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Time trends for prostate cancer mortality in Brazil and its geographic regions: An age–period–cohort analysis

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ABSTRACT

Background: In the 1980s, an increase in mortality rates for prostate cancer was observed in North America and developed European countries. In the 1990s, however, mortality rates decreased for these countries, an outcome related to early detection of the disease. Conversely, an upward trend in mortality rates was observed in Brazil. This study describe the trends in mortality for prostate cancer in Brazil and geographic regions (North, Northeast, South, Southeast, and Central-West) between 1980 until 2014 and analyze the influence of age, period, and cohort effects on mortality rates.

Methods: This time-series study used data from the Mortality Information System (SIM) and population data from Brazilian Institute for Geography and Statistics (IBGE). The effects on mortality rates were examined using age-period-cohort (APC) models.

Results: Crude and standardized mortality rates showed an upward trend for Brazil and its regions more than 2-fold the last 30 years. Age effects showed an increased risk of death in all regions. Period effects showed a higher risk of death in the finals periods for the North and Northeast. Cohort effects showed risk of death was higher for younger than older generations in Brazil and regions, mainly Northeast ($RR_{Adjusted}$ = 3.12, 95% CI 1.29–1.41; $RR_{Adjusted}$ = 0.28, 95% CI 0.26–0.30, respectively).

Conclusion: The increase in prostate cancer mortality rates in Brazil and its regions was mainly due to population aging. The differences in mortality rates and APC effects between regions are related to demographic differences and access of health services across the country.

1. Introduction

Prostate cancer is the second most common male cancer after skin cancers. In general, prostate cancer is primarily a disease of older people, with 75% of cases diagnosed in men aged ≥ 65 years [1].

An estimated 1.1 million men were diagnosed with prostate cancer worldwide in 2012, with nearly 70% of cases occurring in more developed regions [2]. The latest estimate published by National Cancer Institute José Alencar Gomes da Silva (INCA) for the biennium 2016/2017, points to the occurrence of about 61,000 new cases of the disease in Brazil and the increase in prostate cancer incidence rates in the country is due in part to improved diagnostic methods, especially with the dissemination of prostate-specific antigen (PSA) screening in combination with digital rectal examination (DRE) [3]. The US Food and Drug Administration (FDA) approved PSA testing in 1986 and in 1994 it was approved for cancer detection [4]. In Brazil the PSA test was introduced in the 1990s and was adopted by the Unified Health System (SUS) in 1998 in Brazil [5].

Prostate cancer is the fifth leading cause of death from cancer in men worldwide, with an estimated 307,000 deaths in 2012. It is estimated that the number of deaths from prostate cancer is larger in less developed regions than in developed ones [2]. In Brazil, prostate cancer is the second most common type of cancer among men, after non-melanoma skin cancer [3], and the age-standardized mortality rate increased from 7.15/100,000 men in 1980 to 14.06/100,000 men in 2013 [6].

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The frequency distribution of cancer types varies across regions depending on their socio-demographic and socio-economic characteristics, adequate health care availability, and on the population access to diagnostic and treatment of early disease.

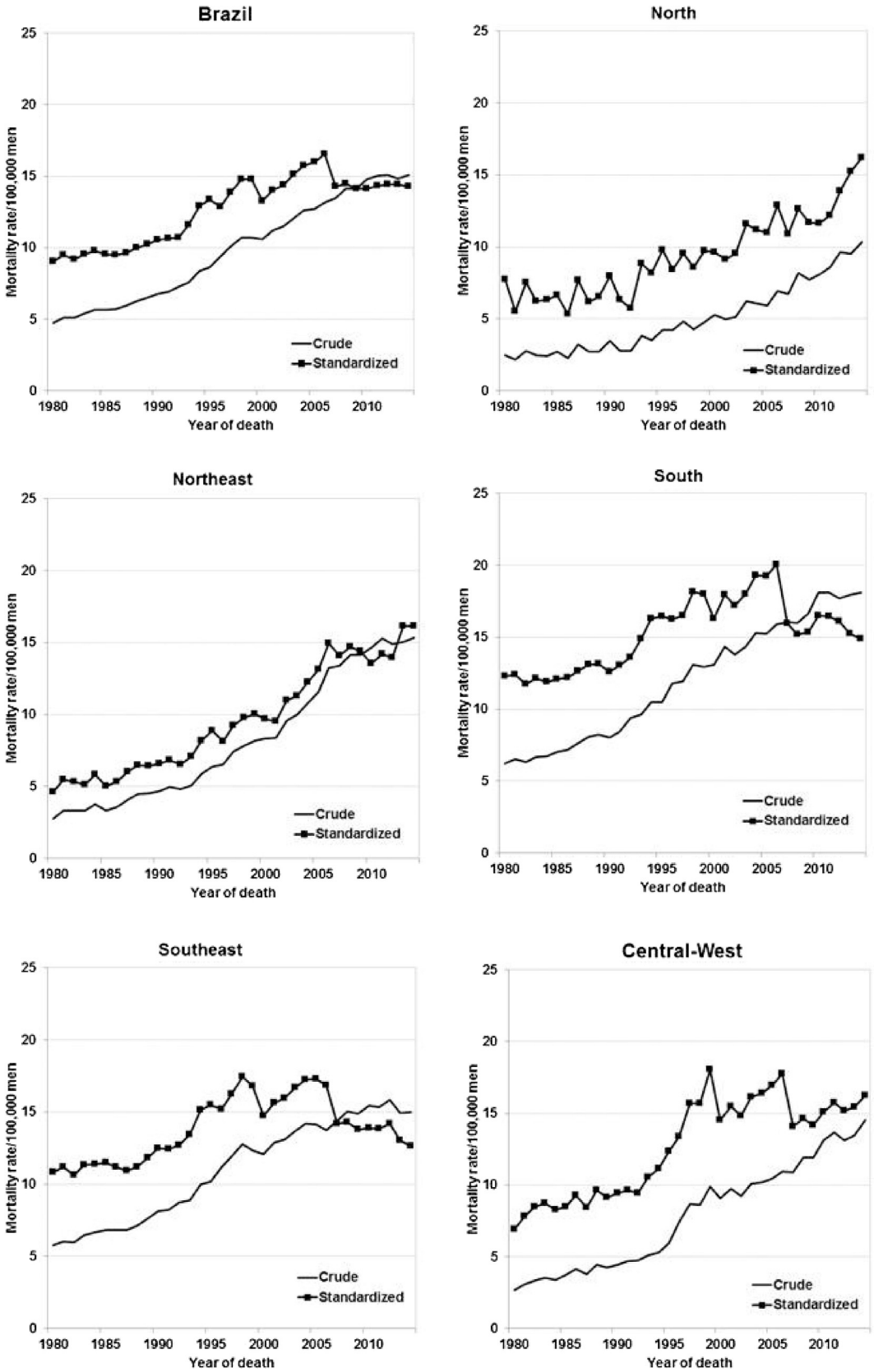

Fig. 1. Prostate cancer mortality rates per 100,000 men: crude and age-standardized for mundial population, Brazil and its regions, 1980–2014.

This underscores the need to study the variations in trends of prostate cancer incidence and mortality for proper monitoring and control [7].

Mortality rates and their variations can be affected by several factors. Age can have an effect on mortality rates, especially from chronic diseases. Some historical events and environmental factors

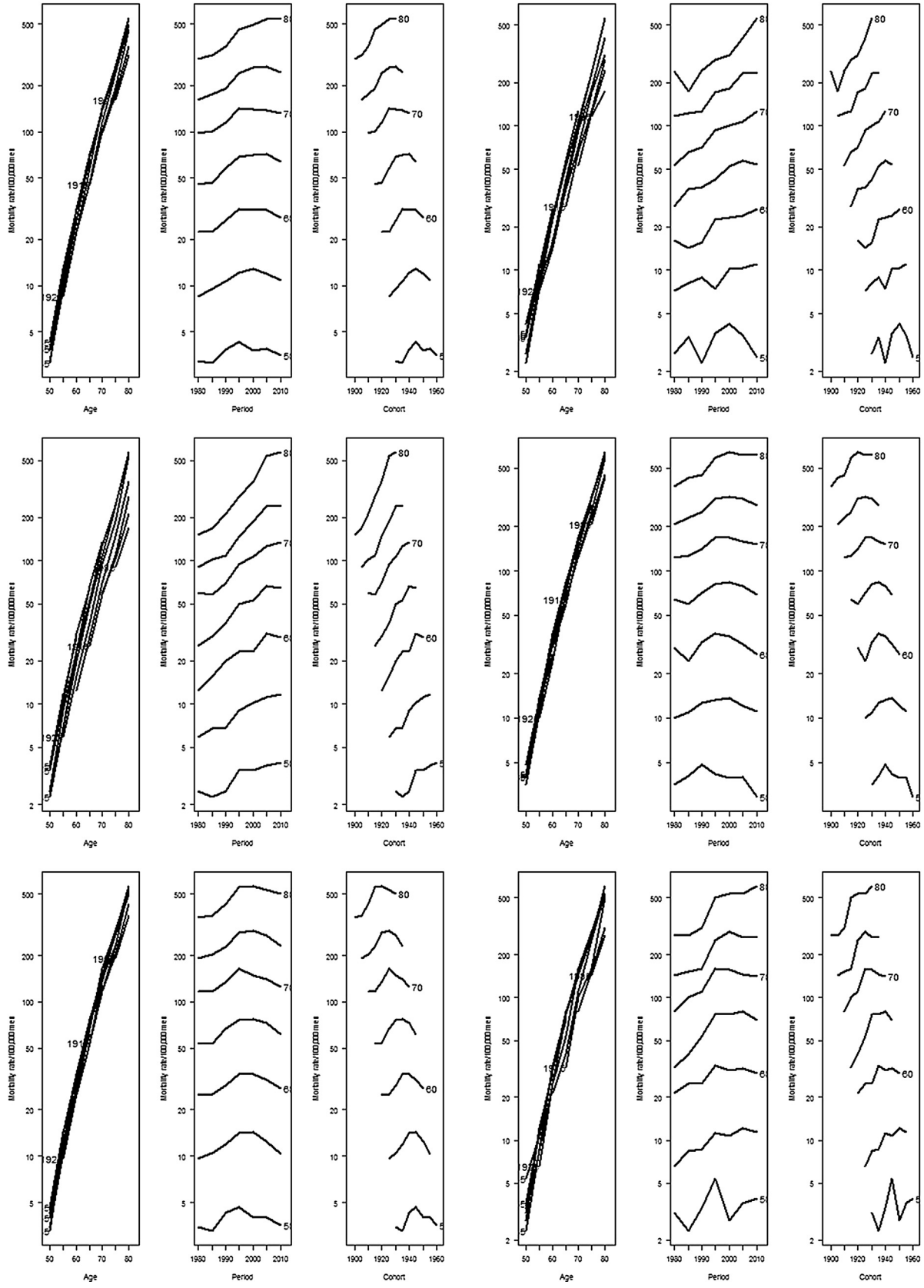

Fig. 2. Age-specific prostate cancer mortality rates per 100,000 men, period of death, and birth cohort. Brazil and its regions, 1980–2014.

can concurrently influence all age groups (period effect). Certain factors affect a generation and promote distinct changes in succeeding cohorts as they age (cohort effect), and are relevant in the examination of mortality risk associated with long-term exposure [8,9].

Several international studies [10–13] on mortality rates have used age–period–cohort (APC) analysis to understand how these factors affect mortality rates over a certain period of time. In Brazil, few studies [14] on prostate cancer have been conducted, especially using data from vital statistics made available by agencies linked to the Ministry of Health.

This study aimed to describe the trends in prostate cancer mortality in Brazil and in its five geographic regions (North, Northeast, South, Southeast, and Central-West) and to determine the influence of age, period, and cohort effects on mortality rates between 1980 and 2014.

2. Methods

2.1. Study design

This is an ecological study of the temporal trend of mortality from prostate cancer in Brazil and its five geographic regions using population-based secondary data.

2.2. Data source

The data used in this study were retrieved from the SUS Computing Department DATASUS, web portal (http://www2.datasus.gov.br/DATASUS/index.php?area=02, accessed on 07/08/2015). Information on deaths was obtained from the Mortality Information System (SIM); information on the resident male population in Brazil and regions was collected or estimated by the Brazilian Institute of Geography and Statistics (IBGE).

Deaths were computed using International Classification of Diseases, Ninth Revision (ICD-9) code 185 for 1980–1995 and ICD-10 code C61 for 1996–2014. For each year, tables were constructed with the number of deaths from prostate cancer and the male population per age group for Brazil and its five geographic regions: North (N), Northeast (NE), South (S), Southeast (SE), and Central-West (CW). Deaths by ill-defined causes were proportionally redistributed to correct mortality rates.

2.3. Data analysis

Crude, specific, and age-standardized rates per 100,000 men were calculated for each year from 1980 to 2014. The specific rates were calculated for five-year age groups for ages 50 and older. Mortality rates were adjusted based on the world standard population for global comparisons as proposed by Segi et al. [15] and modified by Doll et al. [16].

The redistributed number of deaths from prostate cancer and the male population aged ≥ 50 years were computed to construct the age–period–cohort model (APC model). Both age (from 50 to 80 years and older) and period (from 1980 to 2014) were grouped into five-year intervals. Birth cohorts began in 1897 and ended in 1960.

We applied the APC analysis proposed by Yang et al. [8,17] and used in other Brazilian study [18], which estimates the age, period, and cohort effects independently. The model can be written in log-linear regression form as:

$$\log(r_{ijk}) = \log\left(\frac{d_{ijk}}{n_{ijk}}\right) = \tau + a_i + \beta_j + \gamma_k,$$

where r_{ijk} denotes the expected death rate in the age–period–cohort cell (i, j, k); d_{ijk} denotes the number of deaths; n_{ijk} is the population or exposure-at-risk, the log of which is termed as the offset or adjustment for the log-linear contingency table model; τ denotes the intercept or adjusted mean rate; α_i denotes the ith row age effect for $i = 1, \ldots, a$ denotes age groups; β_j denotes the jth column period effect for $j = 1, \ldots,$ p denotes periods; and γ_k denotes the kth diagonal cohort effect for $k = 1, \ldots, (a + p - 1)$ cohorts [8,17].

The birth cohort corresponds to the difference between the period (year of death) and age at the time of the event (cohort = period − age), any model that includes these three variables will have identifying constraints, resulting in the "identification problems." There is no consensus on the best method to solve this problem [8,17,19]; we adopted the weighted parameterization approach proposed by Holford [20].

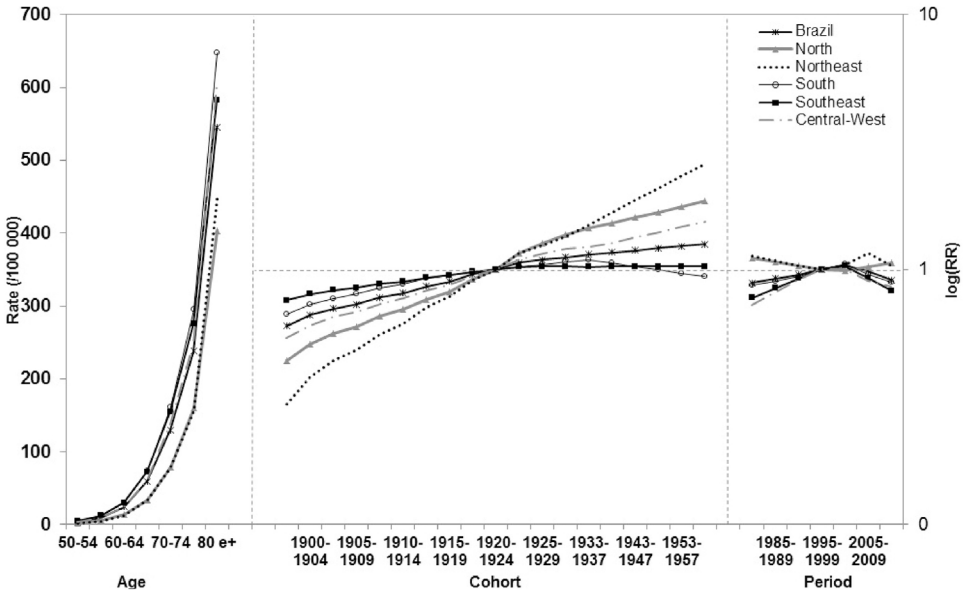

Fig. 3. Results of the fitted APC-model. Brazil and its regions, 1980–2014.

Prostate cancer is rare before age 50 [21,22], mortality rates were examined for ages 50 and older. The period 1995–1999, which corresponds to the widespread dissemination of PSA testing by SUS for detection of prostate cancer in Brazil [5]; was used as reference. The birth cohort (1922) was selected because of the higher incidence of deaths related to this malignant neoplasm.

The APC model was adjusted separately for Brazil and its five geographic regions using a Poisson regression for event counts. In the APC model, the effects act on a multiplicative manner on mortality rates and the log of the expected rate is a linear function of age, period, and cohort effects [8,17].

The association measure generated by the APC model is the relative risk (RR) and 95% confidence intervals (95% CI). The likelihood ratio test compares the goodness-of-fit of models measured by the deviance and the degrees of freedom. The Akaike's information criterion (AIC) was used to compare non-nested models.

APC analyses were performed using the 'Epi 2.0' package in R statistical software version 3.2.2 (2015).

2.4. Ethical aspects

The Research Ethics Committee of the Universidade Federal de Minas Gerais (Protocol ETIC 072/09 of 04/29/2009) approved this project.

3. Results

In 2014, the crude mortality rate for prostate cancer in Brazil was 15/100,000 men. Crude rates of 10 (North), 14 (Central-West), 15 (Southeast), 15 (Northeast), and 18 (South) per 100,000 men were estimated for the geographic regions (Fig. 1).

Age-standardized prostate cancer mortality rates in Brazil increased since 1980, and this increase was more pronounced between 2000 and 2006. After 2006, mortality rates in Brazil showed a trend towards stabilization. In the North region, age-standardized prostate cancer mortality rates rose across the study period with some fluctuations from year to year. The increase in mortality rates in the Northeast was significant and the region had the highest rate of any region after 2013. Mortality rates in the South and Southeast regions were the highest of any region and showed similar trends, with an increase in rates until 2006 followed by a downward trend. To some extent, mortality rates in the Central-West region followed the time trends of national rates (Fig. 1).

Age-specific prostate cancer mortality rates showed an upward trend for ages 50 and older, regardless of birth cohort for all regions. Mortality rates analyzed by period revealed an increase across age groups in the North and Northeast and a decline in the South and Southeast in the last 15 years. In addition, younger cohorts showed a downward trend in age-specific rates in the South and Southeast regions, but an upward trend was observed across age groups and cohorts in the North and Northeast regions (Fig. 2).

Age effects, which are expressed by period and cohort-adjusted rates, increased with aging across all regions. Adjusted rates were lower in the North and Northeast across all age groups compared to the national rates, whereas an opposite result was found for the South and Southeast (Fig. 3). In addition, mortality rates in the Central-West region were higher than the national rates only for ages 60 and older ($p < 0.05$, Supplemental Table 1).

Cohort effects increased in succeeding generations born from 1897 to 1960 across Brazil, except in the South where the risk of death was lower in the 1960 cohort. In addition, the risk of death for the Northeast region increased more sharply across generations compared to Brazil and the other regions (Fig. 3).

Period effects results are expressed as age and cohort-adjusted relative risk (RR). South, Southeast, and Central-West regions followed the national trend and showed an increase in the risk of death from prostate cancer for 1980–2004 and a downward trend after that period (Fig. 3). However, the risk of dying from prostate cancer in the South, Southeast, and Central-West regions was lower than the general national risk ($p < 0.05$, Supplemental Table 1). Conversely, in the North and Northeast regions, results were suggestive of a decline in the risk of death for 1980–1994, with an upward trend after 2000, especially in the Northeast (Fig. 3).

4. Discussion

This study investigated the time trends in prostate cancer mortality in Brazil and in the North, Northeast, South, Southeast, and Central-West Brazilian regions between 1980 and 2014 and the age–period–cohort effects on mortality rates. The results showed that crude and age-standardized mortality rates increased in Brazil and in its five geographic regions. The largest increase in age-standardized rates was observed in the Northeast, even though they were lower than in the South. The age effects on mortality showed an increase in the risk of death from prostate cancer with increasing for ages 50 and older. The period effects showed that the risk of death was lower in the South, Southeast, and Central-West and higher in the North and Northeast regions. In addition, the risk of death increased in succeeding cohorts born after 1897 and was higher in the Northeast.

Similar results were reported for Conceição et al. [23] examined the trends in prostate cancer mortality rates in Brazil, and its regions for 1980–2010, Silva et al. [24] in Central-West region for 1980–2011, and Lima et al. [25] in Aracaju (Northeast) for 1996–2006, all theses studies showed increases in prostate cancer death rates. In turn, Jerez-Roig et al. [14] showed that mortality rates for prostate cancer for 2011–2025 were projected to decline in the country and in the Southeast, South, and Central-West regions, but to increase in the North and Northeast. These authors argued that the highest mortality rates for prostate cancer in less developed Brazilian regions were due to the reduced availability of oncology services, access to early diagnosis, the quality of cancer treatment and the quality of health information compared to more developed regions [14,23–25].

Time trend studies of prostate cancer death rates in the Austria [10], France [11], USA and Canada [26] and Spain [27] revealed that mortality rates have declined over the past 20 years. Multiple factors have been proposed to explain the downward trends observed in these countries, including the introduction of PSA testing for early detection and advances in diagnostic imaging and treatment [10,11,26,27]. In Latin America, a time trend study of prostate cancer death rates for 1955–2001 in Chile [28] identified three periods in the rise of age-standardized rates: a first one from 1955 to 1981 showing a slow increase in rates (0.9% annual increase), a second one starting in 1981 showing a steeper increase (2.6% annual increase), and a third period starting in 1996 showing a slow decline in death rates (1.0% annual decrease). A time trend study of prostate cancer death rates for 1986–2006 in Argentina [12] showed a decline in rates in more developed regions and an increase in more impoverished areas of the country.

The time trend analysis conducted in this study used an age–period–cohort (APC) modeling approach, which revealed a steady increase in the risk of death for men ages 50 and older. The age effects were stronger probably due to the aging process of the Brazilian population [14,23]. In fact, age effects are more significant when considering the actual demographic profile of the Brazilian population, because age, especially 50 and older, is the main risk factor for developing prostate cancer [21,22]. Similar findings were reported in other time trend studies of prostate cancer mortality conducted in Brazil [14,23–25] and other countries [10–13,26–28].

Our results are suggestive of period effects in the 1990s that are possibly related to the dissemination of PSA testing for prostate cancer diagnosis in Brazil, particularly in the Southeast and South regions [5]. The likely increase in the number of diagnosed cases might have led to a rise in mortality rates at the time followed by a decline in subsequent periods due to earlier diagnosis of the disease. In the 1990s, PSA screening for prostate cancer was introduced in more developed countries to reduce mortality in advanced stages. Since then, increased incidence rates have been reported, especially among older men [29,30]. Nevertheless, some studies found no significant changes in death rates after the introduction of PSA screening for prostate cancer whereas others did, and this remains a topic of discussion [31]. In fact, large ongoing international trials investigating the impact of screening on prostate cancer death rates – the European Study of Screening for Prostate Cancer (ERSPC) [32] and the Prostate, Lung, Colorectal and Ovary Screening Trial (PLCO) [33]. The first study showed differences in the rates of mortality between screened and non-screened, while the second did not find differences between the two groups of individuals. In Brazil, population screening for prostate cancer is not systematic [34]. The PSA testing should be administered opportunistically at the time men seek health care services for reasons unrelated specifically to cancer into a perspective of comprehensive care at the men's health, as recommended by the Brazilian National Cancer Institute (INCA) [35].

The cohort effects on mortality showed a higher risk of death in younger than in older cohorts. These findings can be explained by the increased incidence of prostate cancer in Brazil due to population aging in recent decades, a phenomenon termed *"demographic metabolism"* by Yang [17], wherein demographic changes affect succeeding birth cohorts. Similar results were reported in studies in France [11], the Netherlands [36], and Taiwan [13]. Conversely, in Austria [10] and Argentina [12], the risk of death was lower in younger than in older cohorts.

The cohort effects on mortality for the five regions showed that the risk of death was higher in the Northeast, which has fewer oncology services specialized in the diagnosis and treatment of prostate cancer. Additionally, this fact appears to affect younger cohorts from the Northeast, because their risk of death was higher than in young cohorts from other regions, especially compared to those from the South and Southeast, where the quality of care, as represented by better training in diagnosis and treatment, may have contributed to the differences found across Brazilian regions [14,23–25].

Birth cohort effects underscore the importance of early life exposures in explaining disease susceptibility and mortality in the examination of diseases such as cancer, in which long-term exposure to a carcinogen is the major cause of the disease later in the adulthood [8,17]. Even though they are not well established, the effects associated with birth cohorts reflect the accumulation of lifetime exposures to one or more risk factors, including genetic background, increased consumption of fat and meat, alcohol use, and physical inactivity, among others [22]. Some studies have shown an association between the use of pesticides and the risk of developing prostate cancer, especially in occupational exposure groups, but little information exists on the association of environmental exposures to cancer risk in the general male population [37–39].

5. Limitations

Analyses of mortality by cause of death are essential for planning appropriate policies. However, one of the main limitations of these analyses in most developing countries is the quality of vital statistics, especially mortality data. The percentage of deaths from unknown causes has declined in recent decades in all Brazilian regions, indicating an improvement in the quality of information recorded on the Mortality Information System [40,41]. Furthermore, changes in the diagnosis and certification of prostate cancer may partly explain the upward trends in Brazil, particularly among the elderly [42,43].

Another limitation is related to the APC analysis, in which it is still under development, with varying results depending on the assumptions made when building the model. Methodological discussions on model specifications and "identification problems" are contained in papers published over the last 10 years [18–20].

6. Conclusion

The increase in prostate cancer mortality in the last three decades was mainly due to the aging of the Brazilian population. The APC analysis showed that the risk of death was higher in the North and Northeast regions. Differences across regions are possibly related to inequalities in the access and use of health services and the reduced availability of oncology services between more and less developed regions, adversely affecting population health in less developed areas in the country.

Authors' contribution

Study conception and planning: SFMB, MCS, MLC; Data analysis and interpretation: SFMB, MCS; Manuscript preparation and writing: SFMB, MCS, MLC; Critical review of the manuscript and approval of the manuscript's final version: SFMB, MCS, MLC.

Conflict of interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.canep.2017.07.016.

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