased access to this clinical advancement might explain the higher rate of hospitalization in Brazil overtime. It is important to note that both examinations are considered indicative of prostate health and for cancer diagnosis, other specific examinations are required (Sanda *et al.*, 2008).

Several interventions have been employed to treat PCa, including androgen deprivation therapy (Beck *et al.*, 2019), chemotherapy/radionuclide drugs (Cetin, Ozet, 2019) and total or partial prostatectomy (Imber *et al.*, 2019). However, these are often accompanied by adverse effects, including lower urinary tract symptoms, which are present in approximately 80% of men treated for PCa, such as urinary incontinence, urinary obstruction and erectile dysfunction (Alemozaffar *et al.*, 2011; Tang *et al.*, 2019). In addition to urological symptoms, medical conditions related to the cardiovascular system such as myocardial infarction, coronary heart disease and stroke are the most frequently reported events in patients under pharmacological treatment (Riihimaki *et al.*, 2011). Thus, the higher prevalence of PCa in Brazilian men and consequently the increased number of patients undergoing treatment may reflect the increase in hospitalization rates observed in the present study over the years in Brazil (Riihimaki *et al.*, 2011).

To overcome PCa treatment-associated hospitalization and improve treatment efficacy, the Brazilian Ministry of Health has published guidelines addressing PCa diagnosis and therapeutics (Ministry of Health, 2016). Accordingly, one of the suggested clinical protocols to reduce adverse effects related to pharmacological PCa treatment and ensure its efficacy is intermittent treatment with androgenic inhibitors. Although still controversial, some studies have indicated similar efficacy between intermittent and continuous hormonal inhibition clinical protocols, but a better quality of life for patients who are subjected to the intermittent protocol (Magnan *et al.*, 2015). Other clinical alternatives to improve PCa pharmacological treatment and avoid adverse effects are: 1) early onset of androgenic inhibition therapy and 2) docetaxel treatment as the first choice for metastatic PCa resistant to androgen deprivation. Early hormonal treatment is associated with reduced PCa progression and increased overall 10-year patient survival. (Nair *et al.*, 2002; Kunath F *et al.*, 2019). Similarly, docetaxel treatment has been shown to have higher efficacy in PCa treatment, with less impact on the patients' quality of life (Tannock *et al.*, 2004). Collectively, these clinical options may contribute to lower hospitalization and mortality rates in PCa. Moreover, these guidelines are a valuable contribution from the Brazilian government for PCa treatment and may contribute to restraining the increasing number of hospitalization due to PCa over time in Brazil.

Fonseca *et al.* (2021) reported a significant increase in procedures related to patients with cancer in Brazil between 2009-2010 and 2017-2018. Surgical intervention, radiotherapy and chemotherapy increased by 56,8%, 45,3% and 55,2%, respectively. Notably, the proportion of patients commuting to other municipalities for treatment has increased slightly. In 2009-2010, 54.6%, 59.0%, and 49.2% of patients undergoing surgery, radiotherapy and chemotherapy, respectively, traveled to other municipalities. By 2017-2018, these figures increased to 56.9%, 60.7%, and 54.2%, respectively. In both time periods, cancer patients who had to travel for treatment covered an average distance of 166.9 km, 167.8 km, and 139.2 km for surgical, radiotherapy, or chemotherapy treatment, respectively. These travel distances remained similar in 2017-2018, with 152.8 km for surgeries, 167.1 km for radiotherapy, and 139.0 km for chemotherapy. These data showed an increased in the number of procedures over time, which suggests better diagnosis, availability of medical services and better management of reference services. However, it also shows that Brazil still faces a geographic accessibility issue, similar to other low-and middle-income countries such as Malaysia and Colombia (Yahya *et al.* 2019; de Vries *et al.* 2018). A previous report showed that 7.1% of deaths in Brazil were related to a lack of medical support, highlighting the differences between regions (Santo, 2003). This region-dependent phenomenon may be related to massive inequalities and differences in regional health policies, resulting in different levels of access to medical support (Albuquerque *et al.*, 2017; Santo, 2003). In our study, we found that the Northeast and North were the most affected regions, with deaths due to inefficient medical support representing 18.1% and 13.5% of all cases, respectively. Intriguingly, we showed for the first time that the hospitalization and mortality rates associated with PCa, between 2008 and 2018 were higher in the Southeast and lower in the Northern regions of Brazil. However, we must consider the possibility of underestimated rates caused by deficits in medical conditions in regions with less access to basic health care, such as North and Northeast, resulting in fewer hospitalizations and death records.

Finally, it is important to highlight some methodological limitations of the present study: 1) our data were collected from electronic records and, although mandatory, a potential lack of data or incorrect records should be considered, 2) in some regions of Brazil, access to medical care is minimal and the records of accurate data can be underestimated, 3) in this study, we cannot distinguish between first hospitalization and re-hospitalization among the participants and 4) there is no official Brazilian platform/website in which data related to medication prescription and consumption in Brazil are freely available for public consultation. The lack of government information related to medication consumption in Brazil prevents us from establishing a parallel between the number and type of medications used during PCa treatment and the efficacy of these clinical protocols in PCa outcomes.

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Altogether, we present here a comprehensive report on hospitalizations and deaths from PCa in Brazil. The 10-year study period and the numbers exceeding 283000 subjects provide a valuable demonstration of hospitalization and mortality rates divided by age, year and geographic region. The results presented here indicate an increased number of hospitalizations and deaths due to PCa in Brazil, highlighting the need for greater efforts by the Brazilian government to avoid increased rates of morbidity and mortality related to PCa. Moreover, we demonstrated age- and region-related trends in the PCa-associated rates of hospitalization and death. Early prostatic cancer diagnosis and medical intervention in younger patients are crucial for better cancer therapy outcomes.

ACKNOWLEDGMENTS

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