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Geospatial Health 2018; volume 13:732

Trend and spatial analysis of prostate cancer mortality in the state of Sergipe, Brazil

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Abstract

This is an ecological study with exploratory analysis of spatial and temporal data based on mortality data with respect to prostate cancer obtained from the Mortality Information System concerning residents of the state of Sergipe, Brazil between 2000 and 2015. The analysis of temporal trends was performed using the Joinpoint Regression Program through Poisson regression. Spatial analysis was performed using the empirical Bayesian model, Kernel analysis, Global Moran and Local indices. There were 1,986 deaths due to prostate cancer, most of which occurring after 60 years of age. An increasing, non-constant but significant trend in mortality rates was noted. The kernel density estimator showed hotspot densities of the highest rates of prostate cancer mortality in the north-eastern and central regions of the state. High-risk clusters were identified for prostate cancer mortality (I = 0.55, P<0.01). There was an increase in prostate cancer mortality rates and a heterogeneous geographic distribution of risk areas, with high-risk priority areas identified in certain regions of the state. These priority areas include the municipalities located in the Northeast (Amparo do São Francisco, Aquidabã, Canhoba, Cedro de São João and Telha), the West (Frei Paulo and Pedra Mole) and the south-western region of the state (Poço Verde and Simão Dias).

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Key words: Prostatic neoplasms; Mortality; Time series studies; Spatial analysis; Brazil.

Contributions: the authors contributed equally.

Conflict of interest: the authors declare no potential conflict of interest.

Funding: research funding sources: SVS/MS (Ministry of Health - Brazil).

Ethical statement: the research was approved by the Ethics Committee of the Federal University of Sergipe, under the protocol number 1.408.888.

Received for publication: 2 August 2018.
Revision received: 1 September 2018.
Accepted for publication: 9 October 2018.

Geospatial Health 2018; 13:732
doi:10.4081/gh.2018.732

Introduction

Neoplasms are considered a worldwide public health problem and have been highlighted due to the increase in incidence, morbidity/mortality rates and the high costs of prevention, diagnosis and treatment of individuals with this pathology (Ministry of Health, 2006). Among the different types of cancer that affect the male population, prostate cancers characterized by its high incidence and mortality in a global context. It is the second most frequent type of cancer in the male population and represents the third leading cause of cancer death in men worldwide (Ferlay *et al.*, 2015). About 70% of the diagnosed cases occur in economically more developed regions, which can be explained by the better monitoring and diagnosis of the disease in these areas. However, in some middle-income areas, such as countries in Africa and South America, the incidence is also high (National Cancer Institute, 2015). According to estimates by the Brazilian National Cancer Institute, approximately 596,000new cases of cancer were registered in the country between 2016 and 2017, 295,200 of whom males with 61,200 cases being prostate cancer, which represents approximately 6% of all deaths due to neoplasms (National Cancer Institute, 2015).

Prostate cancer occurs due to the hyperplasia of prostate gland cells. The prostrate is located below the bladder in front of the rectum and produces part of the seminal fluid (10-30%) ejaculated during sexual intercourse. Prostate cancer can present both a slow or a rapid evolution; when slow, monitoring is recommended so that any worsening can be picked up. Rapid evolution increases the risk for metastasis eventually death (Haas *et al.*, 2008; National Cancer Institute, 2016). The diagnosis and treatment of prostate cancer affect the daily life of men, due to physiological changes related to aging and/or health conditions, including male sexuality (Vieira, 2010).

Health professionals and managers need accurate epidemiological information on this health problem to plan and implement policies to reduce prostate cancer in the state of Sergipe. Given the lack of local studies addressing this issue, we aimed to visualize and analyze temporal trends and the spatial distributions of prostate cancer mortality in the state of Sergipe between the years 2000 and 2015.

Materials and Methods

This is an ecological, time-series study with spatial analysis techniques using secondary data from the Mortality Information System (SIM) of the Department of Informatics of the Unified Health System (Ministry of Health, 2017). The historical series (2000 to 2015) from the municipalities of the state of Sergipe of the specific mortality for prostate cancer, according to the definition of the International Classification of Diseases, 10th revision (WHO, 2016), codes C61, was used.

Study area

Sergipe is located in the northeast of Brazil, comprises 75 municipalities with Aracaju as state capital. It has a population of 2,265,779 inhabitants and an area of 21,910,354 km² with a population density of 94.3inhab./km (Brazilian Institute of Geography and Statistics - IBGE, 2010). Mortality rates were calculated per 100,000 inhabitants, with the male population as the denominator. Data from the 2010 from the Brazilian Demographic Census and the intercensorial projections produced by the Brazilian Institute of Geography and Statistics Foundation and made available by Datasus (Ministry of Health, 2017) were used.

Statistics

Bayesian estimation was used to minimize the instability caused by the random fluctuation of the cases, smoothing the standardized rates by applying weighted averages and creating a second corrected rate. The Empirical Bayesian Rate illustrated a correction of the multiplicative rate equal to 100,000, taking into account the male population at risk by municipal area and the number of cases for each year analyzed, (Ministry of Health, 2007). Temporal trends for the consecutive series of sixteen years were calculated using the rates of prostate cancer-specific mortality as dependent variables and the year as the independent variable.

The Joinpoint Regression Program Version 4.5.0.1 (National Cancer Institute, 2013) was used to calculate the time frequency trends of departures with a model based on the assumption of a minimum number of points needed to produce statistically significant changes in temporal trends. For this, a linear logarithmic model was created which added Joinpoints and calculated the difference up to a statistically significant value, using the Monte Carlo permutation test (Kim *et al.*, 2001). Annual percent change (APC) was calculated, in addition to the temporal trends in the frequency of departures. In the spatial analysis, the site addresses of the deaths were georeferenced and the points marked by capturing the latitude and longitude coordinates provided by Google Maps (Ministry of Health, 2007; Google Developers, 2016). Thematic maps of the mortality rates for prostate cancer in the municipalities were constructed for the period under analysis. We adopted the kernel intensity estimator which, through statistical smoothing, generated a density surface for the visual detection of hotspots, indicating agglomeration in a spatial distribution and continuous surface from the data (Bailey and Gatrell, 1995).

Spatial autocorrelation between mortality rates was used to investigate whether the spatial distribution of the disease occurs randomly or follows some pattern of occurrence in space. A spatial proximity matrix obtained by the contiguity criterion was adopted, adopting a significance level of 5% and calculating the Moran Global Index (*I*), varying between -1 and +1, representing the spatial autocorrelation expression of prostate cancer mortality in the geographic space analyzed to identify spatial clusters and risk areas. Values close to zero indicate spatial randomness; values between 0 and +1 indicate positive spatial autocorrelation and between -1 and 0 negative spatial autocorrelation (Druck *et al.*, 2004).

Moran's Mirroring Diagram was used to indicate the critical or transitional areas in order to compare the value of each municipality with neighbouring municipalities and to verify the spatial dependence shown by the Local Index of Spatial Association to detect regions with significant spatial autocorrelation (Druck *et al.*, 2004). Spatial quadrants were generated: Q1 (high/high) and Q2 (low/low) municipalities with values similar to those of their neighbours, indicating positive spatial association areas characterizing spatial aggregates; Q3 (high/low) and Q4 (low/high) indicating negative areas of spatial association where the municipalities have distinct values to their neighbours, characterizing discrepant observations, represented visibly by BoxMap (Bailey and Gatrell, 1995; Santos and Raia Junior, 2006). Areas having positive spatial autocorrelation (identified by BoxMap) with statistically significant spaces above 95% were produced, generating a Moran map, used for the visualization of clusters and the identification of priority areas. Moran maps were constructed for spatial representation when the municipalities presented statistically significant differences ($P<0.05$).

The IBGE provided the cartographic base of the state of Sergipe (IBGE, 2010). Thecartographic projection corresponded to the Universal Transverse Mercator system, using the Terra Datum model SIRGAS 2000. The descriptive data were tabulated and analyzed by the programs GraphPad Prism version 5.01 and Microsoft Excel 2010. For the spatial analysis we used the program TerraView 4.2.2 (TerraView, 2010) and QGIS2.18.3 software (Creative Commons Attribution-Share Alike 3.0 license CC BY-SA, Las Palmas, CA, USA).

Results

During the period from 2000 to 2015, a total of 1,986 cases of deaths were identified with prostate cancer being the underlying cause, with an average of 124.1 deaths/year. When analyzing the trend of standardized rates, there was a general and growing trend, ranging from 6.1 (2000) to 16.4 (2015) deaths per 100,000 inhabitants and a growth of 166.1%. Between 2000 and 2006, a trend of more pronounced growth occurred with an APC of 17.5% (CI 10.8-24.6, $P<0.01$). Between 2006 and 2015there was a slight growth trend with a 0.5% APC (Figure 1).

All municipalities in the state of Sergipe recorded cases of prostate cancer deaths. The highest percentage of deaths were in those aged 80 and over (44.7%), mixed-race (46.8%), married (49.7%), non-educated (27.6%), living in metropolitan areas (61.3%), as shown in Table 1. The local empirical Bayesian method generated more stable corrected indicators (Figure 2A).

The average gross rate reached 12.5/100.000 inhabitants, while the smoothed indicator was 12.6/100.000. The smoothed maps showed the majority of municipalities (65.3%) with a mortality rate of 10.0 to 15.0/100.000.

The spatial analysis techniques used demonstrated a conglomerate process in the space, indicating a high variation for the occurrence of prostate cancer mortality in the state of Sergipe during the studied period. The kernel density estimator showed hotspot densities of the highest rates of prostate cancer mortality in the northeastern and central regions of the state (Figure 3). Moran's *I* was positive and significant ($I = 0.55$, $P<0.01$) indicating the existence of clusters and confirming the spatial autocorrelation throughout the analyzed period. The positive value of Moran's *I* allowed us to infer that municipalities with high mortality rates are close to municipalities with the same characteristics, while municipalities with low rates are close to other municipalities with the same pattern.

The BoxMap (Figure 4A) highlights areas according to their position in the Moran mirroring diagram. 29 municipalities had high prostate cancer mortality rates (high-high) with a predominantly contiguous range area from the southwest to the northeast of the state. Another 33 municipalities presented low mortality rates (low-low) and were located in the northwest, central and southern regions of Sergipe. Transition areas were also identified, comprising 6 municipalities with high rates, with neighbours with low rates (high-low) and 7 municipalities with low rates surrounded by municipalities with high rates (low-high), both dispersed throughout the state.

In Figure 4B, the MoranMap presents statistically significant clusters of high-risk areas for prostate cancer mortality, due to the agglomeration of municipalities with high rates (high-high). These priority areas include the municipalities located in the north-eastern (Amparo do São Francisco, Aquidabã, Canhoba, Cedro de São João and Telha), the West (Frei Paulo and Pedra Mole) and the south-western region of the state (Poço Verde and Simão Dias). In addition, clusters of municipalities with low rates of prostate cancer mortality and neighbours with similar values (low-low) are located in the northwest regions of the state (Canindé de São Francisco, Monte Alegre de Sergipe, Poço Redondo and Porto da Folha), the south (Arauá, Cristinápolis, Indiaroba, Itabaianinha, Santa Luzia do Itanhy and Umbaúba), as well as the municipality of Riachuelo, located in the central-eastern regionof the state of Sergipe.

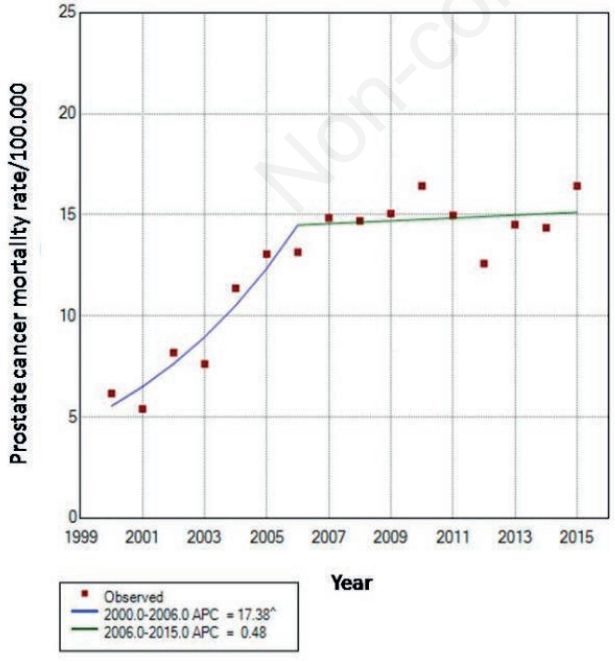

Figure 1. Time trend of standardized mortality rates for prostate cancer in Sergipe, Brazil, 2000 to 2015.

Discussion

Mortality rates due to prostatic neoplasia vary among regions of the world (Bosetti *et al.*, 2005). In recent years, there has been

Table 1. Socio-demographic characteristics of prostate cancer deaths in Sergipe, Brazil, 2000 to 2015.

Demographic variables	n (%)
Age group	
<30	1 (0.05)
30-39	2 (0.10)
40-49	13 (0.65)
50-59	75 (3.78)
60-69	320 (16.11)
70-79	686 (34.54)
≥80	889 (44.76)
Ethnicity	
White	507 (25.53)
Black	223 (11.23)
Asian	4 (0.20)
Multiracial	930 (46.83)
Indigenous	2 (0.10)
Not known	320 (16.11)
Marital status	
Not married	338 (17.02)
Married	988 (49.75)
Widower	333 (16.77)
Divorced	79 (3.98)
Other	52 (2.62)
Not known	196 (9.87)
Education	
None	549 (27.64)
1 to 3 years	411 (20.69)
4 to 7 years	234 (11.78)
8 to 11 years	125 (6.29)
> 12	70 (3.52)
Not known	597 (30.06)
Place of Death	
Hospital	986 (49.65)
Another health facility	8 (0.40)
Home	965 (48.59)
Public space	11 (0.55)
Others	12 (0.60)
Not known	4 (0.20)
Region of Residence	
Metropolitan region	768 (38.67)
Outside the Metropolitan Region	1218 (61.33)

a trend towards moderate growth in prostate cancer mortality throughout Latin America (Hallal *et al.*, 2001). These mortality rates have declined in the United States and other high-income countries, but in low- and middle-income countriestheyhave tended to increase (Jemal *et al.*, 2010; Thun *et al.*, 2010), corroborating the findings of our study.

Prostate cancer usually develops slowly, and some less aggressive tumours may develop asymptomatically over a period of 15-20 years (Bosetti *et al.*, 2005). Men who have this type of cancer commonly present other co-morbidities which makes it difficult to clearly identify the underlying cause of death. The present study shows that there has been a considerable increase of approximately 18% in mortality rates for prostate cancer between the years 2000-2015. This may be related to demographic and epidemiological changes observed in Brazil. Regardless of socioeconomic and cultural factors, population aging exposes the population to a higher probability of being affected by chronic non-transmissible diseases (Gottlieb *et al.*, 2011) including prostate cancer (Ribeiro *et al.*, 2013). In Sergipe, in the years studied, there was an increase in prostate cancer mortality rates in the age group 60-79 years, corresponding to 50.65% of the total cases. This is in line with studies carried out by Cambruzzi *et al.* (2010) and Migowski and Silva (2010) in the states of Rio Grande do Sul and Rio de Janeiro, who reported rates of 44.9% and 48.4% respectively in the range between 60-69 years, and research by Penaforte *et al.* (2009) in the states of Pernambuco and Bahia who reported a higher concentration of cases in the range of 70-79 years.

The results of this study showed that the increase in mortality rates occurred at two distinct time periods, the first relating to the initial years of the series. This finding is consistent with studies by Souza *et al.* (2018) that showed a significantly increasing trend of prostate cancer mortality in the north-eastern region of Brazil between 2003 and 2006. It is believed that this sudden increase is due to improvements in the way cancer was recorded in the state of Sergipe. The second period showed a smaller increase probably related to advances in diagnostic and treatment techniques for prostate cancer (Feletto *et al.*, 2015). Some studies cited the advancement in treatment for men with localized and high-risk prostate cancer was cited as a likely consequence for the behaviour of decreasing trends observed in Australia, England, Canada and the United States between 1994 and 2010 (Feletto *et al.*, 2015).

The majority of deaths were among married men, corroborating the results from other studies indicating higher rates in this marital state (Souza *et al.*, 2013). It is believed that spouses directly influence men seeking treatment, leading to more diagnoses and consequently raising mortality rates attributed to prostate cancer (Rippentrop *et al.*, 2004). There was a predominance of mortality cases in men living outside the metropolitan region, corroborating studies reporting a significant increase in municipalities in the interior of the North, Northeast and Central-West regions of Brazil (Gulnar *et al.*, 2011). Studies show that the identification of high-risk areas, through the combination of different spatial analysis techniques, provides an improved understanding of the disease. It also contributes to delineating areas for classification as priorities for specific interventions, in addition to helping to better evaluate the impacts of targeted actions (Alencar *et al.*, 2012; Martins-Melo *et al.*, 2014). The spatial analysis techniques applied in this study allowed the identification of heterogeneous areas and significant standardization of prostate cancer mortality in Sergipe between the years 2000-2015. High-risk areas for prostate cancer mortality were identified in the Northeast, West and south-western regions of

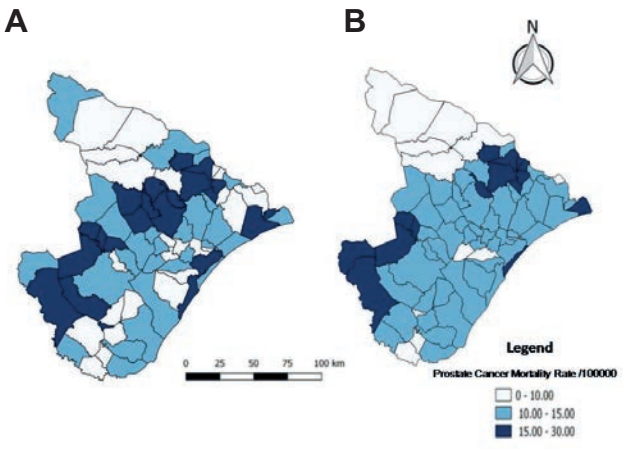

Figure 2. Spatial distribution of prostate cancer mortality rate (per 100,000 inhabitants) in the state of Sergipe, Brazil, between 2000 and 2015: Gross coefficient (A), coefficient smoothed by the local empirical Bayesian method (B).

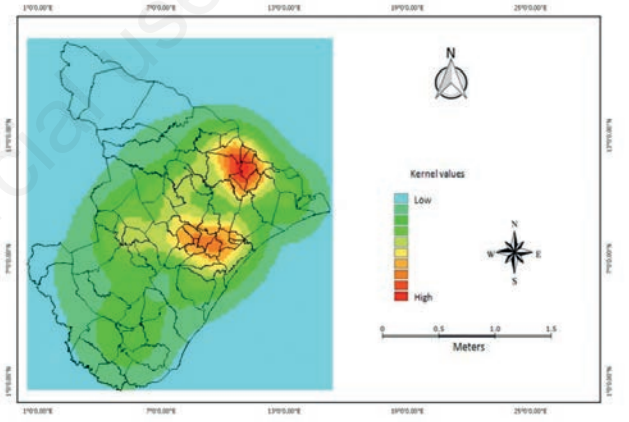

Figure 3. Kernel density map of prostate cancer deaths in the state of Sergipe, Brazil, 2000 to 2015.

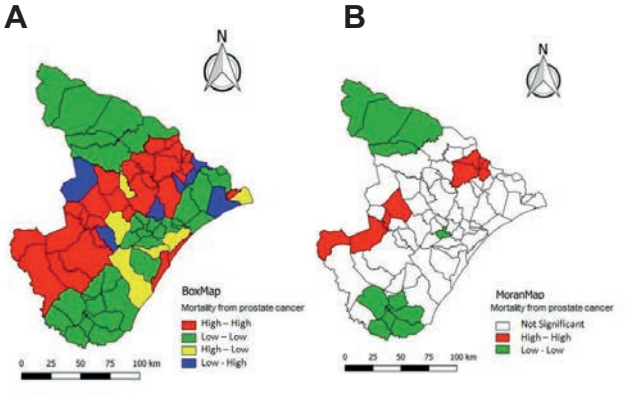

Figure 4. Spatial analysis of mortality rate from prostate cancer (per 100,000 inhabitants) in Sergipe, Brazil, between 2000 and 2015: BoxMap (A) and Moran Maps (B).

the Sergipe state.

These risk areas were far from the metropolitan area of Aracaju, the state capital, where the two High Complexity Units in Oncology are located. The centralization of this service may have contributed to rising mortality rates in some areas far from the capital, possibly hindering access to highly complex care. Factors that make it difficult to access the health care network can lead to a greater number of diagnoses in more advanced stages of the disease, making it impossible to treat adequately, which could eventually contribute to the increase of prostate cancer mortality rates in the areas indicated by the present study. The distribution of the gross indicators reflect the spatial expression of prostate cancer mortality in the state, however, thematic maps with smoothed indicators were better able to show the spatial effects caused by the neighbouring municipalities. Spatial dependence analysis was able to identify statistically significant areas for prostate cancer mortality in the state.

A limitation of this study was the use of secondary data, which may present inconsistencies in relation to its quantity, quality and information processing. In order to minimize any possible systematic errors, information from the national SIM database was compared with data from the state SIM, provided by the Sergipe State Department of Health.

Conclusions

The results of this study revealed the increase prostate cancer mortality rates to be a growing public health problem in the state of Sergipe. The agglomerates of the highest rates (hot spot) were delimited and identified and found to be far from the metropolitan region. Priority high-risk areas were identified (clusters) in certain regions of the state. It points out the urgent need to develop regional health policies, strengthening the network of specialized care for the prevention, early diagnosis and timely treatment of prostate cancer. These findings indicate the need for subsequent studies that raise the understanding of local and regional factors and determinants related to the trends and pattern of the spatial distribution of prostate cancer mortality rates in Sergipe.

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