Trends and predictions for gastric cancer mortality in Brazil

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Abstract

AIM: To analyze the effect of age-period and birth cohort on gastric cancer mortality, in Brazil and across its five geographic regions, by sex, in the population over 20 years of age, as well as make projections for the period 2010-2029.

METHODS: An ecological study is presented herein,
Currently there are no detailed predictions for infection by factors related to the development of gastric cancer. Also, researchers remark that the main etiological factor prevalence, is paramount for vigilance actions. This study presents a high citation potential, due to the innovative methodology and to the scientific development of Brazil, which is among the countries with most publications nowadays.

INTRODUCTION

Gastric cancer incidence has been decreasing globally since 1950[1]. However, its aggressiveness, malignity and, consequently, its prognosis, remain unaltered. Gastric cancer is currently one of the main causes of cancer-related deaths worldwide, and appears as the fourth most frequent cancer in men and sixth in women, being the fifth cancer-related cause of death for both sexes in the world[1].

Regarding risk factors for the development of gastric cancer, a higher incidence is verified in men than in women, in a 2:1 proportion, approximately[2]. Also, researchers remark that the main etiological factors related to the development of gastric cancer are infection by *Helicobacter pylori* (*H. pylori*) and diet, as the elevated consumption of salted foods (preserved or smoked), meat, and refined carbohydrates is directly associated with the risk of developing this neoplasm, while a diet based on fiber, vegetables and fresh fruit presents the inverse association[3,4].

Gastric cancer is usually also associated with low socioeconomic conditions[5], an aspect that highlights the importance of analyzing mortality along with the geographic distribution of the population, especially in countries characterized by high socioeconomic inequalities.

Given the epidemiological importance of gastric cancer, essential measures to support public policy actions include the analysis of the age-period and birth cohort on the distribution of mortality and mortality rate projections. These analyses enable the evaluation of the role of risk factors as well as modifications in therapeutics and diagnosis methods in the evolution of mortality rates[6,7].

Brazil presents demographic and socioeconomic heterogeneity across its five geographic regions, which translates to different mortality and morbidity patterns due to non-transmissible chronic diseases. Addressing cancer, both in prevention and attention to patients, requires differentiated responses that should be adapted to each specific region. Monitoring the trends of incidence and mortality rates, as well as risk factor prevalence, is paramount for vigilance actions and planning of prevention and treatment policies. The objectives of this manuscript are to analyze the effect of age-period and birth cohort in gastric cancer mortality, for Brazil and its five geographic regions, by sex, for the population over the age of 20, and make projections for the period 2010-2029.

MATERIALS AND METHODS

Study design and population

An ecological study is presented herein, on the distribution of deaths by gastric cancer, in Brazil and its five geographic regions, per sex. The study included deaths classified as 151 (stomach neoplasm) and C16 (malignant stomach neoplasm) in the 9th and 10th edition of the International Classification of Diseases (ICD), respectively. The study population included Brazilian men and women over 20 years of age. Mortality data were obtained from the Mortality Information System (MIS/DATASUS). Population data were obtained from the Informatics Department of the Unified Health System (DATASUS), based on the population censuses of 1980, 1991, 2000 and 2010. Inter-census projections for populations on July, 1st of the inter-census years were estimated by the Brazilian Institute of Geography and Statistics (IBGE).

Study variables

After extraction, data were corrected, redistributing 50.0% of the registries classified as ill-defined causes (codes 780-789 in ICD-9, and R00-R99 in ICD-10),
utilizing the redistribution methodology of the World Health Organization (WHO)\[6\]. After redistribution of ill-defined registries, deaths with incomplete diagnosis were redistributed proportionally by year and age group\[9\] (Mello et al\[9\], 2002). Herein gastric cancer deaths were corrected by two death groups with incomplete diagnosis: incomplete diagnosis for general cancer and incomplete diagnosis for gastric cancer. The following codes were considered as incomplete diagnosis for general cancer: C-77 to C-80 and C-97 in ICD-10; and codes 195, 197 to 199, 238 to 239 in ICD-9. For incomplete diagnosis of gastric cancer, the following codes were considered: 150 in ICD-9 and C-26 in ICD-10.

Once death data were corrected, mortality rates for gastric cancer were calculated per 100000 inhabitants, adjusted by the world population\[10\]. Age groups, periods and birth cohorts were grouped in five-year intervals, totaling 13 age groups (20-24 years of age to over 80 years of age), six periods (1980-1984 to 2005-2009) and 20 birth cohorts (1895-1899 to 2005-2009).

Data projections were made by sex for the periods 2010-2014, 2015-2019, 2020-2024 and 2025-2029 based on the three observed periods (1995-1999, 2000-2004 and 2005-2009), with results being presented in three age groups (0-39, 40-59 and ≥ 60 years of age) as well as the total result.

**Statistical analysis**

Age-period and birth cohort (APC) effects were calculated by the Poisson regression method. In this model, effects act in a multiplicative manner on the rates and the logarithm of the expected rate value is a linear function of the effect of age, period and cohort:\[6,7\]

\[
\ln(E[N_{ij}]) = \ln(\phi_i/N_0) = \mu + \alpha_i + \beta_j + \gamma_k
\]

Where \( \mu \) is the mortality rate expected for age \( i \) and period \( j \), \( \phi_i \) is the number of deaths for age \( i \) and period \( j \), and \( N_0 \) expresses the population under risk of death in age \( i \) and period \( j \); \( \mu \) represents the average of the effect, \( \alpha_i \) represents the effect of group age \( i \), \( \beta_j \) represents the effect of period \( j \), and \( \gamma_k \) is the effect of cohort \( k \).

The greatest limitation with the estimation of APC effect parameters is the linear relationship between the factors age, period and cohort, which hinders the estimation of the complete model. Methodologies have been proposed to address this issue; however, there is still no consensus in literature\[11\]. The APC effect parameters were estimated by estimable functions: deviations, curvatures, and \textit{drift}, a method proposed by Holford\[6,7\].

A reference age group was selected (50-54 years of age), along with a reference period (1990-1994), and a reference cohort (which was the median value, as central cohorts are more stable). This manuscript utilized the 1930-1934\[6,7\] cohort as reference. The adjustment of the model was evaluated by the statistical function deviance, defined as twice the logarithm of the likelihood of the complete model in relation to the logarithm of the likelihood function of the estimated model. The contribution of effects was evaluated by the comparison between the deviance of the model with the specific effect in relation to the complete model (age-period-cohort). The results with \( P \leq 0.05 \) were considered statistically significant.

The association measurements, respective confidence intervals (95%CI), and the adjustments of the models were calculated by statistics program R version 3.2.1, with the Epi 1.1.18 library (R Foundation for Computational Statistics, Viena, Austria http://www.r-project.org).

Projections were made for each period utilizing the age-period-cohort model of the Norpred program, inscribed within the program R. Data were compiled in 5-year blocks and the limit age group considered for analysis was the first with more than 10 cases for the combined period. The results of the projections are presented by the observed and expected deaths for each period, for each Brazilian state. Also, for each period, adjusted mortality rates were calculated based on the standard world population to enable comparison with international data, expressed per 100000 inhabitants per year (ASW/100000 inhab). Variations between the number of cases in the last projected year (2025-2029) and the last observed period (2005-2009) were calculated, considering the proportion of variation that occurred in terms of changes in risk or demographics (size and structure of population). Both components can be different from zero and present a positive or negative direction. Calculation is expressed as follows\[11\]:

\[ \Delta \text{tot} = \Delta \text{risk} + \Delta \text{pop} = (N_{\text{ff}} - N_0) + (N_{\text{off}} - N_{00}) \]

Where \( \Delta \text{tot} \) is the total change, \( \Delta \text{risk} \) is change in function of risk, \( \Delta \text{pop} \) is change in function of population, \( N_{\text{ff}} \) is the number of observed cases, \( N_{\text{off}} \) is the number of projected cases, and \( N_0 \) is the number of expected cases when mortality rates increase throughout the observed period.

**RESULTS**

Within the period 1980-2009, there were 314445 deaths registered in Brazil, corresponding to an average standardized mortality rate of 11.71 deaths per 100000 inhabitants. After correction of the number of deaths, there was an increase of 30.8% in the number of deaths (411558), representing an average standardized mortality rate of 15.32 deaths per 100000 inhabitants for gastric cancer, in individuals over 20 years of age. It must be highlighted that, throughout the country, the highest proportion of deaths occurred in the male sex. Also, the highest mortality rates for gastric cancer were observed for the male sex in Brazil and in all geographic regions of the country.
The South and Southeast regions showed decreases in death risks due to this neoplasm, with a protection effect (RR ≤ 1) especially in the period 2005-2009 for both sexes. The Midwest region presented a very specific profile, as despite RR was above 1 in all periods in relation to the reference period, there was a progressive reduction in death risk due to gastric cancer in the analyzed periods (Figure 1). The North and Northeast regions presented decreases in death risks for the period 1995-1999, but in the following periods there was an increase in risk (RR ≥ 1), for both sexes (Figure 2).

Brazil and the Midwest, North, Southeast and South regions presented reductions in death risks for gastric cancer for both sexes, with a protection effect for birth cohorts after 1940-1944, when compared to the reference cohort. This reduction was more expressive in the South and Southeast regions (Figure 2).

Table 1 shows the deviance changes in the sequential construction of APC models. In the evolution of rates for both sexes, in Brazil and its geographic regions, the model with three factors (APC) presented best fit, except for the Midwest region and female sex, for which the most explanatory model was age-cohort (AC).

When comparing the evolution of standardized mortality rates for gastric cancer, increases were observed for the male sex in the North and Northeast regions, and in the female sex in the Northeast region. The projections for the Midwest, South and Southeast regions as well as the pooled analysis for Brazil indicated a reduction in mortality rates for the male sex and stability for the female sex. The number of cases per region, the adjusted rates for the observed period, and projections per sex are presented in Table 2.
Figure 2  Results of the Age-period-cohort model, adjusted for gastric cancer mortality, according to sex and geographical regions, in Brazil, 1980 to 2009.
For Brazilian men, an increase is expected in the number of deaths (30203) when comparing the last observed period with the last projected period, representing a 62% growth, of which 101% is due to population increase and -39% is due to reduction in risk. For women, the expected increase in the number of deaths is 20308, with 99% growth due to changes in population and -23% in reduction of risk. Figure 3 shows the changes in the number of deaths, in function of risk and population increase, when comparing the last observed period and the last projected period for gastric cancer in the Brazilian regions.

**DISCUSSION**

This study evidenced disparities in the evolution of mortality rates due to gastric cancer in Brazilian geographic regions, within the analyzed periods. There was an increase in death risk by this neoplasm in the North and Northeast regions starting from the 2000’s, when compared to the reference period.

Gastric cancer, despite the decrease presented in incidence and mortality rates, is still one of the main cancer-related causes of death globally[12]. This disease presents a bad prognosis, with 5-year survival rates
Table 2  Observed and predicted number of deaths by age and world age-standardized rates in Brazil

|          | Observed | Predicted |
|----------|----------|-----------|
|          | 1995-1999 | 2000-2004 | 2005-2009 | 2010-2014 | 2015-2019 | 2020-2024 | 2025-2029 |
| Males    |          |          |          |          |          |          |          |
| North    |          |          |          |          |          |          |          |
| Age      | 0-39     | 40-59    | ≥ 60     |          |          |          |          |
|          | 99       | 700      | 1287     | 2086     | 13.6     | 13.6     | 13.6     |
| ASW      | 126      | 818      | 1597     | 2541     | 13.3     | 13.3     | 13.3     |
| Total    | 156      | 929      | 2151     | 3236     | 14.3     | 14.3     | 14.3     |
| ASW      | 200      | 1119     | 2792     | 4110     | 15.0     | 15.0     | 15.0     |
| Midwest  |          |          |          |          |          |          |          |
| Age      | 0-39     | 40-59    | ≥ 60     |          |          |          |          |
|          | 94       | 684      | 1404     | 2182     | 13.5     | 12.2     | 12.2     |
| ASW      | 98       | 707      | 1705     | 2682     | 11.6     | 10.6     | 10.6     |
| Total    | 102      | 753      | 1827     | 2920     | 9.3      | 8.4      | 8.4      |
| South    |          |          |          |          |          |          |          |
| Age      | 0-39     | 40-59    | ≥ 60     |          |          |          |          |
|          | 71       | 5515     | 2182     | 7169     | 18.2     | 16.3     | 16.3     |
| ASW      | 616      | 6052     | 2682     | 1464     | 5.6      | 4.6      | 4.6      |
| Total    | 660      | 6862     | 1822     | 2920     | 11.5     | 10.3     | 10.3     |
| Brazil   |          |          |          |          |          |          |          |
| Age      | 0-39     | 40-59    | ≥ 60     |          |          |          |          |
|          | 801      | 6255     | 2016     | 6161     | 17.3     | 16.2     | 16.2     |
| ASW      | 616      | 6304     | 2682     | 16790    | 7.9      | 7.0      | 7.0      |
| Total    | 561      | 7806     | 2282     | 14468    | 9.7      | 9.5      | 9.5      |
| Females  |          |          |          |          |          |          |          |
| North    |          |          |          |          |          |          |          |
| Age      | 0-39     | 40-59    | ≥ 60     |          |          |          |          |
|          | 110      | 324      | 1112     | 7.1      | 18.2     | 16.3     | 16.3     |
| ASW      | 122      | 460      | 1627     | 6.8      | 5.6      | 4.6      | 4.6      |
| Total    | 127      | 557      | 2044     | 6.9      | 5.6      | 4.6      | 4.6      |
| Northeast|          |          |          |          |          |          |          |
| Age      | 0-39     | 40-59    | ≥ 60     |          |          |          |          |
|          | 274      | 943      | 2551     | 11.6     | 17.3     | 16.2     | 16.2     |
| ASW      | 314      | 1114     | 3152     | 6.8      | 5.6      | 4.6      | 4.6      |
| Total    | 380      | 1394     | 4318     | 6.9      | 5.6      | 4.6      | 4.6      |
| Southeast|          |          |          |          |          |          |          |
| Age      | 0-39     | 40-59    | ≥ 60     |          |          |          |          |
|          | 576      | 943      | 2551     | 11.6     | 17.3     | 16.2     | 16.2     |
| ASW      | 652      | 1196     | 3152     | 6.8      | 5.6      | 4.6      | 4.6      |
| Total    | 675      | 1353     | 4318     | 6.9      | 5.6      | 4.6      | 4.6      |
| South    |          |          |          |          |          |          |          |
| Age      | 0-39     | 40-59    | ≥ 60     |          |          |          |          |
|          | 82       | 277      | 603      | 96       | 5.6      | 4.6      | 4.6      |
| ASW      | 92       | 333      | 771      | 5.3      | 4.4      | 4.4      | 4.4      |
| Total    | 96       | 382      | 875      | 5.3      | 4.4      | 4.4      | 4.4      |
| Brazil   |          |          |          |          |          |          |          |
| Age      | 0-39     | 40-59    | ≥ 60     |          |          |          |          |
|          | 576      | 943      | 2551     | 11.6     | 17.3     | 16.2     | 16.2     |
| ASW      | 652      | 1196     | 3152     | 6.8      | 5.6      | 4.6      | 4.6      |
| Total    | 675      | 1353     | 4318     | 6.9      | 5.6      | 4.6      | 4.6      |
| ASW: Age-standardized rates.
Figure 3 World age-standardized rates, changes in numbers of deaths relative change due to risk and changed population, between 2005-2009 (observed) and 2025–2029 (predicted) of gastric cancer mortality in Brazil. ASW: Age-standardized rates; Pop: Population.
under 20%[13].

The mortality rates presented in Brazil, in all regions and for both sexes, are located at intermediate levels, similar to the rates of Venezuela and Argentina, but still superior to those of developed countries such as the United States, Spain, France and Canada. However, Brazilian rates are lower than the mortality rates verified for China, Japan and South Korea[12-20].

This neoplasm can be classified according to its location, in cardia and non-cardia gastric cancer. These diseases present different risk factors and population distributions. While non-cardia gastric cancer presents main risk factors such as H. pylori infection, consumption of salt-preserved food, low consumption of fruit and vegetables, consumption of alcohol and use of tobacco, cardia gastric cancer (esophagogastric junction adenocarcinoma) is a pathology related to obesity, gastroesophageal reflux and Barrett esophagus. Besides, this disease is more common in developed countries and white race individuals, while non-cardia gastric cancer is more incident in Afro-Americans and in developing countries[19,21,22]. There have been important global reductions in incidence and mortality rates for non-cardia gastric cancer; however, an increasing trends have been observed for esophagogastric junction adenocarcinoma, which represents currently 50% of new diagnosed cases of gastric cancer. The prognosis of this type of cancer is worst than non-cardia gastric cancer, as esophagogastric junction adenocarcinoma can disseminate to the abdominal region as well as to the lymph nodes of the thoracic region. Due to the absence of symptoms at the beginning of the disease, esophagogastric junction adenocarcinoma is usually diagnosed in advanced stages[23].

As in other parts of the world, the Brazilian and per region rates for the male sex were approximately twice higher than mortality rates for the female sex[10,21,22]. Some authors believe that this difference is due to the co-existence of other risk factors and that there is unequal exposition according to sex[5,21]. Other authors mention that this reality is related to the fact that women are more aware of health issues than men[18].

Mortality due to this neoplasm in Brazil and in the Midwest, South and Southeast regions presented decreasing trends, along with France, Italy, Spain, Germany, South Korea, Japan and China[1,14]. In the United States and United Kingdom, half of gastric cancers are located in the cardia area, and in the last 30 years, globally, incidence of this disease has increased between 5 and 6 times[22]. A reduction in death risk was evidenced in Brazil and in the South and Southeast regions, starting from the 1990’s, and increased risk was observed in the North and Northeast regions after the 2000’s. Changes in mortality rates of diseases can reflect changes in exposition to risk factors (environmental and/or associated with lifestyle), as well as improvements in diagnosis, treatment, verification and certification of deaths. The differences presented between the North-Northeast regions and other regions of Brazil, especially in the 2000’s, can be a result of the period effect, due to improvement in death registry data and better access to health services. Due to an increase in the possibilities of diagnosing this neoplasm, even if in advanced stages of the disease, these regions presented higher mortality rates in the 2000’s.

Regarding birth cohorts, a progressive reduction in death risk was verified starting in the XX century, in all regions and for both sexes. This result was similar to the results of South Korea, Japan, United States, and Spain[15,17,24,25]. This reality can be explained by the prevalence reduction of H. pylori infection, use of refrigerators (which increased the consumption of fruit and vegetables)[26-29] besides the reduction in the consumption of salt-preserved foods[30] and better sewage collection and treatment, which contributes to reducing the transmission of H. pylori, especially in children and teenagers[19,22]. Reduction of mortality can also be related to new therapeutic strategies implemented within the last decade for the treatment of gastric cancer. These are based on neoadjuvant/adjuvant chemotherapy treatment, which can be associated with radiotherapy[31]. A literature review study with meta-analysis evidenced that patients treated with adjuvant chemotherapy presented better global survival (HR = 0.82; 95%CI: 0.76-0.90; P < 0.001) and disease-free survival (HR = 0.82; 95%CI: 0.75-0.90, P < 0.001) when compared to patients submitted to surgical treatment only[32]. However, there is still no consensus within literature on the best treatment to be utilized, and no studies were found in Brazil that evaluated the implementation of these new therapeutic measures on the survival of patients.

Survival rates are affected by early diagnosis, standardized surgery techniques, nutritional therapy, availability of beds in intensive care units, and the existence of specialized health teams for cancer treatment[13,17]. In this way, the pronounced inequity between Brazilian geographic regions (large urban centers vs the interior) regarding access to cancer diagnosis and treatment services can influence the evolution of mortality rates for this disease. The study by Oliveira et al[33] evidenced sanitary gaps related to breast cancer treatment, especially in North Brazil, with half of health assistance concentrated in few capital cities. The cities of Rio de Janeiro and São Paulo (Southeast Brazil) were responsible for one fifth of attendances, mostly for the resident population. Brazil has a public and universal health system that faces limitations regarding funding and access to diagnosis and treatment services. This reality should not be exclusive to breast cancer treatment and highlights the difficult access to health services that most cancer patients suffer in Brazil[34].

The projections indicated that the least developed
regions of Brazil (North and Northeast) will present increments in gastric cancer mortality rates. These regions present structural challenges in oncology services[34-36]. Also in the North and Northeast regions of the country, the increased mortality can be explained by higher difficulty in the access to diagnosis and treatment services. The ratio medical doctor/inhabitant is lower in the North and Northeast regions (in 2010, approximately 1 doctor per 1000 inhabitants) than in the South and Southeast regions (respectively 2.5 and 2.0 doctors per 1000 inhabitants). The distribution of oncology specialists and oncology hospitals is also unbalanced[37]. Also, there is concentration of oncology services in large urban centers, as a consequence of internal migration and development of these areas. The search for appointments with specialists and access to diagnosis and treatment services generates dislocation from rural areas to large urban centers, which delays diagnosis and therefore, entail in worst prognosis for these patients[32].

A limitation to be considered in the study is the impossibility of separating cardia and non-cardia locations for gastric cancer, which seem to present different behaviors according to most recent studies, as the Brazilian Mortality Information System does not differentiate gastric cancers according to histological type[21]. Another important fact to consider is the lack of historical series for risk factor prevalence, which could aid in the analysis of the observed changes. Finally, it must be highlighted that this is an ecological study, and intra-regional differences can be found in Brazil due to its large continental dimensions, especially regarding the quality of death registries, which the authors attenuated after correcting death data. Limitations related to the APC models must also be mentioned, as these are still under development and there is no consensus in literature on the best methodology to correct the issue of non-identification of the complete model[6,7].

The projections made must be interpreted with caution, as the diagnostic and therapeutic conditions can change in the future, and consequently the mortality trends could be slightly modified. The projection of mortality rates is very important to support the planning of public health measures, as well as to control modifiable risk factors at short and long terms, on the burden of the disease to the population[33]. The main objective of the projections made herein was to provide the required information for health planning purposes, aiming at the selection of vigilance actions for gastric cancer.

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