

Racial disparities in breast cancer survival after treatment initiation in Brazil: a nationwide cohort study



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Summary

Background Breast cancer is a public health priority in Brazil and ensuring equity in health care is one of the cancer control plan goals. Our aim was to present the first assessment on the influence of race or skin colour on breast cancer survival at the national level.

Methods In this nationwide cohort study, data on women who initiated treatment for breast cancer in the public health-care system (Sistema Unico de Saúde), Brazil, were assembled through record linkage of administrative and mortality information systems. The administrative information systems were the Outpatient Information System (data from high complexity procedure authorisations) and the Hospital Information System (data from hospitalisation authorisations). We included women aged 19 years or older who started treatment between Jan 1, 2008, and Nov 30, 2010; self-identified as having White, Black, or Brown race or skin colour; had tumour stage I–IV; and were treated with chemotherapy or radiotherapy, or both. Patients were followed up until Dec 31, 2015. Patients with only hormone therapy records or who underwent only surgery were excluded. The Kaplan-Meier method was used to estimate crude overall survival for race or skin colour by time since treatment initiation, and Cox regression to estimate all-cause mortality hazard ratios (HRs) before and after adjustment for other covariates.

Findings We identified 59 811 women treated for stage I–IV breast cancer. 37 318 (62.4%) women identified themselves as White, 18 779 (31.4%) as Brown, and 3714 (6.2%) as Black. 5-year overall survival probability was higher for White women (74% [95% CI 73–74]) than Black women (64% [62–65]; $p < 0.0001$). In adjusted regression models stratified by the absence of hormone therapy, Black women had a 24% (HR 1.24 [95% CI 1.16–1.34]; $p < 0.0001$) higher risk of all-cause death than White women, and in the presence of hormone therapy Black women had a 25% (1.25 [1.14–1.38]; $p < 0.0001$) higher risk of all-cause death than White women.

Interpretation Black skin colour was identified as a statistically significant risk marker for lower 5-year survival probability and higher risk of all-cause death among women treated for breast cancer by the Sistema Unico de Saúde. Actions to understand and mitigate this unfair difference in health results are urgently needed.

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Introduction

Apart from non-melanoma skin cancer, breast cancer is the most common cancer among women in Brazil, followed by colorectal and cervical cancers. In Brazil, 73 610 new breast cancer cases are expected each year from 2023 to 2025, representing an adjusted incidence rate of 41.89 cases per 100 000 women.¹ Data from 14 Brazilian population-based registries revealed a stable incidence of breast cancer from 2000 to 2010. However, there was an increase in cases in people aged 70 years and older and a decrease in people aged 40–49 years.² This finding contrasts with other transitioning countries where the incidence of breast cancer has been steadily increasing over time.^{3,4} Despite the stable incidence, nationwide data have revealed that, in Brazil, breast cancer is the most common cause of cancer-related deaths in women, and that mortality rates are increasing.⁵

Although advances are being made to identify modifiable risk factors and to establish public health measures to reduce incidence, the reduction of mortality remains the cornerstone of breast cancer control.^{6,7} Global surveillance of trends in cancer survival 2000–14 (CONCORD-3) used data from six Brazilian population-based registries and revealed an increase in 5-year net survival between 2000 and 2004 (68.7%) and between 2005 and 2009 (76.9%), followed by stabilisation in 2010–14 (75.2%).⁶ However, these overall results might mask substantial inequities. After adjusting for income, a hospital-based study revealed significantly lower 10-year breast cancer survival for Brown or Black women than White women. This difference was partially mediated by the stage at diagnosis, with Brown or Black women showing a higher proportion of advanced disease.⁸ A case-only study involving 247 719 women revealed that the prevalence of late-stage (III–IV) breast cancer diagnosis

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Research in context

Evidence before this study

We used PubMed, Embase, and LILACS to search for studies published in any language between database inception and Sept 4, 2023, and that evaluate racial inequality in breast cancer survival in Brazil, using the terms “breast cancer”, “survival”, “racial”, “inequality” and “social determinants”. The studies identified from this search were restricted to subnational datasets and showed that women with Black skin colour presented worse survival than women with White skin colour.

Added value of this study

To our knowledge, this is the first Brazilian nationwide assessment of racial inequity in breast cancer survival. We extracted a cohort of women treated for breast cancer in the public health-care system from a database constructed through the deterministic-probabilistic linkage of two administrative

databases and the mortality database. We have shown that women with Black skin colour presented with a higher risk of all-cause death irrespective of stage at diagnosis in 60 months after treatment initiation. This difference was also seen after adjusting for stage at diagnosis, age at the beginning of treatment, comorbidities, treatment exposure (chemotherapy, radiotherapy, or surgery), Human Development Index, and rural or urban typology of the municipality of residence.

Implications of all the available evidence

This study contributes to the review of the national cancer control plan in Brazil: actions to improve early detection might have a positive effect on racial equity. Additionally, this study encourages researchers to conduct analysis of racial inequality contributing to the debate on the impact of skin colour on people's lives in Brazil.

remained high, at approximately 40%, from 2001 to 2014. Further, this prevalence was higher for women who identified themselves as Black or Brown when compared with White women.⁹

These results are based on data from the public health system, which is the primary provider of cancer care in Brazil, covering screening, diagnosis, treatment, and rehabilitation.^{5,10} The Sistema Único de Saúde (SUS) was established in 1990 to offer free health care, with the goal of achieving universal health coverage.¹¹ 8 years after the implementation of SUS, breast cancer became the focus of a specific health programme and, since then, successive cancer programmes and policies have given special attention to the disease.¹² Although all SUS policies and programmes have to follow the principle of equity, unfair and avoidable differences in access to health care among individuals of different skin colours are recognised.¹³

In Brazil, there has been relatively little research on racial inequities in health care, despite recommendations of the National Commission on Social Determinants of Health and other entities.^{14,15} In contrast, in the USA, several breast cancer survival studies have consistently shown worse outcomes for Black women when compared with non-Hispanic White women.^{16–18} However, unlike in the USA, where race is highly related with ancestry, in Brazil, race is more closely related to skin colour and other physical aspects, so much that the Brazilian census adopts the term “race/skin color”.¹⁹ In this way, race or skin colour is understood as a social construct and not an individual or biological characteristic.²⁰ To the best of our knowledge, no nationwide Brazilian breast cancer study has explored this subject in relation to breast cancer survival. Therefore, we aimed to investigate the impact of race or skin colour on the survival of women treated for breast cancer in the SUS.

Methods

Study design and participants

In this nationwide cohort study, we used a dataset from the National Database on Oncology (BaseOnco), which is a subset of 3.5 million cancer patients from the Brazilian National Database of Health (BNDH). The BNDH covers 15 years of historical data for approximately 200 million inhabitants.²¹ Our dataset consisted of women treated for breast cancer (International Classification of Diseases [ICD]-10 codes: C50.0, C50.1, C50.2, C50.3, C50.4, C50.5, C50.6, C50.8, and C50.9) in the SUS, Brazil, between Jan 1, 2000, and Dec 31, 2015. We included patients who started their first cancer treatment between Jan 1, 2008, and Nov 30, 2010; were aged 19 years or older on the treatment start date; had tumour stage I–IV; were treated with chemotherapy or radiotherapy, or both, and were of White, Black, or Brown race or skin colour. “Race/skin color” is the name of the variable used in official Brazilian information systems. This variable was self-reported by the patient with five options: White, Black, Brown, Yellow (Asian descent), and Indigenous. We did not include Indigenous or Yellow patients in the study because the dynamics of racial discrimination that might affect these groups are different to those that affect the Black and Brown groups. Also, Indigenous people might be under-represented in this cohort as they are often cared for by the armed forces (outside SUS). The Brown skin colour might be understood as a mixed race. In our study, we assigned the race or skin colour as the one most frequently reported in the records of each patient. Patients with only hormone therapy records were not included. Because of the unavailability of TNM stage information in hospitalisation authorisations and to avoid the inclusion of stage 0 patients, women who underwent only surgery were excluded. The end of the follow-up period was Dec 31, 2015.

This study was approved by the Ethics Committee of the Universidade Federal de Minas Gerais (CAAE 44121315.2.0000.5149). The non-anonymised databases used to construct the BNDH were provided by the Ministry of Health of Brazil. After anonymisation, permission was obtained from the database holders (MLC and AAG) to access and use the data.

Procedures

BaseOnco integrates health data from the main SUS information systems: the Outpatient Information System (SIA), the Hospital Information System (SIH), and the Mortality Information System (SIM).

SIA and SIH are systems developed for the collection, storage, and processing of data from high complexity procedure authorisations (APACs) and hospitalisation authorisations, respectively, and SIA and SIH are used for transfer of financial resources between health authorities. APACs and hospitalisation authorisations capture personal, clinical, and procedure data. In oncology, APACs are used to record chemotherapy, radiotherapy, and hormonotherapy authorisations, and hospitalisation authorisations are used to record all hospitalisations including those for or related to surgeries.²² SIM receives, stores, and processes death certificate data issued throughout the country, including the name and date of birth of the deceased, cause of death according to ICD-10 codes, and place of death.^{21,22} The percentage of the deaths registered as garbage codes decreased from 41.3% in 2000 to 33.3% in 2015 in the mortality data in Brazil.²³

Briefly, for the construction of the BNDH, personal data from APACs, hospitalisation authorisations, and death certificates were used for two-by-two comparisons. The records with identical data were considered to be of the same patient (deterministic record linkage). Non-identical pairs received a score according to the probability of being from the same individual (probabilistic record linkage). A random sample of non-identical pairs was assessed manually to establish a cut-off score, a probability from which the pairs of records would be considered to belong to the same individual. Each individual received a unique identification code, and the database was anonymised. A technical description on the deterministic–probabilistic record linkage method used for the construction of BNDH is in the appendix (p 11).

Outcomes and variables of interest

Our primary objective was to estimate the impact of race or skin colour (White, Brown, and Black) in breast cancer 5-year overall (all-cause mortality) survival. As a secondary objective, we described the 5-year disease-specific survival according to race or skin colour.

Other factors were used as independent variables in the regression model: age group at the beginning of treatment (19–39 years, 40–49 years, 50–59 years, 60–69 years, 70–79 years, and ≥80 years); geographical region of residence (North, Northeast, Midwest,

Southeast, and South); if treatment started outside the state of residence (yes or no); year of treatment initiation; number of comorbidities in the first year of treatment (none, 1, 2, 3, or ≥4), as proposed by Elixhauser and colleagues;²⁴ cancer TNM stage (I, II, III, or IV); treatment performed (chemotherapy, radiotherapy, or surgery [conservative or mastectomy]); and if patients were given hormone therapy (yes or no).

For the municipality of residence, we extracted the Human Development Index (HDI) for 2010 from the Atlas of Human Development in Brazil;²⁵ and the 2017 rural or urban classification from the Brazilian Institute of Geography and Statistics (IBGE).²⁶ HDI is a summary measure composed of the geometric mean of life expectancy at birth, years of schooling before the age of 25 years, and the logarithm of income per capita. Municipalities were categorised into five HDI tiers: very high (0.800–1.000), high (0.700–0.799), medium (0.600–0.699), low (0.500–0.599), and very low (0.000–0.499). The 2017 rural or urban classification used data from the 2010 census to classify municipalities according to population size and density (rural, intermediate, or urban) and the geographical isolation index (remote or adjacent).

Statistical analysis

We calculated the frequency distributions of the categorical variables and compared the race or skin colour groups using the χ^2 test. For the survival analysis, we calculated the survival time as the duration (in months) between the date of treatment initiation and the occurrence of an event (death) or the end of the follow-up (Dec 31, 2015). To determine the date of treatment initiation, we selected the earliest date available in the SIH and SIA databases for each patient. This date represents the month of the first recorded procedure for each patient, whether surgery, chemotherapy initiation (neoadjuvant, adjuvant, or palliative), or radiotherapy initiation. Because our study was derived from information systems set up to collect treatment data, we did not have information on women who were diagnosed but never started treatment. Although the date of diagnosis is available in the databases, to prevent immortal bias (inclusion of the immortal time period between diagnosis date and treatment initiation), our time-to-event calculations considered the start of treatment as the start date.

To estimate the probability of overall survival, the date of the event of interest was defined as the date of death from any cause. To estimate the probability of disease-specific survival, the date of the event was defined as the date of death from malignant breast cancer (C50) or from the following malignant neoplasms: brain (C71), liver and intrahepatic bile ducts (C22), bones and articular cartilages of the limbs (C40), bones and articular cartilages from other locations and unspecified locations (C41), and bronchi and lungs (C34). These causes were selected according to the main sites of breast cancer metastasis to

See Online for appendix

	All (n=59 811)	White women (n=37 318)	Brown women (n=18 779)	Black women (n=3714)	p value
Age at treatment start, years	<0.0001
Mean age (SD)	54.6 (12.8)	55.3 (12.9)	53.2 (12.8)	54.1 (12.6)	..
19–39	6810 (11.4%)	3805 (10.2%)	2550 (13.6%)	455 (12.2%)	..
40–49	15 900 (26.6%)	9538 (25.6%)	5403 (28.8%)	959 (25.8%)	..
50–59	16 666 (27.9%)	10 393 (27.8%)	5213 (27.7%)	1060 (28.5%)	..
60–69	12 259 (20.5%)	8020 (21.5%)	3468 (18.5%)	771 (20.7%)	..
70–79	6325 (10.6%)	4258 (11.4%)	1676 (8.9%)	391 (10.5%)	..
≥80	1851 (3.1%)	1304 (3.5%)	469 (2.5%)	78 (2.3%)	..
TNM stage at diagnosis	<0.0001
I	8758 (14.6%)	6149 (16.5%)	2229 (11.9%)	380 (10.2%)	..
II	20 249 (33.8%)	13 028 (34.9%)	6125 (32.6%)	1096 (29.5%)	..
III	25 145 (42.0%)	14 624 (39.2%)	8699 (46.3%)	1822 (49.1%)	..
IV	5659 (9.6%)	3517 (9.4%)	1726 (9.2%)	416 (11.2%)	..
Comorbidities in the first year, Elixhauser score	0.0003
0	57 890 (96.8%)	36 085 (96.7%)	18 235 (97.1%)	3570 (96.1%)	..
1	1808 (3.0%)	1165 (3.1%)	513 (2.7%)	130 (3.5%)	..
2	108 (0.2%)	67 (0.2%)	29 (0.2%)	12 (0.3%)	..
3	5 (0.0%)	1 (0.0%)	2 (0.0%)	2 (0.1%)	..
Chemotherapy	<0.0001
Yes	48 028 (80.3%)	29 564 (79.2%)	15 383 (81.9%)	3081 (83.0%)	..
No	11 783 (19.7%)	7754 (20.8%)	3396 (18.1%)	633 (17.0%)	..
Radiotherapy	<0.0001
Yes	43 166 (72.2%)	27 089 (72.6%)	13 507 (71.9%)	2570 (69.2%)	..
No	16 645 (27.8%)	10 229 (27.4%)	5272 (28.1%)	1144 (30.8%)	..
Breast cancer surgery	<0.0001
Conservative	9961 (16.6%)	6560 (17.6%)	2847 (15.2%)	554 (14.9%)	..
Mastectomy	16 262 (27.2%)	9676 (25.9%)	5453 (29.0%)	1133 (30.5%)	..
No*	33 588 (56.2%)	21 082 (56.5%)	10 479 (55.8%)	2027 (54.6%)	..
Hormone therapy	<0.0001
Yes	36 845 (61.6%)	24 066 (64.5%)	10 724 (57.1%)	2055 (55.3%)	..
No	22 966 (38.4%)	13 252 (35.5%)	8055 (42.9%)	1659 (44.7%)	..
Region of residence at diagnosis	<0.0001
North	2009 (3.4%)	387 (1.0%)	1554 (8.3%)	68 (1.8%)	..
Northeast	12 363 (20.7%)	3942 (10.6%)	7698 (41.0%)	723 (19.5%)	..
Midwest	3395 (5.6%)	1516 (4.1%)	1697 (9.0%)	182 (4.9%)	..
Southeast	29 750 (49.7%)	20 029 (53.7%)	7335 (39.1%)	2386 (64.2%)	..
South	12 294 (20.6%)	11 444 (30.6%)	495 (2.6%)	355 (9.6%)	..
Started treatment in different state of residence	<0.0001
Yes	1357 (2.3%)	722 (1.9%)	563 (3.0%)	72 (1.9%)	..
No	58 454 (97.7%)	36 596 (98.1%)	18 216 (97.0%)	3642 (98.1%)	..
Year of treatment start	0.0005
2008	20 606 (34.4%)	13 062 (35.0%)	6327 (33.7%)	1217 (32.8%)	..
2009	20 419 (34.1%)	12 744 (34.1%)	6392 (34.0%)	1283 (34.5%)	..
2010 (until Nov 30)	18 786 (31.5%)	11 512 (30.9%)	6060 (32.3%)	1214 (32.7%)	..

(Table 1 continues on next page)

account for errors in filling death certificates. Patients who did not have an event of interest during 60 months of follow-up or until Dec 31, 2015, were censored.

The overall and disease-specific survival curves and respective 95% CIs were estimated according to race or skin colour and disease stage using the Kaplan-Meier

method. The curves were compared using the log-rank test at a significance level of 5%. For overall survival outcomes, the association between independent variables and survival time was assessed using the Cox proportional hazards model. For the adjusted model, the independent variables were divided into blocks

	All (n=59 811)	White women (n=37 318)	Brown women (n=18 779)	Black women (n=3714)	p value
(Continued from previous page)					
HDI of the municipality of residence	<0.0001
0.000–0.499	11 (0.0%)	2 (0.0%)	8 (0.0%)	1 (0.0%)	..
0.500–0.599	2326 (3.9%)	583 (1.6%)	1599 (8.6%)	144 (3.9%)	..
0.600–0.699	8842 (14.8%)	4067 (10.9%)	4218 (22.6%)	557 (15.0%)	..
0.700–0.799	36 532 (61.1%)	23 738 (63.7%)	10 388 (55.6%)	2406 (64.9%)	..
>0.799	11 944 (20.0%)	8888 (23.8%)	2456 (13.2%)	600 (16.2%)	..
Data missing	156 (0.3%)	40 (0.1%)	110 (0.6%)	6 (0.2%)	..
Typology of the municipality of residence†	<0.0001
Rural and remote	239 (0.4%)	80 (0.2%)	144 (0.8%)	15 (0.4%)	..
Rural adjacent to an urban area	5951 (10.0%)	3601 (9.6%)	2079 (11.1%)	271 (7.3%)	..
Intermediate and remote	94 (0.2%)	28 (0.1%)	61 (0.3%)	5 (0.1%)	..
Intermediate and adjacent to an urban area	2964 (5.0%)	1806 (4.8%)	1003 (5.4%)	155 (4.2%)	..
Urban	50 407 (84.4%)	31 763 (85.3%)	15 382 (82.4%)	3262 (88.0%)	..
Data missing	156 (0.3%)	40 (0.1%)	110 (0.6%)	6 (0.2%)	..

Data are n (%) unless otherwise indicated. Percentages for categories consider patients with available information and the denominator is the total number of patients with available information. Percentages for data missing refer to the total number of patients. The provided p values refer to the comparison between White, Brown, and Black skin colour groups. Due to the large sample size, statistically significant differences might not reflect clinical or epidemiological differences. HDI=Human Development Index. *Might include surgeries other than breast cancer surgeries. †Municipalities were classified according to population size and density (rural, intermediate, or urban) and geographical isolation index (remote or adjacent).

Table 1: Characteristics of patients with breast cancer included in the study, Brazil, 2008–15

considering their causal influence on the survival time of the patients (hierarchical model). The reference levels of each variable were established as the most frequent, except for the stage at diagnosis, in which stage I was established as the reference level. The first block of variables comprised distal-level characteristics: race or skin colour, geographical region of residence, whether treatment started outside the state of residence, HDI, and rural or urban classification of the municipality of residence. The second block was composed of proximal-level characteristics: age group, TNM stage, treatment variables, and the presence of comorbidities. In the first step of modelling, the distal-level variables were included as a block, and those that obtained a hazard ratio (HR) p value of less than 0.10 were selected for the next step of modelling. In the second step of modelling, the proximal-level variables were included, and those with a HR p value of less than 0.10 remained in the final adjusted model. The proportional hazard assumption was assessed by Schoenfeld residual examination. All analyses were conducted using R software version 3.6.2 and figures were produced using the ggplot2 package version 3.4.4.^{27,28}

Role of the funding source

The funders of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

Results

We identified 59 811 women who started treatment for stage I–IV breast cancer in the SUS between Jan 1, 2008,

and Nov 30, 2010 (appendix p 12). 37 318 (62.4%) women identified themselves as White, 18 779 (31.4%) as Brown, and 3714 (6.2%) as Black (table 1). The mean age at the start of treatment for the entire cohort was 54.6 years (SD 12.8). A higher percentage of Black women (60.3%) were diagnosed with advanced stages (III–IV) of breast cancer than Brown (55.5%) and White women (48.6%; $p < 0.0001$). 57 890 [96.8%] patients did not present with any comorbidities (Elixhauser score) during the first year of treatment. Proportionally more White women (64.5%) underwent hormonal therapy than Brown (57.1%) and Black women (55.3%; $p < 0.0001$). Most women resided in urban areas in the Southeast region and did not move from their state of residence (table 1). Women who were excluded from the study due to having undergone only breast cancer surgery were younger than those who were included (mean 49.8 years [SD 15.9] vs 54.6 years [12.8]) and most of the excluded women underwent conservative surgery (66.5%; appendix p 13).

The overall 5-year survival probability was 73% (95% CI 72–73) and the disease-specific 5-year survival probability was 78% (78–78), with differences among race or skin colour groups (figure 1). 5-year overall survival probability was higher for White women (74% [95% CI 73–74]) than Black women (64% [62–65]; $p < 0.0001$). 5-year overall survival probabilities were 92% (92–93) for stage I, 85% (84–85) for stage II, 65% (64–66) for stage III, and 36% (35–38) for stage IV. The survival of Black women was lower than that of Brown and White women at all disease stages (figure 2). The overall survival curves of women excluded from the study for

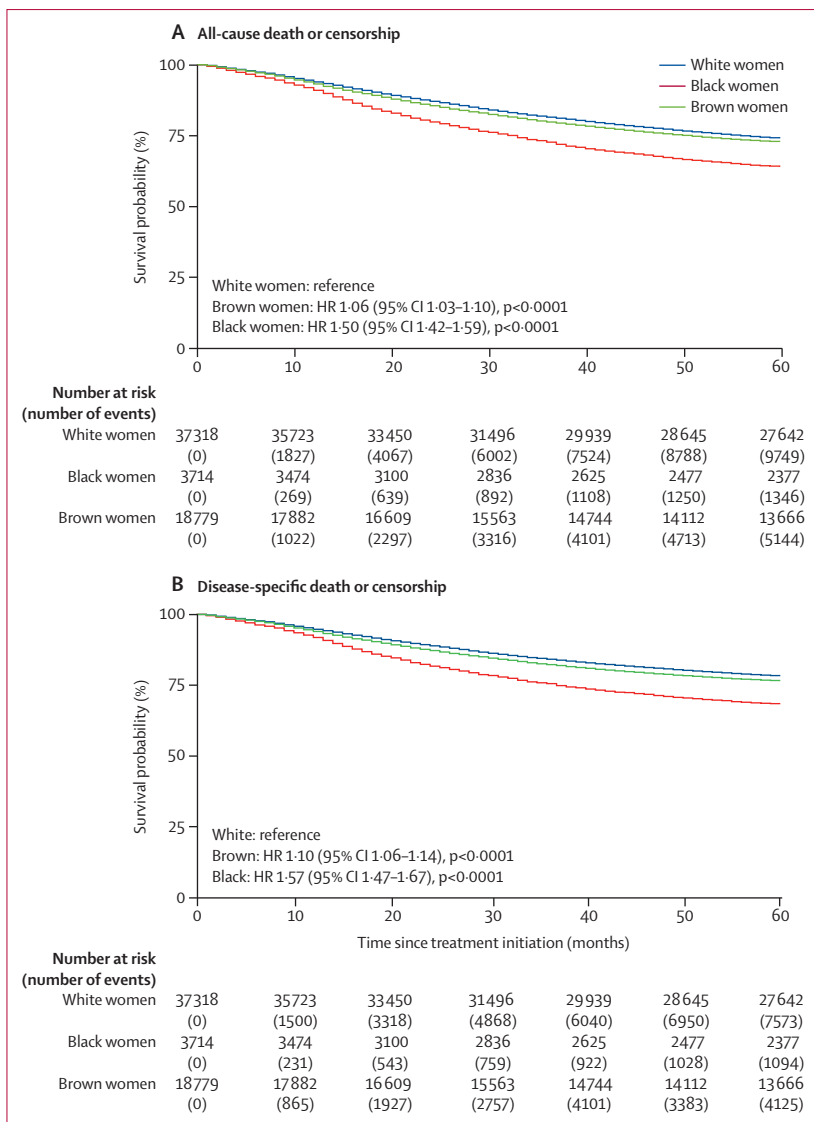


Figure 1: Kaplan-Meier curves of breast cancer 5-year survival from treatment initiation to all-cause death or censorship and from treatment initiation to disease-specific death or censorship of patients treated by the Sistema Único de Saúde, according to race or skin colour in Brazil, 2008–15

Causes of death in disease-specific analysis were malignant neoplasms of the liver and intrahepatic bile ducts (0.7%), bronchi and lungs (18.2%), bones and articular cartilages of the limbs (0.1%), bones and articular cartilages from other locations and unspecified locations (0.2%), breast cancer (80.1%), and brain (0.7%). HR=hazard ratio.

having had only breast cancer surgery also showed that the Black skin colour group had a lower survival probability than the White and Brown skin colour groups (appendix p 16).

Overall survival probabilities for the three race or skin colour groups were lower for patients in the youngest (aged 39 years and younger) and oldest (80 years and older) age groups. Patients who underwent conservative surgery presented with a higher probability of survival than patients who underwent mastectomy or did not undergo surgery; and patients who underwent hormonal therapy presented higher survival probability than those

who did not undergo such treatment, irrespective of race or skin colour (table 2).

In all five geographical regions, the 5-year overall survival probability of women with Black skin colour was the lowest. In the North and Midwest regions, the highest survival probability was observed for Brown women, who represented 77% of the study population in the North and 50% in the Midwest. In the South region, there was no difference in the survival probability between the Black and Brown skin colour groups. In the Southeast and Northeast regions, there was no difference between White and Brown skin colour groups (table 2; appendix pp 17–18). Further, there was a tendency for increased survival with an increase in HDI (table 2).

The Schoenfeld residuals analysis of Cox’s model indicated that the hormone therapy variable violated the proportional hazards assumption. Thus, we conducted a stratified analysis based on this variable. It should be noted that having hormone therapy information recorded indicated that the patient had a positive hormone receptor tumour, and not having hormone therapy information recorded might represent hormone-negative tumours or a patient with hormone receptor-positive tumours without access to appropriate therapy. More women without the hormone therapy claim initiated treatment at stages III (48.0% vs 38.3%) and IV (13.4% vs 7.0%) compared with women with at least one hormone therapy claim. Additionally, there were differences in the geographical distribution. Although most women from both groups resided in the Southeast region of Brazil, the second region where most women resided was the Northeast for those with no hormone therapy claim, and the South for those with a hormone therapy claim. (appendix p 19).

In the adjusted models, Black skin colour had a higher risk of all-cause death when compared with White skin colour, with a 25% higher risk for the model with a hormone therapy claim (HR 1.25 [95% CI 1.14–1.38], p<0.0001) and 24% higher risk for the model without a hormone therapy claim (1.24 [1.16–1.34], p<0.0001). In the model for women without a hormone therapy claim, the Brown skin colour group had a lower risk of death than the White skin colour group. In both models, women living in the South and Midwest geographical regions presented a higher risk of death when compared with women living in the Southwest. In the regression model of patients with a hormone therapy claim, women living in rural municipalities adjacent to urban areas exhibited a lower risk of death than those living in urban municipalities. In the regression model of patients without a hormone therapy claim, women living in municipalities with the two lowest HDI levels presented a higher risk of death compared with women living in municipalities with high a HDI level (0.700–0.799; reference). Further, women living in municipalities with a very high HDI level (0.800–1.000)

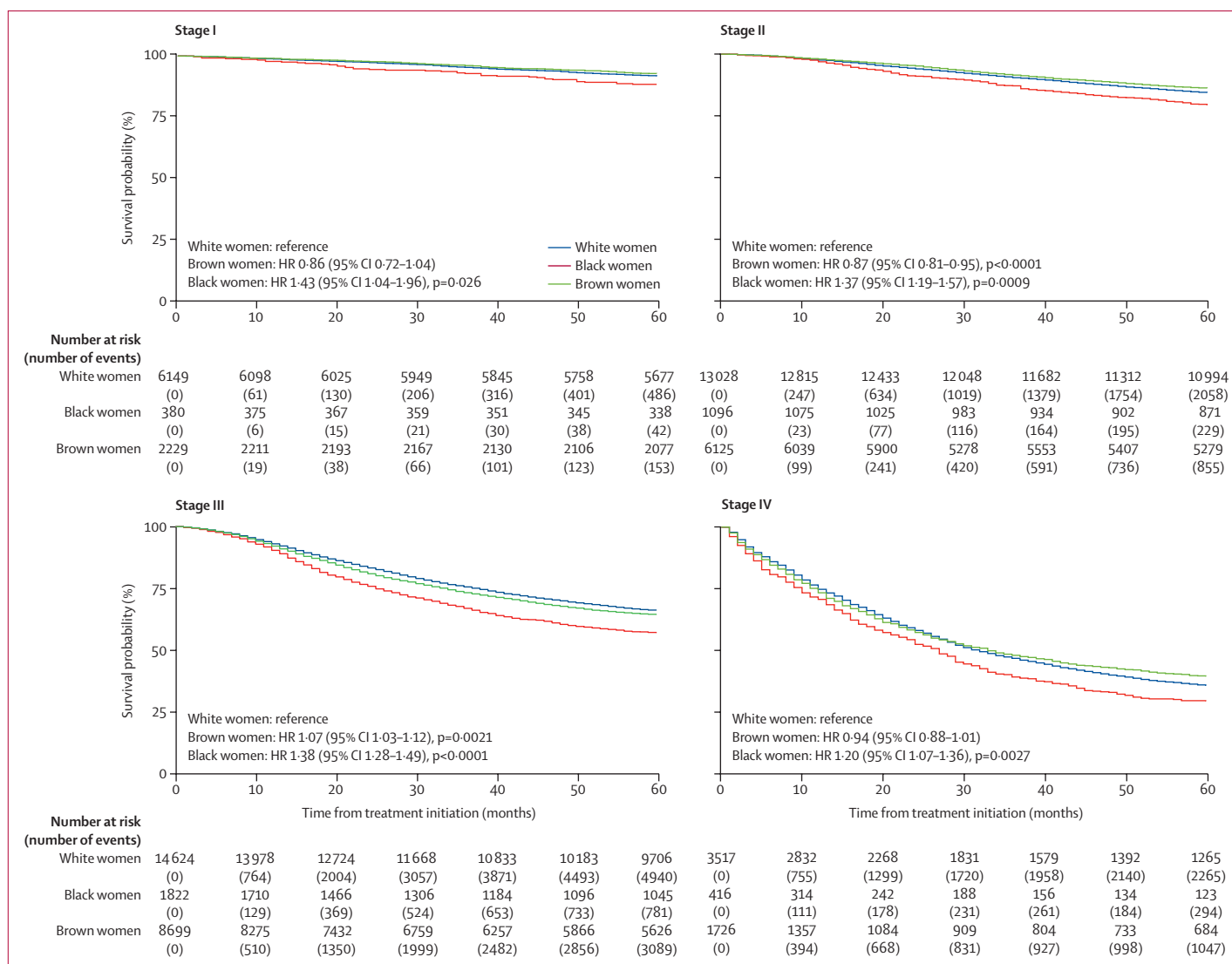


Figure 2: Kaplan-Meier curves of breast cancer 5-year survival from treatment initiation to all-cause death or censorship by cancer stage of patients treated by the Sistema Único de Saúde, according to race or skin colour in Brazil, 2008–15
 HR=hazard ratio.

had a lower risk of death compared with the reference group.

As for the proximal variables, in both models, the oldest age groups (60–69 years, 70–79 years, and ≥80 years) had a higher risk of death than the reference age group of 50–59 years, and women aged 40–49 years had a lower risk of death compared with the reference age group. In the model of patients with a hormone therapy claim, the younger individuals (aged 18–39 years) had a higher risk of death than the reference age group. Further, in both models, patients diagnosed at advanced stages and patients with comorbidities (Elixhauser score) also had a higher risk of death. Also, patients who underwent chemotherapy had a higher risk of death than patients who did not, and patients who underwent mastectomy or did not undergo

breast surgery had a higher risk of death compared to patients who underwent conservative surgery. In the regression model of patients without a hormone therapy claim, having undergone radiotherapy was a protective factor (figures 3, 4; appendix pp 22, 26).

Discussion

In this study, we showed that, among women who initiated treatment for breast cancer in the SUS between 2008 and 2010, those with Black and Brown skin colour had a lower 5-year overall survival probability than White women. When compared with White women, women with Black skin colour presented a higher 5-year risk of all-cause death at all disease stages. Further, women from the North and Midwest regions had a higher risk of cancer-related death compared to those from the Southeast region. We

	White women (n=37 318)		Brown women (n=18 779)		Black women (n=3714)		Log-rank p value†
	Overall survival probability (95% CI)	Log-rank p value	Overall survival probability (95% CI)	Log-rank p value	Overall survival probability (95% CI)	Log-rank p value	
Race or skin colour	74% (73–74)	..	73% (72–73)	..	64% (62–65)	..	<0-0001
Age at treatment start, years	..	<0-0001	..	<0-0001	..	<0-0001	..
19–39	70% (69–72)	..	68% (67–70)	..	59% (55–64)	..	<0-0001
40–49	79% (78–80)	..	76% (74–79)	..	70% (67–72)	..	<0-0001
50–59	76% (75–76)	..	73% (72–74)	..	64% (62–68)	..	<0-0001
60–69	74% (74–75)	..	74% (72–75)	..	63% (59–66)	..	<0-0001
70–79	68% (67–69)	..	68% (66–70)	..	59% (55–64)	..	0-0030
≥80	50% (47–52)	..	63% (59–68)	..	42% (33–55)	..	<0-0001
TNM stage at diagnosis	..	<0-0001	..	<0-0001	..	<0-0001	..
I	92% (91–93)	..	93% (92–94)	..	89% (86–92)	..	0-010
II	84% (84–85)	..	86% (85–87)	..	79% (77–81)	..	<0-0001
III	66% (66–67)	..	65% (64–66)	..	57% (55–60)	..	<0-0001
IV	36% (34–37)	..	40% (37–42)	..	30% (25–34)	..	<0-0001
Comorbidities in the first year, Elixhauser score	..	<0-0001	..	<0-0001	..	<0-0001	..
0	74% (74–75)	..	73% (72–74)	..	64% (63–66)	..	<0-0001
≥1	64% (61–67)	..	62% (58–67)	..	49% (41–58)	..	<0-0001
Chemotherapy	..	<0-0001	..	<0-0001	..	<0-0001	..
Yes	72% (71–72)	..	70% (69–71)	..	62% (60–64)	..	<0-0001
No	83% (82–83)	..	85% (84–86)	..	73% (69–76)	..	<0-0001
Radiotherapy	..	<0-0001	..	<0-0001	..	<0-0001	..
Yes	77% (76–77)	..	76% (75–77)	..	67% (65–69)	..	<0-0001
No	66% (65–66)	..	64% (63–65)	..	57% (54–60)	..	<0-0001
Surgery	..	<0-0001	..	<0-0001	..	<0-0001	..
Conservative	84% (83–85)	..	82% (81–84)	..	75% (72–79)	..	<0-0001
Mastectomy	70% (69–70)	..	68% (67–69)	..	61% (58–64)	..	<0-0001
No	73% (72–73)	..	72% (71–73)	..	62% (60–64)	..	<0-0001
Hormone therapy	..	<0-0001	..	<0-0001	..	<0-0001	..
Yes	82% (81–82)	..	82% (81–82)	..	76% (74–78)	..	<0-0001
No	59% (58–60)	..	60% (59–62)	..	48% (46–51)	..	<0-0001
Region of residence at diagnosis	..	<0-0001	..	<0-0001	..	<0-0001	..
North	57% (52–62)	..	75% (73–77)	..	41% (31–55)	..	<0-0001
Northwest	71% (70–72)	..	72% (71–73)	..	61% (57–65)	..	<0-0001
Midwest	67% (65–69)	..	71% (69–74)	..	65% (58–72)	..	0-008
Southwest	74% (74–75)	..	73% (72–74)	..	65% (63–67)	..	<0-0001
South	75% (74–76)	..	63% (59–68)	..	62% (57–67)	..	<0-0001
Started treatment in different state of residence	..	0-84	..	1-00	..	0-55	..
Yes	74% (71–77)	..	73% (69–76)	..	61% (51–73)	..	0-04
No	74% (73–74)	..	73% (72–73)	..	64% (62–65)	..	<0-0001

(Table 2 continues on next page)

observed that, although the Black skin colour group consistently presented the lowest 5-year survival probability of all the other groups across geographical regions, the best results were not always observed for the White skin colour group; for instance, in the North and Midwest regions, the Brown skin colour group had the best result. This finding might be due to the low proportion of women with Black skin in these regions represented in this study.

In the South, we found a clear difference between survival curves for Black, Brown, and White women, with women with Black skin colour presenting the lowest probability followed by women with Brown skin colour. The South region received an influx of immigrant Europeans in the 19th century—much more recently than other regions—and therefore miscegenation might be lower than in the rest of Brazil. A survival analysis²⁹

	White women (n=37318)		Brown women (n=18779)		Black women (n=3714)		Log-rank p value†
	Overall survival probability (95% CI)	Log-rank p value	Overall survival probability (95% CI)	Log-rank p value	Overall survival probability (95% CI)	Log-rank p value	
(Continued from previous page)							
HDI of the municipality of residence‡	..	<0.0001	..	<0.0001	..	0.01	..
<0.600	63% (59–67)	..	71% (68–73)	..	54% (46–63)	..	<0.0001
0.600–0.699	71% (70–73)	..	71% (70–73)	..	61% (57–65)	..	<0.0001
0.700–0.799	75% (74–75)	..	72% (71–73)	..	65% (63–67)	..	<0.0001
>0.799	74% (73–75)	..	77% (75–78)	..	66% (62–70)	..	<0.0001
Typology of the municipality of residence§	..	0.67	..	0.024	..	<0.0001	..
Urban	74% (73–74)	..	73% (72–74)	..	64% (63–66)	..	<0.0001
Intermediate and adjacent to an urban area	74% (72–76)	..	72% (69–75)	..	57% (50–66)	..	<0.0001
Intermediate and remote	75% (61–93)	..	64% (53–77)	..	20% (03–1.00)	..	<0.0001
Rural adjacent to an urban area	74% (73–75)	..	71% (69–73)	..	60% (54–66)	..	<0.0001
Rural and remote	66% (57–77)	..	65% (58–73)	..	67% (47–95)	..	1.00

HDI=Human Development Index. *Survival from start of treatment until death by any cause or study end. †All log-rank tests of comparisons of variables' categories within each race or skin colour group had p value <0.05, except for the started treatment in different state of residence category for all race or skin colour groups and the typology of the municipality of residence category for the White race or skin colour group. ‡We combined patients from the very low (0.000–0.499) and low human (0.500–0.599) development indices in the <0.600 level. §Municipalities were classified according to their population size and density (rural, intermediate, or urban) and geographical isolation index (remote or adjacent).

Table 2: 5-year overall survival probabilities* of patients with breast cancer treated by Sistema Único de Saúde, by race or skin colour in Brazil, 2008–15

conducted using individual data from two population-based cancer registries from two cities, one from the South region (Curitiba) and one from the Northeast region (Aracaju), including women diagnosed between 1996 and 2012, revealed interesting findings regarding race or skin colour. In Curitiba, the HR for (all-cause) mortality was 1.49 fold higher for Brown women and 1.35 fold higher for Black women compared with white women. However, in Aracaju, there was no difference between race or skin colour groups after race or skin colour data imputation for missing values. Although this finding might reflect a true absence of difference in survival, it might also reflect the low power of the study due to the low representation of Black women in the Aracaju registry.²⁹

In our study, race or skin colour remained a significant predictor of survival in the final regression models, which were stratified according to the presence or absence of a hormone therapy claim. Hormone-receptor-positive tumours have a better prognosis than hormone-receptor-negative tumours.³⁰ In both models, Black women presented a higher risk of death than White women. Interestingly, in the no hormone therapy claim model, Brown women presented a lower risk of death in 60 months compared with White women. Also interestingly, the second geographical region in which most women in the no hormone therapy claim group resided was the Northeast, where there was no difference between White and Brown women regarding 5-year overall survival probability for the entire cohort.

In our study we chose to respect the race or skin colour that the women had self-reported. Had we grouped Brown and Black women, as some authors have done,³¹ we might not have observed significant differences in survival, mainly due to the relatively small number of self-reported Black women in our cohort. In the Pesquisa das Características Étnico-raciais da População, conducted by IBGE, when respondents were asked to indicate their race or skin colour, up to 80 different terms arose. This number contrasts with the five possible options available for inhabitants to identify themselves in official documents.³²

A study using data from the Surveillance, Epidemiology, and End Results Program, between 2004 and 2014, revealed that Black women were less likely to be diagnosed with stage I cancer than non-Hispanic White women in all age groups, and that the risk of death was also higher among Black women. The authors suggested that biological features, such as lymph node metastasis, distant metastasis, and triple-negative behaviour of tumours accounted for much of this difference.³³ An analysis of over 1.1 million women in the USA diagnosed with breast cancer revealed higher odds of triple-negative tumours among non-Hispanic Black women and Hispanic women.³⁴ However, a case-control study in the USA found no difference in prevalence of germline pathogenic variants of breast cancer between Black and non-Hispanic White women. Based on these results the authors recommend that

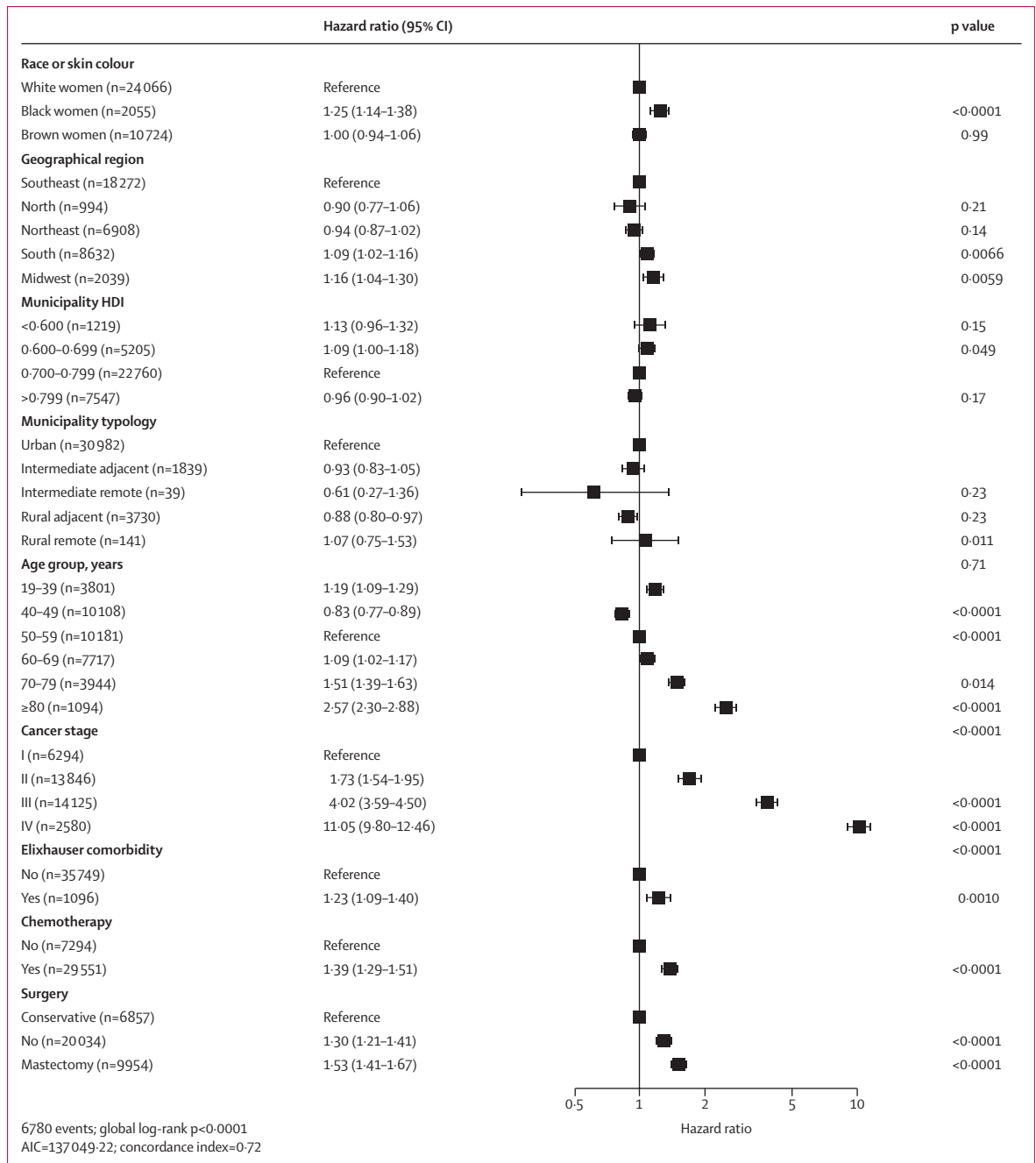


Figure 3: Forest plot of the hazard ratios for risk of death, with 95% CIs, for variables included in the final adjusted model for patients with hormone therapy claim record
 AIC=Akaike information criterion. HDI=Human Development Index.

guidelines for genetic testing should not be tailored according to race.³⁵

In our study, hormone therapy was used less frequently by Black and Brown women, which might indicate a lower frequency of hormone-receptor-positive tumours in these patient groups or a scarcity of access to appropriate therapy.³⁶ One Brazilian study showed a high frequency of luminal tumours in the Southeast

and South regions. Further, more aggressive tumours (epidermal growth factor receptor 2-enriched and triple negative) were most frequent in the North region, and triple-positive tumours were the most frequent in the Midwest region. In the Northeast, a region with high African ancestry, the subtypes presented with an intermediate frequency.³⁷ The relationship between the differences in survival observed in the present study and

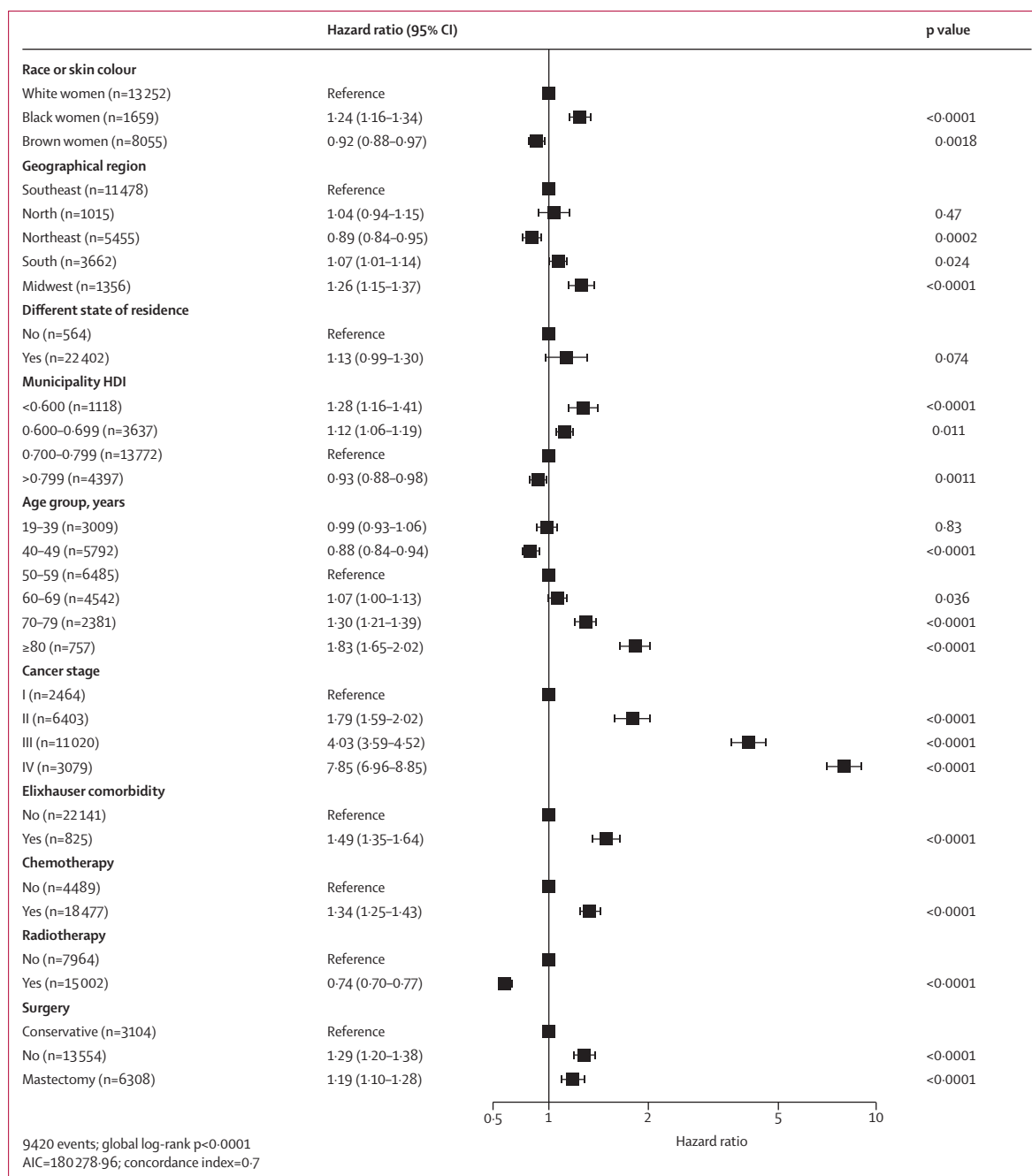


Figure 4: Forest plot of the hazard ratios for risk of death, with 95% CIs, for variables included in the final adjusted model for patients without a hormone therapy claim record
AIC=Akaike information criterion. HDI=Human Development Index.

biological characteristics of the tumours should be the subject of further research.

Thus, in this study, we highlight the use of race or skin colour as a risk marker, which is important for policy making, rather than as a risk factor, where a causal relationship might be suggested.^{20,38,39} The reasons for a lower survival rate among Black women are multifactorial^{29,40} and in addition to the relationship with

socioeconomic position, racial discrimination also plays a crucial role, affecting women’s self-perception, as well as the perception and treatment they receive from health-care professionals, and the health-care system as a whole.²⁰

In our study, a higher proportion of women with Black skin colour were diagnosed with advanced disease compared to women with White skin colour. This result is consistent with that of a previous study.⁸ In Brazil,

guidelines for the early detection of breast cancer are based on results achieved in developed countries.⁴¹ However, national data indicate that this strategy has not been effective.⁹ Inequities in access to breast cancer screening have been acknowledged,⁴² and in 2017 the federal law that warrants mammography screening was altered to establish an active search of women facing social, geographical, or cultural access barriers. However, the implementation of this alteration is still pending regulation.⁴³

Differences in treatment experiences are also thought to explain racial differences in survival. In 2012, the Brazilian parliament issued the 60 days law, establishing 60 days as the maximum interval from diagnosis to treatment initiation in the SUS.⁴⁴ Data from the Registros Hospitalares de Cancer from 2000 to 2017 revealed that, among other factors, being non-White increased the chance of an interval of 60 days or more between diagnosis and treatment initiation.⁴⁵ This finding was also reported in a Southeast state capital, where women in more vulnerable situations, particularly non-White individuals with fewer years of schooling, were more likely to suffer delay to start of treatment.⁴⁶ Due to the unavailability of data, we were unable to explore in depth treatment-related factors that could have contributed to racial differences in survival, such as the use of inappropriate therapy, and treatment delays.

Our study has some other limitations, the major one stemming from the unavailability of life tables stratified by race or skin colour. This unavailability prevented us from estimating relative survival, which would have helped eliminate the influence of differential background mortality. Regarding our main variable, two limitations apply. First, race or skin colour should be self-reported, but we understand that in an unknown number of cases, the assignment might not have been made by the individual. Because we treated the variable as a risk marker, the assignment by administrative staff or by a health-care professional might also influence the care provided to the patient, which in turn influences the health-care results. Second, after applying all inclusion criteria, we lost 4851 individuals (7·5%) due to missing race or skin colour information. It is important to note that SIA and SIH are administrative information systems, and although race or skin colour is a mandatory field in the APAC and hospitalisation authorisation forms, failure to complete it does not prevent the transfer of funds from the Ministry of Health.

Another limitation, derived from the administrative purpose of the SIA and SIH, is that our survival analysis considered the treatment initiation date, not the diagnosis date, as is commonly done in population-based registry studies. Because there are probable differences in treatment access between skin colour groups, we believe that the difference in survival we found would be greater if we were analysing data from a registry. Additionally, we did not have information on treatments

performed outside the SUS. In 2013, 27·9% of the Brazilian population reported coverage by private health insurance schemes, with state capitals reaching 40·10% of the inhabitants reporting such coverage.⁴⁷ This portion of the population typically consists of White individuals who are formally employed, belong to the middle and high socioeconomic classes, and use private health plans or insurances in addition to the SUS.^{48,49}

Our study includes claims data for all Brazilian states, allowing us to retain follow-up information from women who moved from one state to another. However, if women had relocated to another country, they were lost to follow-up and censored at the end of the study. Furthermore, we did not have detailed information on patient characteristics that could have helped explain survival differences among races or skin colours, such as socioeconomic status, schooling, and tumour subtype. It is important to note that claims databases, such as the ones we used, might have inherent errors. Nevertheless, a previous study showed a high concordance between patient medical records and APACs.⁵⁰ It is worth mentioning that our dataset included women who initiated treatment between 2008 and 2010. However, we have no reason to suspect that the scenario presented has changed. In fact, recent studies show racial inequities in health-care access and mortality from COVID-19.^{51,52}

Our findings revealed that, among women treated for breast cancer by the SUS, women with Black skin colour presented a lower 5-year overall survival probability than White women, and a higher risk of all-cause death after controlling for stage at diagnosis, age at the beginning of treatment, comorbidities, treatment exposure, HDI, and rural or urban typology of the municipality of residence for both regression models (women with and without a hormone therapy claim record). We also revealed a higher proportion of advanced-stage diagnoses among Black women. Therefore, the reformulation or implementation of existing policies should focus on understanding the reasons for these unfair differences and mitigating them to reduce health inequality. At the same time, further research is needed to examine racial or skin colour inequities that might occur through the whole breast cancer care continuum from breast cancer awareness and symptom recognition to presentation, diagnosis, treatment uptake and compliance, and rehabilitation.

Contributors

LLPL, MCS, and MLC conceptualised the Article. LLPL, MCS, AAG, and MLC were responsible for the study design. LLPL, AAG, and MLC did the data collection. TP and MCS contributed materials and analysis tools. LLPL and MCS analysed the data. LLPL and MCS created the figures. LLPL drafted the first version of the Article. LLPL, MCS, TP, RMA, AAG, and MLC reviewed and edited the manuscript. AAG and MLC supervised the study process. MLC acquired funding. All authors read and met the International Committee of Medical Journal Editors criteria for authorship and agree with the results and conclusions. LLPL and MLC accessed and verified the study data. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

MLC and AAG received research sponsorship from the National Council of Technological and Scientific Development (CNPq), and from Minas Gerais State Research Foundation, Brazil. LLPL received a PhD scholarship from CNPq. TP received PhD scholarship from the Coordination for the Improvement of Higher Education Personnel (CAPES). All other authors declare no competing interests.

Data sharing

De-identified data can be made available in accordance with the Universidade Federal de Minas Gerais data sharing policies upon reasonable request to the database holders: MLC (mcherchiglia@ufmg.br) and AAG (augustoguerrajr@ufmg.br).

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