Pancreatic Cancer Incidence and Lethality Rates in Brazil

An Ecological Study

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Objectives: To describe incidence and lethality time trends rates of pancreatic cancer (PC) in Brazil.

Methods: Data from Brazilian Health National Public System (SUS) were retrospectively collected with regard to PC from January 2005 to December 2012. Pancreatic cancer incidence and lethality rates were estimated from SUS hospitalizations and in-hospital PC deaths and adjusted to total available hospital beds.

Results: From 2005 to 2012, a total of 36,332 admissions for PC were registered in Brazil. Pancreatic cancer incidence nearly doubled from 2.4/100,000 to 4.5/100,000, particularly among patients older than 70 years, whereas no difference in sex was noted. The greatest incidence rates increase (+109%) occurred in the northeast, a less developed region that has recently achieved significant economic advances. Dynamic changes were observed, notably a shift to increasing PC incidence in rural areas. Lethality rates increased from mean 25% to 27%, the highest rates registered in those 70 years or older.

Conclusions: Overall increase trends in PC incidence and lethality were observed. Pancreatic cancer remains an urban disease in Brazil, the highest incidence found in the most developed regions as in large metropolitan integrated municipalities. Improvement in diagnosis, notification quality, a rapidly aging population, and a great demographic dynamism could in part explain this fact.

Key Words: pancreatic cancer, ecological study, hospitalization rates, lethality rates, time trend analysis

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Cancer figures among the leading causes of morbidity and mortality worldwide, with approximately 14 million new cases and 8.2 million cancer-related deaths in 2012. The number of new cases is expected to rise by approximately 70% for the next 2 decades, in particular in low-income countries.[1] In Brazil, most cases of cancer are diagnosed after the age of 65 years. Estimates of cancer incidence for 2014/2015 biennium in Brazil are approximately 576,000 new cases per year.[2] Pancreatic cancer (PC), although not a highly prevalent cancer, ranks fourth in cancer-related mortality in United States and Europe. In Brazil, PC is the thirteenth most prevalent cancer in men and the tenth most prevalent cancer in women.[3,4] Pancreatic cancer is an aggressive cancer, with a 1-year age-adjusted relative survival of 15% and a 5-year age-adjusted relative survival of only 4%. The survival time is less than 1 year for locally advanced cancer. At the time of diagnosis, 80% to 90% of the tumors are no longer resectable.[5–7]

The incidence of PC increases after the fifth decade of age. Aging is most probably not an independent risk factor but a surrogate of prolonged carcinogen exposure.[8] Increased risk of PC has been associated to hereditary pancreatitis, other inherited cancer syndromes (Peutz-Jeghers syndrome, hereditary breast/ovarian cancer, familial adenomatous polyposis, hereditary nonpolyposis colon cancer/Lynch II syndrome), family history of PC, and nonhereditary chronic pancreatitis. Several environmental factors have been implicated in the risk of PC, including a high saturated fat and meat intake ("western" dietary pattern), obesity, type 2 diabetes, physical inactivity, and, of upmost importance, alcohol and cigarette smoking.[9–14] Cigarette smoking has been recognized as an important risk factor for PC, the magnitude of the association varying among geographic areas.[15,16] Available data suggest that if there is an effect of alcohol consumption, it is limited to heavy drinkers.[17] A meta-analytical study found evidence for a strong association between the risk of PC and tobacco smoking, whereas only a moderate association was found regarding *Helicobacter pylori* infection.[18]

Cancer incidence and mortality patterns have been estimated worldwide. More than 60% of world's new annual cases occur in Africa, Asia, and Central and South America.[1] During the last decade, there has been an overall reduction in cancer-related death in Western Europe and North America, in particular for lung, breast, colorectal, and prostate cancers as well as other tobacco-related neoplasms. With regard to PC, mortality rates have been increasing and trends in the upcoming years and even decades are not favorable.[19,20]

Because little information is available concerning PC in Brazil, this study is proposed in an attempt to evaluate demographic aspects and time trends of PC in Brazil. In particular, the different Brazilian macroregions were taken into account, with focus on the urbanization and conurbation patterns of the 5565 municipalities of this continental country.

MATERIALS AND METHODS

Data Source

Data from the Health Informatics Department of the Brazilian Ministry of Health (DATASUS) from January 2005 to December 2012 (http://www2.datasus.gov.br/DATASUS) were retrospectively searched for patients with an *International Statistical Classification of Diseases and Related Health Problems*, *Tenth Revision* code of PC (*ICD-10* code: C25.0–25.9). The DATASUS is responsible for researching, maintaining, and developing health care systems to support the Brazilian government. The DATASUS collects

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and maintains a population-based health and disease registry that includes hospital admission and discharge information, medical procedures and mortality, reference tables, and vocabulary used in information systems in the whole country. Demographic data (age, sex, municipality) collected by the Instituto Brasileiro de Geografia e Estatística (Brazilian Institute of Geography and Statistics) are also available at the DATASUS Web site. Pancreatic cancer incidence was estimated from hospital discharge medical records and adjusted to available hospital beds. The DATASUS covers approximately the entire Brazilian population, so we assumed that hospital-based registries for PC would truly reflect actual disease numbers.

Study Design, Population, and Variables

An ecological study of PC in Brazil was conducted. Ecological studies are a relatively new area of epidemiology, in which risk factors affecting the health status and the development of diseases in a given population are analyzed geographically and temporally. Registries obtained from the DATASUS from January 2005 to December 2012 were retrospectively searched for hospitalization records of patients with PC classification (*ICD-10* code: 25.0-25.9). The period of study was selected on the basis of the most recent and consistent data available. Relevant data included sex, age, and information of the town of residence at the time of hospital admission and death. Age and sex-standardized rates concerning incidence and lethality (estimated from hospitalizations) were computed. Age groups were stratified as 20 to 49 years, 50 to 69 years, and 70 years or older.

Geographic distribution was the result of individual analysis of pancreatic cancer hospitalization rates per 100,000 inhabitants in each municipality of the country. Results from this exploratory data analysis were included in a platform to plot maps depicting the estimates and distribution of PC.

Statistical Analysis

Pancreatic cancer hospitalization rates were adjusted to the totality of available hospital beds in Brazil, 2012. Estimates of resident population were obtained from Instituto Brasileiro de Geografia e Estatística projections for 2012. Linear regression was applied to evaluate temporal trends in PC incidence and lethality by sex using Microsoft Excel Software (Microsoft Excel for Mac 2011, Version 14.4.9, 2010; Microsoft Corp, Redmond, Wash). Statistical analysis was performed using statistical software package SPSS for Windows (Version 20; SPSS Inc, Chicago, Ill). Exploratory procedures were applied to the data, and summary descriptive statistics and graphical displays were generated by TabWin 3.2 (DATASUS, Brasília, Brazil) either for all cases or separately for groups of cases.

RESULTS

Hospitalizations for PC

Pancreatic cancer incidence in Brazil, estimated from hospitalizations, nearly doubled from 3331 cases in 2005 to 6284 cases in 2012 (see Supplemental Table 1, http://links.lww.com/MPA/A570 that shows the number of PC cases, deaths, and fatality rates from 2005 to 2012).

During the study period, the overall age-standardized incidence rates for PC per 100,000 inhabitants increased from 2.5 to 4.7 in men and from 2.4 to 4.3 in women. Incidence rates by sex were similar, slightly higher in men than in women. The male/female incidence ratio was 1.04:1, men accounting for 51% of cases (Fig. 1).

The observed increase of 87% in PC-adjusted estimated incidence rate in Brazil does not correspond to the number of hospital beds all over the country. On the contrary, from 2005 to 2012, the total number of hospital beds decreased from 499,120 to 456,164 (8.61%). In the same period, Brazilian Health National Public System (SUS) hospital beds decreased from 375,664 to 327,722 (12.76%; see Supplemental Table 2, http://links.lww.com/MPA/A570 that demonstrates number and distribution of hospital beds in Brazil, from 2005 to 2012).

Estimated PC incidence was lowest for people aged 20 to 49 years (<1.7/100,000 in 2012), intermediate for those aged 50 to 69 years (17.03/100,000 and 13.6/100,000 for men and women, respectively, in 2012), and much higher for those 70 years or older (31.68/100,000 and 35.18/100,000 for men and women, respectively, in 2012; Fig. 2).

Lethality Rates From PC

Pancreatic cancer lethality estimated from in-hospital deaths registered in DATASUS from 2005 to 2012 increased in both sexes in a similar way. In men, PC lethality was 26% in 2005, peaked 28% in 2009, 29% in 2011, and 27% in 2012. In women, lethality was 24% in 2005, peaked 29% in 2009 and 2011, and was 27% in 2012 (Fig. 3).

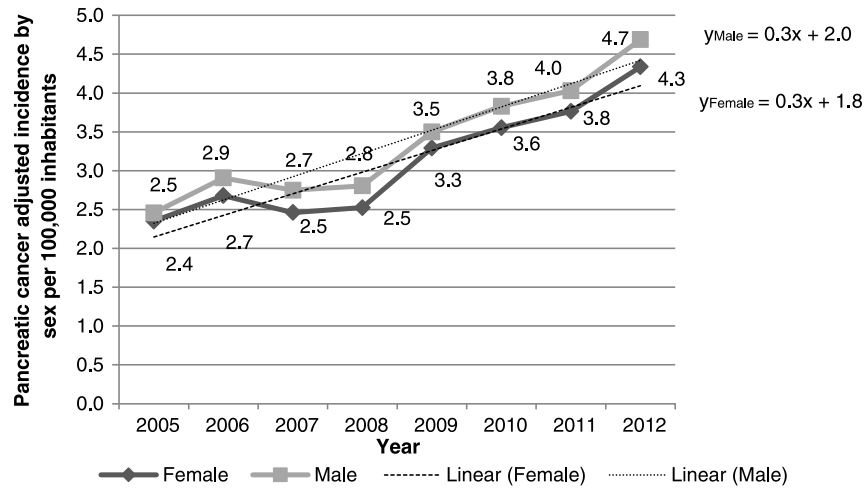

FIGURE 1. Pancreatic cancer incidence by sex, estimated from hospitalizations in Brazil from 2005 to 2012.

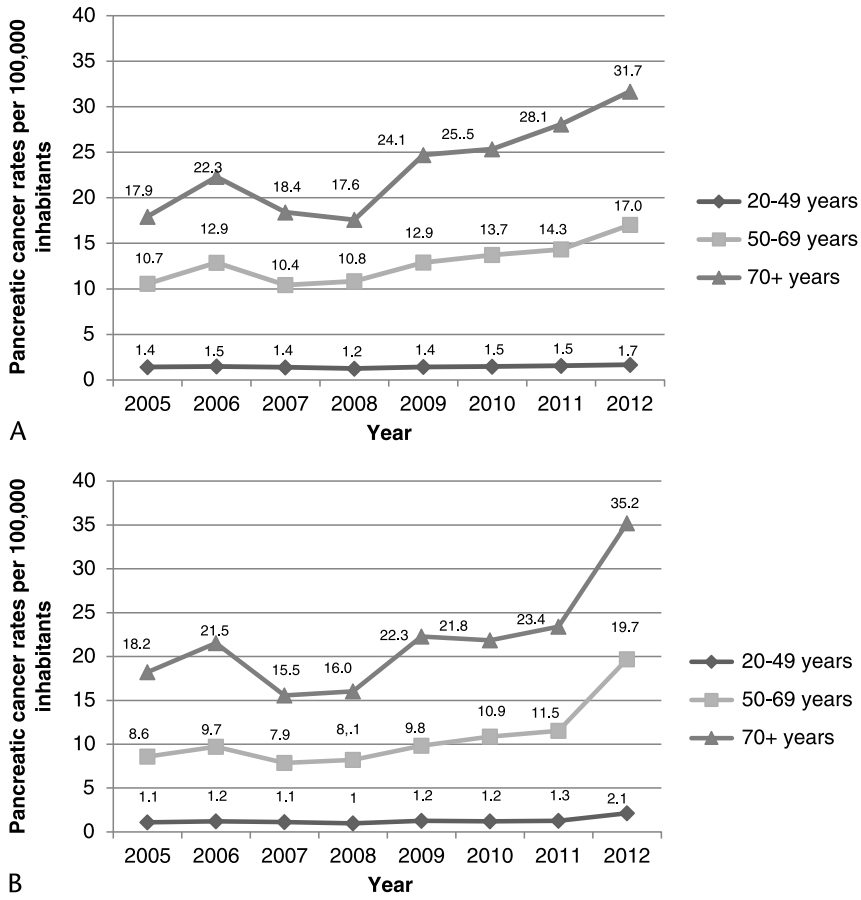

FIGURE 2. Age-standardized PC incidence by sex, estimated from hospitalizations in Brazil from 2005 to 2012, males (A) and females (B).

In-hospital lethality rates were not affected by sex but otherwise increased in proportion to age. For patients from 20 to 49 years, lethality was 21% or less in both sexes. Lethality of patients aged 50 to 69 years ranged from 26% to 30% in males and 18% to 29% in females. The highest lethality rates were registered in those 70 years or older. Throughout 2005 to 2012, there was a +13% change in lethality for age of 20 to 49 years, +1% for age of 50 to 69 years, and +12% for 70 years or older (Fig. 4, Table 1).

Geographic Distribution of PC

The corresponding figures for geographic distribution of PC incidence and lethality resulted from database analysis collected from DATASUS, which included patients' residence address. By the time of the study, all 5565 municipalities distributed in 27 federative units and gathered in 5 macroregions (north, northeast, southeast, south, and central west) were considered (see Supplemental

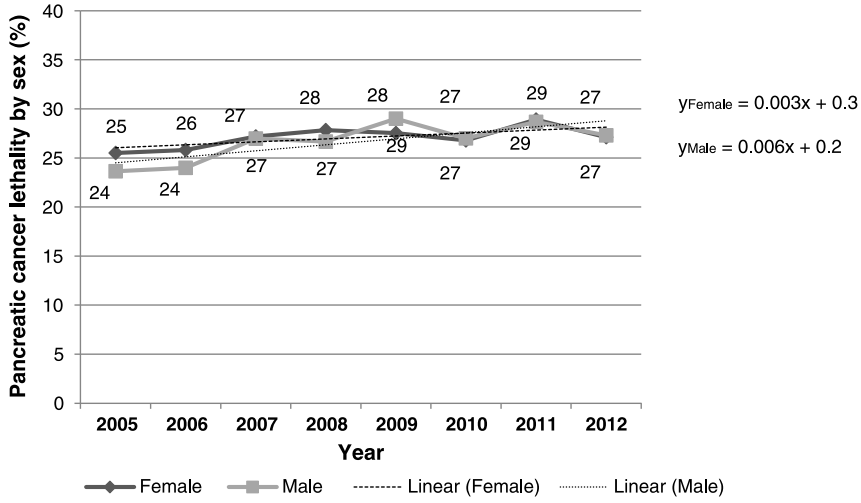

FIGURE 3. Pancreatic cancer lethality rates (%) by sex estimated from in-hospital deaths in Brazil from 2005 to 2012.

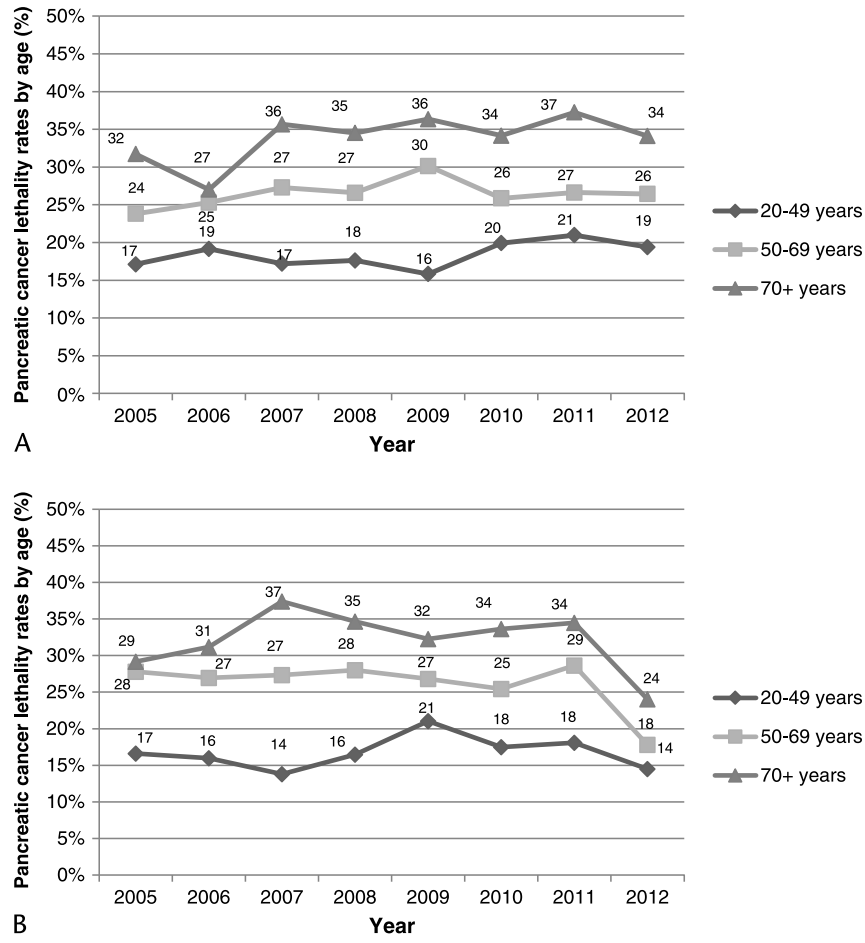

FIGURE 4. Age-standardized PC lethality rates (%) by sex, estimated from in-hospital deaths in Brazil from 2005 to 2012, males (A) and females (B).

Table 3, http://links.lww.com/MPA/A570 that shows the distribution of PC hospitalization rates and lethality in 2005 and 2012 by region, federal unity, and capital).

Throughout the study period (2005–2012), there was an 87% increase in PC-estimated rates in Brazil. This increase was mainly driven by people aged 50 to 69 years (+59.87%) and those 70 years or older (+52.49%). Year after year, estimated incidence was highest in the south (4.0/100,000 in 2005, 7.9/100,000 in 2012) and southeast regions (3.1/100,000 in 2005, 5.6/100,000 in 2012), the most developed country regions, followed by central west, northeast, and north regions (see Supplemental Table 4, http://links.lww.com/MPA/A570).

Based on 2005 data, of the top 10 state capitals with the highest PC incidence rate, 6 are located in the south or southeast. The same pattern was noted in 2012, because 6 of the top 10 capital cities with the highest PC incidence are also located in the south or southeast. Florianópolis and Porto Alegre, both in the south region, were the capitals with the highest estimated rates in 2005. Vitória (in the Southeast) and Porto Alegre (in the South) showed the highest estimated rates in 2012.

South to north incidence rates ratios were greater than 4/100,000 either in 2005 or in 2012. Nevertheless, changes in estimated incidences displayed a different pattern: there was an increase of 109% in the northeast, 98% in the south, 82% in the southeast, 79% in the north, and 76% in the central west regions. Of the 5 cities with the greatest changes in estimated incidence, the following 4 are located in the northeast region: Aracajú (+1,414 %), Natal (+505%), Recife (+288%), and Salvador (+206%).

Geographic analysis of PC-estimated incidence showed higher number of cases in more industrialized and populated municipalities. Pancreatic cancer incidence rates in the capital cities were compared with the general incidence of PC in each Brazilian federal unit (states). Despite that most of the population does not congregate in capitals, PC incidence is higher in almost all capitals. Main exceptions are the states of São Paulo (southeast) as well as Paraná and Santa Catarina (south). These federal units are

TABLE 1. Age-Adjusted Estimated Incidence and Lethality Rates From PC in Brazil and Corresponding Changes in Rates From 2005 to 2012

Rates	Age, y	2005	2012	Changes in Rates, %
Hospitalization, per 100,000	20–49	1.3	1.6	+27
	50–69	9.5	15.2	+60
	≥70	18.1	27.6	+53
Lethality, %	20–49	17	19	+13
	50–69	25.7	26	+1
	≥70	30	34	+12

TABLE 2. Distribution of PC Hospitalization and Lethality Rates in 2005 and 2012 According to Urban and Rural Demographic Data

	2005				2012					
Municipalities	Admission Rates, per 100,000	Population	Adjusted Admission Rates, per 100,000	Lethality, %	Admission Rates, per 100,000	Population	Adjusted Admission Rates, per 100,000	Lethality, %	Changes in Adjusted Admission Rates, %	Changes in Lethality, %
Integrated to metropolitan regions	**2.1**	**91,248,203**	**2.8**	**24**	**3.5**	**95,987,211**	**4.9**	**28**	**74**	**17**
Small	1.9	4,542,857	2.5	19	3.0	4,786,640	4.2	35	65	84
Medium	1.4	9,013,588	1.9	23	2.9	9,802,273	4.0	25	112	9
Large	2.2	77,691,758	2.9	25	3.6	81,398,298	5.0	28	70	12
Not integrated to metropolitan regions	**1.6**	**92,934,991**	**2.1**	**25**	**3.0**	**97,988,512**	**4.2**	**26**	**95**	**4**
Small	1.3	46,661,002	1.7	22	2.5	48,582,072	3.5	22	105	0
Medium	1.4	22,965,072	1.8	29	2.7	24,419,912	4.0	27	120	−7
Large	2.3	23,308,917	3.0	25	4.3	24,986,528	6.0	30	98	20

among the most urbanized and industrialized in Brazil. Of utmost importance, many municipalities in these states show comparatively high Human Development Index (HDI, see Supplemental Table 5, http://links.lww.com/MPA/A570 that shows the capital/federative unit (state) rates ratio of PC in Brazil, 2012).

Taking into account huge economic and demographic disparities present in such a large and unequal country, PC-estimated incidence and lethality rates were reviewed on the basis of demographic and commuting patterns of Brazilian municipalities. A model that classifies municipalities considering the population and demographic density was used in this study. According to this model, municipalities are classified as rural small (<50,000 inhabitants or <80 inhabitants/km), rural medium (≥50,000 inhabitants or ≥80 inhabitants/km, even if the population is <50,000 inhabitants), and true urban centers (>100,000 inhabitants).[21] To analyze the trend of Brazilian population to congregate in large urban centers (associated with the economic opportunities), PC incidence and lethality rates data were collected taking into account municipalities size and relation to metropolitan regions. Large municipalities comprise 85% of metropolitan integrated population. Metropolitan integrated municipalities had the highest PC-adjusted incidence rates, both in 2005 as 2012 (2.8 and 4.9, respectively), mainly the large municipalities (2.9 and 5.0, respectively). These rates are higher than the country average rates (2.4 and 4.5, respectively). Nonintegrated metropolitan municipalities PC-adjusted incidence rates were 2.1 in 2005 and 4.2 in 2012. Pancreatic cancer lethality rates increased 17% in metropolitan integrated municipalities from 2005 to 2012 (24%–28%) and 4% (25–26%) in metropolitan nonintegrated municipalities (Table 2).

Municipalities' hospitalization rates and in-hospital death rates for PC were calculated per 100,000 inhabitants and plotted in maps (2005 and 2012, respectively), shown in Figures 5 and 6. Standardized rates defined 3 ranges for hospitalization rates (<5/100,000, 5–15/100,000, and >15/100,000) and 4 ranges for lethality rates (<25%, 25%–49%, 50%–75%, and >75%).

DISCUSSION

This study, the first one to consider Brazilian nationwide PC data, retrospectively collected from the Health Informatics Department of the Brazilian Ministry of Health (DATASUS) from January 2005 to December 2012, pointed to an 87% increase in PC-estimated

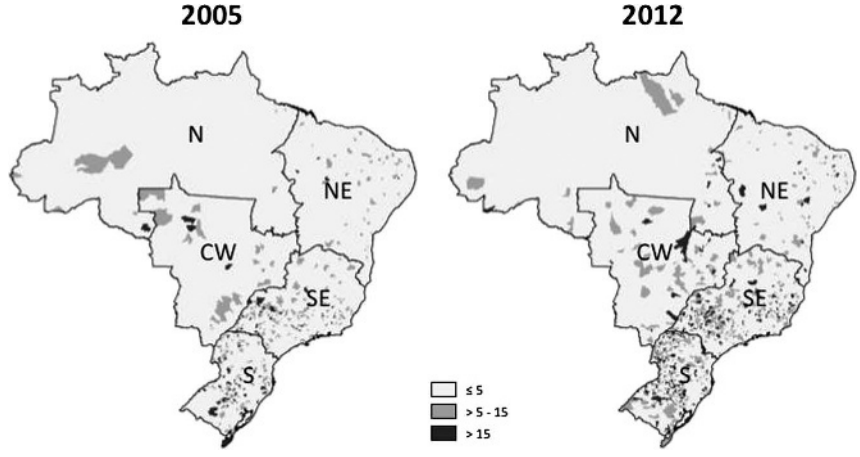

FIGURE 5. Geographic distribution of PC in Brazil according to the municipal hospitalization rates (per 100,000 inhabitants) in 2005 and 2012. Standardized rates defined the following 3 ranges: <5, 5–15, and >15.

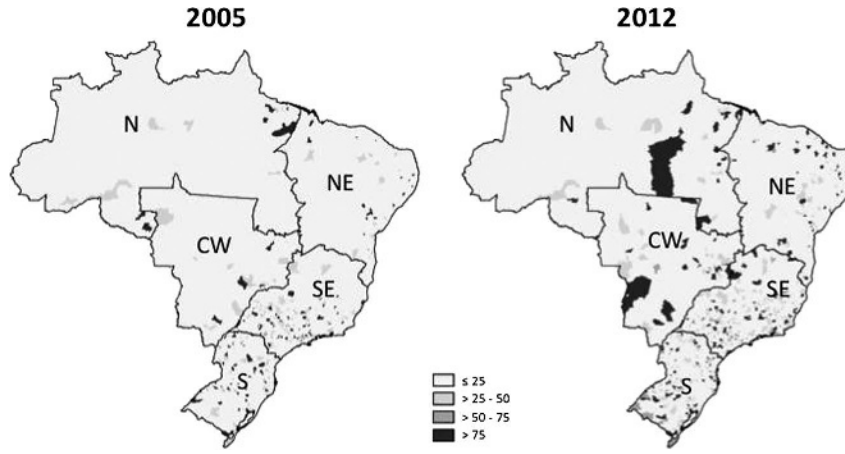

FIGURE 6. Geographic distribution of pancreas cancer lethality in Brazil according to municipal rates of in-hospital deaths in 2005 and 2012. Standardized rates defined the following 4 ranges: <25%, 25%–49.9%, 50%–75%, and >75%. CW indicates central west; N, north; NE, northeast; S, south; SE, southeast.

incidence rates in Brazil, whereas the lethality rates increased modestly. Although there are large differences in PC incidence and mortality among countries,[22] other studies showed unfavorable trends for PC, incidence, and mortality rates increasing especially in more recent years.[3,23]

Regarded as a highly aggressive cancer, PC poses many difficulties in diagnosis. Most of the cases worldwide have not been histologically confirmed, and diagnostic accuracy varies among countries, being probably lower in poorer and middle- or low-income areas of the world. Pancreatic cancer rates are higher in high-income areas, intermediate in South and Central America and Eastern Asia, and lower in low-income areas.[24,25]

Pancreatic cancer mortality has shown different trends from all-cancer mortality during the last decades. Mortality predictions for 2013 and 2014 in the European Union estimated all-cancer age-standardized rates to fall, continuing the favorable trends observed since the late 1980s, a 26% fall for men and 20% for women. Favorable trends have been attributed to early diagnosis, improved efficacy of anticancer treatments, and management of comorbidities.[26] Otherwise, PC mortality has been increasing in American women in recent years[24,27] as in both sexes at all ages in the European Union.[28,29]

Of utmost importance for analysis of PC in Brazil are the actual differences and observed changes in Brazilian demographic pattern, the result of continuous urbanization and industrialization process in the last decades. Brazil is a continental and polarized country. There are huge demographic and development inequalities among the 5565 municipalities and regions, the large metropolitan municipalities and highest development indices associated with the south and southeast regions. Besides adoption of risk factors proper of modern civilizations (as smoking pattern and dietary changes),[2] other factors could explain the increase in PC rates in Brazil: the aging population, the improvement observed in the HDI, and the Human Inequality Coefficient.[30–32]

Risk factors for PC in Brazil are apparently similar to those present in other countries. Tobacco remains the single most important determinant for cancer mortality as is the main recognized risk factor for PC.[28,29] The frequency of smoking in Brazil is 11.3%, versus 17.8% in United States in 2013,[33] higher in men (14.4%) than in women (8.6%).[34] Although smoking in Brazil has dropped 28% in the last 8 years, huge metropolises in the most developed regions, such as Porto Alegre, Florianópolis, São Paulo, and Rio de Janeiro, display the highest smoking frequency[34] and are among the municipalities with the highest rates of PC in Brazil. As in other countries, the prevalence rates of other risk factors (obesity, diabetes) along with improvement in diagnosis, mainly in large cities, are likely contributing to the increases in PC incidence observed in this study.[27] The results of this study are in accordance with international data that correlates the increase in PC rates with age. Brazil, like other developing countries, is dealing with a rapidly growing aging population. Brazil has the sixth largest population of elderly people in the world, which corresponds to 8% of the general population, an increase of 500% in 40 years and a forecast of there being 32 million people 60 years or older by 2020.[35]

In agreement with the results of this study, the south and southeast macroregions were previously shown to have the highest frequency of cancer cases.[2,36] In a similar investigation carried out by our group, the results of an ecological study of gastric cancer in Brazil (2005–2008) also pointed that the south and southeast regions had the highest rates of gastric cancer incidence estimated from hospitalizations, twice the rates registered in the north and northeast regions, the lowest in the country.[37] Regarding PC incidence rates, they are also remarkably higher in metropolitan integrated municipalities, mainly the large ones, reinforcing the importance of economic and social boundaries of metropolitan areas and its relation to public health policies.[38–40]

Of note, when analyzing time trends of PC rates in Brazilian regions in light of HDI and social vulnerability indices (SVI) from 2000 to 2010, the highest PC rates are observed in areas with the highest level of economic development, which also presents the highest HDI and the lowest SVI. Although PC rates in Brazil were higher in the south and southeast regions, the greatest incidence rates increase in the period occurred in the northeast region (+109%). A relative increase in cases of gastric cancer in the northeast region was also present in the referred ecological study of gastric cancer in Brazil.[37] Some hypothesis could support this observation. Although social development indices identify multiple deprivations in the north and northeast regions, Brazil's HDI increased 36.4% in the last decades and 5.24% during this study period[31] and SVI decreased 27% between 2000 and 2010 in Brazil as a whole.[32] Of main importance, the northeast region has achieved the greatest economic advances in the last few years. The northeast gross domestic product increased 3% in 2012, more than the triple average of the country.[41] Difficult access to healthcare and poverty usually go together and continue to represent an important problem in the northeastern of Brazil, but perhaps, the economic improvement

allied to social development allowed better access and quality of registries in health units.

As in other developing countries, the burden of PC in Brazil is increasing. Although several risk factors for PC can be listed, mainly tobacco smoking, obesity, and diabetes mellitus, there are other potential environment and lifestyle factors that could influence the geographical differences of PC incidence in Brazil. In China, population-based cancer registries data indicate more pronounced incidence-increasing trends in rural areas.[42] Likewise, the increasing trend of PC incidence in Brazil is more significant in municipalities not integrated to metropolitan areas compared with those integrated to metropolitan areas. The greatest shift in incidence rates was noted in medium municipalities, either metropolitan integrated or nonintegrated (+112% and +120%, respectively). The differential occurrence of PC in urban versus rural (and coast to in-land) municipalities could raise challenging questions about factors linked to geographical, economical, and demographics differences.

Strengths of this study include the use of National Health Informatics Database (DATASUS), which allowed collecting PC data from all Brazilian municipalities and time trends analysis of PC in Brazil for the first time. However, precision and quality of the registries may be prejudiced. Differences in availability and quality of health care in less developed areas of the country are the most likely explanations for these observations. In spite of the potential limitations, this study might allow the first insight on PC behavior and time trends in Brazil.

In conclusion, PC is a predominantly urban disease with unfavorable trends observed between 2005 and 2012, in Brazil. Among the factors involved, some possible explanations are earlier access to healthcare units, improvement of diagnostic methods and notification quality, along with the phenomenon of a rapidly aging population. Dynamic changes were observed during the period analyzed in this study, notably a shift to increasing PC incidence trends in rural areas, which are largely unexplainable by known risk factors but could be related to greater demographic dynamics in medium cities. The PC negative outlook as a whole for both sexes and ages as its mortality rates strongly suggests that PC will remain a social and economic burden and a critical health problem in Brazil.

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