

# Temporal trends and spatial clusters of gastric cancer mortality in Brazil

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## ABSTRACT

**Objective.** To identify nationwide temporal trends and spatial patterns of gastric cancer-related mortality in Brazil.

**Methods.** An ecological study was performed using death certificates registered from 2000 to 2019 in which gastric cancer was recorded as any cause of death (an underlying or associated cause). Trends over time were assessed using joinpoint regression models. Spatial and spatiotemporal clusters were identified by Kulldorff's space-time scan statistics to identify high-risk areas.

**Results.** In 276 897/22 663 091 (1.22%) death certificates gastric cancer was recorded as any cause of death. Age-adjusted gastric cancer-related mortality increased significantly over time (annual percentage change [APC]: 0.7, 95% confidence interval [CI]: 0.5 to 0.8). The increase in mortality was more pronounced in the less-developed North and Northeast Regions (North Region, APC: 3.1, 95% CI: 2.7 to 3.5; Northeast Region, APC: 3.1, 95% CI: 2.5 to 3.7). Eight spatiotemporally associated high-risk clusters of gastric cancer-related mortality were identified in the North, South, Northeast and Central-West Regions, as well as a major cluster covering a wide geographical range in the South and Southeast Regions of Brazil during the first years of the study period (2000 to 2009).

**Conclusions.** More recently, during 2010 to 2019, clusters of gastric cancer have been identified in the Northeast Region. The nationwide increase in mortality in this analysis of 20 years of data highlights the persistently high burden of gastric cancer in Brazil, especially in socioeconomically disadvantaged regions. The identification of these areas where the population is at high risk for gastric cancer-related mortality emphasizes the need to develop effective and intersectoral control measures.

## Keywords

Stomach neoplasms; time series studies; spatial analysis; epidemiology; mortality.

In the 21st century, cancer will probably be one of the main obstacles to further increasing life expectancy worldwide (1). The third most common cause of cancer mortality is gastric

cancer (GC), leading to an estimated 783 000 deaths globally in 2018 (1 in every 12 deaths worldwide). There were more than 1 000 000 new cases of GC in this year, making it the fifth

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most frequently diagnosed cancer (1). The highest incidence is reported in East Asian countries, Eastern Europe, and Central and South America, whereas North America, northern Europe and Africa report the lowest rates (1).

In most parts of the world, there has been a decline in GC incidence and associated mortality since 2010, which has been attributed to better food preservation, increased accessibility of fruits and vegetables and decreased rates of *Helicobacter pylori* infection, a main risk factor for GC (1, 2). The rapid decrease in the incidence of GC in East Asia has been attributed mainly to reduced *H. pylori* infection (2). The incidence of and mortality from GC continue to decrease in East Asia, likely the result of implementing primary and secondary prevention strategies to control *H. pylori* infection. Prospective control strategies in this context will include the use of an effective vaccine to reduce or prevent infection, the eradication of *H. pylori*, mass endoscopic screening and surveillance of those with high-risk histology (2). In contrast, the incidence of GC in Latin America probably will not decline significantly in the near future because this area has no effective control measures to prevent *H. pylori* infection (2). Global surveillance of GC trends during 2010–2014 has shown a high variation in survival among countries. In Brazil, the survival rate was 20.6% (95% confidence interval [CI]: 18.9% to 22.2%), whereas in Japan the rate was 68.9% (95% CI: 68.6% to 69.2%) and in Korea, 60.3% (95% CI: 59.9% to 60.7%) (3). This disparity in GC survival rates may be related to earlier diagnosis and access to and the quality of health care (3).

In Brazil, GC is the fourth most frequent cancer among men and the sixth among women. The Brazilian National Cancer Institute of the Ministry of Health estimated there were 40 080 GC cases during 2020–2022, with adjusted annual incidences of 7.34/100 000 for women and 12.81/100 000 for men. The incidence of GC varies significantly between and within Brazilian Regions and also among Federal States. For example, the estimated age-standardized incidences were 10.63/100 000 for males and 10.06/100 000 for females in Ceará State in the Northeast Region, contrasting with relatively low rates in Alagoas State, also in the Northeast Region, with rates of 7.94/100 000 for males and 3.49/100 000 for females (4, 5).

A previous study has shown an overall decline in GC mortality in Brazil for both sexes from 1990 to 2015 (6). However, the distribution of GC rates was not uniform, with distinct differences between the five Brazilian administrative macro-regions (7–10). Furthermore, estimates suggest that regional differences in cancer mortality will continue to rise until 2030, with less-developed areas having the highest rates (11).

Studies investigating the geographical distribution of GC and temporal trends in GC-related deaths may help to detect modifiable factors that influence the incidence of and mortality from GC and help to develop strategies to monitor and reduce the burden of disease. These strategies would include the identification of areas where there is a high risk for GC. Mortality from GC usually corresponds to incidence, due to the low rates of survival for GC in low- and middle-income countries (1).

In the present study, temporal and spatiotemporal patterns of GC-related mortality in Brazil during a 20-year period were identified through an analysis of multiple causes of death.

## MATERIALS AND METHODS

### Study design and area

An ecological study was performed, using nationwide data about GC-related mortality, and included analyses of temporal trends, and spatial and spatiotemporal clusters. We included all deaths registered in Brazil between 2000 and 2019 in which GC was mentioned on the death certificate, either as an underlying or associated cause of death (e.g. if there were multiple causes of death).

Brazil is the largest country in South America, with an estimated population of 212 million in 2020. The country is divided into 27 Federal Units (26 States and 1 Federal District) and 5 geographical macro-regions (Central–West, North, Northeast, South and Southeast) (12).

### Data sources

Mortality data were obtained from databases of death certificates, freely available in the nationwide mortality information system (Sistema de Informação sobre Mortalidade) of the Brazilian Ministry of Health. All deaths in the group C16 Malignant neoplasm of stomach, of the tenth revision of the International Statistical Classification of Diseases and Related Health Problems (known as the ICD-10), were selected, namely: C16.0 Cardia; C16.1 Fundus of stomach; C16.2 Body of stomach; C16.3 Pyloric antrum; C16.4 Pylorus; C16.5 Lesser curvature of stomach, unspecified; C16.6 Greater curvature of stomach, unspecified; C16.8 Overlapping lesion of stomach; C16.9 Stomach, unspecified (13).

A total of 540 files were downloaded, corresponding to 27 States of the Federation (26 States and 1 Federal District), with a single file for each of the 20 years of study. The data were grouped using TabWin version 4.1.5 and saved in .dbf format (data and software available from <https://datasus.saude.gov.br/transferencia-de-arquivos/>).

Death certificates provide information about sex, education level, ethnicity, marital status, date of death, place of residence, place of occurrence of death, and causes of death. These data are in the public domain. Details on downloading the data and processing it into data sets have been described previously elsewhere (10). Data from the nationwide mortality information system may vary in coverage, completeness, integration and management support; however, the system is well respected among managers and health professionals, and the data are considered reliable (12).

Census data were obtained from the Brazilian Institute of Geography and Statistics. We used exact information for 2000 and 2010 (the years of demographic censuses in Brazil) and estimates for the intercensus periods (2001–2009 and 2011–2019).

### Time trends

Time trend analyses of GC-related mortality were carried out for 2000 to 2019. Mortality rates adjusted for age and sex were calculated using the direct method of standardization with the population in Brazil in the 2010 census as the standard population. The distributions of mortality in the five macro-regions over time and aggregated by state were analyzed for

the periods 2000–2004, 2005–2009, 2010–2014 and 2015–2019. The total number of GC-related deaths was divided by the estimated population in each calendar year per 100 000 inhabitants by the variables analyzed.

Time trend analyses of mortality were performed using joinpoint regression models with permutation tests (14). Joinpoint analysis provides the best-fit line for a study period using an algorithm that tests whether a multisegmented line is in fact a significantly better fit than a straight or less-segmented line. The joinpoint regression model fitted a series of joined straight lines on a log scale using a log–linear method, determining the direction or the statistical significance with the Monte Carlo permutation method.

The annual percentage change (APC) in mortality with 95% confidence intervals was calculated. The average annual percentage change (AAPC) over the entire period was estimated as the geometric-weighted average of the APC, with the weights reflecting the length of each time interval segment. Temporal trends were considered statistically significant when  $P < 0.05$  for either the APC or AAPC.

We also analyzed GC-related deaths, stratified by variables available from death certificates, including sex (male, female), age group (<15, 15–29, 30–39, 40–49, 50–59, 60–69, ≥70, <45, and ≥45 years), ethnicity (Caucasian, Afro-Brazilian, Asian, Mixed/Pardo-Brazilian, Amerindian) and place of residence.

### Spatiotemporal cluster analysis

Retrospective Kulldorff's space–time scan statistics were used to identify high-risk spatiotemporal clusters (15). We used the Poisson discrete probability model that considers death as a single and rare event, since there was not a homogeneous spatial distribution. The following conditions were applied for the data from 2000 to 2019: 1 year of aggregation, no geographical overlapping of clusters, the use of circular clusters, maximum spatial cluster size of 50% of the exposed population, a radius of 500 km, and a maximum temporal cluster of 50%. We identified

the most likely cluster and secondary clusters using the log likelihood ratio test and relative risk. We defined significance using 99 999 Monte Carlo simulations. After the spatiotemporal analysis, we considered statistically significant clusters in the presence of three or more municipalities as neighbors. We also performed joinpoint analysis for each significant cluster identified in the spatiotemporal analysis using the following dependent variables: sex, age group and ethnicity.

Joinpoint regression analyses were performed with the Joinpoint regression program version 4.0.4 (US National Cancer Institute, Bethesda, MD, USA). We used ArcGIS version 9.3 (Environmental Systems Research Institute, Redlands, CA, USA) for data input, processing, calculation of spatial autocorrelation indicators and elaboration of thematic maps. Scan statistics were analyzed using SaTScan software version 9.1.1 (Harvard Medical School, Boston, MA, and Information Management Services, Silver Spring, MD, USA). Additional statistical analyses were developed using Stata software version 11.2 (Stata Corp., College Station, TX, USA).

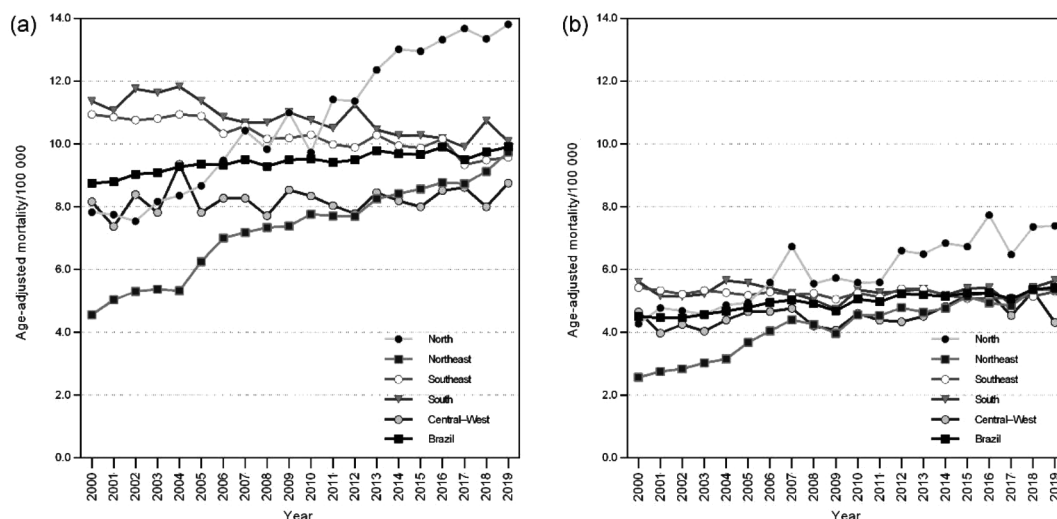
### Ethical considerations

We used publicly available, secondary data, with no identifying information about individuals. According to national regulations, in this case there is no need for approval by an ethics review board (16).

### RESULTS

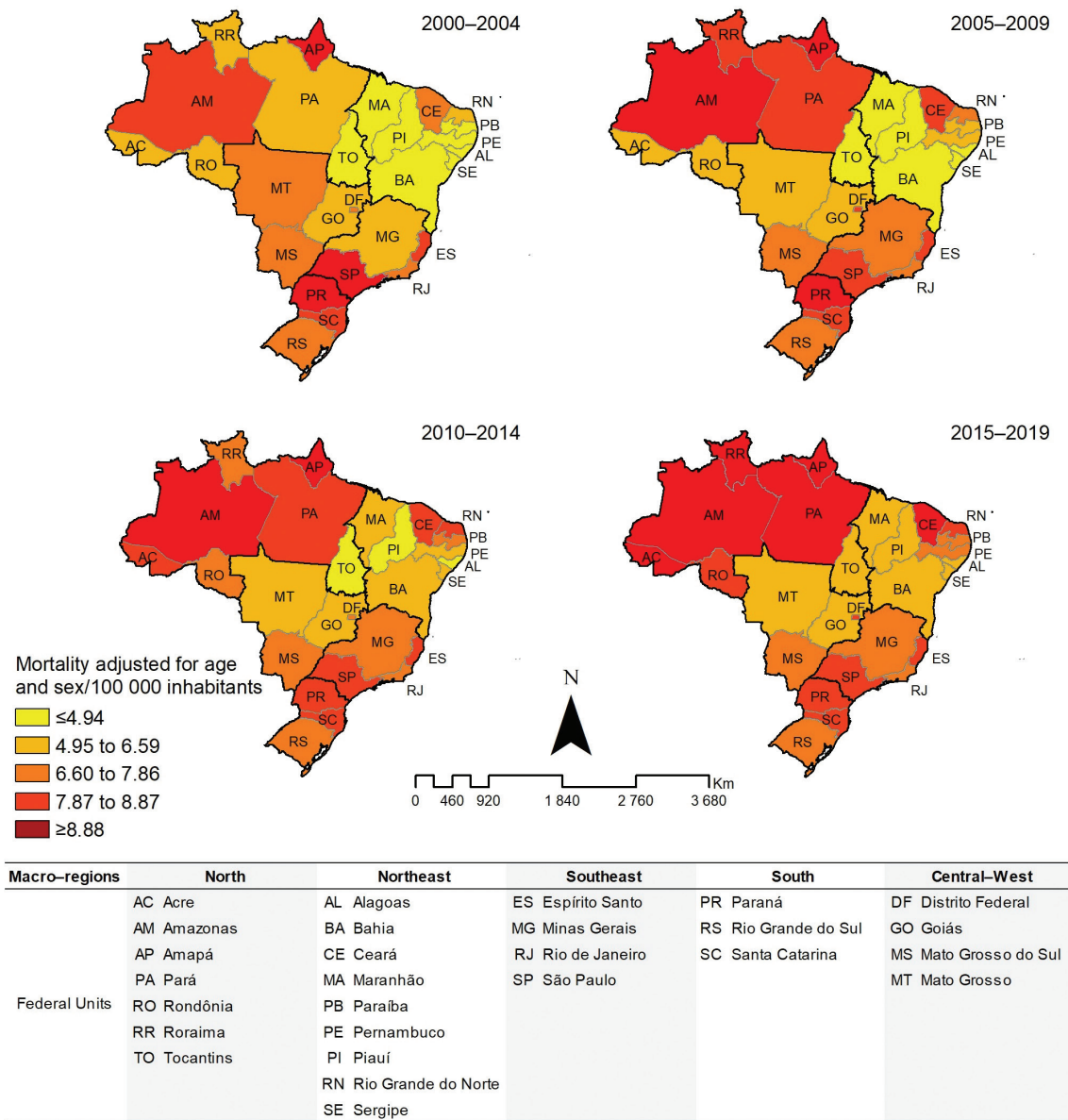
A total of 276 897 (1.22%) out of 22 663 091 deaths were identified that mentioned at least one GC-related condition as an underlying or associated cause of death. GC was identified in 262 478 (94.8%) certificates as an underlying cause of death and in 14 419 (5.2%) as an associated cause. The overall GC-related mortality adjusted for age and sex during the 20-year period was 7.15 deaths/100 000 inhabitants (95% CI: 7.00 to 7.29).

**FIGURE 1. Trends in age-adjusted mortality from gastric cancer per 100 000 inhabitants, Brazil and its regions, for (a) males and (b) females, 2000 to 2019**



Source: Figure prepared by the authors based on the results of their study.

**FIGURE 2. Spatial analysis of mortality related to gastric cancer per 100 000 inhabitants, adjusted for age and sex, Brazil, 2000 to 2019**



Source: Figure prepared by the authors based on the results of their study.

GC-related mortality varied among Brazil’s regions, with an increase in age-adjusted mortality among men and women primarily in the North and Northeast Regions (Figure 1). Among men, in the North in 2000 GC-related mortality was 7.82/100 000 inhabitants compared with 13.81/100 000 inhabitants in 2019, while in the Northeast in 2000 the rate was 4.55/100 000 inhabitants, rising to 9.74/100 000 in 2019 (Figure 1a). Among women, in the North in 2000 GC-related mortality was 4.27/100 000 inhabitants, rising to 7.39/100 000 in 2019, while in the Northeast in 2000 the rate was 2.56/100 000 inhabitants, rising to 5.36/100 000 in 2019 (Figure 1b). The highest rates occurred during 2015–2019 (mortality  $\geq 8.88$ /100 000 inhabitants) in the

States of Acre, Amapá, Amazonas, Ceará, Pará and Roraima (Figure 2). The highest crude mortality was in males (9.37/100 000 population, 95% CI: 9.18 to 9.57) and in those older than 50 years (in those aged 50–59, 12.50/100 000 population, 95% CI: 11.99 to 13.01; in those aged 60–69, 30.36/100 000, 95% CI: 29.35 to 31.36; and in those aged 70 years and older, 67.57/100 000, 95% CI: 65.91 to 69.23) (Table 1).

**Time trend analysis**

Mortality from GC increased nationally during the period studied (AAPC: 0.7, 95% CI: 0.5 to 0.8; in 2000, 11 478 deaths



TABLE 1. Joinpoint regression analysis of mortality related to gastric cancer, Brazil, 2000 to 2019

Indicator or variable	No. (%) deaths	Crude mortality rate (95% CI)	Trend		
			Period	APC (95% CI)	
			Entire period		
			AAPC (95% CI)		
<b>Brazil (total)</b>	276 897 (100.0)	7.10 (6.99 to 7.22)	2000 to 2019	0.7* (0.5 to 0.8)	0.7* (0.5 to 0.8)
<b>Sex<sup>a</sup></b>					
Male	179 013 (64.6)	9.37 (9.18 to 9.57)	2000 to 2004 2004 to 2019	1.6* (0.3 to 2.9) 0.4* (0.2 to 0.5)	0.5* (0.4 to 0.6)
Female	97 859 (35.3)	4.92 (4.79 to 5.06)	2000 to 2019	0.9* (0.7 to 1.2)	0.9* (0.7 to 1.2)
<b>Age group 1 (years)<sup>a</sup></b>					
<15	61 (0.0)	0.01 (0.00 to 0.01)	2000 to 2019	-1.5 (-6.3 to 3.5)	-1.5 (-6.3 to 3.5)
15–29	2 230 (0.8)	0.22 (0.18 to 0.26)	2000 to 2019	0.9* (0.3 to 1.5)	0.9* (0.3 to 1.5)
30–39	8 439 (3.0)	1.41 (1.27 to 1.54)	2000 to 2007 2007 to 2019	1.8 (-0.2 to 3.8) -1.1* (-1.9 to -0.2)	-0.2 (-0.7 to 0.3)
40–49	23 014 (8.3)	4.57 (4.31 to 4.84)	2000 to 2019	-1.5* (-1.8 to -1.2)	-1.5* (-1.8 to -1.2)
50–59	46 665 (16.9)	12.50 (11.99 to 13.01)	2000 to 2019	-1.5* (-1.6 to -1.3)	-1.5* (-1.6 to -1.3)
60–69	69 836 (25.2)	30.36 (29.35 to 31.36)	2000 to 2019	-2.1* (-2.2 to -1.9)	-2.1* (-2.2 to -1.9)
≥70	126 569 (45.7)	67.57 (65.91 to 69.23)	2000 to 2006 2006 to 2019	-0.2 (-1.2 to 0.9) -2.2* (-2.5 to -1.9)	-1.7* (-2.0 to -1.5)
<b>Age group 2 (years)<sup>a</sup></b>					
<45	19 666 (7.1)	0.69 (0.64 to 0.73)	2000 to 2019	0.9* (0.6 to 1.2)	0.9* (0.6 to 1.2)
≥45	257 148 (92.9)	24.95 (24.52 to 25.38)	2000 to 2019	-1.5* (-1.6 to -1.4)	-1.5* (-1.6 to -1.4)
<b>Ethnicity<sup>a</sup></b>					
Caucasian	151 890 (54.9)	8.38 (8.19 to 8.57)	2000 to 2003 2003 to 2019	3.3* (0.3 to 6.4) 0.2 (0.0 to 0.4)	0.4* (0.2 to 0.6)
Afro-Brazilian	21 383 (7.7)	7.45 (7.00 to 7.90)	2000 to 2002 2002 to 2019	6.3 (-1.0 to 14.0) -0.9* (-1.1 to -0.7)	-0.7* (-0.9 to -0.4)
Asian	3 141 (1.1)	7.46 (6.29 to 8.62)	2000 to 2002 2002 to 2019	-28.0* (-46.0 to -4.0) -9.8* (-10.9 to -8.7)	-10.9* (-12.0 to -9.8)
Mixed/Pardo-Brazilian	83 923 (30.3)	5.07 (4.91 to 5.22)	2000 to 2006 2006 to 2014 2014 to 2019	5.9* (4.7 to 7.2) 2.6* (1.8 to 3.3) 0.7 (-0.4 to 1.7)	2.8* (2.3 to 3.3)
Amerindian	451 (0.2)	2.80 (1.66 to 3.94)	2000 to 2019	4.0* (2.2 to 5.7)	4.0* (2.2 to 5.7)
<b>Region of residence<sup>a</sup></b>					
North	18 446 (6.7)	5.68 (5.31 to 6.04)	2000 to 2019	3.1* (2.7 to 3.5)	3.1* (2.7 to 3.5)
Northeast	57 741 (20.9)	5.33 (5.13 to 5.52)	2000 to 2007 2007 to 2019	6.7* (5.1 to 8.2) 1.8* (1.3 to 2.4)	3.1* (2.5 to 3.7)
Southeast	136 198 (49.2)	8.29 (8.09 to 8.49)	2000 to 2019	-0.4* (-0.5 to -0.2)	-0.4* (-0.5 to -0.2)
South	49 012 (17.7)	8.78 (8.43 to 9.13)	2000 to 2019	-0.1 (-0.3 to 0.2)	-0.1 (-0.3 to 0.2)
Central–West	15 500 (5.6)	5.40 (5.02 to 5.78)	2000 to 2019	0.7* (0.4 to 1.0)	0.7* (0.4 to 1.0)
<b>Cluster<sup>a</sup></b>					
Non-cluster areas	92 927 (33.6)	5.30 (5.15 to 5.45)	2000 to 2006 2006 to 2019	3.3* (2.2 to 4.4) 1.4* (1.2 to 1.7)	1.8* (1.6 to 2.1)
All cluster areas	183 768 (66.4)	8.57 (8.39 to 8.74)	2000 to 2019	0.1 (0.0, 0.2)	0.1 (0.0 to 0.2)
1	126 025 (45.5)	8.71 (8.49 to 8.93)	2000 to 2019	-0.6* (-0.7 to -0.5)	-0.6* (-0.7 to -0.5)
2	22 154 (8.0)	7.84 (7.38 to 8.30)	2000 to 2007 2007 to 2019	5.7* (3.5 to 7.9) 1.4* (0.7 to 2.2)	2.6* (2.0 to 3.2)
3	5 330 (1.9)	10.10 (8.89 to 11.31)	2000 to 2019	1.6* (1.1 to 2.2)	1.6* (1.1 to 2.2)
4	9 078 (3.3)	9.37 (8.51 to 10.23)	2000 to 2019	-0.2 (-0.7 to 0.2)	-0.2 (-0.7 to 0.2)
5	3 452 (1.2)	9.21 (7.83 to 10.58)	2000 to 2019	1.9* (1.0 to 2.8)	1.9* (1.0 to 2.8)
6	15 256 (5.5)	7.82 (7.26 to 8.37)	2000 to 2019	1.1* (0.6 to 1.5)	1.1* (0.6 to 1.5)
7	643 (0.2)	8.94 (5.85 to 12.04)	2000 to 2019	2.6* (0.5 to 4.8)	2.6* (0.5 to 4.8)
8	1 830 (0.6)	7.22 (5.75 to 8.70)	2000 to 2019	3.6* (2.6 to 4.6)	3.6* (2.6 to 4.6)

AAPC: average annual percentage change; APC: annual percentage change; CI: confidence interval.

\*  $P < 0.05$ .<sup>a</sup> Data not available in all cases (sex: 25, age group: 83, ethnicity: 16 109).

Source: Table prepared by the authors based on the results of their study.

and in 2019, 16 008 deaths) (Table 1; data about the number of deaths during the first and last years of the trend are not shown in the table). There were distinct differences between the macro-regions (Figure 1; Table 1). The North, Northeast and Central–West Regions had significant increases during the period (AAPC: 3.1, 95% CI: 2.7 to 3.5; in 2000, 1 687 deaths and in 2019, 3 895; AAPC: 3.1, 95% CI: 2.5 to 3.7; in 2000, 558 deaths and in 2019, 1 315; and AAPC: 0.7, 95% CI: 0.4 to 1.0; in 2000, 634 deaths and in 2019, 924, respectively), while mortality in the Southeast Region decreased significantly (AAPC: –0.4, 95% CI: –0.5 to –0.2; in 2000, 6 342 deaths and in 2019, 7 209) (Figure 1; Table 1).

GC mortality significantly increased for both sexes. The increase was higher in women (AAPC: 0.9, 95% CI: 0.7 to 1.2; in 2000, 3 978 deaths and in 2019, 5 824) compared with men (AAPC: 0.5, 95% CI: 0.4 to 0.6; in 2000, 7 497 deaths and in 2019, 10 184). A significant decrease was observed among 40-year-olds and among those aged  $\leq 40$  years.

GC-related mortality decreased significantly among those of Asian descent (AAPC: –10.9, 95% CI: –12.0 to –9.8; in 2000, 229 deaths and in 2019, 144) in contrast to Amerindians and Mixed/Pardo-Brazilians (AAPC for Amerindians: 4.0, 95% CI: 2.2 to 5.7; in 2000, 18 deaths and in 2019, 24 deaths; and AAPC for Mixed/Pardo-Brazilians: 2.8, 95% CI: 2.3 to 3.3; in 2000, 2 203 deaths and in 2019, 6 214) (Table 1).

### Spatiotemporal cluster analysis

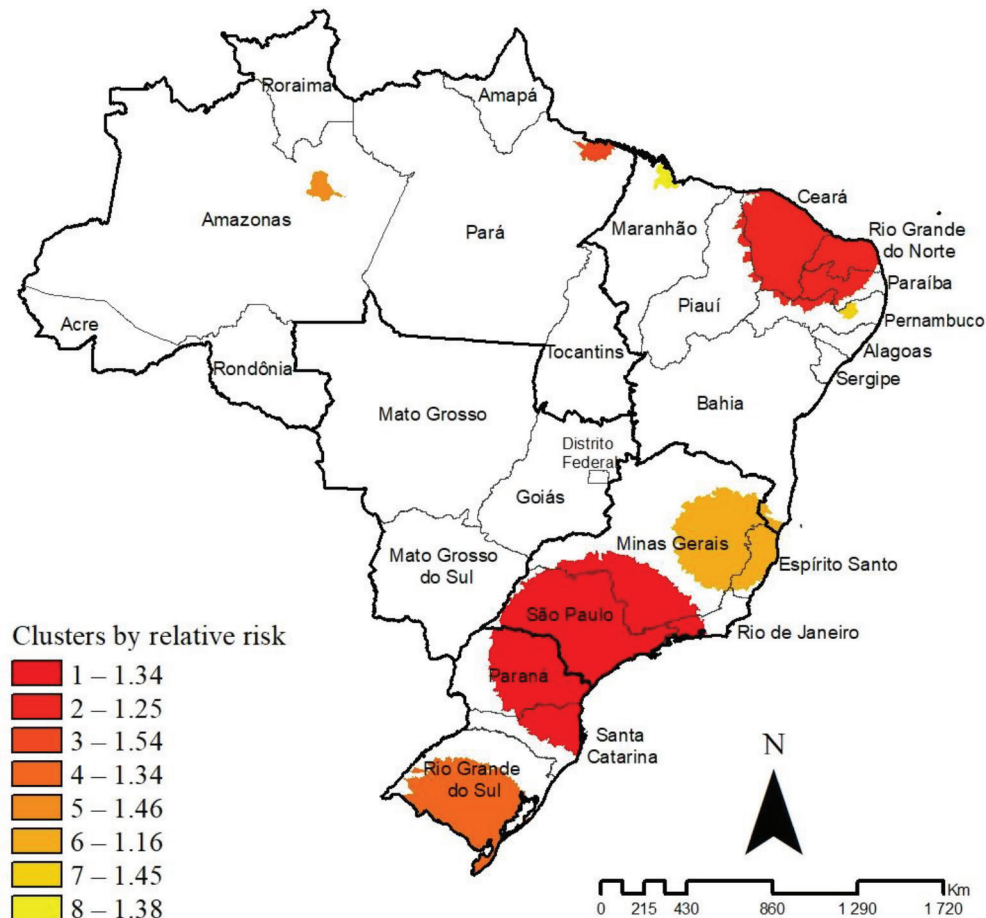
The space–time analysis identified eight significant high-risk clusters of GC-related deaths. The most likely cluster (primary cluster) was verified at the beginning of the study period (2000–2009) and included 1 272 municipalities distributed across five States in the South and Southeast Regions. The crude annual mortality was 9.0/100 000 inhabitants (Figure 3; Table 2). The second most significant cluster occurred from 2010 to 2019, with an annual rate of 8.9/100 000 inhabitants. This cluster included 519 municipalities located in the Ceará, Paraíba, Pernambuco, Piauí and Rio Grande do Norte States (Figure 3; Table 2).

The other six secondary clusters were located within States in the North, Northeast, South and Southeast Regions. The crude annual mortality and risk ratios for these secondary clusters were similar, ranging from 8.3 to 11.0 deaths/100 000 inhabitants (Table 2).

### Time trend analysis of clusters

The eight cluster areas showed a stabilization or decrease throughout the period (Figure 3), but this was not statistically significant (AAPC: 0.1, 95% CI: 0.0 to 0.2; in 2000, 2 736 deaths

**FIGURE 3. Spatiotemporal cluster analysis of the relative risk of mortality from gastric cancer per 100 000 inhabitants, by municipality of residence, Brazil, 2000 to 2019**



Source: Figure prepared by the authors based on the results of their study.

**TABLE 2. Significant spatiotemporal clusters of deaths related to gastric cancer per 100 000 inhabitants, defined using space–time scan statistics, by municipality of residence, Brazil, 2000 to 2019**

Cluster no.	Period	No. of municipalities	States	Region	Radius (km)	No. of deaths	Expected no. of deaths	Annual mortality/100 000 inhabitants during the cluster	RR	LLR	P value
1	2000 to 2009	1 272	Minas Gerais, Paraná, Rio de Janeiro, São Paulo, Santa Catarina	Southeast, South	499.3	61 793	48 981.72	9.0	1.34	1 913.23	<0.00001
2	2010 to 2019	519	Ceará, Pernambuco, Paraíba, Piauí, Rio Grande do Norte	Northeast	361.9	12 915	10 424.58	8.9	1.25	287.95	<0.00001
3	2010 to 2019	27	Pará	North	87.5	3 011	1 964.54	11.0	1.54	241.27	<0.00001
4	2005 to 2014	164	Rio Grande do Sul	South	300.7	4 627	3 469.22	9.6	1.34	177.15	<0.00001
5	2011 to 2019	2	Amazonas	North	57.6	1 947	1 338.22	10.4	1.46	121.92	<0.00001
6	2010 to 2019	357	Bahia, Espírito Santo, Minas Gerais	Northeast, Southeast	258.3	8 308	7 201.31	8.3	1.16	83.26	<0.00001
7	2007 to 2016	10	Pernambuco	Northeast	39.6	374	258.56	10.4	1.45	22.64	0.00016
8	2017 to 2019	13	Maranhão	Northeast	66.5	396	286.81	9.9	1.38	18.58	0.00560

LLR: log likelihood ratio; RR: relative risk for the cluster compared with the rest of the country.  
**Source:** Table prepared by the authors based on the results of their study.

and in 2019, 2 974). In contrast, in the non-clustered areas there was an increase (AAPC: 1.8, 95% CI: 1.6 to 2.1; in 2000, 8 742 death and in 2019, 13 034) (Table 1; data about the number of deaths during the first and last years of the trend are not shown in the table).

The primary cluster (in the Southeast and South Regions) showed significant decreasing trends during all periods (AAPC: –0.6, 95% CI: –0.7 to –0.5; in 2000, 1 832 deaths and in 2019, 1 752). The second most significant cluster (in the Northeast Region in Ceará, Paraíba, Pernambuco, Piauí and Rio Grande do Norte States) had an increasing trend throughout the period (AAPC: 2.6, 95% CI: 2.0 to 3.2; in 2000, 214 deaths and in 2019, 340). A statistically significant increase was observed in clusters 3, 5, 6, 7 and 8, in States in the North, Northeast, South and Southeast Regions (Table 1).

## DISCUSSION

Our study shows that GC-related mortality increased significantly in Brazil during the 20-year study period. The increase was pronounced in the North and Northeast Regions, Brazil's socioeconomically most disadvantaged regions, with significant high-risk clusters mainly in the Northeast. In contrast, in the South, Southeast and Central–West regions, mortality rates decreased (10). In 2012, Bray et al. evaluated global patterns of cancer incidence and mortality, using levels of the Human Development Index, and observed a reduction in

infection-based cancers, an important aspect of the epidemiological transition of cancer. Drops in the incidence of stomach and cervical cancers are consistently seen in populations with medium–to–very-high levels of the Index (17).

The finding of heterogeneity in mortality among the Brazilian regions in the present study is in agreement with the findings of previous studies (7, 9, 10). It is known that indicators of health system performance, education and income; the Gini coefficient; and cancer control strategies and programs play important roles in cancer-related mortality (18, 19). The reduced mortality in the Southeast of Brazil may be explained by different factors including higher socioeconomic levels and their consequences, such as improvements in the health care system and implementation of strategies for early diagnosis and treatment of GC that have occurred since the early 2000s (20).

*H. pylori*, classified as a Group 1 carcinogen by the International Agency for Research on Cancer, has been considered the most important risk factor for GC. Notably, the prevalence of infection is higher in Northeast Brazil (21) than in the South and Southeast (22, 23). Futures studies are warranted to evaluate the dynamics of *H. pylori* prevalence during the past decade (2011 to 2020) in Brazil.

In addition, geographical differences within regions must be taken into account, for example, in regard to genetics and dietary habits. Consuming fruits and vegetables protects against developing GC, whereas consuming foods with high

levels of salt and those with high levels of *N*-nitroso compounds is considered a risk factor (24). Smoking is another well-known risk factor for GC. Studies conducted in Brazil, including in the Northeast Region, have found that tobacco use declined during the study period after the implementation of control and education measures (25, 26).

Another possible cause of increasing GC mortality in specific areas of North and Northeast Brazil is the excessive use of pesticides and agricultural chemicals containing compounds including chrome, arsenic and nitrites, with residues ending up in food and drinking water. It has been suggested that occupational exposure in specific geographical areas may be a major risk factor for gastric carcinogenesis (27-29). During the past 15 years (2008 to 2022), agribusiness has grown considerably in Northeast Brazil, especially in semiarid regions like Ceará (27). This is relevant in view of the increased GC mortality observed among agricultural workers in Brazil (26). Studies from China have shown that an increased risk of GC is associated with occupational exposure to crystalline silica, talc and chromium, especially among carpenters, steelworkers and tin miners, while Chinese farmworkers are reported to be exposed to large amounts of pesticides and fertilizers (29, 30).

Worldwide, the average incidence of and mortality from GC in men is twice as high as those in women (1, 8, 9). There has been a trend towards a reduction in the differences between GC mortality in men and women, due to the marked increase in GC mortality in women. A previous study observed a reduction in the ratio of hospitalization rates between men and women and suggested that this may be associated with lower exposure of men to risk factors in recent years (7). However, our study showed that mortality from GC was increasing in both sexes, and the reduction in the difference between men and women might be due to the greater exposure of women to risk factors.

In our study there was a decline in GC mortality for all age groups except for those aged 15 to 29 years, in agreement with previous studies that showed GC mortality rates proportionally increased among the younger Brazilian population between 2005 and 2010 (7). A study from the United States has also reported that the incidence of GC in young patients (i.e. those <40 years) increased from 1973 to 2015 (31). The reasons for the increase in younger adults remain unclear; intestinal-type tumor cells occur more often in older people, whereas the diffuse type is associated with younger patients and females (32). A study from Ceará State, a GC cluster area, has shown that the diffuse type of GC was significantly more prevalent in patients younger than 45 years when compared with older patients (33). In recent years (2008 to 2014), the incidence of both histological types has decreased, but a shift has been observed, with a decline in the diffuse type that has been more gradual than in the intestinal type.

We found increasing GC mortality among Pardo-Brazilians (individuals with varying ethnic ancestry) and Amerindians. Similar results were found in studies conducted in Indigenous populations from different places, such as Siberians; the Mapuche in South America; the Inuit in the Arctic areas of Greenland, Canada and Alaska; and the Maori in New Zealand (32, 34). These findings call for improved surveillance measures and investigations into the risk factors involved in GC, which may

include household sanitation, eating habits and the prevalence of *H. pylori* infection in addition to limited access to health care, especially among Indigenous populations. Conversely, there was a reduction in the incidence of GC among individuals of Asian ethnicity that may be related to better socioeconomic conditions and better availability of health services. Most of the population of Asian ethnicity in Brazil comes from East Asia, an area of high GC incidence.

There are some limitations to our study due to the fact that it was based on the analysis of secondary data. The coverage of mortality data may be suboptimal and the data may be inconsistent. Thus, data about trends should be interpreted with care, especially because registration of deaths and their causes has improved recently. Improvements in the health care system increased the registration of causes of mortality mainly in less-developed areas (18). Consequently, variations among Brazilian regions in the quality of mortality surveillance may have influenced the results, mainly in the North and Northeast Regions. The underlying causes of death may have been registered as GC-related complications (or another cause), with GC recorded as an associated cause of death. We used data related to multiple causes of death to reduce this possible bias and included all death certificates in which GC was mentioned. Another limitation is the impossibility of evaluating the dynamics of GC mortality in terms of the topographic location of a tumor that is classified as proximal (cardia) or distal (non-cardia). Overall, the location of tumors has changed due to an increase in the incidence of GC of the cardia and a decrease in non-cardia GC (33, 35).

In conclusion, the nationwide increase in GC mortality in this analysis of 20 years of data highlights the persistent burden of GC in Brazil in socioeconomically disadvantaged regions. The identification of high-risk areas for GC-related mortality emphasizes the need to improve effective intersectoral control measures.

**Authors' contributions.** LLBCB, AFF, ANR and JH designed the project, analyzed and interpreted the data, and wrote, critically reviewed and gave final approval to the article. FASP, TGSB, DBC, DMMQ and FM collaborated in analyzing and interpreting the data, drafting the article, and critically reviewing and giving final approval. All authors reviewed and approved the final version.

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## Tendencias temporales y conglomerados espaciales de mortalidad por cáncer gástrico en Brasil

### RESUMEN

**Objetivo.** Identificar las tendencias temporales y los patrones espaciales de la mortalidad relacionada con el cáncer gástrico a nivel nacional en Brasil.

**Métodos.** Se realizó un estudio ecológico, empleando certificados de defunción registrados entre los años 2000 y 2019 en los que se notificó cáncer gástrico como cualquier causa de muerte (subyacente o asociada). Se evaluaron las tendencias con el transcurso del tiempo mediante modelos de regresión de punto de inflexión (*joinpoint*). Se identificaron los conglomerados espaciales y espaciotemporales mediante la técnica estadística de exploración espaciotemporal de Kulldorff para determinar cuáles eran las áreas de alto riesgo.

**Resultados.** En 276 897 de 22 663 091 certificados de defunción (1,22%), se registró cáncer gástrico como cualquier causa de muerte. La mortalidad relacionada con el cáncer gástrico ajustada por edad aumentó significativamente con el tiempo (cambio porcentual anual: 0,7; intervalo de confianza [IC] del 95%: 0,5 a 0,8). El aumento de la mortalidad fue más acusado en la regiones Norte y Noreste, menos desarrolladas, (región Norte, cambio porcentual anual: 3,1, IC del 95%: 2,7 a 3,5; región Noreste, cambio porcentual anual: 3,1, IC del 95%: 2,5 a 3,7). Durante los primeros años del período de estudio (del 2000 al 2009), se identificaron ocho conglomerados de alto riesgo de mortalidad relacionada con el cáncer gástrico y con asociación espacial y temporal en las regiones Norte, Sur, Noreste y Centro-Oeste, así como un conglomerado importante que cubría un amplio rango geográfico en las regiones Sur y Sureste de Brasil.

**Conclusiones.** Más recientemente, del 2010 al 2019, se han identificado conglomerados de cáncer gástrico en la región noreste. El aumento nacional de la mortalidad en este análisis de veinte años de datos destaca la carga persistentemente alta del cáncer gástrico en Brasil, especialmente en las regiones socioeconómicamente desfavorecidas. La identificación de estas áreas en que la población presenta un alto riesgo de mortalidad relacionada con el cáncer gástrico subraya la necesidad de elaborar medidas de control intersectoriales y efectivas.

### Palabras clave

Neoplasias gástricas; estudios de series temporales; análisis espacial; epidemiología; mortalidad.

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## Tendências temporais e aglomerados espaciais de mortalidade por câncer gástrico no Brasil

### RESUMO

**Objetivo.** Identificar tendências temporais e padrões espaciais de mortalidade relacionada ao câncer gástrico em todo o Brasil.

**Métodos.** Realizou-se um estudo ecológico a partir de declarações de óbito registradas de 2000 a 2019 em que o câncer gástrico foi indicado como qualquer causa de morte (causa básica ou associada). As tendências ao longo do tempo foram avaliadas a partir de modelos de regressão por pontos de inflexão (*joinpoint*). Os aglomerados espaciais e espaço-temporais foram identificados por estatística de varredura espaço-temporal de Kulldorff para detectar áreas de alto risco.

**Resultados.** O câncer gástrico foi registrado como qualquer causa de morte em 276.897/22.663.091 (1,22%) declarações de óbito. A mortalidade relacionada ao câncer gástrico ajustada por idade aumentou significativamente ao longo do tempo [variação percentual anual (VPA): 0,7, intervalo de confiança (IC) de 95%: 0,5 a 0,8]. O aumento da mortalidade foi mais acentuado no Norte e Nordeste, regiões menos desenvolvidas (região Norte, VPA: 3,1, IC 95%: 2,7 a 3,5; região Nordeste, VPA: 3,1, IC 95%: 2,5 a 3,7). Identificaram-se oito aglomerados de alto risco de mortalidade relacionada ao câncer gástrico em associação espaço-temporal nas regiões Norte, Sul, Nordeste e Centro-Oeste, além de um grande aglomerado que abrangia uma larga faixa geográfica nas regiões Sul e Sudeste do Brasil durante os primeiros anos do período de estudo (2000 a 2009).

**Conclusões.** Mais recentemente, no período de 2010 a 2019, identificaram-se aglomerados de câncer gástrico na região Nordeste. O aumento da mortalidade em todo o país nesta análise de dados relativos a 20 anos evidencia a persistência da alta carga de câncer gástrico no Brasil, sobretudo em regiões desfavorecidas do ponto de vista socioeconômico. A identificação dessas áreas em que a população corre alto risco de morte relacionada ao câncer gástrico enfatiza a necessidade de desenvolver medidas de controle efetivas e intersectoriais.

**Palavras-chave** Neoplasias gástricas; estudos de séries temporais; análise espacial; epidemiologia; mortalidade.