Ecological study of gastric cancer in Brazil: Geographic and time trend analysis

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Abstract

AIM: To investigate the geographic distributions and time trends of gastric cancer (GC) incidence and mortality in Brazil.

METHODS: An ecological study of the DATASUS registry was conducted by identifying hospitalizations for GC between January 2005 and December 2010. The data included information on the gender, age, and town of residence at the time of hospital admission and death.

RESULTS: The GC rates, adjusted according to available hospital beds, decreased from 13.8 per 100000 in 2005 to 12.7 per 100000 in 2010. The GC rates decreased more among the younger age groups, in which the male-to-female difference also decreased in comparison to the older age groups. Although the lethality rates tended to increase with age, young patients were proportionally more affected. The spatial GC distribution showed that the rates were higher in the south and southeast. However, while the rates decreased in the central-west and south, they increased in the northern regions. A geographic analysis showed higher rates of GC in more urbanized areas, with a coast-to-inland gradient. Geographically, GC lethality overlapped greatly with the hospital admission rates.

CONCLUSION: The results of this study support the hypothesis of a critical role for environmental factors in GC pathogenesis. The declining rates in young patients, particularly males, suggest a relatively recent decrease in the exposure to risk factors associated with GC. The spatial distribution of GC indicates an ongoing dynamic change within the Brazilian environment.

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Key words: Gastric cancer; Ecological study; Hospitalization; Lethality rate

Core tip: Declining rates in young patients and changes in the geographic distribution of gastric cancer suggest a recent decrease in the exposure to risk factors within the Brazilian environment.
INTRODUCTION

Gastric cancer (GC) is among the most common cancers worldwide and is estimated to be the second-leading cause of cancer-related death[1]. At the time of diagnosis, most patients already present with late-stage disease, resulting in an overall low survival rate[2,3]. Although the mechanisms that underlie gastric carcinogenesis development are not completely understood, GC likely results from complex interactions between host and environmental factors[3].

Multiple risk factors for GC have been recognized, including smoking and diet[4,5] but *Helicobacter pylori* (H. pylori) infection and the resulting development of intestinal metaplasia appear to be of crucial importance[6,7]. Chronic inflammation secondary to H. pylori infection is thought to be responsible for the development of a step-wise progression from chronic gastritis to pre-malignant changes that eventually result in GC[8,9].

Although epidemiological data appear to indicate a progressive reduction in the incidence of GC, particularly in developed countries within North America and Western Europe, significant geographical[10] and ethnic[11] variations exist. However, data from developing countries remain limited, which renders global analyses difficult. The aim of this study was to analyze the geographic distributions and time trends of GC incidence and mortality in Brazil to identify the areas with differential risks and outcomes for GC.

MATERIALS AND METHODS

Data source

Data from the Health Informatics Department of the Brazilian Ministry of Health (DATASUS) were utilized for this study (http://www2.datasus.gov.br/DATASUS). DATASUS is a fundamental tool for the coordination of the National Health Information System and maintains reference tables and vocabularies used in information systems throughout the entire country. This population-based health and disease registry includes important information such as medical procedures, hospital admission and discharge, and mortality, and it covers approximately the entire Brazilian population. In addition, demographic data, such as age, gender, and municipality, collected from the Instituto Brasileiro de Geografia e Estatística (IBGE; Brazilian Institute of Geography and Statistics), are also available at the DATASUS website.

In this study, we used hospital discharge records for GC patients as an estimate of the GC incidence. We assumed that hospital-based procedures for either GC diagnosis or treatment would in fact reflect the actual disease numbers. Variables for which DATASUS does not collect information, such as co-morbidities and treatment details, were not evaluated.

Study design, population, and variables

We conducted an ecological study with the DATASUS registry by identifying hospitalizations for GC patients diagnosed between January 2005 and December 2010. The analysis period was based on the most recent and consistent information and contained complete data entries. We included patients for whom a diagnosis of malignant neoplasm of the stomach was assigned; these patients were classified as C16 (from C16.0 to C16.9), according to the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10).

The data included information on the town of residence at the time of hospital admission and death, and the patients were categorized by gender and age; for the latter, patients were stratified as < 20 years, 20-49 years, 50-69 years, and > 70 years of age (for whom coexisting co-morbidities might render meaningful comparisons more difficult).

For the geographic distribution analysis, the GC hospitalization rates were obtained per 100000 inhabitants in the individual municipalities. The results from this exploratory model were included in a platform to plot maps depicting the estimates and distribution of GC.

Statistical analysis

The statistical analysis was performed with the statistical software package SPSS for Windows (Version 10.0.1, SPSS Inc., Chicago, IL, United States). Exploratory procedures were applied to the data, and summary descriptive statistics and graphical displays were generated either for all cases or separately for groups of cases.

RESULTS

In this study, we first present an overall picture of GC in Brazil over time (from 2005-2010) by showing the total cases registered per year, the rates per 100000 inhabitants, and the lethality rates, including the distribution by gender.

Hospitalizations for gastric cancer

The total numbers of hospitalizations for GC were 19085 in 2005 and 17602 in 2010, of which 3232 and 3305 resulted in death, respectively. Nevertheless, in terms of cases per 100000 inhabitants, the rates adjusted according to available hospital beds decreased from 13.8 per 100000 in 2005 to 12.7 per 100000 in 2010 (Figures 1 and 2 and Table 1). Regarding gender, the Brazilian numbers confirm the world trend for male predominance, as male patients accounted for 65% of all GC cases (Figure 1).

Next, we analyzed the population distribution of GC according to the age at diagnosis, using nationwide age-standardized rates of hospitalizations (Figure 3). Relatively low rates of GC cases were detected within the population < 50 years of age, whereas the rates were higher among those > 50 years, as expected. However, given the differences between 2005 and 2010, GC-related
hospitalizations decreased proportionally more among the < 50 years groups, in which the male-to-female difference also markedly decreased in comparison with the older age groups (Table 2).

**Lethality rates from gastric cancer**

Regarding GC-associated mortality, although the differences were not significant, the lethality rates appeared to indicate an increasing trend during the period from 2005-2010 (Figure 1 and Table 1). Although GC lethality was not related to gender, the use of standardized age groups seemed to reveal differences. As expected, the mortality rates increased linearly with age, ranging from approximately 10% among patients < 50 years to 25% among patients > 70 years (Figure 3). Nevertheless, lethality was proportionally greater among patients < 50 years, compared to the older groups (Table 2).

**Geographic distribution of gastric cancer**

Regarding the geographic distribution, this study analyzed the GC hospitalization rates per 100000 inhabitants within the individual municipalities. The obtained results were plotted in maps that depicted the estimates and distributions of GC per region, including the south, southeast, north, northeast, and central-west regions, in the years 2005 and 2010. The standardized rates defined three ranges of 0-10, 10-65, and > 65. The spatial distribution of GC showed that the rates were higher in the south and southeast, in contrast to those in the north and northeast regions. However, while the GC hospitalization rates decreased in the central-west and southern regions from 2005 to 2010, they increased in the northern regions. A geographic analysis of the distribution of GC cases indicated the presence of higher rates in municipalities with urbanized residency, those located in more industrialized areas, and those with greater urban population concentrations. Moreover, the GC rates also demonstrated a coast-to-inland gradient, which greatly overlaps with the urban-to-rural areas of the country (Figure 4). With respect to GC lethality, the standardized rates defined four ranges of < 25, 25-50, 50-75, and > 75. The geographic distribution of lethality overlapped considerably with the GC hospitalization rates (Figure 5).

In 2005, the towns with the highest rates of GC per 1000000 inhabitants were Cuiabá (38.0) in Mato Grosso (central-west) and Curitiba (36.0) in Paraná (south), whereas in 2010, the highest rates were observed in Vitória (42.1) in Espírito Santo (southeast) and Boa Vista (24.9) in Roraima (north). Notably, of the municipal areas with the highest GC rates, 2 of the top 4 areas in 2005 were located in the south, in contrast to 2 of the top 6 that were located in the north in 2010. Table 1 includes the hospitalization and lethality rates and populations of each country region, federal unity, and capital.

**DISCUSSION**

This study was the first to analyze the spatial distributions and demographics of GC incidence rates and lethality estimates over time in Brazil to identify the areas with differential risks and outcomes. Overall, the results of this study indicate that the nationwide GC incidence declined overall, whereas the lethality rate increased between 2005 and 2010. In particular, we observed a proportional decrease in GC hospitalization rates and the male-to-female ratio among young individuals. Nevertheless, the GC lethality rates proportionally increased among the younger population between 2005 and 2010. The geographic...
distribution of GC indicates a higher concentration throughout the south, southeast and central-west regions, in contrast to the lower rates in the northern regions. Interestingly, this study detected a decrease in the GC inci-
ence in regions of higher concentration over time, but it also unveiled a contrasting relative increase in cases in the northern regions during the same period.

Several studies support the notion that the GC incidence is declining worldwide \cite{12,13}. In accordance with those findings, in the current study, we have presented data from estimates of the GC incidence in Brazil to show that although the population increased from 2005 to 2010, hospitalizations for GC consistently declined. The time trends of the age-stratified groups show an increase in the GC incidence in patients > 50 years with an overall male predominance, a well-recognized phenomenon in GC that is usually attributed to possible differential environmental exposure \cite{14,15}. This suggests that the risk factors for GC have been present in our environment, but the exposure statuses to the relevant

Figure 3  Age-standardized gastric cancer incidences by gender, estimated from hospitalizations and lethality trends, in Brazil from 2005-2010.

| Ages: 0-19 yr | Male | Female | General |
|---------------|------|--------|---------|
| 2005          | 0.80 | 0.60   | 0.70    |
| 2006          | 0.60 | 0.40   | 0.50    |
| 2007          | 0.40 | 0.20   | 0.30    |
| 2008          | 0.20 | 0.00   | 0.10    |
| 2009          | 0.00 | 0.00   | 0.00    |
| 2010          | 0.00 | 0.00   | 0.00    |

| Ages: 20-49 yr | Male | Female | General |
|----------------|------|--------|---------|
| 2005           | 10.0 | 8.0    | 9.0     |
| 2006           | 8.0  | 6.0    | 7.0     |
| 2007           | 6.0  | 4.0    | 5.0     |
| 2008           | 4.0  | 2.0    | 3.0     |
| 2009           | 2.0  | 0.0    | 1.0     |
| 2010           | 0.0  | 0.0    | 0.0     |

| Ages: 50-69 yr | Male | Female | General |
|----------------|------|--------|---------|
| 2005           | 60.0 | 40.0   | 50.0    |
| 2006           | 40.0 | 20.0   | 30.0    |
| 2007           | 20.0 | 10.0   | 20.0    |
| 2008           | 10.0 | 5.0    | 10.0    |
| 2009           | 5.0  | 2.5    | 5.0     |
| 2010           | 2.5  | 1.25   | 2.5     |

| Ages: > 70 yr  | Male | Female | General |
|----------------|------|--------|---------|
| 2005           | 120  | 100    | 110     |
| 2006           | 100  | 80     | 90      |
| 2007           | 80   | 60     | 70      |
| 2008           | 60   | 40     | 50      |
| 2009           | 40   | 20     | 30      |
| 2010           | 20   | 10     | 15      |
factors most likely differed between male and female patients. However, our finding of decreasing GC rates, especially in the younger age groups and proportionally more among males, support the idea of relatively recent environmental modifications in Brazil and appear to be in accordance with a previous Japanese study, in which the decreasing trend in younger groups was additionally associated with intestinal-type GC[20,21].

Overall, more than 90% of the GCs are adenocarcinomas and comprise two well-differentiated types, namely intestinal and diffuse[17]. The intestinal type, to which the decrease in GC has been attributed[20,21], is usually more prevalent among men and the elderly and is predominant in the lowest socioeconomic groups; diet and H. pylori infection are major risk factors. The diffuse type, in contrast, is more frequent among the young, with an equal male-female distribution, and has been associated with constitutive-related factors[18]. Considering the well-known differences in the pathogenic mechanisms of the two GC subtypes, our results appear to corroborate the trends of a 25-year study of a reference center in Southern Brazil that showed a decrease in the intestinal subtype paralleled by a steady increase in the diffuse subtype of GC, predominantly in women <45 years[21]. This fact might explain the tendency to select more severe or advanced cases with increasing lethality, which are also compatible with the diffuse subtype of GC[21]. In agreement with our results, young patients in a large population-based study of age-related GC outcomes in the United States also presented with more advanced disease. However, the prognosis of young patients with GC remained better than that of the older patients[22]. Although this information appears paradoxical and might also contradict our results, it is likely that the adjusted stage-stratified relative survival would be more favorable among young patients, compared to older patients, due to their general health condition and possibly to differences in the availability and quality of health care.

With respect to the incidence and associated mortality, marked geographic differences are characteristic of worldwide GC epidemiology. The highest incidence rates have been reported in Japan and Korea, whereas the lowest are in the United States and Western and Northern European countries; Brazil has been considered to have an intermediate-high pattern[10,22,24]. Although the precise etiology of GC remains unknown, studies have identified potential genetic, environmental, and lifestyle risk factors that might also account for the geographical differences. Several risk factors have been associated with GC, including H. pylori infection, smoking, and diet[41,52]. Regarding dietary factors, ecologic studies have suggested associations of GC incidence and mortality with salt consumption[26-28]. Studies of immigrants have shown that changing patterns of incidence according to the location where people live appear to reinforce the critical role of dietary habits in the development of GC[26,29].

The differential occurrence in urban versus rural municipalities constitutes another intriguing factor that could contribute to additional geographical variations in GC. In contrast to our results, a study conducted in southern Spain showed a reduction in the mortality rates in the most rural municipalities[8,30,31]. However, geographic GC clustering remains evident in China, and high-risk areas are located in rural areas, especially in the north[32,33]. Similar results from studies conducted in Lithuania[34], South Korea[35], and Brazil[36], which reported higher risks of GC incidence and mortality in rural areas, also appear to agree with our findings and with those of another previous Brazilian study that estimated a specific reduction in GC would occur in the state capitals ten years earlier than in the inland municipalities[34]. These differences might be explained at least in part by gaps in education and preventive measures, together with lower access to health-care services for populations residing outside of larger urban centers.

H. pylori infection has been established as the most important risk factor for GF, but its presence alone is not sufficient to explain GC development[30,37]. H. pylori is commonly observed and widely distributed throughout the populations of developing countries[18,39], including Brazil[40], and the low socioeconomic level, which includes variables indicative of a crowded environment and deficient sanitation or habitation conditions, have been confirmed in population-based studies to be critical for infection acquisition[41,42]. Therefore, it is reasonable to suppose that H. pylori infection would also account for the high prevalence of GC in Brazil. In fact, GC has been associated with socioeconomic status and, at an individual level, this variable might be linked not only with H. pylori infection but also with dietary patterns, smoking, and possibly environmental and occupational exposures[15,31,43,44]. However, the socioeconomic condition and its influence on H. pylori infection alone cannot explain, for example, the high frequency of GC in Japan or Korea, both of which have a high socioeconomic level. Because of these discrepancies, potential synergistic associations of H. pylori infection with different variables have also been investigated with respect to GC development. Previously, in a cross-sectional study in Japan, investigators found an association between H. pylori infection and the consumption of salted food[25]. Nevertheless, the potential association between salt consumption and H. pylori infection with respect to GC development was also

**Table 2  Changes in gastric cancer-associated hospitalizations and lethality rates among the standardized age ranges from 2005-2010**

| Age ranges  | 2005   | 2010   | Difference |
|------------|--------|--------|------------|
| Hospitalization | < 20 yr | 0.54   | 0.28       | -48.1%     |
|             | 20-49 yr | 6.23   | 3.91       | -37.2%     |
|             | 50-69 yr | 38.06  | 29.67      | -22.0%     |
|             | > 70 yr  | 75.97  | 55.40      | -27.1%     |
| Lethality   | < 20 yr  | 6.5    | 9.5        | +46.2%     |
|             | 20-49 yr | 12.1   | 14.8       | +23.3%     |
|             | 50-69 yr | 16.9   | 17.8       | +5.3%      |
|             | > 70 yr  | 22.5   | 23.5       | +4.4%      |
investigated in epidemiological studies and yielded inconsistent results\textsuperscript{[14,45,46]}. Despite the potential limitations of this study, which are basically related to the lack of disease details and information regarding co-morbidities and therapy, and the fact that the data were based on hospitalization rates and mortality, all procedures were thoroughly applied to generate a large database that contained nationwide information that was collected in a single, common, electronic data-based system. Therefore, although an ecological fallacy would still be possible in this study, this possibility was mitigated by the use of municipalities and the simplicity and straightforwardness of the data entered in the electronic system. However, it is important to cautiously interpret the results of this study because of some additional methodological limitations. For example, the concept of a municipal unit might be very different in Brazil, compared to most countries. In addition to clear geographic heterogeneities, Brazilian cities might present great differences in terms of population. In addition to the well-known global tendency towards urban concentration, considerable differences are observed among the 5435 Brazilian municipalities. For example, populations might vary from one thousand to twenty million inhabitants per city and yet, these would be considered municipal units of the same level in our database. An-
other potential caveat of this study is the precision of the registries, which is likely related to the geographic socio-economic differences, with repercussions on health-care quality. Nevertheless, it is clear that GC will remain a significant societal burden and will unfortunately continue to constitute a critical health issue in Brazil for many years. Therefore, despite all the potential limitations and criticism regarding this type of study, the information generated by this unified database might allow the first insights regarding the dynamics of GC in Brazil.

In conclusion, the results of this study appear to support the hypothesis that environmental elements are fundamental determinants of GC pathogenesis. Furthermore, the decline in GC incidence among younger patients, along with less discrepancy in the gender distribution during the analysis period, likely suggests a relatively recent decrease in the population-level exposure to the environmental risk factors associated with GC. However, the differential spatial distribution of GC suggests a possible ongoing dynamic change within the Brazilian environment, with shifts in incidence from the south towards the north and from more urbanized coastal areas to inland areas.

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