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BRIEF ARTICLE

# 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.



**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.

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## 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[1,2]. 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 stepwise 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

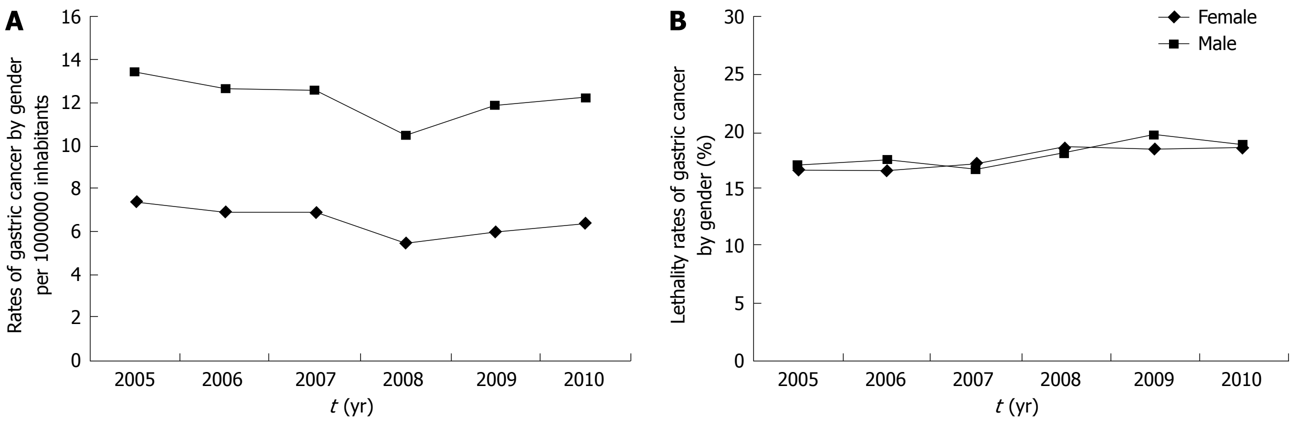


**Figure 1 Gastric cancer incidence by gender (A), estimated from hospitalizations and lethality trends (B), in Brazil from 2005-2010.**

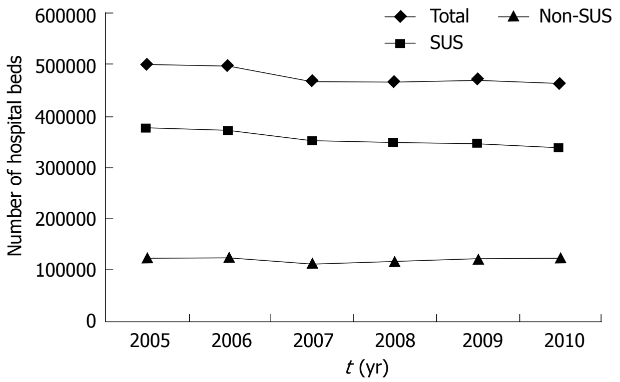


**Figure 2 Number and distribution of hospital beds in Brazil from 2005-2010.**

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 100000 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

**Table 1 Distributions of gastric cancer hospitalization rates and lethality in 2005 and 2010**

| Region, Federal Unity and Capital | 2005 | | | | 2010 | | | |
|---|---|---|---|---|---|---|---|---|
| | Hospitalization rate (per $10^5$) | Population | Adjusted hospitalization rates (per $10^5$) | Lethality | Hospitalization rate (per $10^5$) | Population | Adjusted hospitalization rates (per $10^5$) | Lethality |
| Brazil | 10.4 | 184184074 | 13.8 | 17.0% | 9.2 | 190755799 | 12.7 | 18.8% |
| North | 6.0 | 14698834 | 7.4 | 16.0% | 6.7 | 15864454 | 8.4 | 16% |
| Rondônia | 2.9 | 1534584 | 4.2 | 11.4% | 4.7 | 1562409 | 6.5 | 10.8% |
| Porto Velho | 2.4 | 373917 | 4.0 | 33.3% | 4.2 | 428527 | 6.1 | 11.1% |
| Acre | 9.7 | 669737 | 10.5 | 13.8% | 7.1 | 733559 | 7.8 | 9.6% |
| Rio Branco | 11.4 | 305730 | 13.1 | 17.1% | 11.0 | 336038 | 12.9 | 13.5% |
| Amazonas | 8.9 | 3232319 | 10.8 | 12.1% | 8.9 | 3483985 | 10.3 | 9.1% |
| Manaus | 16.2 | 1644688 | 22.0 | 11.6% | 16.4 | 1802014 | 21.0 | 9.5% |
| Roraima | 1.5 | 391318 | 1.6 | 0.0% | 18.0 | 450479 | 18.5 | 12.3% |
| Boa Vista | 1.7 | 242179 | 1.7 | 0.0% | 23.9 | 284313 | 24.9 | 11.8% |
| Pará | 5.4 | 6970591 | 6.7 | 22.0% | 4.6 | 7581051 | 6.1 | 28.3% |
| Belém | 11.9 | 1405873 | 17.4 | 23.4% | 9.6 | 1393399 | 17.2 | 31.3% |
| Amapá | 2.9 | 594577 | 3.3 | 29.4% | 6.9 | 669526 | 8.1 | 28.3% |
| Macapá | 2.8 | 355405 | 3.4 | 30.0% | 8.0 | 398204 | 10.0 | 34.4% |
| Tocantins | 6.8 | 1305708 | 7.9 | 10.1% | 11.3 | 1383445 | 13.0 | 6.4% |
| Palmas | 9.1 | 208168 | 11.6 | 5.3% | 4.8 | 228332 | 6.2 | 0.0% |
| Northeast | 6.4 | 51018983 | 7.6 | 16.0% | 6.5 | 53081950 | 7.8 | 17% |
| Maranhão | 5.5 | 6103338 | 6.4 | 12.5% | 4.2 | 6574789 | 4.9 | 17.9% |
| São Luís | 9.4 | 978822 | 12.3 | 21.7% | 12.3 | 1014837 | 15.8 | 18.4% |
| Piauí | 4.5 | 3006886 | 5.0 | 12.7% | 6.8 | 3118360 | 7.8 | 9.0% |
| Teresina | 4.7 | 788770 | 6.0 | 18.9% | 9.8 | 814230 | 13.0 | 18.8% |
| Ceará | 9.4 | 8097290 | 11.4 | 13.1% | 8.9 | 8452381 | 11.2 | 13.7% |
| Fortaleza | 15.2 | 2374944 | 20.3 | 15.8% | 9.5 | 2452185 | 13.3 | 14.2% |
| Rio Grande do Norte | 15.7 | 3003040 | 18.7 | 20.0% | 10.2 | 3168027 | 11.9 | 22.5% |
| Natal | 20.1 | 778038 | 29.5 | 32.7% | 12.6 | 803739 | 16.9 | 25.7% |
| Paraíba | 8.8 | 3595849 | 10.5 | 13.2% | 7.1 | 3766528 | 8.3 | 11.3% |
| João Pessoa | 8.9 | 660797 | 11.9 | 15.3% | 6.8 | 723515 | 9.1 | 6.1% |
| Pernambuco | 2.9 | 8413601 | 3.5 | 10.5% | 7.4 | 8796448 | 9.0 | 15.2% |
| Recife | 3.7 | 1501010 | 4.7 | 16.4% | 8.7 | 1537704 | 11.4 | 20.9% |
| Alagoas | 7.6 | 3015901 | 8.7 | 13.9% | 3.0 | 3120494 | 3.5 | 13.7% |
| Maceió | 10.0 | 903464 | 12.2 | 10.0% | 3.1 | 932748 | 3.9 | 13.8% |
| Sergipe | 3.3 | 1967818 | 3.8 | 27.7% | 2.9 | 2068017 | 3.6 | 25.4% |
| Aracajú | 6.6 | 498618 | 8.1 | 30.3% | 2.5 | 571149 | 3.6 | 21.4% |
| Bahia | 5.2 | 13815260 | 6.3 | 19.2% | 5.8 | 14016906 | 6.9 | 22.1% |
| Salvador | 6.2 | 2673557 | 8.7 | 25.7% | 8.5 | 2,675,656 | 11.8 | 27.3% |
| Southeast | 11.9 | 78472036 | 17.0 | 18.0% | 11.0 | 80364410 | 16.6 | 20.0% |
| Minas Gerais | 14.3 | 19237434 | 18.7 | 17.0% | 12.0 | 19597330 | 16.5 | 18.9% |
| Belo Horizonte | 14.5 | 2375330 | 22.7 | 20.0% | 12.3 | 2375151 | 20.5 | 21.2% |
| Espírito Santo | 9.3 | 3408360 | 12.4 | 13.6% | 10.6 | 3514952 | 14.9 | 21.7% |
| Vitória | 13.1 | 396324 | 18.0 | 12.2% | 29.3 | 414586 | 42.1 | 16.7% |
| Rio de Janeiro | 8.8 | 15383422 | 12.5 | 26.4% | 7.6 | 15989929 | 11.5 | 23.9% |
| Rio de Janeiro | 9.0 | 6094182 | 14.5 | 33.9% | 7.1 | 6320446 | 12.6 | 24.8% |
| São Paulo | 12.1 | 40442820 | 18.4 | 17.1% | 11.9 | 41262199 | 18.8 | 19.5% |
| São Paulo | 11.1 | 10927985 | 19.6 | 19.6% | 11.2 | 11253503 | 21.1 | 21.8% |
| South | 15.9 | 26973432 | 21.4 | 16.0% | 11.5 | 27386891 | 16.1 | 18.0% |
| Paraná | 17.2 | 10261840 | 22.7 | 15.7% | 14.3 | 10444526 | 19.9 | 16.9% |
| Curitiba | 20.0 | 1757903 | 36.0 | 13.6% | 11.5 | 1751907 | 20.1 | 17.8% |
| Santa Catarina | 17.1 | 5866590 | 21.9 | 16.8% | 5.6 | 6248436 | 7.6 | 17.0% |
| Florianópolis | 22.2 | 487047 | 28.0 | 23.9% | 1.7 | 515288 | 2.2 | 42.9% |
| Rio Grande do Sul | 14.1 | 10845002 | 19.8 | 15.1% | 12.1 | 10693929 | 17.4 | 18.3% |
| Porto Alegre | 11.9 | 1428694 | 16.7 | 21.8% | 9.9 | 1409351 | 14.9 | 24.5% |
| Central-West | 10.2 | 13020789 | 13.8 | 15.0% | 7.9 | 14058094 | 11.1 | 21.0% |
| Mato Grosso do Sul | 10.6 | 2264489 | 13.8 | 17.0% | 11.0 | 2449024 | 17.1 | 22.6% |
| Campo Grande | 8.0 | 749770 | 11.9 | 23.3% | 13.5 | 786797 | 22.7 | 24.5% |
| Mato Grosso | 13.2 | 2803272 | 17.4 | 14.0% | 7.4 | 3035122 | 10.1 | 22.1% |
| Cuiabá | 23.6 | 533801 | 38.0 | 17.5% | 10.3 | 551098 | 15.9 | 26.3% |
| Goiás | 8.0 | 5619919 | 10.9 | 12.7% | 6.0 | 6003788 | 8.3 | 20.6% |
| Goiânia | 8.8 | 1201007 | 13.4 | 17.9% | 7.5 | 1302001 | 12.0 | 22.4% |
| Distrito Federal | 11.2 | 2333109 | 16.2 | 19.8% | 9.8 | 2570160 | 13.9 | 17.9% |
| Brasília | 11.2 | 2333109 | 16.2 | 19.8% | 5.0 | 2570160 | 7.1 | 10.9% |

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-

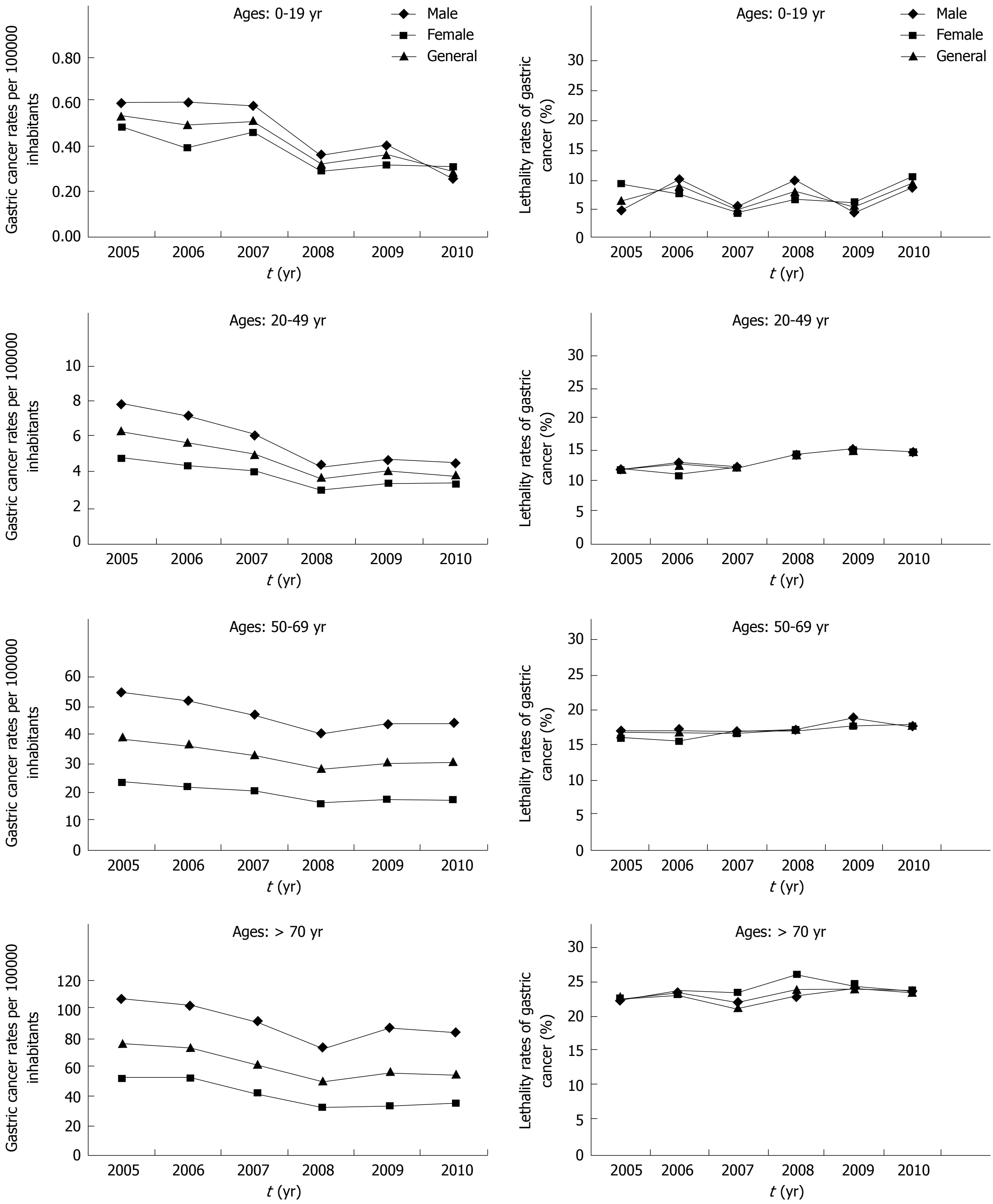


**Figure 3 Age-standardized gastric cancer incidences by gender, estimated from hospitalizations and lethality trends, in Brazil from 2005-2010.**

dence 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[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[14,15]. This suggests that the risk factors for GC have been present in our environment, but the exposure statuses to the relevant

**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 | +22.3% |
| | 50-69 yr | 16.9 | 17.8 | +5.3% |
| | > 70 yr | 22.5 | 23.5 | +4.4% |

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[16].

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[18,19], 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[15]. 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[20]. 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[10,23,24]. Although the precise etiology of GC remains unknown, studies have identified potential genetic, environmental, and lifestyle risk factors that might also account also for the geographical differences. Several risk factors have been associated with GC, including *H. pylori* infection, smoking, and diet[4,15,25]. 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[28,29].

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[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[24]. 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[9,37]. *H. pylori* is commonly observed and widely distributed throughout the populations of developing countries[38,39], 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[29]. Nevertheless, the potential association between salt consumption and *H. pylori* infection with respect to GC development was also

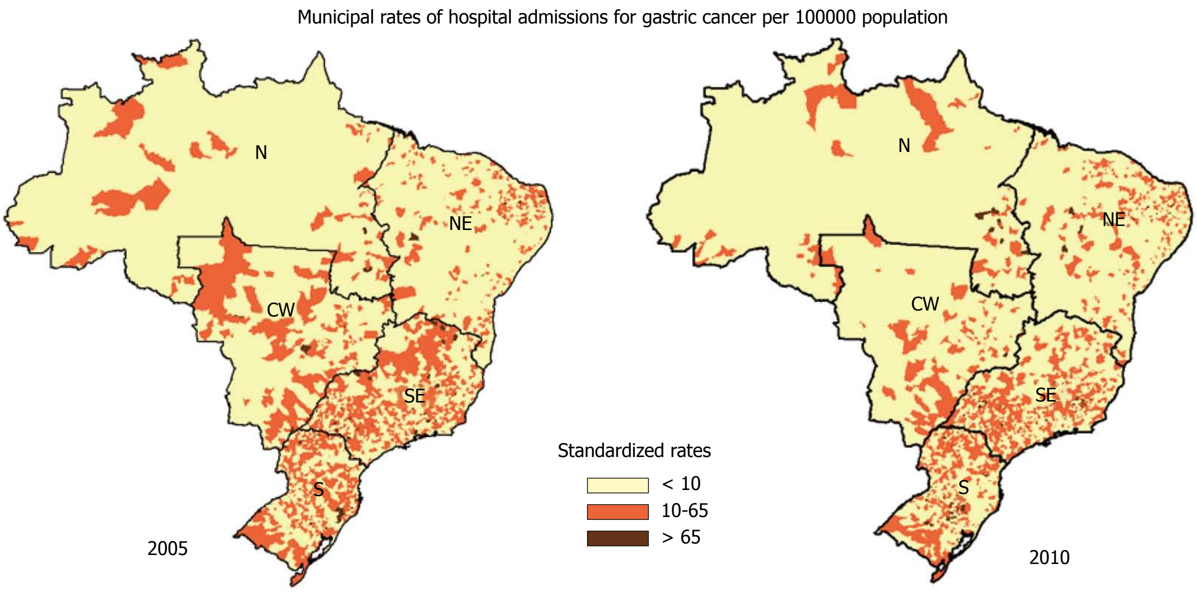


**Figure 4 Geographic distribution of gastric cancer in Brazil according to the municipal hospitalization rates (per 100000 inhabitants) in the years of 2005 and 2010.** Standardized rates defined three ranges of 0-10, 10-65 and > 65. S: South; SE: Southeast; N: North; NE: Northeast; CW: Central-west.

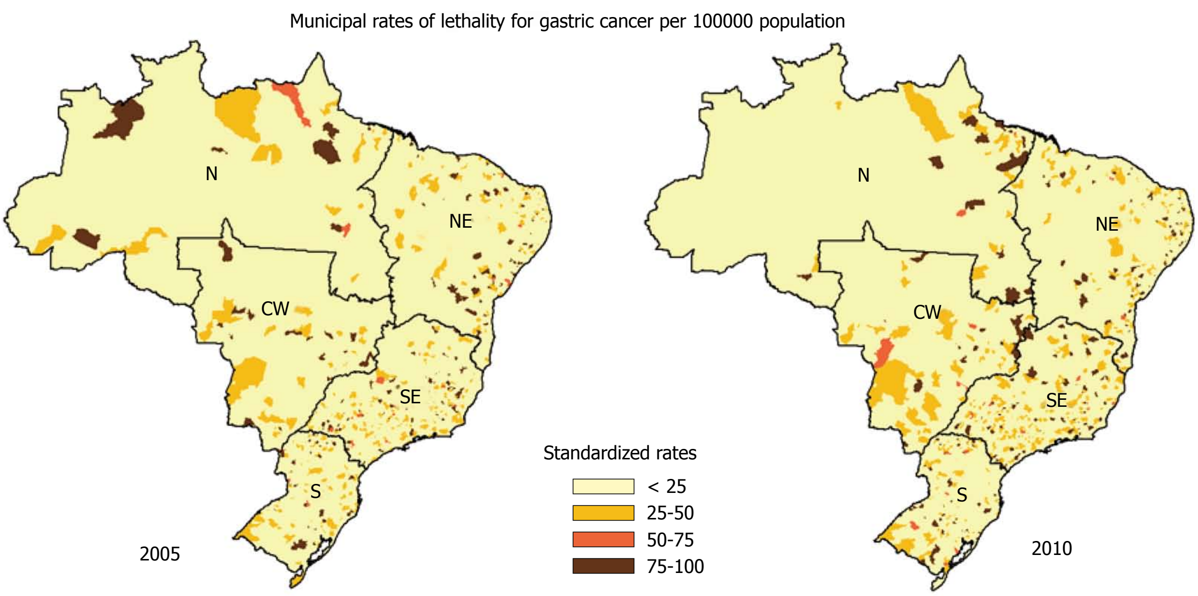


**Figure 5 Geographic distribution of gastric cancer lethality in Brazil according to the municipal rates (per 100000 inhabitants) in the years of 2005 and 2010.** Standardized rates defined four ranges of < 25, 25-50, 50-75 and > 75. S: South; SE: Southeast; N: North; NE: Northeast; CW: Central-west.

investigated in epidemiological studies and yielded inconsistent results[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. Another 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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## COMMENTS

### Background

Gastric cancer (GC) is among the most common cancers worldwide and is the second leading cause of cancer-related deaths. The underlying pathogenic mechanisms of GC are not completely understood, but they likely result from host-environmental factor interactions.

### Research frontiers

Although epidemiological data indicate a progressive reduction in the GC incidence in developed countries, remarkable geographical and ethnic variations exist. However, data from developing countries remain limited, which renders global analysis difficult.

### Innovations and breakthroughs

This study is the first to analyze the spatial distributions and demographics of the GC incidence and lethality estimates over time in Brazil to identify the areas with differential risks and outcomes. An ecological study of data from the Health Informatics Department of the Brazilian Ministry of Health registry identified the GC hospitalization rates between January 2005 and December 2010. The data included information about the town of residence at hospital admission and death, and the patients were categorized by gender and age. 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 that depicted the GC estimates and distributions.

### Applications

The ecological analysis provided by this study identified changes in the GC geographic distribution and declining GC rates in young patients, suggesting a recent decrease in the exposure to risk factors within the Brazilian environment.

### Peer review

This database-based study explores variations in the GC rates and consequent deaths in Brazil from 2005-2010. In addition, this study provides information about the nationwide geographic localization. Hospital discharge records associated with a GC diagnosis, regardless of the duration or reason for hospitalization and including outpatient procedures, were utilized to estimate the GC rate, distribution, and lethality. Another novel finding of this study is that of a coast-to-inland gradient that greatly overlaps with the urban-to-rural areas of the country. The authors believe that this observation reflects the geographic and social-economic features of Brazilian society within the analysis period. In addition, this information might reinforce the notion that the interaction of people with their geographic environments could determine or at least modulate economic and social development, with consequent influences on demographics and health issues.

## REFERENCES


1 **Kamangar F**, Dores GM, Anderson WF. Patterns of cancer incidence, mortality, and prevalence across five continents: defining priorities to reduce cancer disparities in different geographic regions of the world. *J Clin Oncol* 2006; **24**: 2137-2150 [PMID: 16682732 DOI: 10.1200/JCO.2005.05.2308]

2 **Hartgrink HH**, Jansen EP, van Grieken NC, van de Velde CJ. Gastric cancer. *Lancet* 2009; **374**: 477-490 [PMID: 19625077 DOI: 10.1016/S0140-6736(09)60617-6]

3 **Wu MS**, Chen CJ, Lin JT. Host-environment interactions: their impact on progression from gastric inflammation to carcinogenesis and on development of new approaches to prevent and treat gastric cancer. *Cancer Epidemiol Biomarkers Prev* 2005; **14**: 1878-1882 [PMID: 16103430 DOI: 10.1158/1055-9965.EPI-04-0792]

4 **Forman D**, Burley VJ. Gastric cancer: global pattern of the disease and an overview of environmental risk factors. *Best Pract Res Clin Gastroenterol* 2006; **20**: 633-649 [PMID: 16997150 DOI: 10.1016/j.bpg.2006.04.008]

5 **Jakszyn P**, Bingham S, Pera G, Agudo A, Luben R, Welch A, Boeing H, Del Giudice G, Palli D, Saieva C, Krogh V, Sacerdote C, Tumino R, Panico S, Berglund G, Simán H, Hallmans G, Sanchez MJ, Larrañaga N, Barricarte A, Chirlaque MD, Quirós JR, Key TJ, Allen N, Lund E, Carneiro F, Linseisen J, Nagel G, Overvad K, Tjonneland A, Olsen A, Bueno-de-Mesquita HB, Ocké MO, Peeters PH, Numans ME, Clavel-Chapelon F, Trichopoulou A, Fenger C, Stenling R, Ferrari P, Jenab M, Norat T, Riboli E, Gonzalez CA. Endogenous versus exogenous exposure to N-nitroso compounds and gastric cancer risk in the European Prospective Investigation into Cancer and Nutrition (EPIC-EURGAST) study. *Carcinogenesis* 2006; **27**: 1497-1501 [PMID: 16571648 DOI: 10.1093/carcin/bgl019]

6 **Hunt RH**. Will eradication of Helicobacter pylori infection influence the risk of gastric cancer? *Am J Med* 2004; **117** Suppl 5A: 86S-91S [PMID: 15478858]

7 **Talley NJ**, Fock KM, Moayyedi P. Gastric Cancer Consensus conference recommends Helicobacter pylori screening and treatment in asymptomatic persons from high-risk populations to prevent gastric cancer. *Am J Gastroenterol* 2008; **103**: 510-514 [PMID: 18341483 DOI: 10.1111/j.1572-0241.2008.01819.x]

8 **Correa P**, Shiao YH. Phenotypic and genotypic events in gastric carcinogenesis. *Cancer Res* 1994; **54**: 1941s-1943s [PMID: 8137316]

9 **Uemura N**, Okamoto S, Yamamoto S, Matsumura N, Yamaguchi S, Yamakido M, Taniyama K, Sasaki N, Schlemper RJ. Helicobacter pylori infection and the development of gastric cancer. *N Engl J Med* 2001; **345**: 784-789 [PMID: 11556297 DOI: 10.1056/NEJMoa001999]

10 **Parkin DM**, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin* 2005; **55**: 74-108 [PMID: 15761078]

11 **Haenszel W**, Correa P. Developments in the epidemiology of stomach cancer over the past decade. *Cancer Res* 1975; **35**: 3452-3459 [PMID: 1104154]

12 **Kelley JR**, Duggan JM. Gastric cancer epidemiology and risk factors. *J Clin Epidemiol* 2003; **56**: 1-9 [PMID: 12589864 DOI: 10.1016/S0895-4356(02)00534-6]

13 **Ferlay J**, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBO-

CAN 2008. *Int J Cancer* 2010; **127**: 2893-2917 [PMID: 21351269 DOI: 10.1002/ijc.25516]
14 **Lee SA**, Kang D, Shim KN, Choe JW, Hong WS, Choi H. Effect of diet and Helicobacter pylori infection to the risk of early gastric cancer. *J Epidemiol* 2003; **13**: 162-168 [PMID: 12749604]
15 **Crew KD**, Neugut AI. Epidemiology of gastric cancer. *World J Gastroenterol* 2006; **12**: 354-362 [PMID: 16489633]
16 **Kaneko S**, Yoshimura T. Time trend analysis of gastric cancer incidence in Japan by histological types, 1975-1989. *Br J Cancer* 2001; **84**: 400-405 [PMID: 11161407 DOI: 10.1054/bjoc.2000.1602]
17 **Lauren P**. The two histological main types of gastric carcinoma: diffuse and so-called intestinal-type carcinoma. an attempt at a histo-clinical classification. *Acta Pathol Microbiol Scand* 1965; **64**: 31-49 [PMID: 14320675]
18 **Craanen ME**, Dekker W, Blok P, Ferwerda J, Tytgat GN. Time trends in gastric carcinoma: changing patterns of type and location. *Am J Gastroenterol* 1992; **87**: 572-579 [PMID: 1306644]
19 **Laurén PA**, Nevalainen TJ. Epidemiology of intestinal and diffuse types of gastric carcinoma. A time-trend study in Finland with comparison between studies from high- and low-risk areas. *Cancer* 1993; **71**: 2926-2933 [PMID: 8490820]
20 **Rampazzo A**, Mott GL, Fontana K, Fagundes RB. Gastric adenocarcinoma trends in the central region of Rio Grande do Sul (Southern Brazil): what has changed in 25 years? *Arq Gastroenterol* 2012; **49**: 178-183 [PMID: 23011238 DOI: 10.1590/S0004-28032012000300002]
21 **Smith BR**, Stabile BE. Extreme aggressiveness and lethality of gastric adenocarcinoma in the very young. *Arch Surg* 2009; **144**: 506-510 [PMID: 19528381 DOI: 10.1001/archsurg.2009.77]
22 **Al-Refaie WB**, Hu CY, Pisters PW, Chang GJ. Gastric adenocarcinoma in young patients: a population-based appraisal. *Ann Surg Oncol* 2011; **18**: 2800-2807 [PMID: 21424881 DOI: 10.1245/s10434-011-1647-x]
23 **Howson CP**, Hiyama T, Wynder EL. The decline in gastric cancer: epidemiology of an unplanned triumph. *Epidemiol Rev* 1986; **8**: 1-27 [PMID: 3533579]
24 **Chatenoud L**, Bertuccio P, Bosetti C, Levi F, Curado MP, Malvezzi M, Negri E, La Vecchia C. Trends in cancer mortality in Brazil, 1980-2004. *Eur J Cancer Prev* 2010; **19**: 79-86 [PMID: 20009937 DOI: 10.1097/CEJ.0b013e32833233be]
25 **Armstrong B**, Doll R. Environmental factors and cancer incidence and mortality in different countries, with special reference to dietary practices. *Int J Cancer* 1975; **15**: 617-631 [PMID: 1140864]
26 **Joossens JV**, Hill MJ, Elliott P, Stamler R, Lesaffre E, Dyer A, Nichols R, Kesteloot H. Dietary salt, nitrate and stomach cancer mortality in 24 countries. European Cancer Prevention (ECP) and the INTERSALT Cooperative Research Group. *Int J Epidemiol* 1996; **25**: 494-504 [PMID: 8671549]
27 **Ngoan LT**, Mizoue T, Fujino Y, Tokui N, Yoshimura T. Dietary factors and stomach cancer mortality. *Br J Cancer* 2002; **87**: 37-42 [PMID: 12085253 DOI: 10.1038/sj.bjc.6600415]
28 **Tsugane S**, Sasazuki S. Diet and the risk of gastric cancer: review of epidemiological evidence. *Gastric Cancer* 2007; **10**: 75-83 [PMID: 17577615 DOI: 10.1007/s10120-007-0420-0]
29 **Tsugane S**, Tei Y, Takahashi T, Watanabe S, Sugano K. Salty food intake and risk of Helicobacter pylori infection. *Jpn J Cancer Res* 1994; **85**: 474-478 [PMID: 8014104]
30 **Ocaña-Riola R**, Sánchez-Cantalejo C, Fernández-Ajuria A. Rural habitat and risk of death in small areas of Southern Spain. *Soc Sci Med* 2006; **63**: 1352-1362 [PMID: 16647792 DOI: 10.1016/j.socscimed.2006.03.016]
31 **Aragonés N**, Pérez-Gómez B, Pollán M, Ramis R, Vidal E, Lope V, García-Pérez J, Boldo E, López-Abente G. The striking geographical pattern of gastric cancer mortality in Spain: environmental hypotheses revisited. *BMC Cancer* 2009; **9**: 316 [PMID: 19737377 DOI: 10.1186/1471-2407-9-316]
32 **Yang L**. Incidence and mortality of gastric cancer in China. *World J Gastroenterol* 2006; **12**: 17-20 [PMID: 16440411]
33 **Guo P**, Huang ZL, Yu P, Li K. Trends in cancer mortality in China: an update. *Ann Oncol* 2012; **23**: 2755-2762 [PMID: 22492700 DOI: 10.1093/annonc/mds069]
34 **Smailyte G**, Kurtinaitis J. Cancer mortality differences among urban and rural residents in Lithuania. *BMC Public Health* 2008; **8**: 56 [PMID: 18267035 DOI: 10.1186/1471-2458-8-56]
35 **Lee WJ**, Son M, Chun BC, Park ES, Lee HK, Coble J, Dosemeci M. Cancer mortality and farming in South Korea: an ecologic study. *Cancer Causes Control* 2008; **19**: 505-513 [PMID: 18197459 DOI: 10.1007/s10552-008-9112-2]
36 **Silva GA**, Gamarra CJ, Girianelli VR, Valente JG. Cancer mortality trends in Brazilian state capitals and other municipalities between 1980 and 2006. *Rev Saude Publica* 2011; **45**: 1009-1018 [PMID: 22127651 DOI: 10.1590/S0034-89102011005000076]
37 **Helicobacter and Cancer Collaborative Group**. Gastric cancer and Helicobacter pylori: a combined analysis of 12 case control studies nested within prospective cohorts. *Gut* 2001; **49**: 347-353 [PMID: 11511555 DOI: 10.1136/gut.49.3.347]
38 **Parkin DM**. The global health burden of infection-associated cancers in the year 2002. *Int J Cancer* 2006; **118**: 3030-3044 [PMID: 16404738 DOI: 10.1002/ijc.21731]
39 **Prinz C**, Schwendy S, Voland P. H pylori and gastric cancer: shifting the global burden. *World J Gastroenterol* 2006; **12**: 5458-5464 [PMID: 17006981]
40 **Magalhães Queiroz DM**, Luzza F. Epidemiology of Helicobacter pylori infection. *Helicobacter* 2006; **11** Suppl 1: 1-5 [PMID: 16925604]
41 **Zaterka S**, Eisig JN, Chinzon D, Rothstein W. Factors related to Helicobacter pylori prevalence in an adult population in Brazil. *Helicobacter* 2007; **12**: 82-88 [PMID: 17241306 DOI: 10.1111/j.1523-5378.2007.00474.x]
42 **Dattoli VC**, Veiga RV, da Cunha SS, Pontes-de-Carvalho LC, Barreto ML, Alcântara-Neves NM. Seroprevalence and potential risk factors for Helicobacter pylori infection in Brazilian children. *Helicobacter* 2010; **15**: 273-278 [PMID: 20633188 DOI: 10.1111/j.1523-5378.2010.00766.x]
43 **Resnik DB**, Roman G. Health, justice, and the environment. *Bioethics* 2007; **21**: 230-241 [PMID: 17845481 DOI: 10.1111/j.1467-8519.2007.00547.x]
44 **Evans GW**, Kantrowitz E. Socioeconomic status and health: the potential role of environmental risk exposure. *Annu Rev Public Health* 2002; **23**: 303-331 [PMID: 11910065 DOI: 10.1146/annurev.publhealth.23.112001.112349]
45 **Machida-Montani A**, Sasazuki S, Inoue M, Natsukawa S, Shaura K, Koizumi Y, Kasuga Y, Hanaoka T, Tsugane S. Association of Helicobacter pylori infection and environmental factors in non-cardia gastric cancer in Japan. *Gastric Cancer* 2004; **7**: 46-53 [PMID: 15052440 DOI: 10.1007/s10120-004-0268-5]
46 **Shikata K**, Kiyohara Y, Kubo M, Yonemoto K, Ninomiya T, Shirota T, Tanizaki Y, Doi Y, Tanaka K, Oishi Y, Matsumoto T, Iida M. A prospective study of dietary salt intake and gastric cancer incidence in a defined Japanese population: the Hisayama study. *Int J Cancer* 2006; **119**: 196-201 [PMID: 16450397 DOI: 10.1002/ijc.2182]

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