RESEARCH ARTICLE

Disparities in Epidemiological Profile of Gastric Adenocarcinoma in Selected Cities of Brazil

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Abstract

Background: Despite decreasing global incidence trends, gastric cancer is still among the five most incident cancers in the world and the third cancer-related cause of death. In Brazil, differences in incidence and mortality exist depending on the geographic region studied. **Objective:** To describe the incidence, mortality, trends and age-period-cohort of gastric cancer in three cities of Brazil (Sao Paulo, Belem and Fortaleza), in the period 1990-2012. Mortality for gastric cancer in Brazil overall and by region was described. **Methods:** 33,462 incident cases of gastric cancer were identified from the population-based cancer registries and 23,424 deaths from mortality information system in residents of the three cities and in Brazil were included in the study. Data for incident cases were extracted from the Population Based Cancer Registries from the National Cancer Institute (INCA). Mortality data on gastric cancer were extracted from Information Technology Department of Brazilian Public Health Care System/Health Ministry (DATASUS/MS). Mortality and incidence age standardized rates were calculated. For trends analysis the Joinpoint Regression and age-period-cohort model were applied. **Results:** Belem presented the highest incidence rates for gastric adenocarcinoma. Decreasing incidence trends were identified in Sao Paulo (-7.8% in men; -6.3% in women) and in Fortaleza (-1.2% in men). Increasing incidence trends were observed for women in Belem (1.8%) and Fortaleza (1.1%). In Belem (Amazon area), there was an increased risk for gastric cancer in women born after the 1960s. Overall in Brazil mortality for gastric cancer is decreasing. Mortality trends showed significant reduction, for both sexes, in the three Brazilian cities. **Conclusion:** Incidence of gastric cancer is increasing in women born in the sixties in Belem (Amazon region) and Fortaleza (Northeast region). In Brazil there was increase in mortality in Northeast region and decrease in others regions. More update data on incidence for Amazon and Northeast region is needed.

Keywords: Incidence- mortality- trends- gastric neoplasm- cohort effect

Introduction

Gastric cancer is the fifth most incident cancer and the third cancer-related cause of death in the world. Despite decreasing incidence and mortality rates, high incidence have been observed in Eastern Asia, Europe, South and Central America. There are gender-related differences, with men:women ratio of 2:1 (Ferlay et al., 2017; Luo et al., 2017).

In 2018, 21,290 gastric cancer cases were estimated in Brazil. Adjusted incidence rates varied between 6/100,000 for women and 15/100,000 for men. Incidences vary according to the Brazilian region; in men, is the second most incident in the North and Northeast regions, and fifth in the Southeast region. In women, gastric cancer is the fourth most common in the North region, and the sixth in the Southeast (Brasil, 2017).

Globally, the highest mortality rates were found in Eastern Asia (24.0 and 9.8 per 100,000 men and women, respectively), followed by Eastern Europe and South and Central America. The lowest rates were observed in North America (2.8 and 1.5 per 100,000 men and women) (Ferlay et al., 2015). Mortality rates in Brazil were 12.2 and 5.2 per 100,000 men and women. Trends are decreasing, but mortality rates remain high for both sexes and unequal across geographic regions (De Souza Giusti et al., 2016).

Africa and Asia continents still present relatively

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low risk for gastric cancer, despite high prevalent of Helicobacter pylori (*H. pylori*) infection. This indicates that *H. pylori* infection are not always necessary for carcinogenesis, and other risk factors are associated with this malignancy (Uemura et al., 2001; Ferrari and Reis, 2013; Mihmanli et al., 2016; Zamani et al., 2018). Among the risk factors, it is believed that lifestyle contributes with an excessive ingestion of salt and salted foods, tobacco smoking, low consumption of fruits and vegetables, but genetic risk and low socioeconomic level (Crew and Neugut, 2006; Ferrari and Reis, 2013) are also associated. In Brazil, the estimated population attributable fraction (PAF) for gastric cancer regarding *H. pylori* in 2020 is 56% for both sexes. The combined PAF for non-cardia gastric cancer ranges from 88.0% in males to 83.6% in females; and for cardia gastric cancer PAF is 65.5% in males and 62.2% in females (Azevedo e Silva et al., 2016).

Our aim was to describe the incidence, mortality, trends and age-period-cohort of gastric cancer in three cities from different regions of Brazil: São Paulo (Southeast), Belem (North) and Fortaleza (Northeast). Mortality for gastric cancer in Brazil overall and by region was described.

Materials and Methods

Incident cases of gastric cancer were obtained from the Population Based Cancer Registries available at Brazilian National Cancer Institute Website (http://www2. inca.gov.br/wps/wcm/connect/estatisticas/site/home/ rcbp) for the three cities: Belem [Belem and Ananindeua cities] (1996-2010), Fortaleza (1990-2006) and Sao Paulo (1997-2012). Data was extracted for both gender, aged >20 years old. Death for gastric cancer (C16 stomach, ICD-10) were obtained from the Mortality Information System (http://www2.datasus.gov.br/DATASUS/index. php?area=0205&id=6937) for these cities; deaths for Brazil overall and regions for the period 1996-2012.

Sao Paulo, Belem and Fortaleza concentrate 8% of the Brazilian population, with approximately 15 million inhabitants, evidencing the importance of these cities for the description of the epidemiology of gastric adenocarcinoma (Brazilian Institute of Geography and Statistics, 2015).

Gastric adenocarcinoma cancer classification (Fritz et al., 2000) was classified according to Lauren (Lauren, 1965; Hu et al., 2012). Incident cases were stratified by gender, age group (20-49, 50-69, and 70+), topographies were grouped as proximal (C16.0-C16.6), distal (C16.3-C16.4) and stomach (NOS) (C16.8-C16.9) (Fritz et al., 2000). Descriptive analysis was carried out for all incidence data.

Population distribution for the studied cities was obtained from the Brazilian Institute of Geography and Statistics Census (2010), for ages 20 to 70 plus, it was composed of 8,074,610 inhabitants in São Paulo, 1,674,350 inhabitants in Fortaleza and 1,246,387 inhabitants in Belem, (http://tabnet.datasus.gov.br/cgi/ tabcgi.exe?ibge/cnv/popuf.def), for the calculation of incidence and mortality rates. Age standardized rates (smoothed for 3 years) were calculated using SEGI's world standard population (1966) (Doll et al., 1966).

Trends in incidence and mortality were calculated through a linear regression model within software Joinpoint Regression, version 4.5.0.0 (May, 2017) (Kim et al., 2000).

The effects of age, period and birth cohort on incidence and mortality rates for gastric cancer were estimated by the age-period-cohort model. This model is applied as temporal trends are usually subjected to effects regarding the age of the individual, date of diagnosis or death (period) and year of birth (cohort) (Holford, 1991). The models were estimated for incidence and mortality, according to gender. All individuals aged over 20 years old were included in analyses and the age groups comprehended five-year intervals (20-24, 25-29, ..., 80 years old or over), resulting in 13 age groups. The period was grouped in five-year intervals, totaling three periods. Cohort was calculated by the difference between the occurrence year (new case or death) and the age, yielding 15 cohorts. Estimation of the relative risk (RR=1) considered the median cohort as reference (most stable cohort). The four models (age, age-cohort, age-period and age-period-cohort) were compared and the statistically significant results were those with p-values <0.05. Calculations were carried out using the Epi (version 2.19) (Carstensen et al., 2017) package of software R (version 2.12.2).

Results

The overall number of incident cases of gastric cancer in the studied periods were 3,843 in Belem (1996-2010), 3,430 in Fortaleza (1990-2006) and 26,189 in São Paulo (1997-2012), it accounts 33,462 cases. The number of deaths in the cities, for the period 1996-2012, were 3,135 in Belem, 2,862 in Fortaleza and 17,427 in São Paulo.

Gastric cancer was more frequent in males (60%) for the three cities. The most affected age group was 50-69 years old, for both genders. Stomach NOS were most frequent in three cities (79-86%). The intestinal type was most common in Belem and Sao Paulo, while in Fortaleza distribution of diffuse/intestinal types was similar (Table 1).

The highest gastric cancer incidence were in Belem, 69.1/100,000 (2003) in men, 26.7/100,000 (2006) in women. The lowest rates occurred in Fortaleza (Figure 1A, Supplementary Table 1). The highest incidence rates per histological type was to Adenocarcinoma NOS (Supplementary Figure 1).

Increasing incidence trends for adenocarcinoma were identified in the women of Belem 1.8% (CI95%:0.6;3.0) and Fortaleza 1.1% (CI95%:0.7;1.5), while decreasing trends were verified for men and women of Sao Paulo -7.8% (CI95%:-8.1;-7.4) and -6.3% (CI95%:-6.5;-6.0), respectively. Sao Paulo presented the most pronounced decline in the studied period (Figure 1). Women presented increasing incidence trends for the diffuse and intestinal types in Belem and Fortaleza (Supplementary Figure 1).

The highest mortality rates for gastric cancer were in Belem in the 1990's (43.8 in men and 19.2/100,000 in women) (Supplementary Table 1). Fortaleza reported the lowest rates for both sexes. Mortality trends presented significant reductions for both sexes in the cities (Figure

Table 1. Distribution of Gastric Cancer Incident Cases in three Brazilian Cities (Sao Paulo, Fortaleza and Belem), in Adults Aged ≥20 Years Old

Variables	Belem (1996-2010) n=3,843	Fortaleza (1990-2006) n=3,430	Sao Paulo (1997-2012) n=26,189
	n (%)	n (%)	n (%)
Gender			
Male	2,477 (64.5)	2,120 (61.8)	15,730 (60.1)
Female	1,366 (35.5)	1,310 (38.2)	10,459 (39.9)
Age group			
20-49	726 (18.9)	624 (18.2)	4196 (16.0)
50-69	1,765 (45.9)	1,621 (47.3)	11,376 (43.4)
70+	1,352 (35.2)	1,185 (34.5)	10,617 (40.5)
Topography			
Proximal	494 (12.9)	213 (6.2)	2,399 (9.2)
Distal	314 (8.2)	239 (7.0)	1,380 (5.3)
Stomach, NOS	3,035 (79.0)	2,978 (86.8)	22,410 (85.6)
Histological type			
Intestinal	737 (19.2)	566 (16.5)	5,138 (19.6)
Diffuse	449 (11.7)	578 (16.9)	2,081 (7.9)
Undetermined	27 (0.7)	82 (2.4)	390 (1.5)
NOS Adenocarcinoma	1,200 (31.2)	824 (24.0)	11,540 (44.1)
Other morphologies	1,430 (37.2)	1,380 (40.2)	7,040 (26.9)

Source: RCBP/INCA NOS: Not Otherwise Specified

Table 2. Age-Standardized Mortality Rates for Gastric Cancer and Trends in Adults Aged ≥20 Years Old, for Brazil and Regions, by Sex, Smoothed for Three Years, 1996 to 2012

Regions	AMSR*/100,000		AAPC (95%CI)
	1996	2012	
Male			
North	17.3	19.0	0.6 (-0.7;1.9)
Northeast	8.6	12.4	2.3 (1.3;3.4)
Southeast	27.4	16.1	-3.8 (-5.6;-1.9)
South	25.6	18.9	-2.6 (-4.8;-0.3)
Central-West	17.2	13.4	-2.2 (-3.0;-1.3)
Brasil	20.6	15.6	-2.2 (-3.4;-1.0)
Female			
North	9.5	9.0	-0.8 (-2.5;0.9)
Northeast	4.5	6.4	1.9 (0.8;3.0)
Southeast	10.8	7.1	-3.1 (-3.6;-2.6)
South	10.5	7.2	-2.4 (-4.2;-0.7)
Central-West	7.6	6.2	-1.9 (-4.9;1.3)
Brasil	8.8	7.0	-2.1 (-3.5;-0.8)

*Age-standardized mortality rates

1B). In Brazil the highest mortality rates, in both sexes, were observed in Southeast and South regions. Trends in mortality was significant increasing in Northeast region and decreasing in Southeast, South, for both genders

(Table 2).

Age-period-cohort analysis showed a significant increase in incidence in the women of Belem, who were born after the 1960's. In São Paulo the decrease was significant for both sexes, in cohorts born up to 1940. In Belem for both sexes and in São Paulo for men, the complete model (age-period-cohort) was the best adjusted
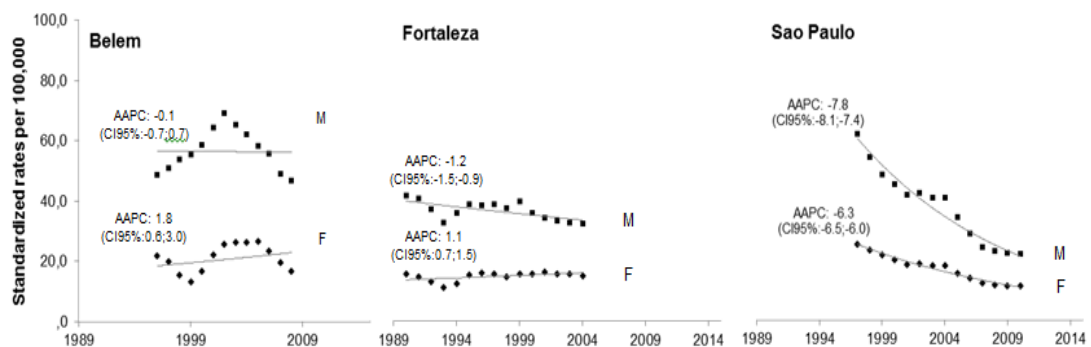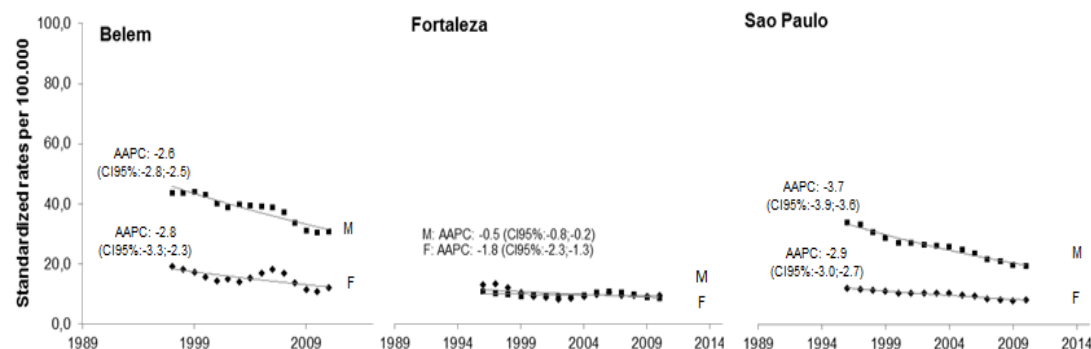

Figure 1. Incidence and Mortality (1996-2012) for Gastric Cancer According to Sex in Adults Aged ≥20 Years Old, in Three Brazilian Cities: Belem (1996-2010), Fortaleza (1990-2006) and Sao Paulo (1997-2012).
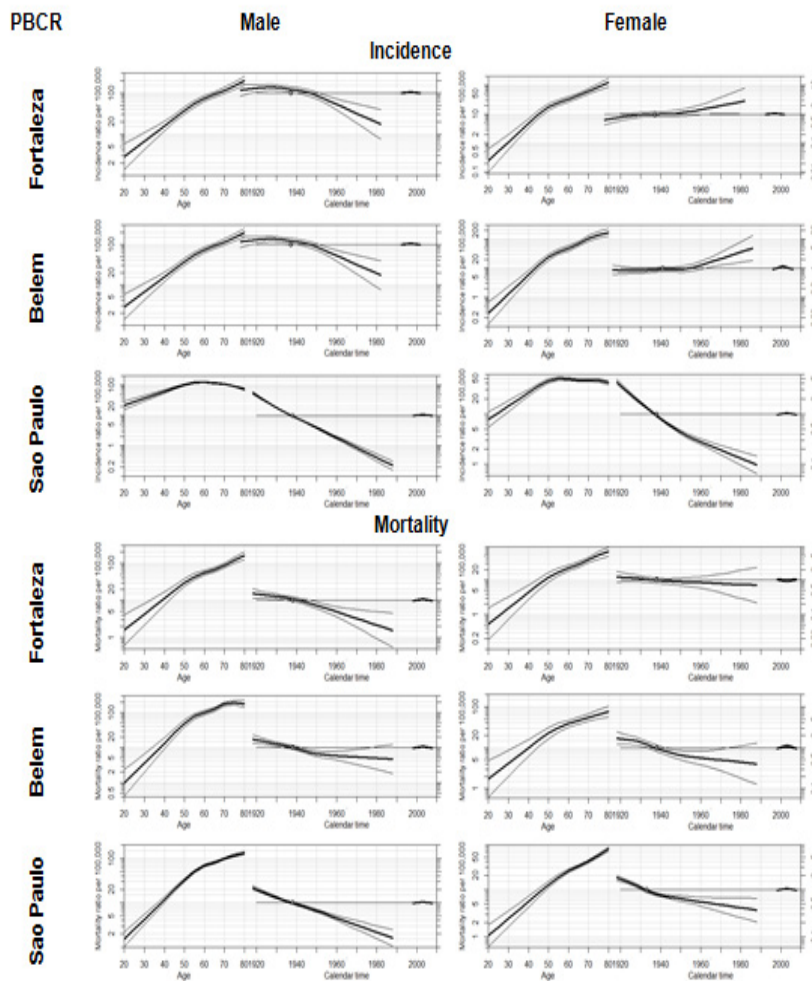
Figure 2. Age, Period, and Cohort Effects on the Incidence and Mortality (1996-2012) of Gastric Cancer by Sex, in Adults Aged ≥20 Years Old, in Three Brazilian Cities: Belem (1996-2010), Fortaleza (1990-2006) and Sao Paulo (1997-2012). Abbreviations: PBCR, population-based cancer registry.

(p<0.001). Regarding mortality, risk of death was higher in both genders, for the three cities. The age-drift model was significant in three cities for men and in Belem for women (p<0.001); in women of São Paulo, the model age-period-cohort (p<0.001) presented the best fit (Figure 2, Supplementary Table 2).

Discussion

The highest incidence of gastric cancer was observed in Belem, which was similar to those reported for Eastern and Western Asia (Luo et al., 2017). The incidence rates of Sao Paulo and Fortaleza were comparable to those of Latin America and European countries such as Italy, Croatia and Slovenia (Ferlay et al., 2015; Ferro et al., 2014; Sierra et al., 2016; Luo et al., 2017).

Incidence rates of Belem were three times higher than the rates for Sao Paulo and two times higher than the rates for Fortaleza (males). The highest incidence rates among men were in Latin American countries (Sierra et al., 2016; Luo et al., 2017). These incidence differences between genders have not been well studied (Song et al., 2015; Luo et al., 2017). Despite the Brazilian disparities, regarding self-declared race as indigenous or Asian Brazilians it varies 1% to 2.3% of the residents (Belem,

Fortaleza and Sao Paulo) (Brazilian Institute of Geography and Statistics, 2015). Therefore, skin color would not be a factor to explain the differences observed herein.

Gastric adenocarcinoma is more common after the fifties year old age however about 20% of the cases occurred for age 20-49. This could be due to early diagnosis or an aggressive carcinogenic effect such as more aggressive *H. Pylori* genotypes. More investigation is need for the young age group risk factors and carcinogenic mechanism (Uemura et al., 2001; Wong et al., 2004; Luo et al., 2017).

Decreasing trends were observed for gastric adenocarcinoma incidence in Sao Paulo (both genders) and for men in Fortaleza. Since the 1950's there has been a decrease in gastric cancer incidence in North America, Europe and more recently, in some Asian and Latin American countries (Ferro et al., 2014; Song et al., 2015; Sierra et al., 2016; Luo et al., 2017). However, the decline in incidence observed in these three Brazilian geographic regions appears to be somehow delayed in comparison with others regions of the world. Reasons for this disparities in declining rates includes a slow socioeconomic transition occurred late in the North and Northeast cities (UNDP, 2013).

In Brazil, the prevalence of *H. pylori* varies between

60% and 95% within the regions (Plummer et al., 2015; Azevedo e Silva et al., 2016). Timely treatment of *H. pylori* infection is essential to reduce the risk of gastric cancer (Choi et al., 2018). The attributable fraction of this carcinogen was 56% for all gastric cancers (Azevedo e Silva et al., 2016). Although there are no studies on the temporal trends of *H. pylori* prevalence in Brazil, improvements in socioeconomic conditions and antibiotic treatments could have contributed to reduce this infection across the country (Guggenheim and Shah, 2013; Herrero et al., 2014). A study on *H. pylori* infection rates in Belem demonstrated this bacterium is involved in the pathophysiology of more severe gastric lesions (de Souza et al., 2014).

In Brazil, the human development index increased by 38% (1980-2014); Sao Paulo has the highest municipal human development index (MHDI) (0.805), followed by Fortaleza (0.754) and Belem (0.746) in 2010 (UNDP, 2013). Decreasing incidence trends in Sao Paulo and Fortaleza, and decreasing mortality for the three cities could be attributed to improvements in socioeconomic levels.

A decrease in the prevalence of smoking has been observed among Brazilians changing from 34.8% in 1989 to 14.7% in 2013 (Monteiro et al., 2007; Malta et al., 2015). The most evident decline in smoking prevalence was observed in the North and Northeast regions, including Belem and Fortaleza, when compared to the decrease verified in the Southeast region (São Paulo) (Malta et al., 2015). Moreover, Brazil presents a high consumption of processed and minimally processed foods, ranging from 2.67% to 5.63% in the Northeast (Marchioni et al., 2011; Levy et al., 2012). The consumption of fruit and vegetables (2008-2009) was 2.84% for Brazil overall; in the North region consumption was 1.82%, for the Northeast 2.59%, while in the Southeast was 3.13%. These disparities in relation to the Amazon region (Belem) could explain the difference in risk across geographic regions (Levy et al., 2012). These risk factors definitely influenced the decrease in gastric cancer incidence and mortality, as described above.

Changes in food preservation processes also occurred (Ferrari and Reis, 2013; Luo et al., 2017). In Brazil, in 1960, only 11% of households had a refrigerator (Brazilian Institute of Geography and Statistics, 2009); however, between 1981-2010 this number increased to 37%, and in 2010, 94% of Brazilian households had refrigerators, meaning that food conservation improved approximately by 95% in the three cities (Brazilian Institute of Geography and Statistics, 2015).

Trend in incidence by Lauren's classification verified that Sao Paulo presented a decline for the intestinal type, while Fortaleza and Belem presented increases for both intestinal and diffuse types. Intestinal and diffuse types are associated with *H. pylori* infection (Shah et al., 2011). However, the intestinal type is more frequent in high-risk populations and is associated with dietary habits and tobacco consumption, while the diffuse type presents a stronger genetic component (You et al., 2000; Ferrari and Reis, 2013; Ferro et al., 2014; Karimi et al., 2014). This result has a limitation due to high percentage of cases

classified as Adenocarcinoma NOS.

Decreasing mortality rates were also verified for the three cities. The differences in mortality trends between the cities could be related to unequal distribution of specialized health services, as the majority of health services are located in the South and Southeast regions (Curado and De Souza, 2014). Despite the mortality decline verified in the world and confirmed for Brazil. Projections for 2017 based on seven Latin American countries evidenced that mortality rates will remain high (Carioli et al., 2017). One of the most important factor for the reduction of gastric cancer mortality was the access to health services, for diagnosis and treatment (Mihmanli et al., 2016). In countries of Asia, such as South Korea (Song et al., 2015) and Japan (Hamashima et al., 2013), mobile screening programs were implemented due to high incidences of gastric cancer and were an important instrument to reduce mortality.

The cities studied covered the North, Northeast and Southeast regions of Brazil and presented heterogeneous incidence and mortality rates and trends for gastric cancer. Increasing risk in a cohort of women born in 60's in amazon area of Brasil was observed. The same findings were described in USA and in Japan for cohorts born since 1950 and in Canada, China, Croatia, Latvia, Russia and Thailand for cohorts born since 1960 (Luo et al., 2017), which suggests the impact of early exposure in these birth cohort s of women.

The limitations of this study concern the quality of the secondary database. The anatomical location of the gastric cancers was based on PBCRs data, it showed that the majority of the lesions has other not specified topography (Ferlay et al., 2015). This is a limitation from the PBCRs in identify the subsite of the tumors. It is recommended that the PBCRs should improve subsite coding for gastric cancer.

Moreover, these results describe the magnitude of gastric cancer in the three studied cities. Differences regarding the histological classification were identified, with most cases being classified as Adenocarcinoma NOS (24% to 44%). The morphological Lauren's classification was therefore limited to incidence data. Differences in mortality trends observed by Regions could be related with the improvement of information in the mortality system.

Incidence of gastric cancer is increasing in women born in the sixties in Belem (Amazon region) and Fortaleza (Northeast region). In Brazil there was increase in mortality in Northeast region and decrease in others regions. More update data on incidence for Amazon and Northeast region is needed.

Acknowledgments

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