Temporal Trend and Spatial Distribution of Oral Cancer Mortality in Sergipe

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Tendência Temporal e Distribuição Espacial da Mortalidade por Câncer de Boca em Sergipe

Tendencia Temporal y Distribución Espacial de la Mortalidad por Cáncer de Boca en Sergipe

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ABSTRAT

Introduction: Annually, in Brazil, 15 thousand individuals are diagnosed with oral cancer and almost half of them die. Sergipe is among the seven Brazilian states with the highest rates. **Objective:** To analyze the temporal trend and the spatial distribution of oral cancer mortality in Sergipe between 2007 and 2016. **Method:** Population-based time series ecological study, using techniques of spatial analysis. Mortality data were obtained from the Mortality Information System (SIM). The analysis of temporal trends was performed with the Joinpoint regression model using Poisson regression. Spatial analyzes were carried out using the Kernel intensity estimator and the Moran Global and Local indexes. **Results:** 543 oral cancer deaths were analyzed. The most frequent cases were in men (74%), with an average age of 64 years and low education. The overall and male's mortality rates (annual percent change − APC=2.5; 95% CI 0.9-6.7 and APC=2.96; 95% CI 1.2-5.6), respectively, increased. There was also an increasing trend of mortality by tongue cancer (APC=10.05; 95% CI 3.8-16.7). Mortality related to other anatomical locations was stable. There was a concentration of deaths in the Metropolitan, Midsouth and Mid-rural regions. **Conclusion:** During the period investigated, the general mortality rate showed an increasing trend, with concentration in the Midsouth, Mid and Metropolitan regions, and it is necessary to maintain preventive and control measures against oral cancer throughout the State of Sergipe.

Key words: mouth neoplasms/mortality; spatio-temporal analysis; spatial analysis; ecological studies; demography.

RESUMO

Introdução: Anualmente, no Brasil, 15 mil pessoas são diagnosticadas com câncer de boca, e quase metade delas morre. Sergipe está entre os sete Estados brasileiros com maiores índices. **Objetivo:** Analisar a tendência temporal e a distribuição espacial da mortalidade por câncer de boca em Sergipe entre 2007 e 2016. **Método:** Estudo ecológico de série temporal de base populacional, utilizando técnicas de análise espacial. Os dados de mortalidade foram obtidos no Sistema de Informação sobre Mortalidade (SIM). A análise das tendências temporais foi realizada no modelo de regressão de *Joinpoint* por meio da regressão de *Poisson*. Foram realizadas análises espaciais utilizando o estimador de intensidade *Kernel* e os índices de Moran Global e Local. **Resultados:** Foram analisadas 543 mortes por câncer de boca. Os casos mais frequentes ocorreram em homens (74%), com idade média de 64 anos e baixa escolaridade. As taxas de mortalidade global (variação percentual anual − APC=2,5; IC 95% 0,9-6,7) e masculina (APC=2,96; IC 95% 1,2-5,6) aumentaram. Houve também uma tendência crescente de mortalidade por câncer na língua (APC=10,05; IC 95% 3,8-16,7). A mortalidade relacionada a outras localizações anatômicas foi estável. Houve concentração de óbitos nas Regiões Metropolitana, Centro-Sul e Centro-Agreste. **Conclusão:** Durante o período analisado, a taxa de mortalidade geral mostrou uma tendência crescente, com concentração nas Regiões Centro-Sul, Central e Metropolitana, sendo necessário manter medidas de prevenção e controle contra o câncer de boca em todo o Estado de Sergipe.

Palavras-chave: neoplasias bucais/mortalidade; análise espaço-temporal; análise espacial; estudos ecológicos; demografia.

RESUMEN

Introducción: Cada año en Brasil, 15.000 personas son diagnosticadas con cáncer de boca y casi la mitad de ellas mueren. Sergipe es uno de los siete Estados brasileños con las tasas más altas. **Objetivo:** Analizar la tendencia temporal y la distribución espacial de la mortalidad por cáncer de boca en Sergipe entre 2007 y 2016. **Método:** Estudio ecológico de series temporales basadas en la población, utilizando técnicas de análisis espacial. Los datos de mortalidad se obtuvieron del Sistema de Información sobre Mortalidad (SIM). *Poisson* realizó el análisis de las tendencias de tiempo en el modelo de regresión de Punto de unión. Fueron realizadas análisis espaciales utilizando el estimador de intensidad del *Kernel* y los índices Moran Global y Local. **Resultados:** Se analizaron un total de 543 muertes por cáncer de boca. Los casos más frecuentes se dieron en hombres (74%), con una edad media de 64 años y baja escolaridad. Aumentaron las tasas de mortalidad global (porcentual cambio anual − PCA=2,5; IC 0,9-6,7) y masculinas (PCA=2,96; IC 95% 1,2-5,6). También hubo una tendencia creciente de mortalidad por cáncer en la lengua (PCA=10,05; IC 95% 3,8-16,7). La mortalidad relacionada con otros lugares anatómicos fue estable. Hubo una concentración de muertes en las regiones Metropolitana, Central-Sur y Centro-Agreste. **Conclusión:** Durante el período analizado, la tasa general de mortalidad mostró una tendencia creciente, con concentración en las Regiones Centro-Sur, Centro y Metropolitano, y es necesario mantener medidas de prevención y control contra el cáncer de boca en todo el Estado de Sergipe.

Palabras clave: neoplasias de la boca/mortalidad; análisis espacio-temporal; análisis espacial; estudios ecológicos; demografía.

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INTRODUCTION

Oral cancer is considered one of the main problems for health services worldwide due to its high morbimortality[1,2]. A malignant tumor affects lips, mouth structures, gingiva, cheeks, palate, tongue and floor of the mouth. Only in the last two decades the incidence raised 68%, likely attributed to poor healthy habits[3]. Annually, 22 thousand new cases are diagnosed in Brazil, with rate of mortality of approximately six deaths per 100 thousand population[4].

Despite nearly one century of public policies with the implementation of cancer attention programs and preventive campaigns, it is still high the incidence of oral cancer in Brazil[5]. For each year of the triennium 2020-2022, 11,180 new cases of oral cancer are previewed in men and 4,010 in women, corresponding to an estimated risk of 10.69 new cases per 100 thousand men and 3.71 per 100 thousand women. In Brazil's Northeast, excluding non-melanoma skin cancer, oral cancer is the fifth most frequent in men (6.72 cases/100 thousand) and the 11th in women (3.12 cases/100 thousand). Sergipe – Brazil's smallest federative unit with only 21,910 km^2 – has one of the highest incidence rates with 8.48 cases per 100 thousand men and 2.23 cases per 100 thousand women[4].

The profile of the population at risk of squamous cell carcinoma (SCC), the most common malignant epithelial neoplasms affecting oral cavity comprehends male individuals older than 50-years old, low education and income, smokers and living in rural areas[6]. In addition, it is clear that factors related to the patient's medical status and to the primary tumor are important indicators of oral cancer[7,8].

Mortality is an important indicator of the burden of diseases and reflects the risk of death in a certain period for a specific population. The systematic collection of information about death certificates is the most simple and accessible manner of collecting data about mortality of a population[9]. The Brazilian rate of mortality by oral cancer (C00 to C10, according to ICD-10) is 2.64/100 thousand population and Sergipe is ranked 11th with a rate of mortality of 2.58/100 thousand population[4].

To determine deaths by oral cancer within a context of individual-space-time can help to identify its causes and reduction of onset[10]. The analysis of the population-based space distribution of oral cancer is essential to identify areas of risk and vulnerability. In addition, the evaluation of the rates of mortality by oral cancer and social determinants in the geographical space allows to identify specific necessities of interventions in public health to prevent the disease in a direct and equitable manner. The objective of this study was to analyze the time trend and space distribution of mortality by oral cancer in Sergipe, Brazil, from 2007 to 2016.

METHOD

The present study was conducted in the State of Sergipe in Brazil's Northeast region. Its estimated population is 2,265, 779 inhabitants and populational density of 94.3 inhabitants per km^2[11] with 75 municipalities divided in eight macroregions comprehending a population with several socioeconomic and environmental aspects[12,13]. Nearly 50% of the population is classified as below the Poverty Index and life expectancy is 72.1 year[11] (Figure 1).

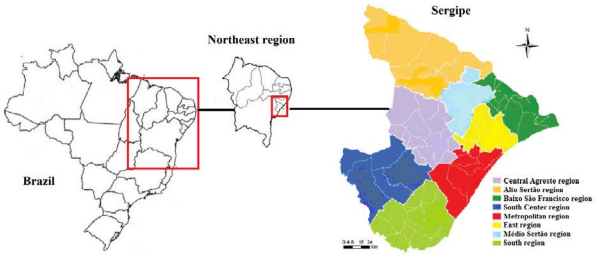

Figure 1. Geographical location. Sergipe, Brazil

It is a population-based time series ecological study utilizing techniques of spatial analysis. The sample was formed with secondary data of deaths by oral cancer registered in the Mortality Information System (SIM)[14] of all the 75 municipalities of the State of Sergipe from 2007 to 2016. The rates of mortality refer to 100 thousand population and the residing inhabitants was utilized as denominator.

The socioeconomic data were extracted from the death certificate of Sergipe's population selected because of the basic cause of death as "disease or condition which triggered the chain of pathological effects leading directly to death"[13]. Therefore, the primary location of the neoplasm or origin cancer follows the American Cancer Society[12].

The following codes of malignant neoplasms according to Chapter II of the International Classification of Disease and Related Health Problems 10th Edition (ICD-10)[15], were utilized: C00 (lip); C01 (base of the tongue); C02 (other and unspecified parts of the tongue); C03 (gingiva); C04 (mouth); C05 (palate); C06 (other and unspecified parts of the mouth); C07 (parotid gland); C08 (other and unspecified major salivary glands); C09 (amygdala); and C10 (oropharynx)[15].

The temporal trend for 10-years consecutive series was calculated with the annual rate of specific mortality of oral cancer as dependent variable and the period of

the study in years as independent variable. Initially, the software Joinpoint, version 4.0 (Surveillance Research, National Cancer Institute, USA) was utilized to analyze the trends, it estimates the annual percent change (APC) of a segmented linear regression (Joinpoint regression) and identifies the inflection points, each point reflects the changes of increase or decrease of the mortality rates.

This regression allowed the adjustment of a series of lines and their inflection points in a logarithmic scale through the annual test of trends. The Monte Carlo permutation test was utilized to obtain the adjustment based in the best line of each segment analyzed. The APC and the mean annual percent change (MAPC), with their respective confidence intervals of 95% were estimated and tested. The study periods were analyzed in separate with the occurrence of inflection points with reverse direction. The number of inflections utilized in the analysis resulted from models defined by the software to allow better representation of the trend with the lower number of inflection points. Poisson regression was utilized to determine the number of required segments to correctly explain the relation between two variables. The points of change of trend with $p<0.05$ were considered.

For the spatial analysis, the addresses of the residences were georeferenced and the points were marked with the latitude and longitude from Google Earth Pro[16]. Thematic maps of distribution of deaths by oral cancer in the municipalities for the period analyzed were elaborated with the software QGIS 2.1.4. The Kernel techniques were applied to identify the intensity of the distribution of deaths in the State of Sergipe. It shows the density of the surface generated statistically for visual detection of feature points, which indicates the agglomeration of cases in the spatial distribution. The distribution of points was transformed in smooth surface as a continuous map representing different levels of intensity of death. The level of smoothing, that is, the width of the radius of influence was defined as three thousand meters because this value generated a correct representation of the distribution of deaths by oral cancer in the municipalities, minimizing the bias of overlap.

The following formula was utilized to estimate the Kernel density:

$$\hat{f}_h(x) = \frac{1}{n}\sum_{i=1}^{n} K_h \sum_{i=1}^{n} (x - x_i) = \frac{1}{nh}\sum_{i=1}^{n} K\left(\frac{x - x_i}{h}\right)$$

Where n is the number of samples and h, the kernel smoothing parameter and K (xt, xi), the kernel operator[17]

Spatial autocorrelation analysis was performed among the mortality rates by cancer in the municipalities. Moran Global Index (MGI)[18] was calculated to identify clusters with risks of this occurrence. A spatial proximity matrix obtained by the criteria of contiguity was developed, adopting a level of significance of 5%. The values of the index ranged from -1.0 to +1.0, which represented the expression of spatial autocorrelation of mortality by oral cancer in the geographical space analyzed to identify spatial agglomerates and areas of risk. Values close to 0 indicate spatial randomness; values between 0 and +1 indicate positive spatial autocorrelation and between -1 and 0, negative spatial autocorrelation[19].

The Moran's index of global spatial autocorrelation is based in cross-products of deviations of the mean calculated for the features as follows:

$$I = \frac{\left[(n\sum_i^n \sum_j^n \omega_{ij}(y_i - \tilde{y})(y_j - \tilde{y})\right]}{\left[\sum_i^n (y_i - \tilde{y})^2 \sum_i^n \sum_j^n \omega_{ij}\right]}$$

Where ω_{ij} is an element of the matrix of contiguity (ω); y_i is the rate of mortality of the municipality i; y_j is the rate of incidence of the municipality j; $\breve{y}$ is the mean of the sample and the symbol n represents the total number of municipalities[18,20].

Moran's Scatter Plot Frame was utilized to indicate critical or transient areas in order to compare the value of each municipality with its neighbors and verify the spatial dependence shown by the Local Index of Spatial Association (LISA) to detect regions with significant spatial correlation. Thus, to evaluate the local spatial grouping, it would be useful to obtain a measure of association of each unit if the hypothesis of stationarity of the process occurs locally[19].

$$I = \frac{n\left[(Z_i \sum_j^n \omega_{ij} Z_j)\right]}{(\sum_j^n Z_j^2)}$$

Where $Z_i = y_i - \breve{y}$; $Z_j = y_j - \breve{y}$; ω_{ij} is the element of the contiguous matrix ω; y_i is the rate of mortality of the municipality i; y_j is the rate of incidence of the municipality j; $\breve{y}$ is the mean of the sample and the symbol n represents the total number of cities[18,20].

The spatial dependence and risk patterns were analyzed with the creation of spatial quadrants: Q1 (high/high) and Q2 (low/low) indicate municipalities with values similar to its neighbors; Q3 (high/low) and Q4 (low/high) indicate negative points of spatial association where the municipalities have different values from their neighbors, characterizing discrepant observations. Areas with positive spatial correlation with statistically significant spaces above 85% were generated through Moran Map utilized

to visualize clusters and identification of priority areas. Moran Maps were constructed for spatial representation when statistically significant differences were detected in the municipalities ($p<0.05$)[21].

The "*Instituto Brasileiro de Geografia e Estatística* (IBGE)[11]" provided the cartographic base of the State of Sergipe. The cartographic projection followed the Universal Transverse Mercator = (UTM) and utilized Terra Datum, model "*Sistema de Referência Geocêntrico para as Américas 2000* (SIRGAS2000)". The descriptive data were tabulated and analyzed with GraphPad Prism version 5.01 and Microsoft Office Excel 2010. TerraView 4.2.2 and QGis 2.14 were utilized for spatial statistics.

The Institutional Review Board of "*Universidade Federal de Sergipe*" (CAAE 68035317.3.0000.5546) approved the study.

RESULTS

From 2007 to 2016, 543 deaths by oral cancer in the State of Sergipe were registered. Of these, 74% (n=400) in men and 26% (n=143) in women. The mean age was 63 years (±14.36 years, ranging from 10 to 104 years), 56% of the individuals had three years or less of education (n=305), 63% were Brown or Black. The frequency of deaths at the hospital and at home was 53.4% (n=290) and 448% (n=243), respectively.

The rate of mortality by 100 thousand population by oral cancer increased 2.50 cases in 2007 to 2.99 in 2016 (APC=2.5; CI 95% 0.9-6.7) as shown in Figure 2 (A). Men presented rising rates of mortality while women rates were stable (4.08 to 4.65 per 100 thousand men, APC=2.96; CI 95% 1.2-5.6) and 0.97 to 1.4 per 100 thousand women, APC=0.84; CI 95% -4.4-6.3) as portrayed in Figure 2 (B and C).

The distribution of deaths according to the anatomic site (ICD-10[15]) is depicted in Table 1. There was rising trend of mortality by tongue cancer (APC=10.05; CI 95% 3.8-16.7). Mortality related to other sites remained stable.

The estimator Kernel identified high density of deaths in the regions *Metropolitana, Central-Sul* and *Central Agreste* (Figure 3). Moran's Map showed local agglomerates of risk ($p<0.01$) in nine municipalities (*Itabaiana, Areia Branca, Riachuelo, Santa Rosa de Lima, Canhoba, Amparo de São Francisco, Malhada dos Bois* and *Telha*) as shown in Figure 4 (A and B).

DISCUSSION

The epidemiological characteristics and the spatial-temporal distribution of mortality by oral cancer were investigated. The sample followed the pattern described in the literature with most of the deaths occurring with middle-aged men and low education level[2,22,23]. The mortality rate increased for men likely related to lifestyle, smoking and drinking habits which potentialize the risk if simultaneous[24].

Among women, the trend was stable, different from a multicenter study conducted with database of 14 countries which found trend of change of the incidence of oral cancer in women across several world regions[25]. Similarly, in a historical series carried out in Brazil from 2002 to 2013, it was found decline of the mortality rate of men and women, possibly due to social alterations related to women's smoking and drinking habits[26].

The incidence of squamous cell carcinoma (SCC) of the tongue has been increasing in the last decades and the current sample showed a rising trend for this anatomic site. A study with 22 cancer registries worldwide showed increase of incidence of SCC of the tongue, ranging from

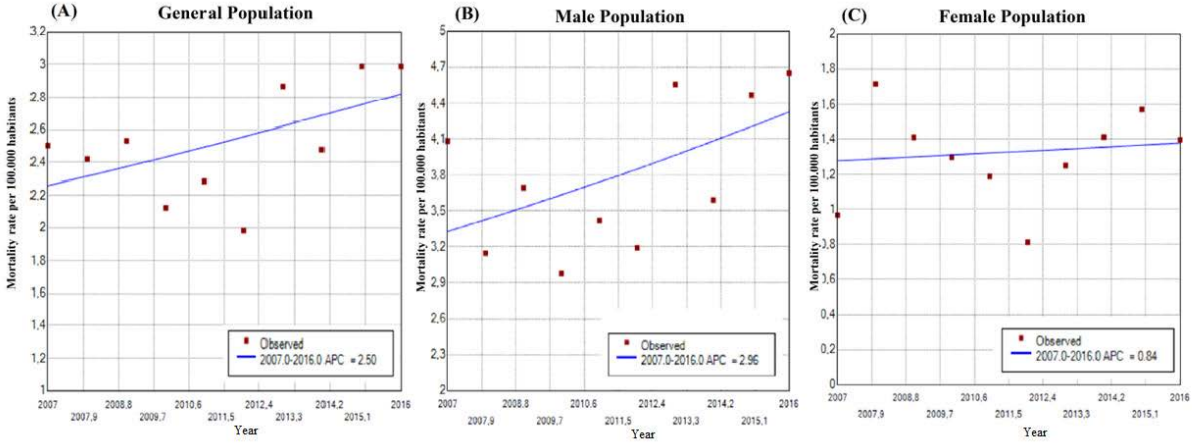

Figure 2. Analysis of the general trend of mortality and by sex, 2007-2016. Sergipe, Brazil

Table 1. Distribution of deaths and trends of oral cancer according to ICD-10[15] classification, Sergipe, 2007-2016

ICD-10	n	%	APC	CI	Trend
C00 – Lip	6	1.1	10.15	(-1.9 to 23.7)	Stable
C01 and C02 – Tongue	149	27.4	10.05	(3.8 to 16.7)	Rising
C03 – Gingiva	6	1.1	11.36	(-8.1 to 35)	Stable
C04 – Floor of the mouth	10	1.8	-0.12	(-17.1 to 24.4)	Stable
C05 – Palate	23	4.2	-6.03	(-23.7 to 15.7)	Stable
C06 – Cheek mucosa	170	31.3	1.85	(-3.2 to 7.2)	Stable
C07 and C08 – Major salivary glands	33	6.1	7.75	(-6.3 to 23.9)	Stable
C10 – Oropharynx	146	26.9	-1.7	(-8.8 to 5.9)	Stable
Total	543	100.0	10.15	(-1.9 to 23.7)	Stable

Caption: ICD-10th = International Classification of Diseases and Related Health Problems 10th Edition.

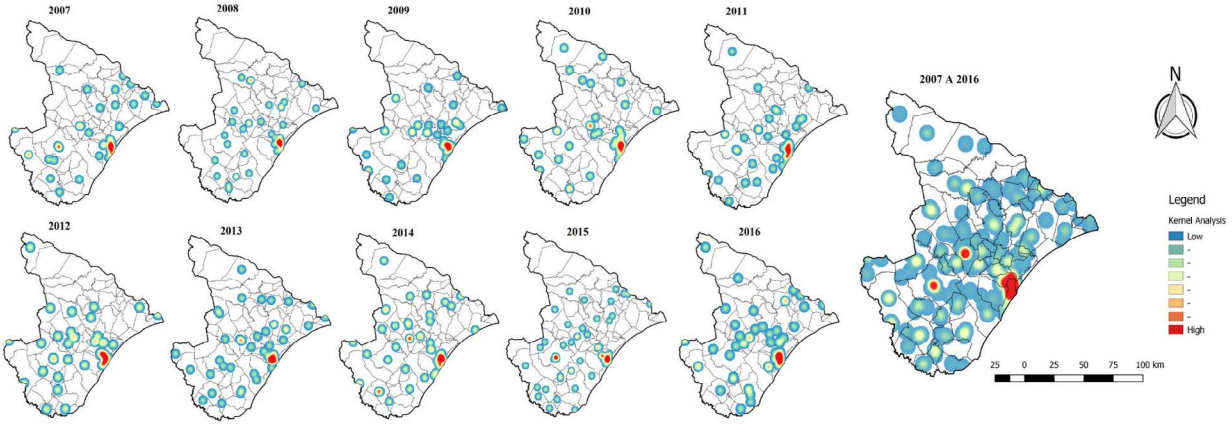

Figure 3. Kernel Analysis of the deaths by oral cancer, 2007-2016. Sergipe, Brazil

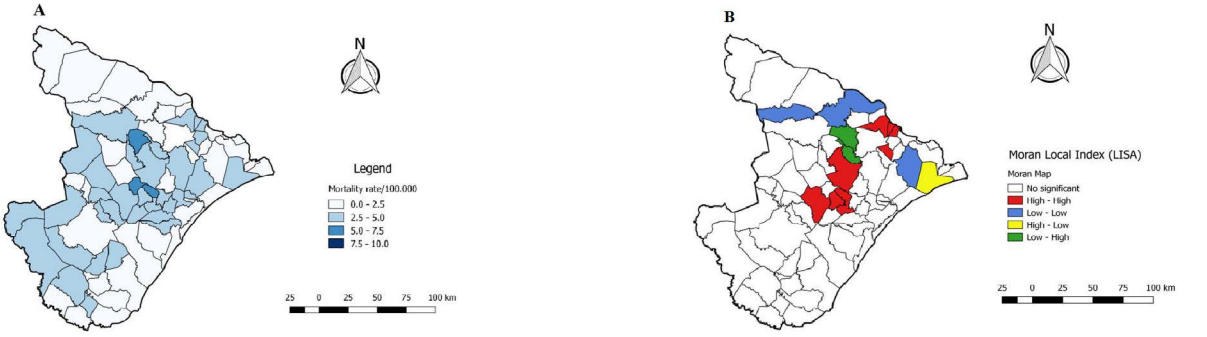

Figure 4. Cumulative mortality rate (A) and cumulative mean mortality rate analyzed by Moran method (B) for oral cancer, 2007-2016. Sergipe, Brazil

0.4% to 3.3% annually in most of the areas[25]. Lesions of the tongue and floor of the mouth are localized in areas of rich vascularization and full of lymph nodes, which contributes for locoregional or remote metastatic spread, worsening the prognosis and defining the necessity of aggressive treatment[7,27]. In addition, these areas are more exposed to carcinogenic agents and papillomavirus infection (HPV), which is being described as an independent factor for SCC of head and neck, mainly for oropharynx tumors, specifically tonsils and tongue cancer[28,29].

Improvement of the access to oral health services in the last decades in Brazil was found, mainly within the program Family Health implemented in 1997, likely impacting positively the identification and notification of oral health related deaths in Sergipe[5]. It is known that it

takes decades of well implemented public health policies to ameliorate health indicators. Furthermore, the decline of mortality rates, increase of survival years and upgrade of oral cancer related quality-of-life are contingent upon early identification and diagnosis, immediate treatment and multi-disciplinary team monitoring[30], reason why the medium and high complexity levels of the public health in the country from which depend the process of diagnosis and treatment need to improve in Sergipe.

According to Law number 12,732/2012[31] implemented in 2014, cancer treatment must be initiated in up to 60 days from the day of the diagnosis. However, in despite of this, changes were not significant because the patients have to deal with the usual problems like low investment, insufficient structure and staff with poor technological skills. A hospital-based descriptive, analytical study between 2009 and 2015 in Brazil concluded that the Northeast Region had the second percent (23.46%) of patients who had no access within 60 days from the diagnosis with the North Region ranked first with 23.57%[32].

The study of Ferlay et al.[33] evaluated the rates of incidence and mortality of different types of cancer in 184 countries and concluded that the incidence of oral cancer has been increasing in the most developed countries while mortality increased in less developed ones. Likely, the increase may be related to the difficulty of early access and immediate beginning of the treatment, since in Brazil the cases are diagnosed at advanced stage in more than 75% while in USA, the percent is 42%[34].

In addition, the steady increase of deaths may also have been influenced over the years by improved reporting on the Mortality Information System (SIM)[14], which is remarkable in the number of ignored information. Santos et al.[35] who assessed mortality from 2000 to 2009 in the capital of Sergipe presented variables with 20% to 35% of information ignored in the death certificate, which did not occur in the present study, which obtained less than 15% of ignored information. Still, studies[35,36] evaluating the integrity of the data of SIM noticed a decreasing trend of non-completion of data for most of the variables in the death certificate in different regions of the country.

The Moran's spatial dependence analysis from 2007 to 2016 draws attention to the fact that the municipalities of *Itabaiana* and *Areia Branca* presented agglomerates of sites of risk ($p<0.01$) because these are two of the three with gold mining (*Itabaiana, Areia Branca* and *Itaporanga D'Ajuda*) according to the geological map and mineral resources of the State of Sergipe[37]. Mercury is utilized in gold extraction to separate particulates and arsenic is naturally present in the ground and released during the extraction process, contaminating the soil, rivers and fishes which may contribute to increased risk of cancer[38,39].

However, given the limitations of an ecological study, more studies are necessary to check any relation among the onset of oral cancer and the presence of these substances in *Itabaiana* and *Areia Branca*, since oral cancer has other risk factors as its location in sites exposed to carcinogenic agents of different types as tobacco, alcohol, ultraviolet radiation, genetic factors and HPV, recently.

In addition, limitations common to ecological studies exist because only secondary data were utilized and several information were missed while filling out the death certificate which results in incomplete register of data negatively affecting the epidemiological analyzes. Thus, it was not possible to evaluate some very important variables as clinical staging and delay of diagnostic and treatment.

CONCLUSION

Mortality by oral cancer is rising for the general and male population and for females, it kept stable in the period investigated. Only malignant neoplasms of the tongue presented rising trend as concluded from the analysis of the anatomic location, which can be related to the improvement of the identification of the disease because of decentralization of oral health services or even in the registration of death certificates. In the Metropolitan, Mid-Southern and Mid-East regions it was detected concentration of deaths.

CONTRIBUTIONS

All the authors contributed to the study conception/design, acquisition, analysis and interpretation of the data, wording and critical review. They approved the final version to be published.

DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interests to declare.

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None.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394-424. doi: https://doi.org/10.3322/caac.21492
2. Moro JS, Maroneze MC, Ardenghi TM, et al. Oral and oropharyngeal cancer: epidemiology and survival

analysis. Einstein (São Paulo). 2018;16(2):eAO4248. doi: https://doi.org/10.1590/s1679-45082018ao4248

3. Aquino RCA, Lima MLLT, Menezes CRCX, et al. Aspectos epidemiológicos da mortalidade por câncer de boca: conhecendo os riscos para possibilitar a detecção precoce das alterações na comunicação. Rev CEFAC. 2015;17(4):1254-61. doi: https://doi.org/10.1590/1982-0216201517414914
4. Atlas de Mortalidade por Câncer [Internet]. Rio de Janeiro: Instituto Nacional de Câncer José Alencar Gomes da Silva. c1996-2014 - . Taxas de mortalidade por câncer, brutas e ajustadas por idade, pelas populações mundial e brasileira, por 100.000, segundo sexo, localidade e período selecionado; [acesso 2018 dez 18]. Disponível em: https://mortalidade.inca.gov.br/MortalidadeWeb/pages/Modelo05/consultar.xhtml#panelResultado
5. Martins Filho PRS, Santos TS, Silva LCF, et al. Oral cancer in Brazil: a secular history of Public Health Policies. Rev Gaúcha Odontol. 2014;62(2):159-64. doi: https://doi.org/10.1590/1981-86372014000020000091688
6. Martins JD, Mascarenhas Andrade JO, Freitas VS, et al. Determinantes sociais de saúde e a ocorrência de câncer oral: uma revisão sistemática de literatura. Rev Salud Pública. 2015;16(5):786-98. doi: http://doi.org/10.15446/rsap.v16n5.40083
7. Almeida FCS, Cazal C, Nunes FD, et al. Fatores prognósticos no câncer de boca. Rev Bras Cienc Saude. 2011;15(4):471-8.
8. Haraj NE, Bouri H, El Aziz S, et al. Evaluation of the quality of life in patients followed for differentiated cancer of the thyroid. Ann Endocrinol (Paris). 2019;80(1):26-31. doi: https://doi.org/10.1016/j.ando.2018.01.003
9. Instituto Nacional de Câncer. Atlas de mortalidade por câncer no Brasil 1979-1999. Rio de Janeiro: INCA; 2002.
10. Czeresnia D, Ribeiro AM. O conceito de espaço em epidemiologia: uma interpretação histórica e epistemológica. Cad Saúde Pública. 2000;16(3):595-617. doi: https://doi.org/10.1590/S0102-311X2000000300002
11. Cidades@ [Internet]. Rio de Janeiro: Instituto Brasileiro de Geografia e Estatística. c2017 - [acesso 2017 dez 18]. Disponível em: https://cidades.ibge.gov.br/
12. American Cancer Society [Internet]. Atlanta: American Cancer Society; c2022. What is a cancer of unknown primary? [revised 2018 Mar 9; cited 2019 Jan 2]. Available from: https://www.cancer.org/cancer/cancer-unknown-primary/about/cancer-of-unknown-primary.html
13. Ministério da Saúde; Fundação Nacional de Saúde. Manual de instruções para o preenchimento da declaração de óbito. 3. ed. Brasilia (DF): Ascom; 2001.
14. SIM: Sistema de Informação sobre Mortalidade [Internet]. Versão 3.2.1.2. Brasília, DF: DATASUS. [data desconhecida] - [acesso 2017 maio 10]. Disponível em: http://sim.saude.gov.br/default.asp
15. Organização Mundial da Saúde. CID-10: classificação estatística internacional de doenças e problemas relacionados à saúde. São Paulo: Edusp; 2008.
16. Google Earth. 2017. Sergipe. [acesso 2017 ago 2]. Disponível em: https://earth.google.com/web/
17. Parzen E. On estimation of a probability density function and mode. Ann Math Statist. 1962;33(3):1065-76. doi: https://doi.org/10.1214/aoms/1177704472
18. Chen Y. New approaches for calculating Moran's index of spatial autocorrelation. PLoS One. 2013;8(7):e68336. doi: https://doi.org/10.1371/journal.pone.0068336
19. Moran PAP. The interpretation of statistical maps. J R Stat Soc Series B Stat Methodol [Internet]. 1948 [cited 2018 May 12];10(2):243-51. Available from: https://www.jstor.org/stable/2983777
20. Santos MB, Santos AD, Barreto AS, et al. Clinical and epidemiological indicators and spatial analysis of leprosy cases in patients under 15 years old in an endemic area of Northeast Brazil: an ecological and time series study. BMJ Open. 2019;9(7):e023420. doi: https://doi.org/10.1136/bmjopen-2018-023420
21. Fischer M, Scholten H, Unwin D. Spatial analytical perspectives on GIS. London: Routledge; 1996.
22. Le Campion ACOV, Santos KCB, Carmo ES, et al. Caracterização do atraso no diagnóstico do câncer de boca e orofaringe em dois centros de referência. Cad Saúde Colet. 2016;24(2):178-84. doi: https://doi.org/10.1590/1414-462X201600020004
23. Bonfante GMS, Machado CJ, Souza PEA, et al. Sobrevida de cinco anos e fatores associados ao câncer de boca para pacientes em tratamento oncológico ambulatorial pelo Sistema Único de Saúde, Brasil. Cad Saude Publica. 2014;30(5):983-97. doi: https://doi.org/10.1590/0102-311X00182712
24. Marur S, Forastiere AA. Head and neck cancer: changing epidemiology, diagnosis, and treatment. Mayo Clin Proc. 2008;83(4):489-501. doi: https://doi.org/10.4065/83.4.489
25. Ng JH, Iyer NG, Tan MH, et al. Changing epidemiology of oral squamous cell carcinoma of the tongue: a global study. 2017;39(2):297-304. doi: https://doi.org/10.1002/hed.24589
26. Perea LME, Peres MA, Boing AF, et al. Tendência de mortalidade por câncer de boca e faringe no Brasil no período 2002-2013. Rev Saude Publica. 2018;52:10. doi: https://doi.org/10.11606/S1518-8787.2018052000251
27. Brandizzi D, Gandolfo M, Velazco ML, et al. Clinical features and evolution of oral cancer: a study of 274 cases in Buenos Aires, Argentina. Med Oral Patol Oral Cir Bucal [Internet]. 2008 [cited 2018 May];13(9):E544-8. Available from: http://www.medicinaoral.com/pubmed/medoralv13_i9_pE544.pdf
28. Nguyen NP, Chi A, Nguyen LM, et al. Human papillomavirus-associated oropharyngeal cancer: a new

clinical entity. QJM. 2010;103(4):229-36. doi: https://doi.org/10.1093/qjmed/hcp176

29. Kabeya M, Furuta R, Kawabata K, et al. Prevalence of human papillomavirus in mobile tongue cancer with particular reference to young patients. Cancer Sci. 2012;103(2):161-8. doi: https://doi.org/10.1111/j.1349-7006.2011.02149.x
30. Johnson NW, Warnakulasuriya S, Gupta PC, et al. Global oral health inequalities in incidence and outcomes for oral cancer: causes and solutions. Adv Dent Res. 2011;23(2):237-46. doi: https://doi.org/10.1177/0022034511402082
31. Ministério da Saúde (BR). Lei n.º 12.732, de 22 de novembro de 2012. Dispõe sobre o primeiro tratamento de paciente com neoplasia maligna comprovada e estabelece prazo para seu início [Internet]. Diário Oficial da União, Brasília, DF. 2012 nov 23 [acesso 2018 maio 12]; Seção 1:1. Disponível em: https://www.planalto.gov.br/ccivil_03/_ato2011-2014/2012/lei/l12732.htm
32. Observatório de Oncologia [Internet]. São Paulo: Observatório de Oncologia; [data desconhecida]. 60 dias para o câncer e o direito do paciente; 2017 ago 15 [acesso 2018 maio 12]. Disponível em: http://observatoriodeoncologia.com.br/60-dias-para-o-cancer-e-o-direito-do-paciente
33. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015;136(5):E359-86. doi: https://doi.org/10.1002/ijc.29210
34. Liao DZ, Schlecht NF, Rosenblatt G, et al. Association of delayed time to treatment initiation with overall survival and recurrence among patients with head and neck squamous cell carcinoma in an underserved urban population. JAMA Otolaryngol Head Neck Surg. 2019;145(11):1001-9. doi: https://doi.org/10.1001/jamaoto.2019.2414
35. Santos VTG, Santos VS, Carvalho RAS, et al. Mortality from oral cancer in Aracaju/SE, Brazil: 2000-2009. Rev Odontol UNESP. 2013;42(3):204-10. doi: https://doi.org/10.1590/S1807-25772013000300010
36. Marques LJP, Oliveira CM, Bonfim CV, et al. Avaliação da completude e da concordância das variáveis dos sistemas de informações sobre nascidos vivos e sobre mortalidade no Recife-PE, 2010-2012. Epidemiol Serv Saúde. 2016;25(4):849-54. doi: https://doi.org/10.5123/S1679-49742016000400019
37. Santos RA, Martins AAM, Neves JP, et al (organizador). Geologia e recursos minerais do estado de Sergipe: texto explicativo do Mapa geológico do Estado de Sergipe: escala 1:250.000 [Internet]. Brasília (DF): CPRM; 1998 [acesso 2018 maio 18]. Disponível em: https://rigeo.cprm.gov.br/jspui/bitstream/doc/5024/1/Rel_Sergipe.pdf
38. Rhodes VP. Distribuição de mercúrio e arsênio nos sedimentos da área afetada por garimpo de ouro - Rio Gualaxo do Norte, Mariana, MG [dissertação na Internet]. Ouro Preto (MG): Universidade Federal de Ouro Preto; 2010 [acesso 2018 maio 18]. Disponível em: http://www.repositorio.ufop.br/handle/123456789/2274
39. Kumar V, Abbas A, Aster J, editors. Robbins basic pathology. 10th ed. Amsterdã: Elsevier; c2017.

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