Late-Stage Diagnosis of Breast Cancer in Brazil: Analysis of Data from Hospital-Based Cancer Registries (2000–2012)

Diagnóstico de câncer de mama em estado avançado no Brasil: análise de dados dos registros hospitalares de câncer (2000–2012)

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Abstract

Objective To analyze the time trend and the factors regarding the diagnosis of late-stage breast cancer in Brazil from 2000 to 2012.

Methods We conducted a retrospective cohort study using data from hospital-based cancer registries. Joinpoint regression was used to analyze the time trends of stage at diagnosis. The risk of late-stage presentation was estimated using multinomial logistic regression.

Results A total of 170,757 cases were analyzed. The median time from diagnosis to treatment was of 43 days (range: 0–182 days). The percentage of cases with late-stage diagnosis decreased from 2000 to 2002, with an annual percent change (APC) of -6.6% (95% confidence interval [95%CI]: -7.6–-5.5%); it increased from 2002 until 2009, with an APC of 1.1% (95% CI: 0.9–1.3%), and remained stable up to 2012. Women with college education (compared with illiterate women) had less chance of having a late-stage diagnosis (odds ratio [OR]: 0.32; 95%CI: 0.29–0.35). The odds were greater among brown women (OR: 1.30; 95%CI: 1.21–1.41) and black women (OR: 1.63; 95%CI: 1.47–1.82), compared with white women. The odds were also higher for women treated in facilities located and in the Northern region of Brazil (OR: 1.23; 95%CI: 1.04–1.45) and in the Midwest (OR: 1.61; 95%CI: 1.34–1.94), compared with those treated in the southern region of the country. Age, histological type, and marital status were some of the other factors that were positively related to staging at the diagnosis.

Conclusion Access to diagnosis of breast cancer is uneven in Brazil, and women with lower socioeconomic status present a greater probability of having an advanced stage at diagnosis.

Keywords
- breast neoplasms
- women's health service
- disease registries
- health services accessibility
- oncology

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Resumo

Objetivo Analisar a tendência temporal e os fatores relacionados ao diagnóstico do câncer de mama em estágio avançado no Brasil entre 2000 e 2012.

Métodos Foi feito estudo de tendência temporal e de coorte retrospectiva e com dados do registro hospitalar de câncer. A análise de tendência temporal foi feita usando o modelo de regressão *joinpoint*. A chance de apresentação em estágio avançado foi estimada pelo modelo de regressão logística multinomial.

Resultados Um total de 170.757 casos foram analisados. O tempo médio entre o diagnóstico e o início do tratamento foi de 43 dias (variação: 0–182 dias). O percentual de casos com estadiamento avançado ao diagnóstico diminuiu de 2000 a 2002, com uma variação percentual anual (VPA) de -6,6% (intervalo de confiança de 95% [IC95%] -7,6–-5,5%); esse percentual aumentou entre 2002 e 2009, com um VPA de 1,1% (IC95%: 0,9–1,3%), e se manteve estável de 2009 a 2012. Mulheres com ensino superior (comparadas a analfabetas) apresentaram chance menor de terem doença avançada ao diagnóstico (razão de chances [OP]: 0,32; IC95%: 0,29–0,35). As chances foram maiores entre mulheres pardas (OR: 1,30; IC95%: 1,21–1,41) e negras (OR: 1,63; IC95%: 1,47–1,82) em comparação com as brancas. Mulheres tratadas nas regiões Norte (OR: 1,23; IC95%: 1,04–1,45) e Centro-oeste (OR: 1,61; IC95%: 1,34–1,94) apresentaram maior chance de terem doença avançada ao diagnóstico quando comparadas com as tratadas na região Sul. Outros fatores positivamente associados ao estadiamento no momento do diagnóstico foram: idade, tipo histológico e estado civil.

Conclusão O acesso ao diagnóstico de câncer de mama é desigual no Brasil, e mulheres com nível socioeconômico mais baixo têm uma probabilidade maior de ter uma doença avançada ao diagnóstico.

Palavras-Chave

- neoplasias da mama
- serviços de saúde da mulher
- registros de doenças
- acesso aos serviços de saúde
- oncologia

Introduction

Breast cancer is the most prevalent malignant neoplasm among women worldwide, and according to 2012 estimates, it accounted for 36.3% of all cases of cancer, and for 14.7% of all deaths from cancer in women.[1,2] For 2016, 57,960 new cases of this type of cancer were expected in Brazil, representing 28.1% of all cases of cancer in Brazilian women. The national incidence is estimated at 56.20 cases per 100,000 women, but it rises to 74.30 cases per 100,000 women when the Southern region of Brazil is considered separately.

Breast cancer is the most frequent type of cancer among women in the Southeastern, Midwestern, Southern and Northeastern regions, and the second most frequent type in the Northern region of Brazil.[3] In 2012, the total mortality from breast cancer was estimated at 13,591 deaths nationwide, representing 15.79% of all deaths from cancer that year.[4] Breast cancer mortality rates tend to be higher in developing countries, in part due to late diagnosis and barriers to the initiation of the treatment once the diagnosis is confirmed. The lack of an organized screening program in most of these regions contributes to this gap in mortality rates when compared with more affluent countries.[5]

Even in high-income regions, the mortality rates are higher for ethnic minorities and poorer women. This phenomenon is mediated by stage at diagnosis, and has been reported in several locations, including the United Kingdom and the United States of America.[6,7] A study of mortality trends in Brazil from 1980 to 2010[8] shows a rise in total mortality from breast and cervical cancers as a result of rising rates in the smaller municipalities and in the states of the Northern and Northeastern regions.

In 1998, given the growing importance of cancer as a public health problem, the Brazilian Ministry of Health (MOH) issued order no. 3.535, which specified minimum criteria in order for health facilities to register to provide cancer care in Brazil's unified health system (SUS, in the Portuguese acronym).[8] Since then, a series of measures have been taken to assure comprehensive care for cancer patients in Brazil.

In this context, the ministerial order no. 2.439 is notable; it launched Brazil's national cancer care policy (PNAO, in the Portuguese acronym), emphasizing the importance of prevention, early diagnosis, rehabilitation, palliative care and timely multidisciplinary care for people with cancer.[9]

Hospital cancer registries (HCRs) are one source of information on cancer care that is provided by Brazil's health facilities.[10,11] Designed to gather information from the cases reported by health institutions, HCRs came into operation in the 1960's, and have been increasing in number even since, particularly following the institution of the PNAO, in 2005.[12,13]

Based on the information drawn from the HCRs, the objectives of the present study are to estimate the time interval between diagnosis and treatment, to evaluate the time trend of stage at diagnosis, as well as to analyze the determinants of stage at diagnosis of breast cancer in Brazil from 2000 to 2012.

Methods

Study Design

We performed a time trend analysis and a retrospective cohort study based on secondary data from HCRs in Brazil from 2000 to 2012.

Data Sources

The HCR database contains information on cancer cases treated at the majority of Brazil's health facilities, including 91% of the facilities that are part of the SUS cancer care network.

The information for health facilities nationwide, except for the state of São Paulo (in the Southeastern region), was obtained via the HCR integrator, which is available on the website (https://irhc.inca.gov.br/ RHCNet) of Brazil's National Cancer Institute (INCA, in the Portuguese acronym).

Data for the facilities in São Paulo State were obtained via the website (http://www.fosp.saude.sp.gov.br/publicacoes/acessobancodados) of the São Paulo Oncocentro Foundation (FOSP, in the Portuguese acronym). These websites were accessed for current data on January 21st, 2016.

Study Population

The study population comprised women with a diagnosis of breast cancer (code C50 in the 10th edition of the International Classification of Diseases), aged 18 years or older at the date of the diagnosis, for whom information on the stage at diagnosis was available.

Only cases of invasive tumors confirmed by microscopic examination were considered eligible for the study. All cases of histopathological diagnoses of "in situ" neoplasms and benign or non-invasive tumors were excluded. All cases of sarcomas, lymphomas and neuroendocrine tumors, as well as cases of skin neoplasms of the breast region, were also excluded, because they are entities whose occurrence, diagnosis, risk factors and treatment are different from those of the pathology addressed in this study.

As a way of minimizing the inclusion of duplicate records, the study considered only cases classified as analytical on the HCRs. That selection was necessary because some cases might have been recorded by different institutions (once as analytical and again as non-analytical), and would thus be counted more than once.

Study Variables

Intervals were calculated in days from the date of the diagnosis (date of the histopathology report) to the starting date of the first specific treatment for the disease, as well as from date of the first appointment at the recording institution to the beginning of the treatment. The percentage of cases for which the time from the diagnosis exceeded 60 days was calculated. Cases in which the patient's place of birth differed from the state where the hospital care facility was located were also recorded. That procedure was designed to achieve an approximation to the hypothetical barrier-to-access situation, in which patients have to travel to a location different from their place of residence to seek care.

The study variables also included the following: level of schooling, region of the recording institution, region of birth, occurrence of previous diagnosis and treatment, histological type, stage, treatment accomplishment, age, clinical status at the end of the treatment, exposure to tobacco and alcohol, marital status, and race/skin color.[12]

The patients were classified by disease stage at diagnosis, and they were subsequently separated into three groups according to the international tumor, node and metastasis (TNM) stage classification.[14] In the category called initial disease, we included patients at stages I to IIa; in the category called localized disease, those patients at stages IIb to IIIc were included; and in the advanced disease category, we included those at stage IV. That classification was designed to gather together groups of patients with similar prognosis and to facilitate the interpretation of the results.[15]

Data Analysis

Measurements of central tendency and dispersion were calculated for time in days from the diagnosis to the beginning of the treatment, and for the interval between the first appointment and the beginning of the treatment. Time trends for breast cancer stage over the observation period were studied using a joinpoint regression model, with stage as the outcome (expressed as a percentage of cases at stages III and IV) and year of diagnosis as the independent variable. In order to fit the model, joinpoints from 0–3 (tendencies indicated by straight line segments) were admitted, and, for each type of cancer, annual percentage changes (APCs) were estimated, with 95% confidence intervals (95%CIs).[16]

The factors associated with breast cancer stage at diagnosis were examined using a multinomial logistic regression model for stage, which was divided into three categories. The 'localized disease' and 'advanced disease' categories were compared with the 'initial disease' category. After a univariate analysis was performed, the variables selected for the multiple model were those displaying an association with the outcome, with $p \leq 0.20$,[17] and with fewer than 35% of records with missing information. The odds ratios (ORs) and their respective 95%CIs were then calculated.

The influence of smoking, alcohol use, marital status, race/skin color and family history of cancer (variables unavailable for institutions in the state of São Paulo), was examined in a second analysis conducted using a similar methodology, but excluding cases originated from health facilities in São Paulo. In the univariate analysis, the variables that displayed correlation with the disease stage ($p \leq 0.20$) and had less than 35% of missing data were studied in a multivariate model.

The analyses were performed using the R software (R Foundation for Statistical Computing, Vienna, Austria), version 3.0.3, while the regression model coefficients were extracted with the assistance of the texreg package.[18] The Joinpoint software (National Cancer Institute, Rockville, MD, US), version 4.2.02, was also used for the time trend analyses. All spreadsheets were edited using the Apache OpenOffice software (Apache Software Foundation, Forest Hill, ND, US), version 4.1.1. The study was approved by the

Research Ethics Committee of Instituto de Medicina Social, Universidade do Estado do Rio de Janeiro, under resolution 196/96, no. CAAE: 50685115.9.0000.5260.

Results

A total of 170,757 cases of malignant breast cancer that met the study's criteria were included. The time from the date of the diagnosis to the beginning of the treatment ranged from 0–182 days, with a median of 43 days for the studied population. The interval between the first appointment at the facility and the beginning of the treatment ranged from 7–180 days (median of 32 days). In 36.2% of the cases, the time from the diagnosis to the beginning of the cancer treatment exceeded 60 days.

The percentage of cases with stages III and IV decreased over the period between 2000 and 2002 (from 43.1% to 37.7%). From 2002 to 2009, we observed an increase, with a peak of 40.2% in 2010, with apparent stability until the end of the study period, in 2012. This change was confirmed in the joinpoint regression analysis (►**Fig. 1**). Two statistically significant points of inflection were found in the changing percentages of advanced cases of breast cancer. The first trend, from 2000 to 2002, showed an APC of -6.6% (95%CI: -7.6–-5.5%) in the percentages of cases at stages III and IV.

In the second trend, from 2002 to 2009, the percentage grew, with an APC of 1.1% (95%CI: 0.9–1.3%). Lastly, the third trend, which extended from 2009 to 2012, showed a new inflexion in the curve: a downturn, showing an APC of 0.3% (95%CI: -0.9–0.2%). This trend, however, lacked statistical significance.

The median age at diagnosis was 55 years (ranging from 18–113 years), with 19% of the patients aged 70 years or older. More than half of the patients (52.7%) were born in Brazil's Southeastern region, and 27.6% of them were from the state of São Paulo. São Paulo also accounted for the highest percentage of registered cases, with 42.5% of observations originating from facilities in that state.

Of the patients included, 28.5% had incomplete primary education, and 6.9% had higher education, while for 30.9% of the cases, this information was not available. In 19.6% of the cases, the patients had been born in a state that was different from the state where the health facility that recorded the case was located, and in 7.6% of the cases, data on the birthplace was missing, as shown in ►**Table 1**.

The number of breast cancer cases recorded per year increased during the study period, peaking in 2010, with 17,080 cases, which is equivalent to 10.5% of the total cases. The initial treatment proposed was completed by 86.3% of the patients, and 18.2% showed no evidence of cancer at the end of the treatment. Of the records analyzed, 54.9% lacked information for the variable "disease state at end of treatment." Of the patients included, 48.1% declared never being tobacco users, and 52.7% denied any history of alcohol use. Married women accounted for 47.6% of the cases studied. As for data on race/skin color taken from the patients' hospital records, the distribution was as follows: 50.7% of the patients were white, 33.4% were brown, and 6.6% were black. The characteristics of the patients studied are shown in ►**Tables 1** and **2**.

In the univariate analysis, the explanatory variables that were significantly related with breast cancer stage at diagnosis were age, level of schooling, the state in which the hospital facility was located, place of birth outside the state where the treating facility was located, histology and year of diagnosis (if established up to 2005 or after 2006).

►**Table 3** shows the results of the multivariate analysis. Age at diagnosis continued to display a significant relationship with the stage after adjustments were made. The odds of having a localized or advanced disease diminished with increasing age. In comparison with the cases in the $\leq$ 30 years of age group, the greatest relative difference for both categories (localized or advanced disease) occurred in the 65–69 years of age group, for whom the ORs were 0.38 (95%CI: 0.33–0.43) for localized disease, and 0.32 (95%CI: 0.26–0.39) for advanced disease. That trend continued for the other age groups, with ORs decreasing as age increased, in relation to the reference category.

Women with more advanced levels of schooling presented lower estimated odds for both categories. Cases with

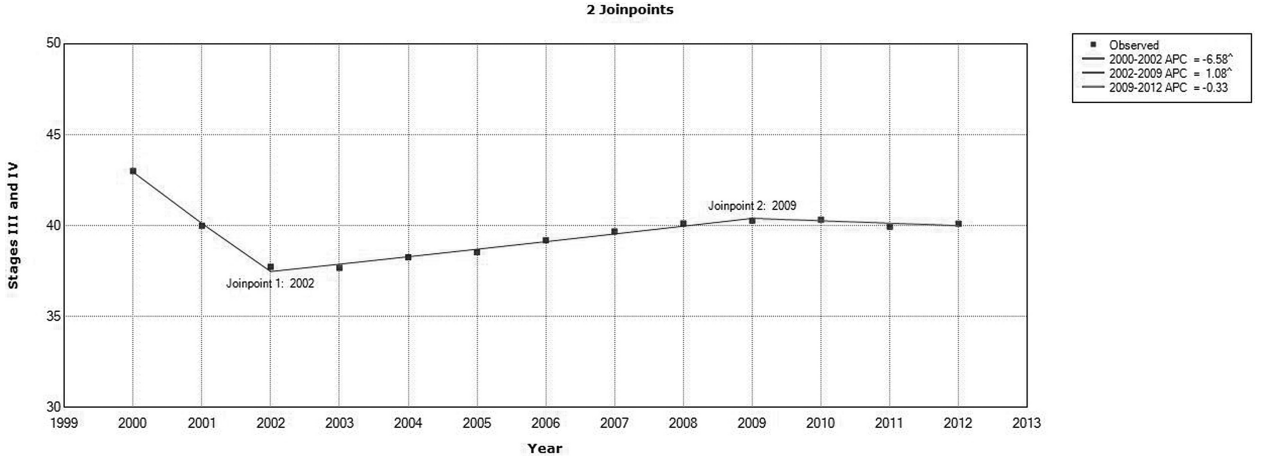

Fig. 1 Time trend of the percentage of cases of women registered by the hospital cancer registries (HCRs) with diagnosis at stages III and IV. Abbreviations: APC, Annual Percent Change.

Table 1 Sociodemographic characteristics of the women with invasive breast cancer diagnosis, registered by the hospital cancer registries and meeting inclusion criteria, Brazil 2000–2012

Level of schooling	n (%)
No formal education	12,037 (6.8)
Primary education (incomplete)	50,476 (28.5)
Primary education (complete)	23,433 (13.2)
Secondary education	24,144 (13.6)
College (higher education)	12,296 (6.9)
Missing information	54,849 (30.9)
Region of the institution	**n (%)**
Midwest	2,802 (1.6)
Northeast	29,547 (17.3)
North	4,433 (2.6)
Southeast	106,711 (62.5)
South	27,264 (15.9)
Region of birth	**n (%)**
Midwest	2,401 (1.5)
Northeast	41,358 (26.0)
North	4,250 (2.7)
Southeast	83,861 (52.7)
South	25,838 (16.2)
Another country	1,361 (0.9)
Region of birth differs from region of institution	**n (%)**
No	124,237 (72.8)
Yes	33,471 (19.6)
Missing information	13,049 (7.6)
Smoking	**n (%)**
Former	2,486 (2.5)
Never	47,196 (48.1)
Current	16,927 (17.2)
Missing information	31,595 (32.2)
Alcoholism	**n (%)**
Former	723 (0.7)
Never	51,768 (52.7)
Current	8,802 (8.9)
Missing information	36,911 (37.6)
Marital status	**n (%)**
Single	20,155 (20.5)
Married	46,716 (47.6)
Civil union	341 (0.3)
Divorced	6,396 (6.5)
Widow	14,516 (14.8)
Missing information	10,080 (10.3)
Race/skin color	**n (%)**
Asian	665 (0.7)
White	49,825 (50.7)
Indigenous	86 (0.1)
Brown	32,801 (33.4)
Black	6,477 (6.6)
Missing information	8,350 (8.5)

(*Continued*)

schooling classified as higher education presented an OR of 0.34 (95%CI: 0.32–0.36) for localized disease, and an OR of 0.32 (95%CI: 0.29–0.35) for advanced disease, when compared with those with no schooling. That effect remained uniform after the adjustment for the other variables of the model, and the OR was observed to decrease as the level of schooling increased.

There was a relationship between the region where the recording health facility was located and the stage at diagnosis. Using the Southern region as reference, the OR for localized disease was of 1.10 (95%CI: 1.06–1.14) in the Southeastern region, of 1.64 (95%CI: 1.57–1.72) in the Northeastern region, of 1.69 (95%CI: 1.50–1.90) in the Midwestern region, and of 1.81 (95%CI: 1.68–1.96) in the Northern region of Brazil. That trend remained the same for the advanced disease. In addition, being born in a region different from that of the treatment institution was associated with 12% higher odds of being in the localized category than in the initial category (OR: 1.12; 95%CI: 1.09–1.16), and with 15% greater odds of belonging to the advanced category (OR: 1.15; 95%CI: 1.09–1.21).

In comparison with ductal tumors, lobular tumors presented in early stages, with lower odds for localized disease (OR: 0.94; 95%CI: 0.90–0.98). No statistically significant difference was observed between ductal and lobular tumors in the advanced disease category.

In the second analysis, excluding the facilities located in the state of São Paulo, we examined the effects of race/skin color and marital status on staging. These were the only variables, among those unavailable for facilities in the state of São Paulo, that met the criteria for inclusion in the multivariate analysis.

After adjustment for age, schooling, region of the health facility, histological type and year of diagnosis, we observed that cases classified as brown had an OR of 1.16 (95%CI: 1.11–1.21) for localized disease, and an OR of 1.30 (95% CI 1.21–1.41) for advanced disease. Those classified as black had an OR of 1.46 (95%CI: 1.36–1.57) for localized disease, and an OR of 1.63 (95% CI: 1.47–1.82) for advanced disease, in comparison with the initial disease category (►**Table 4**).

Discussion

Breast cancer is diagnosed late in Brazil, and women with lower socioeconomic status, non-whites, and those treated in the Northern and Northeastern regions are prone to greater estimated risk of presenting at an advanced stage.

Table 2 Clinical- and treatment-related characteristics of the women with breast cancer diagnosis included in the study

Treatment accomplishment	n (%)
Complete treatment	147,375 (86.3)
Incomplete treatment	5,211 (3.0)
Missing information	18,171 (10.6)
Status at the end of treatment	**n (%)**
Without evidence of disease	31,107 (18.2)
Partial remission	5,481 (3.2)
Stable disease	25,653 (15.0)
Disease in progression	6,793 (3.9)
End-of-life care	989 (0.6)
Death	4,535 (2.6)
Not applicable	2,500 (1.5)
Missing information	93,699 (54.9)
Diagnosis and treatment at admission	**n (%)**
Diagnosis stabilized, treatment initiated	30,911 (18.1)
Diagnosis stabilized, no treatment	58,219 (34.0)
Without diagnosis and treatment	78,791 (46.1)
Missing information	431 (0.2)
Histological type	**n (%)**
Adenocarcinoma	3,049 (1.8)
Ductal differentiation	143,261 (84.0)
Lobular differentiation	15,013 (8.8)
Epithelial without any other specifications	4,860 (2.8)
Squamous	1,130 (0.6)
Medullary	1,106 (0.6)
Mucinous	2,078 (1.2)
Mucoepidermoid	14 (0.01)
Invasive neoplasm without any other specifications	246 (0.1)
Stage	**n (%)**
I	32,942 (19.3)
II	70,268 (41.1)
III	51,636 (30.2)
IV	15,911 (9.3)

In addition, once the diagnosis is made, the time until the beginning of the treatment is excessively long for a large proportion of patients. Breast cancer is a complex disease whose genesis is multifactorial and involves biological, environmental and social determinants. This study sought to identify characteristics associated with disease stage, given its relationship to prognosis and the fact that it is considered an effect mediator of several factors bearing on cancer mortality.

In 2014, MOH order no. 1220 set a maximum delay of 60 days from the diagnosis for the cancer treatment to begin. Although in our study the median times from diagnosis to the beginning of the treatment were below that limit, that time was exceeded in a significant proportion of cases. These findings evidence the need for measures that help overcome barriers and ensure a prompt treatment for diagnosed cases, leading to a potential reduction in morbidity and mortality.[19]

A tendency was also observed for the percentage of diagnoses at stages III and IV to increase over the study period. The percentage of breast cancer cases at advanced stages increased significantly from 2002 to 2009; after that period, this rate stabilized. That finding conflicts with the results reported in another study,[20] which also used data from the HCRs, and that showed a tendency for the percentage of advanced cases to decline between 2000 and 2009.

This difference can be explained by the different methodology those authors used, particularly their classification of cases as localized and advanced. In their study, however, the smaller number of cases included and the retention of cases of non-invasive tumors tended to increase the percentage of cases at an early stage.

We can hypothesize that the reversal in the upward trend in the percentage of diagnoses at stages III and IV, which was observed for the last 2 years of the observation period, may be related to effects of the MOH order no. 2439. This idea is reinforced by the fact that women diagnosed after 2005 had lower odds of having an advanced disease. However, due to the relatively short period of time since the edition of the ministerial order, and keeping in mind the natural history of breast cancer, additional studies are needed to confirm this hypothesis.

The odds of developing breast cancer in more advanced stages decreased with age in our study, a finding that is in agreement with the findings reported by other authors. A recent study focusing on locally advanced cases in a population-based cancer registry in the United States found higher occurrence in young women.[15] The prognosis for pre-menopausal breast cancer is characteristically worse than that for post-menopausal patients. That is probably because of the higher prevalence of more aggressive tumor subtypes in younger women.[21] Accordingly, the age effect found reflects, in part, the influence of the biological characteristics of breast tumors on stage.

The level of schooling showed a significant relationship with the advanced stage. In the multivariate analysis that relationship held for both the localized and advance disease categories, and it did so when the variables race/skin color and marital status were included in the model. Recent studies have reported (in agreement with our findings) that the level of schooling is associated with access to breast cancer screening, the stage of the disease, and mortality.[22,23]

A cross-sectional study[20] examining a sample of 59,317 cases of breast cancer recorded on HCRs from 2000 to 2009 found a significant relationship between low level of schooling (cases with 7 years or less of formal schooling) and advanced stage (defined in that study as stage IIIb or higher at diagnosis). In addition to level of schooling, the authors also found that age, region of residence and histological type

Table 3 Results of the multivariate analysis: OR and 95%CI calculated for the localized and advanced disease categories in relation to the initial disease category

Variables	Localized disease - OR (95%CI)	Advanced disease - OR (95%CI)
Age (years)		
< 30	1	1
30–34	0.98 (0.85–1.15)	0.78 (0.63–0.97)
35–39	0.80 (0.70–0.93)	0.64 (0.52–0.78)
40–44	0.66 (0.57–0.75)	0.44 (0.36–0.53)
45–49	0.55 (0.48–0.63)	0.39 (0.32–0.47)
50–54	0.51 (0.44–0.58)	0.38 (0.32–0.47)
55–59	0.46 (0.40–0.53)	0.36 (0.30–0.44)
60–64	0.40 (0.35–0.46)	0.34 (0.28–0.41)
65–69	0.38 (0.33–0.43)	0.32 (0.26–0.39)
≥ 70	0.41 (0.36–0.47)	0.34 (0.28–0.42)
Level of schooling		
No formal education (illiterate)	1	1
Primary education (incomplete)	0.67 (0.64–0.70)	0.65 (0.60–0.70)
Primary education (complete)	0.56 (0.54––0.60)	0.51 (0.46–0.55)
Secondary education	0.45 (0.43––0.48)	0.41 (0.38–0.45)
College (higher education)	0.34 (0.32––0.36)	0.32 (0.29–0.35)
Region of the institution		
South	1	1
Midwest	1.69 (1.50–1.90)	1.88 (1.58–2.23)
Northeast	1.64 (1.57–1.72)	1.06 (0.98–1.15)
North	1.81 (1.68–1.96)	1.31 (1.15–1.49)
Southeast	1.10 (1.06–1.14)	1.11 (1.04–1.18)
State of birth		
Same as the institution	1	1
Different from the institution	1.12 (1.09–1.16)	1.15 (1.09–1.21)
Histology		
Ductal differentiation	1	1
Lobular differentiation	0.94 (0.90–0.98)	1.01 (0.93–1.08)
Other	0.71 (0.68–0.75)	1.16 (1.08–1.25)
Year of diagnosis		
2000–2005	1	1
2006–2012	0.98 (0.96–1.01)	0.88 (0.85–0.92)

Abbreviations: 95%CI, 95% confidence interval; OR, odds ratio.

had an association with the odds of having an advanced disease at diagnosis.

Women treated at health facilities in the Northern, Northeastern and Midwestern regions had a greater likelihood of having advanced-stage cancer at diagnosis than those in the Southern and Southeastern regions. For women treated at facilities in the Northeast, we found a significant increase in risk for localized disease, but not for advanced disease, when compared with those treated in the Southeastern region. That situation is compatible with the findings of other studies, which have pointed to inequality in the rates of mortality from these diseases among the various regions of Brazil.[24]

Tumors exhibiting lobular differentiation were related to reduced risk of having localized cancer at diagnosis, but no significant difference was detected in relation with the risk of advanced cancer in comparison with tumors with ductal differentiation. Meanwhile, tumors of other histological types were observed to have an association with reduced

Table 4 Results of the multivariate analysis excluding the state of São Paulo: OR and 95%CI calculated for the localized and advanced disease categories compared with the initial disease category

Variables	Localized disease - OR (95%CI)	Advanced disease - OR (95%CI)
Age		
< 30	1	1
30–34	0.93 (0.76–1.15)	0.64 (0.47–0.86)
35–39	0.79 (0.65–0.96)	0.61 (0.46–0.80)
40–44	0.66 (0.55–0.80)	0.42 (0.32–0.55)
45–49	0.56 (0.46–0.67)	0.38 (0.30–0.50)
50–54	0.53 (0.44–0.63)	0.39 (0.30–0.50)
55–59	0.46 (0.38–0.55)	0.36 (0.27–0.47)
60–64	0.42 (0.35–0.51)	0.34 (0.26–0.45)
65–69	0.39 (0.32–0.48)	0.33 (0.25–0.43)
≥ 70	0.38 (0.32–0.46)	0.31 (0.24–0.41)
Level of schooling		
No formal education (illiterate)	1	1
Primary education (incomplete)	0.67 (0.63–0.71)	0.65 (0.59–0.72)
Primary education (complete)	0.62 (0.57–0.66)	0.60 (0.54–0.67)
Secondary education	0.46 (0.43–0.50)	0.43 (0.38–0.48)
College (higher education)	0.38 (0.35–0.42)	0.32 (0.28–0.37)
Region of the institution		
South	1	1
Midwest	1.48 (1.31–1.68)	1.61 (1.34–1.94)
Northeast	1.36 (1.28–1.44)	0.77 (0.70–0.85)
North	1.82 (1.64–2.01)	1.23 (1.04–1.45)
Southeast	1.17 (1.12–1.23)	1.03 (0.95–1.11)
State of birth		
Same as the institution	1	1
Different from the institution	1.06 (1.01–1.11)	1.06 (0.99–1.15)
Histology		
Ductal differentiation	1	1
Lobular differentiation	0.96 (0.90–1.02)	0.89 (0.80–0.99)
Other	0.81 (0.76–0.87)	1.19 (1.07–1.33)
Year of diagnosis		
2000–2005	1	1
2006–2012	0.89 (0.86–0.92)	0.77 (0.72–0.82)
Race/skin color		
White	1	1
Asian	1.16 (0.96–1.41)	1.24 (0.88–1.75)
Indigenous	0.94 (0.52–1.69)	1.25 (0.50–3.15)
Brown	1.16 (1.11–1.21)	1.30 (1.21–1.41)
Black	1.46 (1.36–1.57)	1.63 (1.47–1.82)
Marital status		
Married	1	1
Divorced	1.05 (0.98–1.12)	0.97 (0.86–1.09)
Single	1.24 (1.19–1.30)	1.46 (1.35–1.56)
Widow	1.17 (1.11–1.23)	1.16 (1.07–1.28)

Abbreviations: 95%CI, 95% confidence interval; OR, odds ratio.

risk for localized disease and increased risk for advanced disease, probably reflecting the heterogeneous population included in this category, which comprises rare histological types, but also tumors whose histological type is poorly defined (such as "malignant neoplasm with no other specification"), which occurred frequently in the records.

The stage at diagnosis was influenced by race/skin color and marital status. Black and brown women, as well as single and legally separated women, were more likely to be in the localized and advanced categories than white and married women. That fact, which is in agreement with the evidence found in the literature, highlights the importance of social barriers and family support to promote proper women's health care.[25–27]

This study has limitations. As the data were obtained from a secondary source, the analyses were restricted to the information provided in the HCRs. As a result, important considerations relating to the natural history of the disease could not be directly analyzed. In addition, for some data items, low completion rates precluded their inclusion in the analyses. Of particular note in this context was the absence of data on expression of hormone receptors and human epidermal growth factor receptor 2 (HER-2), whose relationship to prognosis cannot be disregarded.

Another important issue was the total coverage of cancer cases in Brazil achieved by the HCRs. When compared with the estimated annual incidence of the disease, the number of observations available is relatively small, even given the increasing coverage and inclusion of data by health facilities in recent years.

A study published in 2015,[20] for example, included significantly fewer cases (50,317) than the present study (170,757), despite using the same database and working with similar study periods. This suggests that the system is constantly updated, and indicates a tendency for coverage to increase progressively. It is also worthy of note that the HCRs cover primarily patients treated by the SUS, excluding nearly all patients covered by the supplementary health system.

Conclusion

Cancer care in Brazil can be evaluated from data drawn from the HCRs, which are designed to yield information on the treatment offered at health facilities, to enable quality control of the service being provided, and to be included in epidemiological surveillance platforms, in addition to serving as a source for public health research. Coverage by the HCR system has been increasing in recent years, and the system constitutes an increasingly useful source to assist monitoring on cancer prevention and control issues in Brazil. Access to breast cancer diagnosis in Brazil is unequal. The finding that socioeconomics factors may influence the stage at diagnosis highlights the need to promote broader access to cancer diagnosis in Brazil. The gaps between clinical suspicion, establishment of the diagnosis and beginning of the treatment are key issues to be dealt with by health managers and policy promoters. We believe that special attention should be paid to women with lower socioeconomic status.

Conflicts of Interest
The authors have no conflicts of interest to declare.

Contributions
Renna Junior NL and Azevedo e Silva G contributed with the conception and design, data collection and analysis, interpretation of data, writing of the article, critical review of the intellectual content, and final approval of the version to be published.

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References

1 Ferlay J, Soerjomataram I, Ervik M, et al. *GLOBOCAN 2012 v10: Cancer Incidence and Mortality Worldwide*. Lyon: International Agency for Research on Cancer; 2013. (IARC CancerBase No. 11)
2 Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015;136(05):E359–E386. Doi: 10.1002/ijc.29210
3 Ministério da Saúde. Instituto Nacional de Câncer José Alencar Gomes da Silva. *Estimativa 2016: Incidência de Câncer no Brasil*. Rio de Janeiro, RJINCA2015http://www.inca.gov.br/estimativa/2016/estimativa-2016-v11.pdf. Accessed November 13, 2015
4 Ministério da Saúde. Instituto Nacional de Câncer José Alencar Gomes da Silva. *Atlas de Mortalidade por Câncer*. Rio de Janeiro, RJINCA2012https://mortalidade.inca.gov.br/MortalidadeWeb. Accessed April 6, 2015.
5 Porter PL. Global trends in breast cancer incidence and mortality. Salud Publica Mex 2009;51:S141–S146
6 Akinyemiju T, Moore JX, Ojesina AI, Waterbor JW, Altekruse SF. Racial disparities in individual breast cancer outcomes by hormone-receptor subtype, area-level socio-economic status and healthcare resources. Breast Cancer Res Treat 2016;157(03): 575–586. Doi: 10.1007/s10549-016-3840-x
7 Morris M, Woods LM, Rogers N, O'Sullivan E, Kearins O, Rachet B. Ethnicity, deprivation and screening: survival from breast cancer among screening-eligible women in the West Midlands diagnosed from 1989 to 2011. Br J Cancer 2015;113(03):548–555. Doi: 10.1038/bjc.2015.204
8 Ministério da Saúde. Portaria No 3.535, de 02 de setembro de 1998. Estabelece critérios para cadastramento de centros de atendimento em oncologia. Brasília: Diário Oficial da União, 3 de setembro de; 1998:75–77
9 Ministério da Saúde. Portaria No 2.439, de 08 de dezembro de 2005. Institui a Política Nacional de Atenção Oncológica: promoção, prevenção, diagnóstico, tratamento, reabilitação e cuidados paliativos, a ser implantada em todas as unidades federadas, respeitadas as competências das três esferas de gestão. Brasília: Diário Oficial da União, 9 de dezembro de; 2005:80–81
10 Terracini B, Zanetti R. A short history of pathology registries, with emphasis on cancer registries. Soz Praventivmed 2003;48(01):3–10
11 Ministério da Saúde. Instituto Nacional de Câncer José Alencar Gomes da Silva. *Informação dos Registros Hospitalares de Câncer como Estratégia de Transformação: Perfil do Instituto Nacional de Câncer José Alencar Gomes da Silva em 25 anos*. Rio de Janeiro, RJINCA2012http://bvsms.saude.gov.br/bvs/publicacoes/inca/Informacao_dos_registros_hospitalares.pdf. Accessed May 3, 2015.

12 Ministério da Saúde. Instituto Nacional de Câncer. *Registros Hospitalares de Câncer: Planejamento e Gestão*. 2ª ed. Rio de Janeiro, RJ: INCA; 2010
13 Mirra AP. *Registros de Câncer no Brasil e sua História*. São Paulo, SP: TOMGRAF; 2005
14 Edge S. *AJCC Cancer Staging Manual*. 7th ed. New York, NY: Springer; 2010
15 Newman LA. Epidemiology of locally advanced breast cancer. Semin Radiat Oncol 2009;19(04):195–203. Doi: 10.1016/j.semradonc.2009.05.003
16 Kim HJ, Fay MP, Feuer EJ, Midthune DN. Permutation tests for joinpoint regression with applications to cancer rates. Stat Med 2000;19(03):335–351. Doi: 10.1002/(SICI)1097-0258(20000215)19:3<335:AID-SIM336>3.0.CO;2-Z
17 Maldonado G, Greenland S. Simulation study of confounder-selection strategies. Am J Epidemiol 1993;138(11):923–936. Doi: 10.1093/oxfordjournals.aje.a116813
18 Leifeld P. texreg: conversion of statistical model output in R to LaTeX and HTML tables. J Stat Softw 2013;55:1–26. Doi: 10.18637/jss.v055.i08
19 Brito C, Portela MC, Vasconcellos MTL. Survival of breast cancer women in the state of Rio de Janeiro, Southeastern Brazil. Rev Saude Publica 2009;43(03):481–489. Doi: 10.1590/S0034-89102009000300012
20 Abrahão KdeS, Bergmann A, Aguiar SS, Thuler LCS. Determinants of advanced stage presentation of breast cancer in 87,969 Brazilian women. Maturitas 2015;82(04):365–370. Doi: 10.1016/j.maturitas.2015.07.02
21 Anders CK, Hsu DS, Broadwater G, et al. Young age at diagnosis correlates with worse prognosis and defines a subset of breast cancers with shared patterns of gene expression. J Clin Oncol 2008;26(20):3324–3330. Doi: 10.1200/JCO.2007.14.2471
22 Boone SD, Baumgartner KB, Joste NE, Pinkston CM, Yang D, Baumgartner RN. The joint contribution of tumor phenotype and education to breast cancer survival disparity between Hispanic and non-Hispanic white women. Cancer Causes Control 2014;25(03):273–282. Doi: 10.1007/s10552-013-0329-3
23 Novaes CdeO, Mattos IE. [Prevalence of non-utilization of mammography and associated factors in elderly women]. Cad Saude Publica 2009;25(Suppl 2):S310–S320. Doi: 10.1590/S0102-311X2009001400013
24 Girianelli VR, Gamarra CJ, Azevedo e Silva G. Disparities in cervical and breast cancer mortality in Brazil. Rev Saude Publica 2014;48(03):459–467. Doi: 10.1590/S0034-8910.2014048005214
25 Bairros FS, Meneghel SN, Dias-da-Costa JS, et al. Racial inequalities in access to women's health care in southern Brazil. Cad Saude Publica 2011;27(12):2364–2372. Doi: 10.1590/S0102-311X2011001200008
26 Ferrante JM, Gonzalez EC, Roetzheim RG, Pal N, Woodard L. Clinical and demographic predictors of late-stage cervical cancer. Arch Fam Med 2000;9(05):439–445. Doi: 10.1001/archfami.9.5.439
27 Schinkel JK, Zahm SH, Jatoi I, et al. Racial/ethnic differences in breast cancer survival by inflammatory status and hormonal receptor status: an analysis of the Surveillance, Epidemiology, and End Results data. Cancer Causes Control 2014;25(08):959–968. Doi: 10.1007/s10552-014-0395-1