Factors Associated with Delay between Diagnosis and Initiation of Breast Cancer Treatment: a Cohort Study with 204,130 Cases in Brazil

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Fatores Associados ao Atraso entre o Diagnóstico e o Início do Tratamento de Câncer de Mama: um Estudo de Coorte com 204.130 Casos no Brasil

Factores Asociados con el Retardo entre el Diagnóstico y el Inicio del Tratamiento del Cáncer de Mama: un Estudio de Cohorte con 204.130 Casos en Brasil

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ABSTRACT

Introduction: Breast cancer is considered a public health problem with an increasing incidence worldwide. Several factors contribute to late diagnosis and hinder the initiation of the treatment, resulting in a worse prognosis. **Objectives:** To analyze the time interval between diagnosis and the beginning of the first oncologic treatment in the Brazilian population, in addition to assessing the factors associated with the longest time intervals. **Method:** Retrospective cohort study with 540,529 patients registered in the Hospital Cancer Registry System (SisRHC) from 2000 to 2017. The outcome was the time between diagnosis and the beginning of the first oncologic treatment, considering the interval greater than 60 days as delay. Descriptive analysis and simple logistic regression were performed (95% CI; p <0.05) to analyze the variables. **Results:** 204,130 cases were analyzed, mean age of 55.8 years (± 13.24), predominantly females (99.1%), 55.1% were from the southeast region and 71% lived in non-capital cities. The median of the time interval between diagnosis and the beginning of the first oncologic treatment was 63 days (interquartile range = 36-109). Sociodemographic, clinical and treatment-related variables affect the time interval, except the gender variable. **Conclusion:** The time between diagnosis and the beginning of the first oncologic treatment was high. Sociodemographic, clinical and treatment-related factors influence time intervals. Their early identification can contribute to guide the actions toward these most vulnerable groups to delay.

Key words: Breast Neoplasms/diagnosis; Time-to-Treatment; Risk Factors; Hospital Records.

RESUMO

Introdução: O câncer de mama é considerado um problema de saúde pública, tendo crescente incidência mundial. Diversos fatores contribuem para o diagnóstico tardio e dificultam o início do tratamento, repercutindo em um pior prognóstico. Objetivos: Analisar o intervalo de tempo entre o diagnóstico e o înício do primeiro tratamento oncológico na população brasileira, além de avaliar os fatores associados aos maiores intervalos. Método: Trata-se de um estudo de coorte retrospectivo com 540.529 pacientes cadastrados no Sistema de Registros Hospitalares de Câncer (SisRHC) no período de 2000 a 2017. Utilizou-se como desfecho o intervalo de tempo entre o diagnóstico e o início do primeiro tratamento oncológico, considerando-se como atraso o intervalo maior do que 60 dias. Para análise das variáveis, foram realizadas análise descritiva e regressão logística simples (IC95%; p<0,05). **Resultados:** Foram analisados 204.130 casos que apresentaram média de idade de 55,8 anos (±13,24), sendo predominantemente do sexo feminino (99,1%), 55,1% eram da Região Sudeste e 71,4% residiam em cidades não capitais. A mediana do intervalo de tempo entre o diagnóstico e o início do primeiro tratamento oncológico foi de 63 dias (variação interquartil = 36-109). As variáveis sociodemográficas, clínicas e relacionadas ao tratamento mostraram impacto no intervalo de tempo, com exceção da variável sexo. Conclusão: O tempo entre o diagnóstico e o início do primeiro tratamento oncológico foi elevado. Fatores sociodemográficos, clínicos e relacionados ao tratamento influenciam nos intervalos de tempo. Identificá-los precocemente pode contribuir para o direcionamento de ações a esses grupos mais vulneráveis ao atraso.

Palavras-chave: Neoplasias da Mama/diagnóstico; Tempo para o Tratamento; Fatores de Risco; Registros Hospitalares.

RESUMEN

Introducción: El cáncer de mama se considera un problema de salud pública con una incidencia mundial creciente. Varios factores contribuyen al diagnóstico tardío y dificultan el inicio del tratamiento, resultando en un peor pronóstico. Objetivos: Analizar el intervalo de tiempo entre el diagnóstico y el comienzo del primer tratamiento oncologico en la población brasileña, además de evaluar los factores asociados con los intervalos de tiempo más largos. Método: Este es un estudio de cohorte retrospectivo con 540.529 pacientes registrados en el Hospital Cancer Registry System (SisRHC) desde 2000 hasta 2017. El resultado fue el intervalo de tiempo entre el diagnóstico y el comienzo del primer tratamiento oncologico, considerando como retraso el intervalo superior a 60 días. Para el análisis de las variables, se realizó un análisis descriptivo y una regresión logística simple (IC 95%; p <0,05). Resultados: Se analizaron 204,130 casos, con una edad media de 55,8 años (±13,24), predominantemente mujeres (99,1%), 55,1% de la región sureste y 71,4% residentes en ciudades no capitales. La mediana del intervalo de tiempo entre el diagnóstico y el comienzo del primer tratamiento contra el cáncer fue de 63 días (rango intercuartil = 36-109). Las variables sociodemográficas, clínicas y relacionadas con el tratamiento tuvieron un impacto en el intervalo de tiempo, con la excepción de la variable de género. Conclusión: El intervalo de tiempo promedio entre el diagnóstico y el comienzo del primer tratamiento oncologico fue alto. Además, se observó que los factores sociodemográficos, clínicos y relacionados con el tratamiento influyen en los intervalos de tiempo, por lo que identificarlos temprano puede contribuir a acciones directas para estos grupos más vulnerables al retraso.

Palabras clave: Neoplasias de la Mama/diagnóstico; Tiempo de Tratamiento; Factores de Riesgo; Registros de Hospitales.

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INTRODUCTION

Breast cancer (BC) is considered a public health problem¹. It is ranked second biggest incidence worldwide among the types of cancer, and first in females, except non-melanoma skin cancers². In 2018, 2.1 million new cases of BC were estimated in the world and more than 626 thousand cancer related deaths. The biggest incidence rates of BC were noticed in developed countries (41.1 per 100 thousand) when compared to developing countries (32.8 per 100 thousand), although there is an inversion of this scenario in relation to mortality rates, which are 17.1 and 10.3 per 100 thousand, respectively².

In Brazil, 66,280 new cases of BC are estimated for each year of the triennium 2020-2022, being the most incident cancer in women in the South, Southeast, West-Central and Northeast regions not considering non-melanoma skin cancer¹. BC is the main cause of death by cancer among women in four of the five Brazil's macroregions, except the Northern Region, where it ranks second³. The five-year survival rate in the country is approximately 68.7%⁴. From 1988 to 2008, BC incidence in Brazilian males tripled⁵. Sociodemographic, clinical and treatment-related features differ significantly among men and women diagnosed with BC in the country, despite similar prognosis⁶.

The inequalities among developed and in development countries are attributed to various clinical and sociodemographic factors that result in poor access of the population to health services⁷⁻⁹. This context contributes for the late diagnosis of BC^{4,5}. Social, geographical and health services related barriers favor the delay to initiate the treatment^{7,10}. Despite the uncertainties about the actual impact of the delay in survival of women with BC, studies have demonstrated that the long intervals of time between the diagnosis of BC and beginning of the first treatment are associated to worse prognosis^{11,12}.

In Brazil, in 2013, it was published Ordinance number 876/13¹³, which disposes about the application of the Law 12,732/12, that determines the period of until 60 days to initiate the oncologic treatment post diagnosis confirmation at National Health System (SUS)¹⁴.

The high proportion of women with advanced clinical staging (CS) at the diagnosis and raising increase of the rates of mortality indicate that the actions to control BC in Brazil may not been effective^{15,16}. Brazilian investigators noticed that the first oncologic treatment is initiated with delay, for most of the cases^{17,18,19}. The hurdles to access oncologic assistance have significant consequences for the health of this population^{20,21}.

In this context, the present study has the objective of analyze the time interval between diagnosis and beginning of the first oncologic treatment of the Brazilian population and evaluate the associated factors to the delay.

METHOD

Retrospective cohort study with secondary data originated from Brazil's National Cancer Hospital Registries (SisRHC). The information was obtained through download of the database found in the web system 'Integrator RHC', performed on November 30, 2019. Patients with BC diagnosed and treated from 2000 to 2017 were included. The cases registered in this database are originated from 336 hospital units. Exclusion criteria were: non-analytic cases (cases diagnosed and treated partially or totally - out of the hospital where the RHC is installed and cases enrolled in the hospital with RHC but that failed to initiate antineoplastic treatment in the unit)²², age <18 or >99 years, cases without information about gender, patients with non-invasive cancer, without information of CS or with CS IV, whose first treatment was decided for palliation, without information of the diagnosis or treatment date, those who did not submit to treatment or did not have information about the first treatment performed, cases where treatment was dated as prior to diagnosis (negative time) and with time interval over 365 days.

The sociodemographic variables utilized for the analysis were: gender, age-range, race/skin color according to the Brazilian Institute of Geography and Statistics (IBGE), education, Municipal Human Development Index (HDI-M), identified from the code of the municipality and classified according to the United Nations Development Programme (UNDP)²³; marital status, use of alcohol, use of tobacco, origin city, region of residence, region of the hospital unit and origin of referral (SUS and others). The clinical variables and related to the first treatment were: histological type, CS, year of diagnosis (categorized in the periods pre-law: 2000-2005 and 2006-2011 and post-law: 2012-2017); city of residence and treatment, unit of treatment and first oncologic treatment performed.

The study outcome was defined as the time interval between diagnosis and beginning of the first oncologic treatment with intent to cure. Time interval over 60 days was defined as delay based in Directive 876/13¹³.

The descriptive analysis of the study population was performed. The continuous variables were analyzed through distribution (absolute and relative frequencies) and measures of central tendency (mean and median). The analysis of the association between the clinical and sociodemographic factors with the outcome (delay) was performed utilizing the simple regression logistic.

Variables with p<0.05 were considered as statistically significant. The results were described utilizing odds ratio (OR) and considering confidence interval of 95% (CI 95%). The data were analyzed through Statistical Package for the Social Sciences (SPSS) version 23.0 (IBM Corp., Armonk, United States).

RESULTS

Initially, 540,529 individuals diagnosed with BC registered at SisRHC who initiated oncologic treatment from 2000 to 2017 were included. Based in the eligibility criteria, 322,891 cases were excluded, reaching the final population of 204,130 for analysis (Figure 1). The mean age of the patients was 55.8 (±13.24) years, with predominance of females (99.1%); 55.1% were from Southeast regions; 49.6% had less than eight years of education, 44.0% were referred by SUS and 71.4% lived out of the capital (table 1).

Mostly (87.4%) the population consisted of patients with invasive ductal carcinoma (IDC), 58.8% were submitted to surgery as first treatment, 52.0% were at advanced staging, 56.5% were treated in "other units" and 54.8% were treated out of the living city (Table 2). 43 Oncology High Complexity Assistance Centers (CACON) (14.5%) and 252 "other units" (85.4%) were identified in this database which conducted BC treatments (not tabulated data).

The median time interval between the diagnosis and the first treatment was 63 days (interquartile range [IQR]: 36-109), 52.8% of the patients presented time interval over 60 days.

It is possible to notice that all the sociodemographic and clinical variables present statistically significant association with delay, except gender (OR=0.99; CI=0.91-1.09; p=0.862). The patients submitted to radiotherapy or hormone therapy as first treatment presented 2.11 (CI95% 2.04-2.18; p<0.001) and 2.13 (CI95% 2.03-2.24; p<0.001) more chance of delay to initiate the treatment, respectively when compared to those submitted to surgery. The patients diagnosed in the period of 2006-2011 and 2012-2017 had more chance of delay when compared to those diagnosed between 2000 and 2005 (Table 2).

Figure 2 shows the distribution of the number of cases registered at RHC per year. It is noticed that there was a gradual increase along 17 years with expressive growth in 2013 and 2014.

It is possible to observe in Figure 3 that between 2000 and 2012 the frequency of the cases that had interval between the diagnosis and treatment over 60 days increased gradually along the time. In 2012, it was noticed

the peak of the delay, indicating that nearly 60% of the individuals had access to oncologic therapy more than 60 days after diagnosed with BC. This delay continued in the subsequent years, however since 2015 it appears that a slight reduction of the delay is happening although the percent continues high.

DISCUSSION

In the present study, it was observed that the delay (46.4%) was more frequent among patients diagnosed from 2012 to 2017, being this the period when Law 12,732/12¹⁴, also known as "Law of 60 days", entered into force. The analysis of simple logistic regression revealed that receiving the diagnosis of BC after the publication of the law increased in 64% the chance of delay to start the treatment when compared to the period from 2000 to 2005. Medeiros et al.9 analyzed the national data from RHC and suggested that the increase of the delay between 2006 to 2011 in comparison to the period from 2000 to 2005, may be related to the increase of incidence of BC in the country, together with the poor adequacy in increasing the offer of specialized services to meet the demand for consultation⁹. In 2011, a survey conducted by the Division of Early Detection and Support to the Organization of the Network of the National Cancer Institute José Alencar Gomes da Silva (INCA), showed that the installed capacity and the production of the oncologic network necessary for the whole national territory was of 375 CACON or Oncology High Complexity Care Units (UNACON). However, the actual capacity was nearly 30% lower than the necessary, with 264 units approved at the time. The deficit of the installed capacity added to the peak of the number of cases registered in RHC in 2013 and 2014 can justify the biggest delays in this period²⁴. Ordinance number 140/1425, which determines that CACON or UNACON approved health units should mandatorily update RHC information may have increased the number of registries and improved the quality of the data²⁵. In 2011, the audit conducted by INCA found that less of the half of the units forwarded data about the waiting time to perform the procedures²⁴.

In Brazil, the growth of BC monitoring initiatives is not impacting the reduction of mortality positively. This happens because in addition to the low mammography cover in the target-population, there is discrepancy of the follow up of suspected lesions and deficit of access to surgical treatment²⁰.

Despite the "Law of 60 days" is a progress in oncologic attention in Brazil, the results of the present study indicate that the law is not being complied with. Sousa et al. ¹⁷ noticed that 71.6% of the women with BC diagnosed

Table 1. Sociodemographic variables of patients with breast cancer. Hospital Cancer Registry System (SisRHC). Brazil, 2000-2017 (N=204,130)

Variables	Overall 204,130 (100.0)	Time interval N (%)			
		≥61 days 107,741 (52.8)	0 to 60 days 96,389 (47.2)	OR (CI95%)	p value
Gender					
Male	1,931 (0.9)	1,023 (0.9)	908 (0.9)	Reference	
Female	202,199 (99.1)	106,718 (99.1)	95,481 (99.1)	0.99 (0.91-1.08)	0.862
Age					
≤ 49 years	75,771 (37.1)	37,126 (34.5)	38,645 (40.1)	Reference	
50 to 69 years	96,935 (47.5)	52,750 (49.0)	44,185 (45.8)	1.24 (1.22-1.27)	< 0.001
70 years or more	31,424 (15.4)	17,865 (16.6)	13,559 (14.1)	1.37 (1.34-1.41)	< 0.001
Race/skin color					
Caucasian	65,556 (32.1)	34,290 (31.8)	31,266 (32.4)	Reference	
Non-Caucasian*	58,543 (28.7)	31,337 (29.1)	27,206 (28.2)	1.05 (1.03-1.07)	0.001
No information	80,031 (39.2)	42,114 (39.1)	37,917 (39.3)	1.01 (0.99-1.03)	0.230
Marital Status					
Live with partner	64,185 (31.4)	33,327 (30.9)	30,858 (32.0)	Reference	
Live without partner	56,145 (27.5)	30,580 (28.4)	25,565 (26.5)	1.11 (1.08-1.13)	< 0.001
No information	83,800 (41.1)	43,834 (40.7)	39,966 (41.5)	1.02 (0.99-1.04)	0.142
Alcohol user					
Never	72,781 (35.7)	38,520 (35.8)	34,261 (35.5)	Reference	
Ex or current user	16,031 (7.9)	9,053 (8.4.	6,978 (7.2)	1.15 (1.11-1.19)	< 0.001
No information	115,318 (56.5)	60,168 (55.8)	55,150 (57.2)	0.97 (0.95-0.99)	0.002
Tobacco user					
Never	68,063 (33.3)	35,982 (33.4)	32,081 (33.3)	Reference	
Ex or current user	28,496 (14.0)	15,542 (14.4)	12,954 (13.4)	1.07 (1.04-1.10)	< 0.001
No information	107,571 (52.7)	56,217 (52.2)	51,354 (53.3)	0.98 (0.96-0.99)	0.013
Region of residence					
South	36,128 (17.7)	18,671 (17.4)	17,457 (18.2)	Reference	
Southeast	112,381 (55.2)	60,609 (56.4)	51,772 (53.9)	1.09 (1.07-1.12)	< 0.001
West-Central	5,355 (2.6)	2,882 (2.7)	2,473 (2.6)	1.09 (1.03-1.15)	0.003
Northeast	42,917 (21.1)	21,166 (19.7)	21,751 (22.6)	0.91 (0.88-0.94)	< 0.001
North	6,821 (3,4)	4,148 (3.9)	2,673 (2.8)	1.45 (1.38-1.53)	< 0.001
Origin of Referral					
SUS	89,784 (44.0)	49,298 (45.8)	40,486 (42.0)	Reference	
Others	29,874 (14.6)	14,639 (13.6)	15,235 (15.8)	0.79 (0.77-0.81)	< 0.001
No information	84,472 (414)	43,804 (40.7)	40,668 (42.2)	0.88 (0.87-0.90)	< 0.001
City of origin**					
Capital	58,269 (28.6)	31,521 (29.3)	26,748 (27.8)	Reference	
Non capital	145,333 (71.4)	75,955 (70.7)	69,378 (72.2)	0.93 (0.91 - 0.95)	< 0.001
IDHM of the city of					
origin***					
Very high (0.800-1.000)	43,337 (21.3)	21,754 (20.2)	21,583 (22.5)	Reference	< 0.001
Others £ (0.000-0.779)	160,249 (78.7)	85,713 (79.8)	74,536 (77.5)	1.14 (1.12-1.16)	

 $\textbf{Captions: *} Non \ Caucasian: \ Black, \ Brown, \ Asian \ and \ Native; **Capital: corresponds to the 26 \ Brazilian capitals \ and \ Federal \ District; \ Non \ capital: \ other \ cities; ***IDHM= Municipal \ Index \ of \ Human \ Development; \ \pounds = Others: \ Very \ low, \ mean, \ high; \ OR= \ Odds \ ratio; \ CI= \ Confidence \ Interval.$

and treated in the State of Piauí, between 2016 and 2017, had delay over 60 days. These authors suggest that the disarticulation between health services hampers that patients with BC have access to their right secured

by law. As a counterpart, in a study conducted in Belo Horizonte¹⁸, from a cohort of patients registered at RHC diagnosed in the period from 2010 to 2013 it was noticed that little more of half of the population investigated

Table 2. Clinical variables and related to the treatment of patients with breast cancer. Hospital Cancer Registry System (SisRHC). Brazil, 2000-2017 (N=204,130)

Variables	Overall 204,130	Time interval N (%)		OR (CI95%)	p value
variables	(100.0)	≤61 days 107,741(52.8)	0 to 60 days 96,389 (47.2)		
Histological Type					
IDC	178,384 (87.4)	93,728 (87.0)	84,656 (87.8)	Reference	
Others	25,746 (12.6)	14,013 (13.0)	11,733 (12.2)	1.08 (1.05-1.10)	< 0.001
First treatment					
Surgery	119,929 (58.8)	62,992 (58.5)	56,937 (59.1)	Reference	
Radiotherapy	17,921 (8.8)	12,544 (11.6)	5,377 (5.6)	2.11 (2.04-2.18)	< 0.001
Chemotherapy	57,624 (28.2)	26,255 (24.4)	31,369 (32.5)	0.75 (0.74-0.77)	< 0.001
Hormone therapy	8,115 (4.0)	5,699 (5.3)	2,416 (2.5)	2.13 (2.03-2.24)	< 0.001
Others	541 (0.3)	251 (0.2)	290 (0.3)	0.78 (0.66-0.93)	0.004
Clinical Staging					
Initial (0 to IIA)	97,961 (48.0)	55,847 (51.8)	42,114 (43.7)	Reference	
Advanced (IIB to IIIC)	106,169 (52.0)	51,894 (48.2)	54,275 (56.3)	0.72 (0.71-0.93)	< 0.001
Unit of Treatment					
Other units *	115,359 (56.5)	58,530 (54.3)	56,829 (59.0)	Reference	
Cacon	88,771 (43.5)	49,211 (45.7)	39,560 (41.0)	1.20 (1.18-1.22)	< 0.001
Same city of					
residence and					
treatment	91,778 (45.1)	46,555 (43.3)	45,223 (47.0)	Reference	< 0.001
Yes	111,824 (54.9)	60,921 (56.7)	50,903 (53.0)	1.16 (1.14-1.18)	
No					
Year of diagnosis					
2000-2005	41,671 (20.4)	18,218 (16.9)	23,453 (24.3)	Reference	
2006-2011	73,320 (35.9)	39,532 (36.7)	33,788 (35.1)	1.51 (1.47-1.54)	< 0.001
2012-2017	89,139 (43.7)	49,991 (46.4)	39,148 (40.6)	1.64 (1.61-1.68)	< 0.001
Region of the					
hospital unit					
South	36,344 (17.8)	18,778 (17.4)	17,566 (18.2)	Reference	
Southeast	114,665 (56.2)	62,082 (57.6)	52,583 (54.6)	1.10 (1.08-1.13)	< 0.001
West-Central	4,287 (2.1)	2,076 (1.9)	2,211 (2.3)	0.88 (0.82-0.94)	< 0.001
Northeast	42,609 (20.9)	20,996 (19.5)	21,613 (22.4)	0.91 (0.88-0.94)	< 0.001
North	6,225 (3.0)	3,809 (3.5)	2,416 (2.5)	1.47 (1.40-1.56)	<0.001

Captions: IDC = Invasive ductal carcinoma; *Other units: Unacon = Oncology High Complexity Units, radiotherapy services and general hospitals; Cacon = Oncology High Complex Centers; OR= Odds ratio; CI = Confidence Interval.

(54.3%) had interval of up to 60 days between diagnosis and beginning of the treatment; however, it was proven that as high the social vulnerability profile of women, higher are the chance of delay (p<0.001). This result reveals the existence of inequities in the access of treatment of BC in the country, even after barriers to access health services have been apparently overcome¹⁸.

In other countries, time intervals were lower than the identified in the present study²⁶⁻²⁸. McLaughlin et al.²⁶ noticed that the women population of North Carolina (USA) had median of time between the diagnosis and treatment of 22 days (minimum: 0, maximum: 177 days). Most of the patients (90%) initiated the treatment in a

time interval lower than 60 days and in 81% of the cases, surgery was the first treatment performed. Comparing the results, it is observed that there is great discrepancy between the studies that may be related to the differences of the structure of the health studies among the countries. However, despite the responsibility being often attributed to the institutional current barriers, Travassos e Bahia²⁹ suggest that this reality is the result of the professional relation health-patient.

Although it has not been identified association between gender and delay, possibly this difference between men and women can be visualized in the stages prior to diagnosis³⁰. Because of the rarity of the disease in

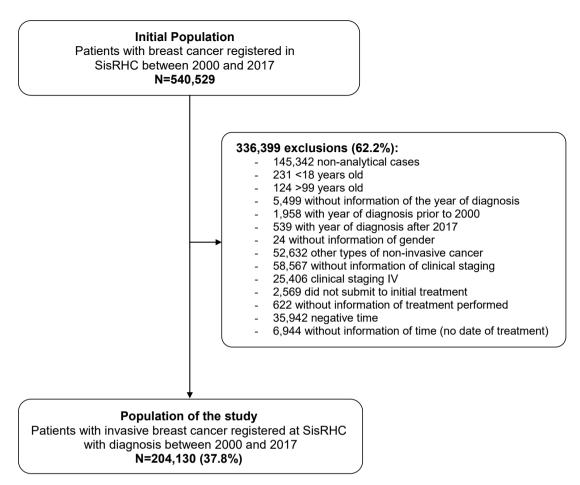


Figure 1. Flow diagram of the study inclusion and exclusion criteria

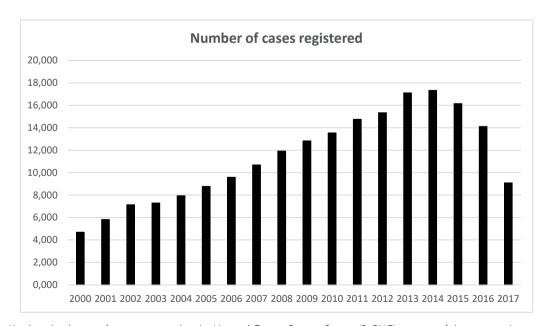


Figure 2. Absolute distribution of cases registered at the Hospital Cancer Registry System (SisRHC) per year of diagnosis in the period 2000-2017 (N=204,130)

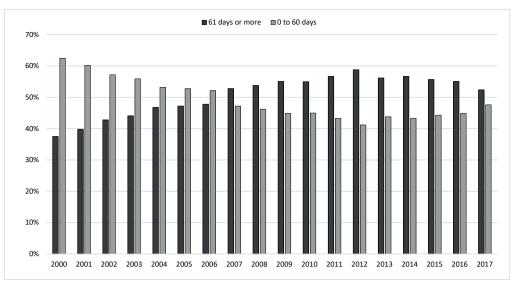


Figure 3. Distribution of the frequency of time intervals between diagnosis and beginning of the treatment, Hospital Cancer Registry System (SisRHC). Brazil, 2000-2017 (N=204,130)

males, it can be expected that the patient and the health professional delay in determining the suspicion of the disease, postponing the seek for care and beginning of the diagnosis investigation³¹. In addition, methods and lines of treatment of BC in males are still based in the methods used for females, which justifies the similarities among genders³². In a recent study, it was proved that the annual mean of BC incidence in males increased considerably³³. As a consequence, it is important to analyze the flow of consultations of men diagnosed with BC since the onset of the symptoms until the access to health services to make these processes more effective for this gender.

Patients of non-Caucasian race/skin color with less than eight years of education, aged between 50 and 69 years and who live without partner had more chance of delay compared to other categories. These factors have already been usually associated to delay^{7,9,10}. The results observed can be attributed to socioeconomic and ethnic inequalities that define the profile of more social vulnerability, impacting the search and access of health services negatively^{18,34}. Family structure and social support network also influence this context^{35,36}.

The fact that patients with $CS \ge 2B$ have less chance of delay than those with initial disease as noticed by other authors, reinforces the possibility that physicians must act fast in severer cases¹¹. In the present study, advanced $CS (\ge 2B)$ was the most frequent (52.0%). This data is corroborated by other authors that indicate that, in Brazil, most of the cases is diagnosed at advanced disease⁹. This reality is alarming because it is known that CS is an important diagnosis prognosis. As seen by Höfelmann et al.³⁷, in a study conducted in Santa Catarina, there was a drop of survival with the increase of staging (CS I: 98%; CS II: 81%; CS III and CS IV: 60%). In addition,

this clinical characteristic interferes in the quality of life of individuals with BC. That is, patients diagnosed in initial stages are submitted to less aggressive treatments and have less complications related to oncologic therapy and consequently lower risk of death³⁸. Because of this problematic, it is important to prioritize the policies of monitoring, early diagnosis and guarantee of timely treatment in order to increase the survival and better outcomes^{15,20}.

The categories of treatment based in the therapeutic conducts occurring according to CS differ in relation to the likelihood of exposure to delay. When compared to those who submitted to surgery – most frequent treatment in this study – it was noticed that patients who underwent chemotherapy and radiotherapy had approximately twofold more chance of delay. In Brazil, there are inequalities in the offer of specialized assistance for diagnosis and treatment of patients with BC^{20,34,39}. The distribution of chemotherapy and radiotherapy services within SUS indicates concentration in the biggest urban centers of the country^{20,34}. In addition, because of the concentration of the treatments offered by SUS in the large cities, many patients need to travel long distances to access the oncologic treatment^{20,21,34}.

The inequalities of the offer of specialized care for diagnosis and treatment of BC mirror the differences of access to health service among the country's macroregions^{20,40}. In 2010, 40% of the total of consultations within SUS were concentrated in only seven Brazilian capitals located in the South, Southeast and Northeast of Brazil³⁴. In addition, the biggest number of CACON and UNACON allowed by SUS are located in these regions⁴¹. This reality can justify the high chance of delay in the treatment for the residents of the West-

Central and North regions where sanitary structure is barely sufficient³⁴. In Brazil's Southeast where there is great offer of chemotherapy and radiotherapy services, the high chance of delay can be attributed to high demand for consultation because of high rates of incidence of BC in this region^{20,34,41}. Actually, living in the Northeast Region was a protection for the delay of beginning the treatment. Recent findings corroborate this result when it was observed in this region lower time intervals compared with other country regions^{9,41}.

It was observed in this study that 54.9% of the population did not live in the same municipality of the treatment unit and that the individuals who needed to journey to another city had 16% more chance of delay than those who were treated in the same municipality they lived. This data is similar to another Brazilian study where 51.34% of the SUS patients needed to go to another city seeking for treatment²¹. It is clear that the geographical barriers influence the access to health, which was reported in the State of Minas Gerais in the study of Alves et al. 42. The inequal access to monitoring, diagnosis and treatment initiatives can justify the increase of the mortality rate of women living out of the capitals⁴³. According to Oliveira et al.,34 the offer of transportation and accommodation to the needy patients can be strategies to minimize the barrier caused by the distance between the city of residence and of treatment.

In relation to the variable origin of referral, despite the fragility of this data because of the great percent of lack of information, it was observed that patients referred by SUS had more chance of delay than those who accessed the health service by their own means or were referred otherwise. According to Ferreira et al.44, who analyzed the time between the diagnosis and beginning of the treatment of BC in Ceará from 2009 to 2011, the patients referred by SUS waited more than those originated from private services with intervals of 71.5 days and 39 days (p=0.031), respectively. Medeiros et al.9 verified through data registered at RHC, from 2000 to 2011 that patients referred by SUS had 1.34 more chance of delay than those not referred by SUS. SUS patients also had disadvantages in relation to access to diagnosis and treatment of BC9. Liedke et al.¹⁶ verified that women treated in SUS had more chance of being diagnosed with advanced CS than those from private services. These authors affirm that the early access to diagnosis and treatment of BC could improve the outcome of the patients of health public services. Kaliks et al.45 e Oliveira et al.34 report that the structural limitation of the public health system hampers the access to the treatment and consequently, impact the prognosis negatively.

The structure of the health services can affect the period of diagnostic investigation and the treatment of patients with BC significantly⁴⁶. When the treatment unit was evaluated, patients treated in CACON had 20% more chance of delay when compared to those treated in other units. The more complex centers, further to being compelled to perform the definitive diagnosis and treat all types of cancer, must offer surgical treatment, chemotherapy and radiotherapy. These attributions in only one center may be creating overload that can interfere in this result^{34,42}. On the other hand, the fragilities in the process of regionalization of the care can favor the concentration of the volume of the consultations and procedures in the units of greater complexity^{21,34,42}.

In studies conducted in a CACON in Rio de Janeiro, it was observed that the patients referred without diagnosis and who were biopsied in the own CACON, had more chance of delay for diagnostic confirmation^{36,47}. In these cases, wait for the diagnosis of a tertiary hospital specialized in BC treatment can favor the waiting time for the procedure to be longer than for the patients diagnosed in less complex units³⁶.

Some limitations of the present study need to be highlighted. The study data originated from cancer cases previously registered in Brazil's SisRHC and the utilization of retrospective secondary data can interfere in the results attained. The negative aspects are the great quantity of cases with unfilled variables and secondary data whose quality of collection and storage cannot be warranted. As an example, the variables race/skin color, marital status, use of tobacco and alcohol and origin of the referral that, despite being significant in relation to the investigated outcome, presented a considerable percent of missed information, mostly, because in the State of São Paulo these data are not routinely collected. Therefore, it is paramount to fill the data of SisRHC correctly, since its analysis can help monitor the care provided to oncologic patients and guide the public policies.

The robust sample size may have favored possible errors in the test of hypothesis that can be characterized by the elevated frequency of statistically significant associations, narrow confidence intervals even when the associations between exposure and outcomes were weak. This factor contributed for the decision of not performing adjusted analysis since practically every variable were inserted in the multiple regression analysis and would remain biased in the final model.

The positive aspect that stands out is the good external validity of this study. Because data of all the Brazilian states were included, the results presented can be extrapolated to patients diagnosed with BC across the entire national territory. In addition, the heterogeneity of the population investigated herein allows the comparability of the data with populations from countries with similar profiles

of Brazil. As strong aspect of the study, it is possible to highlight the comparison between the periods before and after the publication of the "Law of the 60 days", that shows that, even after the legal fixation of the time to initiate the oncologic treatment, the majority of the population with BC is not being benefitted with this law. And, more worrying still is that after the regulation of the Law the chance of delay increased. On the other hand, it must be considered that the five-year period after the publication of the law might not have been sufficient to change the scenario of access to oncologic treatment in Brazil, since this involves a complex process of reorganization and adjustment of the public network to the new rule of the Ministry of Health. New studies must be conducted in the future to evaluate the impact of the Law along the time.

CONCLUSION

It was verified that the median of the time interval between the diagnosis and beginning of the first oncologic treatment with BC registered at SisRHC, diagnosed between 2000 and 2017 was 63 days. For most of the cases the delay was over 60 days (52.8%). Sociodemographic, clinical and treatment-related factors influenced the delay.

Based in the identification of the profile of patients more vulnerable to delay, it is possible to contribute with actions targeted to these specific groups. In addition, it was identified that even after the establishment of the 60 days Law, this delay continues being noticed, suggesting that reorganization and inspection of the attention to the patients with BC must be prioritized.

CONTRIBUTIONS

Anke Bergmann, Luiz Claudio Santos Thuler, Giselle Coutinho Medeiros, Clarice Gomes Chagas Teodózio, Erica Alves Nogueira Fabro and Suzana Sales de Aguiar contributed for the conception and design of the study, gathering, analysis and interpretation of the data and wording of the manuscript. Artur Henrique Machado Lopes, Bárbara Cordeiro de Conte, Erisvan Vieira da Silva, Lyssandra Luiza Pestana Coelho, Nitza Ferreira Muniz and Sara Isabel Pimentel de Carvalho Schuab contributed for the analysis and interpretation of the data and wording of the manuscript. All the authors approved the final version to be published.

DECLARATION OF CONFLICT OF INTERESTS

The author Anke Bergmann declares potential conflict of interests because she is scientific editor of INCA Brazilian Journal of Cancerology. The other authors have no conflict of interests.

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