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## CLINICAL SCIENCE

# Disparities in female breast cancer mortality rates in Brazil between 1980 and 2009

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**OBJECTIVE:** To describe the temporal trends in female breast cancer mortality rates in Brazil in its macro-regions and states between 1980 and 2009.

**METHODS:** This was an ecological time-series study using data on breast cancer deaths registered in the Mortality Data System (SIM/WHO) and census data on the resident population collected by the Brazilian Institute of Geography and Statistics (IBGE/WHO). Joinpoint regression analyses were used to identify the significant changes in trends and to estimate the annual percentage change (APC) in mortality rates.

**RESULTS:** Female breast cancer mortality rates in Brazil tended to stabilize from 1994 onward (APC=0.4%). Considering the Brazilian macro-regions, the annual mortality rates decreased in the Southeast, stabilized in the South and increased in the Northeast, North, and Midwest. Only the states of Sao Paulo (APC=-1.9%), Rio Grande do Sul (APC=-0.8%) and Rio de Janeiro (APC=-0.6%) presented a significant decline in mortality rates. The greatest increases were found in Maranhao (APC= 12%), Paraiba (APC= 11.9%), and Piaui (APC= 10.9%).

**CONCLUSION:** Although there has been a trend toward stabilization in female breast cancer mortality rates in Brazil, when the mortality rate of each macro-region and state is analyzed individually, considerable inequalities are found, with rate decline or stabilization in states with higher socioeconomic levels and a substantial increase in those with lower socioeconomic levels.

**KEYWORDS:** Breast Cancer; Mortality; Trends; Brazil.

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## INTRODUCTION

Breast cancer is the principal cause of cancer deaths in women worldwide (1-2). The patterns of mortality rates generally follow the incidence patterns of the disease (3). The trend in breast cancer incidence and mortality rates has remained stable or declined in some developed countries (1,4,5), largely as a result of a reduction in the use of menopausal hormone therapy (6), early detection through mammography screening, and advances in the treatment of the disease (1,2). However, breast cancer incidence and mortality have been increasing rapidly among women in many of the countries of Eastern Europe, Asia, and Latin America and some African countries (1,2).

The incidence of breast cancer is directly associated with older age groups (7,8). The Brazilian population is currently

undergoing an accelerated aging process, with changes in the epidemiological profile of the population reflecting the slower growth rate in the number of children and adolescents together with an increase in the economically active population and the elderly (9).

As a developing country with an emerging economy, the pattern of breast cancer in Brazil has been changing, and an increase in incidence has been reported (10). The estimated number of new cases for 2012 is 52,680, with a risk of 52 cases for every 100,000 women (10). This transition, however, is occurring in an extremely unbalanced manner, which is, to a large extent, associated with the different social conditions present within the country (11). In the Southeast region, breast cancer is the most common type of malignancy in women, with an estimated risk of 69 new cases per 100,000 women, followed by the South (65/100,000), the Midwest (47/100,000), and the Northeast (32/100,000). In the North region, it is the second most common form of cancer in women, with an incidence of 19/100,000 (10).

In the last decade, opportunistic breast cancer screening in some areas of Brazil and the use of mammography (12,13)

have allowed the reduction of local advanced diseased and an increase in early breast cancer detection (14). However, as of 2004, this modification in the pattern of diagnosis had not affected breast cancer mortality (15,16), morbidity, or quality of life, considering different types of surgical treatment (17).

The continental dimensions of this vast country (9) and large social and economic disparities might play a role in breast cancer mortality. However, to date, this question has not been addressed, limiting the understanding of the impact of the disease and not allowing for a better use and allocation of resources according to the needs of each individual state. Therefore, the objectives of the present study were to analyze female breast cancer mortality trends in Brazil considering individual macro-regions and states for the 1980-2009 period.

## METHODS

### Study design

This is an ecological time-series study conducted by collecting data on the number of deaths due to female breast cancer in Brazil between 1980 and 2009. Because this study was carried out using secondary open data, there was no need for Ethics Committee approval.

### Brazilian macro-regions and states

Brazil encompasses a total area of 8,514,876 km<sup>2</sup> in South America and consists of 27 states in five geographical macro-regions: the South, Southeast, Midwest, North, and Northeast (9). The total population in 2009 was approximately 191 million inhabitants, and the population density was 22.5 people/km<sup>2</sup>.

The South region, consisting of the states of Parana, Santa Catarina and Rio Grande do Sul, comprises 15% of the country's population and has the highest human development index (HDI). The Southeast region is composed of the states of Sao Paulo, Minas Gerais, Rio de Janeiro, and Espirito Santo and is the most populous (42%) and most affluent region of Brazil. The states of Mato Grosso, Mato Grosso do Sul, and Goias and the Federal District, where Brasilia, the capital of the country, is situated, constitute the Midwest. This is the least populated region (7%), with the second lowest population density in the country. The North region, which is the least densely populated, consists of the states of Acre, Amapa, Amazonas, Para, Rondonia, Roraima, and Tocantins. This region includes 45% of the total area of Brazil and 8% of its total population. The Northeast region is made up of the states of Bahia, Alagoas, Ceara, Maranhao, Paraiba, Pernambuco, Piaui, Rio Grande do Norte, and Sergipe. The population of this region represents 29% of the total population of the country, and it is the region with the lowest HDI in Brazil (9).

### Data sources

The number of deaths from female breast cancer in the different Brazilian states and macro-regions and for the country as a whole was obtained from the reports of deaths registered in the Mortality Data System (SIM/WHO) and made available by the DATASUS database (18). The states of Acre, Roraima, and Amapa were excluded from the study because data for the period to be analyzed were missing, while Tocantins was excluded because it only became an independent state in 1989 (9). During this study,

the International Classification of Diseases (ICD) underwent two revisions; therefore, data up to 1996 were based on the ICD-9, and data from 1996 onward were based on the ICD-10. The consolidated mortality data from 1980 to 2008 and preliminary data for 2009 were included in this study.

Data on the resident population, which were obtained from the national censuses conducted in 1980, 1991, and 2000, were extracted from DATASUS. For the intermediate years, population estimates were derived from the National Household Sample Surveys (PNAD), which are conducted annually by the Brazilian Institute of Geography and Statistics IBGE/WHO (18).

### Statistical analysis

Once the data on deaths and the resident population were obtained, age-specific mortality rates, which were classified into seven different age groups (20-29, 30-39, 40-49, 50-59, 60-69, 70-79 and  $\geq 80$  years of age), were calculated, and the age-standardized mortality rates were estimated using an indirect method with the hypothetical world population proposed by Segi (1960) and modified by Doll et al. (1966) as a reference (19).

To identify significant changes in trends, we performed a joinpoint regression analysis with the software provided by the Surveillance Research Program of the US National Cancer Institute (20). With this analysis, it is possible to identify the years in which a significant change in the linear slope of the trend (on a log scale) was detected during the study period (21). The best-fitting points, called "joinpoints", are chosen when the rate changes significantly. The analysis starts with the minimum number of joinpoints (e.g., 0 joinpoints, which is a straight line) and tests whether one joinpoint is significant and must be added to the model. To describe linear trends by period, the estimated annual percentage change (APC) is then computed for each of those trends by fitting a regression line to the natural logarithm of the rates using calendar year as a regressor variable [i.e., given  $y = a + bx$ , where  $y = \ln(\text{rate})$  and  $x = \text{calendar year}$ , the APC is estimated as  $100 \times (e^b - 1)$ ] (20,21).

An increase in mortality rates was considered to have occurred when the trend was toward growth and the minimum value of the confidence interval was  $>0$ . Conversely, a reduction was considered to have occurred when there was a decline in the trend and the maximum value of the confidence interval was  $<0$ . Stability was defined when, regardless of the trend, the confidence interval included zero.

## RESULTS

Between 1980 and 2009, 213,486 cases of death from female breast cancer were registered in Brazil. The standardized mortality rate increased from 9.2 per 100,000 women in 1980 to 11.3 per 100,000 in 2009. A change occurred in the mortality trend in Brazil. Initially, between 1980 and 1994, an annual increase of 1.6% was registered; however, from 1994 onward, the rates tended to stabilize, with an annual increase of 0.4%, as shown in Table 1. The highest mortality rates were found in the South and Southeast regions of the country, with maximum values of 14.6/100,000 women in 1997 and 14.4/100,000 in 1994, respectively. Nevertheless, these were the regions in which the female breast cancer mortality rates

**Table 1 - Female breast cancer mortality trends between 1980 and 2009 in Brazil and the macro-regions of the country.**

Brazil and its macro-regions	Trend 1						Trend 2					
	Period		Mortality Rate		APC	(95% CI; p-value)	Period		Mortality Rate		APC	(95% CI; p-value)
	Initial	Final	Initial	Final			Initial	Final	Initial	Final		
Brazil	1980	1994	9.2	11.7	1.6*	(1.1-2.1; p<0.01)	1994	2009	11.7	11.3	0.4	(-0.1-0.8; p=0.08)
South	1980	1994	10.9	14.4	2.2*	(1.5-3.0; p<0.01)	1994	2009	14.4	12.7	-0.3	(-1.0-0.3; p=0.31)
Southeast	1980	1997	12.3	14.6	1.2*	(0.8-1.6; p<0.01)	1997	2009	14.6	12.6	-0.9*	(-1.6-0.2; p<0.01)
Midwest	1980	2009	5.3	10.4	1.9*	(1.5-2.4; p<0.01)						
North	1980	2009	4.1	6.6	2.4*	(1.9-3.0; p<0.01)						
Northeast	1980	2000	4.2	6.1	2.1*	(1.7-2.5; p<0.01)	2000	2009	6.1	9.0	5.3*	(3.9-6.7; p<0.01)

Standardized mortality rate per 100,000 women.

\*Statistically significant; p<0.05.

tended to decline or stabilize (Table 1). In the South, stabilization occurred from 1994 onwards. In the Southeast, a significant change occurred in the mortality rates in 1997, from an increase of 1.2% between 1980 and 1997 to a decrease of -0.9% between 1997 and 2009.

In the Midwest and North regions, increases in the breast cancer mortality rates in women of 1.9% and 2.4%, respectively, were found during the period analyzed. An increase in mortality was also registered in the Northeast region of the country, with an increase of 2.1% between 1980 and 2000 and 5.3% from 2000 onward.

When female breast cancer mortality trends were analyzed in the different states in Brazil (Table 2), a significant decrease was found in three states: Sao Paulo (-1.9% from 1999 onward), Rio Grande do Sul (-0.8% from 1993 onward),

and Rio de Janeiro (-0.6% from 1994 onward). In all of these states and in the Federal District, the capital of the country, the breast cancer mortality rates for women were higher. The maximum value for Rio de Janeiro was 18.8/100,000 women in 1994, followed by the Federal District (18.4/100,000 in 2006), Rio Grande do Sul (17.1/100,000 in 1993), and São Paulo (16.7/100,000 in 1999) (Figure 1).

In the states of Parana and Santa Catarina and the Federal District, the breast cancer mortality rates stabilized, as shown in Table 2. An increase occurred in the breast cancer mortality rates in women in 17 states, primarily those situated in the Northeast region of the country, particularly the states of Maranhao (APC of 12% from 2002 onward), Paraiba (APC of 11.9% from 2000 onward), and Piaui (APC of 10.9% from 1997 onward).

**Table 2 - Trends in female breast cancer mortality rates between 1980 and 2009 in the states of Brazil.**

States	Trend 1						Trend 2					
	Period		Mortality Rate		APC	(95% CI; p-value)	Period		Mortality Rate		APC	(95% CI; p-value)
	Initial	Final	Initial	Final			Initial	Final	Initial	Final		
Parana	1980	2002	8.3	13.1	2.2*	(1.7-2.8; p<0.01)	2002	2009	13.1	11.8	-1.3	(-4.0-1.6; p=0.35)
Santa Catarina	1980	1998	8.9	12.5	2.1*	(1.4-2.8; p<0.01)	1998	2009	12.5	11.3	-0.6	(-2.0-0.9; p=0.43)
Rio Grande do Sul	1980	1993	13.4	17.1	2.1*	(1.1-3.1; p<0.01)	1993	2009	17.1	13.9	-0.8*	(-1.4- -0.1; p=0.03)
Espirito Santo	1980	2009	6.5	10.3	2.1*	(1.5-2.7; p<0.01)						
Rio de Janeiro	1980	1994	17.0	18.8	1.2*	(0.6-1.8; p<0.01)	1994	2009	18.8	16.3	-0.6*	(-1.1- -0.1; p=0.03)
São Paulo	1980	1999	12.5	16.7	1.2*	(0.9-1.6; p<0.01)	1999	2009	16.7	12.7	-1.9*	(-2.9- -0.9; p<0.01)
Minas Gerais	1980	2009	7.7	9.2	0.7*	(0.4-1.0; p<0.01)						
Goiás	1980	2009	4.1	9.8	2.0*	(1.3-2.6; p<0.01)						
Mato Grosso do Sul	1980	2009	6.3	11.8	2.2*	(1.4-3.1; p<0.01)						
Mato Grosso	1980	2009	2.5	8.9	4.3*	(3.4-5.1; p<0.01)						
Federal District	1980	2006	11.5	18.4	1.1*	(0.4-1.8; p<0.01)	2006	2009	18.4	12.1	-11.0	(-25.9-7.0; p=0.20)
Amazonas	1980	2009	4.3	6.4	2.1*	(1.0-3.2; p<0.01)						
Para	1980	2009	4.6	6.4	1.6*	(0.9-2.4; p<0.01)						
Rondonia	1980	2009	1.3	9.5	4.5*	(2.9-6.2; p<0.01)						
Bahia	1980	2001	4.7	5.7	1.3*	(0.7-1.8; p<0.01)	2001	2009	5.7	7.7	4.4*	(2.0-6.1; p<0.01)
Rio Grande do Norte	1980	1986	3.1	5.4	9.7*	(0.9-19.2; p=0.03)	1986	2009	5.4	9.7	2.3*	(1.2-3.4; p<0.01)
Maranhao	1980	2002	1.2	2.5	3.0*	(1.4-4.7; p<0.01)	2002	2009	2.5	5.8	12.0*	(2.5-22.3; p=0.01)
Piaui	1980	1997	2.2	2.7	0.3	(-2.2-2.8; p=0.80)	1997	2009	2.7	8.5	10.9*	(6.3-15.7; p<0.01)
Paraiba	1980	2000	3.5	3.3	1.6*	(0.4-2.9; p=0.01)	2000	2009	3.3	9.5	11.9*	(7.3-16.7; p<0.01)
Alagoas	1980	1996	5.1	2.6	-1.1	(-2.4-0.2; p=0.08)	1996	2009	2.6	8.7	6.1*	(4.2-8.0; p<0.01)
Sergipe	1980	1983	5.5	2.7	-17.4	(-39.7-12.9; p=0.21)	1983	2009	2.7	12.5	4.2*	(3.0-5.4; p<0.01)
Ceara	1980	2009	3.6	9.9	3.8*	(3.2-4.3; p<0.01)						
Pernambuco	1980	2009	6.2	11.1	2.7*	(2.4-3.1; p<0.01)						

Standardized mortality rate per 100,000 women.

\*Statistically significant; p<0.05.

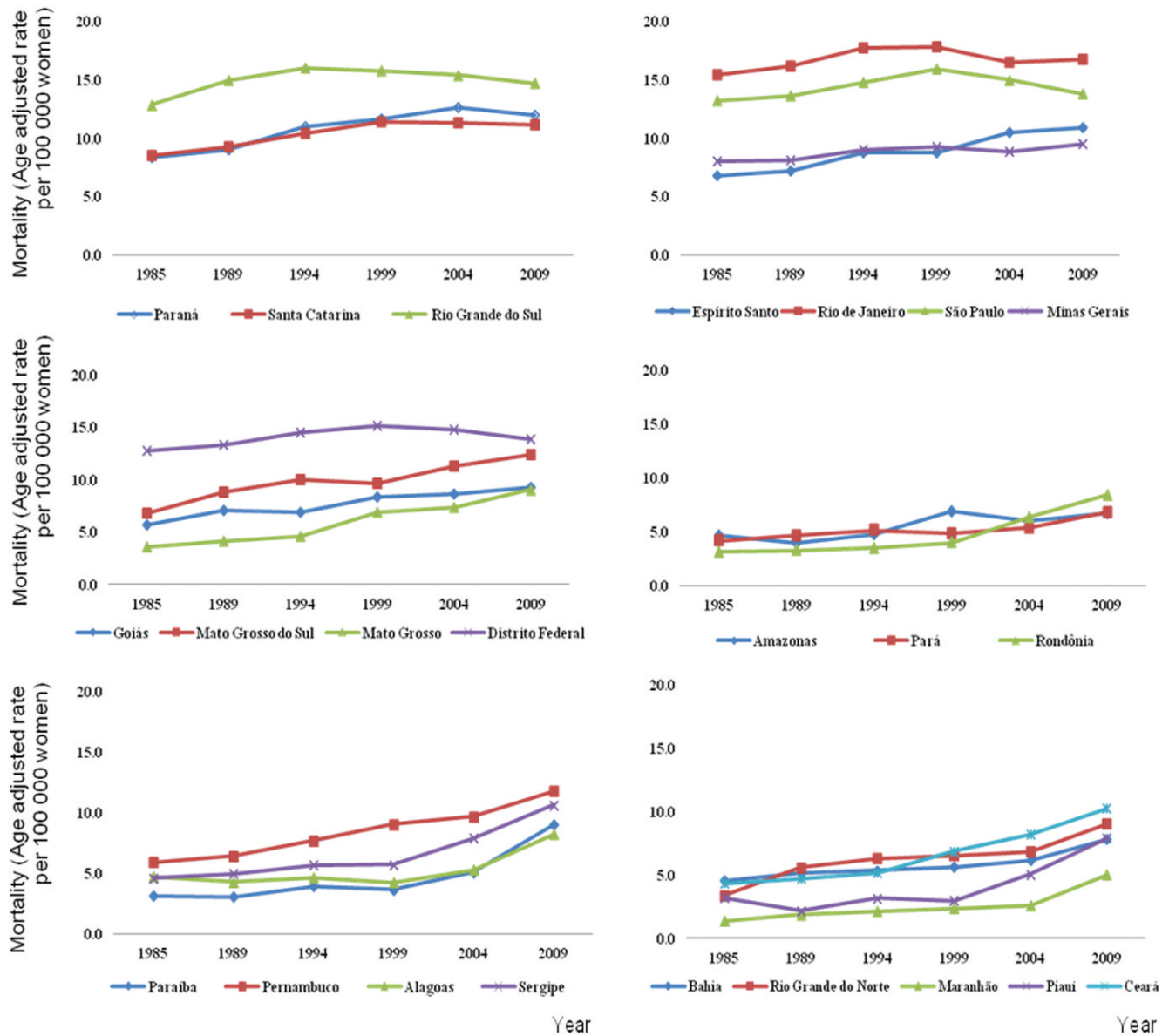


Figure 1 - Female breast cancer mortality rates in the states of Brazil from 1980 to 2009 (5-year average annual mortality rates). The states are grouped in accordance with their macro-regions.

## DISCUSSION

This analysis of the trends in female breast cancer mortality in Brazil reveals a positive pattern in recent years, reflecting a leveling of the rates. These findings contradict the expected patterns for developing, low-income countries (1,2) and differ from some studies that reported an increase in mortality in other periods (4,22). However, the present results correlate with other studies (15,16) in which a general trend toward stabilization was found in breast cancer rates up to 1994, indicating that advances were being achieved in the treatment of breast cancer and the availability of mammography screening programs, resulting in earlier detection (1,5). Despite this supposedly favorable scenario and although breast cancer mortality rates remain constant, considerable increases will occur in the absolute number of deaths as a result of population growth and increased life expectancy because

of the strong association between the risk of cancer and age (23).

The exact number of breast cancer deaths registered in the country as a whole and the North region in particular is unknown due to incomplete notification in some states. Irregularities are known to have occurred in the registration of deaths in the majority of the states in the North region and in some states in the Northeast in 1980 (24). However, a significant improvement was achieved in the quality of reports in 1990, with the coverage of deaths increasing, thus enabling reliable mortality indicators to be produced.

Currently, there are 19 hospital population-based cancer registries in Brazil. Over time, a significant improvement in the quality of mortality data in the country has been noted, which is indicated by the reduction in the deaths classified as "ill-defined causes", mostly from 2005. However, there is still a certain degree of underreporting (10). The database quality in a cancer registry depends on the quality of its

sources and its registration criteria. These methods should follow the international standard so that the worldwide population can be compared consistently (25).

It is crucial that cancer mortality data are standardized, updated, properly recorded, representative of the population, and disseminated in a timely manner as a tool for the epidemiologic surveillance of cancer in the country. In this way, careful interpretation and usage of the estimates are necessary when analyzing time trends. Such an approach is important due to changes in the methodology and the best quality of data over time (10).

As shown, significant regional differences exist in Brazil with respect to female breast cancer mortality rates, reproducing a similar pattern to those observed around the world (1-6). Although the Southeast (the most developed region) generally has the highest mortality rates, when temporal trends are analyzed, a pattern of decline is found, which is in line with trends identified in a large proportion of developed countries over the past 25 years (1,2,5). In the United States, an annual decrease of 2.5% has been observed, with similar findings in various European countries, such as France (-1.4%), Italy (-1.6%), and Germany (-1.5%) (1,2,5). However, the greatest increase (5.3%) was found in the Northeast, a region of medium and low development, in agreement with trends observed in some African and Asian countries, including South Korea and India (2).

Breast cancer is associated with industrialization, and the risk of the disease is related to higher socioeconomic levels, older age groups, low parity, early menarche and late menopause, obesity and alcohol consumption (10,26). Accordingly, the results of the present study show that the risk of dying from female breast cancer in Brazil is at least twofold higher in states such as Sao Paulo, Rio de Janeiro, Rio Grande do Sul and the Federal District, where HDIs are higher, compared with the states of Alagoas, Maranhao and Piaui. Social inequalities regarding the access to and use of healthcare services are also present in this country, as reflected in the different breast cancer mortality trends found within Brazil.

Mammography screening is known to reduce breast cancer mortality rates through early diagnosis (27). In Brazil, mammography coverage is lower in the North and in some states of the Northeast, with coverage levels that range from 64% to 84% (28). According to the National Cancer Institute (INCA), mammography coverage ranges from 37% to 67% (29) in 15 state capital cities and the Federal District, which partially explains the different trends in breast cancer mortality shown in this paper, ranging from a decrease of 0.9% in the Southeast to an increase of 5.3% in the Northeast. These inequalities are even greater when the different states of Brazil are analyzed separately, with values ranging from a decline of 1.9% in Sao Paulo to a substantial increase of 12% in Maranhao.

Due to the immense inequalities between regions in Brazil, the specifications of each individual region need to be considered because they indicate different patterns within the demographic transition. In the South, mortality from breast cancer is higher in Rio Grande do Sul compared with the states of Santa Catarina and Parana, as has also been shown in other studies (10,30), suggesting heterogeneity in the profiles of exposure to risk factors and in lifestyle and genetic factors (30). However, contrary to the results of these previous studies, the present findings suggest stabilization and a decline in breast cancer mortality

in women in the South, principally in Rio Grande do Sul, where a decline of 0.8% has occurred since 1993.

In the Southeast, the mortality rates are higher in Rio de Janeiro and Sao Paulo, confirming data published by INCA (10). However, there was a significant decline in breast cancer mortality in women in the states of Rio de Janeiro and Sao Paulo. The 1.9% decline found in Sao Paulo from 1999 onward is particularly noteworthy and suggests advances in treatment. The Sao Paulo State Health Department, in collaboration with the Women's Health Referral Center, the Department of Breast Diseases of the Federal University of Sao Paulo (UNIFESP) and the Oncocenter Foundation, is developing a strategic plan to reduce breast cancer mortality. This type of action in association with a center for efficient case resolution (CARE) may help provide immediate and individualized treatment (29).

In the Midwest region, the Federal District, the capital of the country, has the highest mortality rates from breast cancer in women compared with Mato Grosso do Sul, Goias, and Mato Grosso, following patterns similar to those found in Sao Paulo, Rio de Janeiro, and Rio Grande do Sul. Nevertheless, the 11% decline in mortality registered over the past four years in the Federal District may be due to advances in the Brazilian National Health System (SUS) (30,31) in addition to regulations and guidelines within the SUS network that prevent the migration of residents from other states. This would explain the steep decline in mortality in the Federal District and justify the increase in mortality rates in recent years in the northeastern states because patients with breast cancer would migrate from the states with poorer healthcare conditions to the Federal District, where the public healthcare network is well established and well developed.

In the North, breast cancer is the second cause of mortality from cancer in women, preceded only by cervical cancer (10). These data show an annual increase of 2.4% in the mortality rate. The profile of the individual states is similar, with increases that range from 4.5% in Rondonia to 1.6% in Para. This vast region is composed of extensive areas of unpopulated territory such as that occupied by the Amazon forest (11); however, it is a region in which the population is increasing rapidly (11). Considering these facts and the unfavorable trend in mortality, breast cancer continues to be of fundamental importance to public health in this region.

Socioeconomic indicators in the Northeast region are precarious (9). In parallel, the greatest increase in female breast cancer mortality was found in this region. An increase of 5.3% occurred between 2000 and 2009, with variation between the states that ranged from a 1.1% decline in Alagoas between 1980 and 1996 (thereafter increasing by 6.1%) to a 12% increase in Maranhao between 2002 and 2009. It is possible that some of these fluctuations may be the result of changes in the practices of codification and registration and modifications to regulations concerning migration within the SUS network because the inverse occurred in the Federal District (30). Nevertheless, in these states, breast cancer mortality was found to follow the patterns expected for developing and less developed regions (1,2). The maximum mortality rates ranged from 5.8 per 100,000 women in Maranhao to 12.5/100,000 in Sergipe.

In 2004, a consensus document was drawn up to promote the early detection of breast cancer in Brazil, with the development of public policies adapted to the reality of the infrastructure in the country (32). The current major

challenge facing Brazil is related to the difficulty encountered by patients in accessing the few centers in the country that specialize in breast cancer treatment. Furthermore, even these centers are often inadequately equipped to provide speedy diagnosis and treatment, resulting in patients migrating from areas in which healthcare is deficient to areas where access is easier, consequently overloading and burdening existing centers (29). In many regions of the country, the distribution of consultations was found to be poor, and access to treatment was difficult for women of lower socioeconomic levels (28,33,34).

The socioeconomic inequalities present in this country are most likely affecting mortality patterns despite the increased knowledge of risk factors for breast cancer, the improvement in mammography screening programs, resulting in the early detection of cases, and the advances achieved in the treatment of the disease (26,35,36). Therefore, although the risk of breast cancer is higher among women living in areas in which socioeconomic conditions are better (35,36), economically deprived women are at an increased risk of dying from breast cancer (36).

### Conclusions and policy implications

Although there has been a trend toward stabilization in the female breast cancer mortality rates in Brazil, when the mortality rate of each state is analyzed individually, considerable inequalities are found, with rate decline or stabilization in states with higher socioeconomic levels and a substantial rate increase in those with lower socioeconomic levels. In the majority of developing states, the mortality rates are increasing. Therefore, female breast cancer mortality should be studied in greater detail in view of the significant changes in the annual percentages, particularly in regions where the level of development is low.

The epidemiological data presented in this study provide further scientific knowledge on the temporal trends of female breast cancer in Brazil in each macro-region of the country and in each state. These data highlight important differences in the pattern of breast cancer mortality in Brazil and, for the first time, show a decline in female breast cancer mortality in some states and macro-regions of the country.

The relevance of these findings lies in the fact that they provide scientific data on which to base future decision making, primarily with respect to the northeast of the country, where the greatest increases in mortality were found. Therefore, although Brazil must be considered as a whole, the priority in terms of primary and secondary preventive actions should be established for the less developed regions of the country.

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### AUTHOR CONTRIBUTIONS

Freitas-Junior R was responsible for manuscript writing and the intellectual and scientific content of the study. Gonzaga CM was responsible for manuscript writing, the methodology applied, and revisions. Freitas NM was responsible for the methodology applied and critical revisions. Martins E was responsible for the statistical analysis. Dardes RC was responsible for the critical revisions.

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