Ethnic, racial and socioeconomic disparities in breast cancer survival in two Brazilian capitals between 1996 and 2012

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Abstract

Objective
To study the impact of socio-economic status and ethno-racial strata on excess mortality hazard and net survival of women with breast cancer in two Brazilian state capitals.

Method
We conducted a survival analysis with individual data from population-based cancer registries including women with breast cancer diagnosed between 1996 and 2012 in Aracaju and Curitiba. The main outcomes were the excess mortality hazard (EMH) and net survival. The associations of age, year of diagnosis, disease stage, race/skin colour and socioeconomic status (SES) with the excess mortality hazard and net survival were analysed using multi-level spline regression models, modelled as cubic splines with knots at 1 and 5 years of follow-up.

Results
A total of 2,045 women in Aracaju and 7,872 in Curitiba were included in the analyses. The EMH was higher for women with lower SES and for black and brown women in both municipalities. The greatest difference in excess mortality was seen between the most deprived women and the most affluent women in Curitiba, hazard ratio (HR) 1.93 (95%CI 1.63-2.28). For race/skin colour, the greatest ratio was found in Curitiba (HR 1.35, 95%CI 1.09-1.66) for black women compared with white women. The most important socio-economic difference in net survival was seen in Aracaju. Age-standardised net survival at five years was 55.7% for the most deprived women and 67.2% for the most affluent. Net survival at eight years was 48.3% and 61.0%, respectively. Net survival in Curitiba was higher than in Aracaju in all SES groups."

Conclusion
Our findings suggest the presence of contrasting breast cancer survival expectancy in Aracaju and Curitiba, highlighting regional inequalities in access to health care. Lower survival among brown and black women, and those in lower SES groups indicates that early detection, early diagnosis and timely access to treatment must be prioritized to reduce inequalities in outcome among Brazilian women.

1. Introduction

Breast cancer is the most common malignant neoplasm and the main cause of cancer-related mortality among women worldwide. Global estimates for 2018 indicate the occurrence of 2,088,849 new cases and 684,996 deaths(1). The clinical expressions of the disease are strongly related to biological factors and characteristics such as age at menarche, parity, age at first full-term birth, and contraceptive use and perimenopausal hormone replacement are all related to its occurrence and may reflect social and economic characteristics of the population (2). Incidence rates have historically been higher in high-income regions such as North America and Western Europe, but 46% of deaths from breast cancer each year now occur in low- and middle-income countries (1,3).

While breast cancer is more common in developed regions, its consequences are felt proportionally more in low-income areas. In Brazil, an estimated 66,280 cases occurred in 2020 (4). It was the most frequent neoplasm in women in all the macro-regions of Brazil except the North region, where it ranked second. Although the conditions of health of the Brazilian population have improved in the past 30 years, most of the improvements have occurred in higher-income areas, accentuating regional inequalities in the distribution of disease (5).

The association between lower socioeconomic status (SES) and cancer survival has been demonstrated for various types of tumour, in several regions of the world (6). Breast cancer survival is lower for women in less-developed regions of the world (7), but even for women living in high-income regions, where by international standards, survival is generally high, educational level (8) and race or skin colour (9,10) are associated with prognostic disparities. Few studies have addressed this association in Brazil (11–13), a country with high indices of social inequality (14). There is, however, indirect evidence suggesting that SES impacts breast cancer survival. Non-white women, especially those living in the least developed regions of the country, tend to present with more advanced disease, with a worse prognosis (15–17). Most population data sources lack individual information on SES, and analyses of health outcomes by SES require the use of ecological indicators (such as indices of socio-economic deprivation or human development), which are attributed to individuals using the place of residence as a proxy (18,19).

In population-based studies, analyses are usually performed using relative survival techniques (20). In these methods, the excess mortality hazard associated with a diagnosis of cancer can be determined through the relation between the survival observed among cancer patients and the survival that would have been expected in the general population, which can be obtained from population life tables of all-cause mortality by age, sex and calendar year. From the excess mortality hazard (EMH), it is possible to estimate relative survival, defined as an estimate of survival from breast cancer after correction for other causes of death (competing hazards), which increase rapidly with age(21,22).

Regional disparities are still among the most relevant public health issues in Brazil and access to screening and treatment are key factors in breast cancer prognosis (23). Given the lack of a national, or even a macroregional, Population

Based Cancer Registry in Brazil, in order to compare the influence of the socioeconomic development on cancer survival, we selected two capitals, Aracaju and Curitiba, in which the the Population Based Cancer Registries achieve good quality standards of data collection and reporting. These capitals are located in regions with very different levels of socioeconomic development (24) Comparing cancer survival between these two cities could help to indicate regional inequities in breast cancer prognosis in Brazil as a whole.

Given the public health importance of breast cancer in Brazil and the growing socio-economic inequalities seen in the country in the last 10 years, as well as the lack of studies in the Brazilian literature, study of the socio-economic and ethno-racial determinants of breast cancer survival can contribute to the evidence base for cancer strategies designed to reduce inequalities in survival. In this study, we have examined the impact of socio-economic status (SES) and ethno-racial group on the excess mortality hazard and on net survival from breast cancer among women residing in Aracaju and Curitiba.

2. Methods

With a population of 664.908 inhabitants in 2020, Aracaju presented a Municipal Human Development Index (MHDI) of 0.770. As in other parts of the North and Northeast regions, the challenges of reducing socioeconomic disparities and improving access to health services are still ongoing and socioeconomic differences remain wide. Curitiba is located in the South region, one of the wealthiest regions in Brazil, the estimated population in 2020 was of 1,751,907 inhabitants. It is among the most affluent locations in the country with a MDHI of 0.823, and was among the top 5 cities in Brazil for its gross domestic product in 2020.(24,25)

We obtained individual data on women diagnosed with breast cancer from the population-based cancer registries of Aracaju and Curitiba. The epidemiological and clinical characteristics of the study population, including dates of cancer diagnosis and death, were obtained directly from the cancer registries. Population estimates required to constitute the life tables, as well as maps, geographical coordinates, information on the division of municipal territories into statistical wards, and information on educational level and income for each territorial division, were drawn from the official statistics bureau (*Instituto Brasileiro de Geografia e Estatística - IBGE*) from the 12th Brazilian Population Census (26), taken in 2010.

The life tables for the municipalities of Aracaju and Curitiba used in this study, containing annual survival probabilities by sex and age, were provided by the CONCORD programme (27). For many of the women, geographical coordinates for the residential address at the time of diagnosis were provided by the registry. When these coordinates were not available, geocodes were derived by matching the woman's residential address with the Google Maps (28) data base.

The study population comprised 2,208 women who were diagnosed with breast cancer aged 18 to 85 years in Aracaju during the 17 years 1996-2012, and 7,969 women diagnosed during the 15 years 1998-2012 in Curitiba. Other criteria for inclusion were histopathological confirmation (99.0% in Aracaju and 99.1% in Curitiba), either from the primary tumour or a metastatic lesion, or by cytology from fine-needle biopsy. Cases diagnosed only from an autopsy or registered only from a death certificate were excluded from survival analyses, because their date of diagnosis is unknown. We also excluded *in situ* tumours and other non-invasive neoplasms, as well as lymphomas, sarcomas, and neuroendocrine tumours since the natural history and clinical behaviour of these malignancies is distinct from that of epithelial malignancies of the breast.

Dates of birth, diagnosis and death were obtained directly from the registries. The date of diagnosis was taken as the date of the histopathology report. Independent variables examined were age at diagnosis, race/skin colour, SES, year of diagnosis and extent of disease. Race/skin colour was categorised as yellow, white, indigenous, brown and black.

When this study was conducted, individual data on income and educational level were not available in the Aracaju or Curitiba registries. Instead, an ecological variable indicating socio-economic status (SES) was constructed, using as reference the geographical area (statistical ward) of residence of each woman, following the model used by the United Nations Development Program (UNDP) for the composition of the Municipal Human Development Index (MHDI) (24). The variable was constructed from census data on educational level and income. The educational dimension was subdivided into two indicators. The first indicator was designed to estimate the educational level of the adult population by using the percentage of persons aged 18 years or over who had completed lower secondary school. The second indicator reflected percentage school attendance in the population under 20 years of age. The two indicators were calculated separately for each statistical ward in each municipality. These indicators were then combined into the final dimension of the educational level as a weighted mean, with weight 1 for the educational level in the adult population and weight 2 for school attendance in the youth population. The income dimension was derived from the per capita household income of the population in each statistical ward, considering as references the mean per capita income in Brazil's Federal District in 2010 and the standard minimum income used in the composition of the global Human Development Index.

The final socioeconomic index was obtained as the geometric mean of the educational and income dimensions, and the value could range from 0 to 1. The index was calculated for each statistical ward in both cities. Statistical wards in each city were then classified into five groups by quintile of the SES index, ordered from the lowest (1) to the highest (5) socio-economic status. The SES index was attributed to each woman according to the Cartesian coordinates of her residential address at diagnosis. When the coordinates were unavailable in the data source, they were obtained through the Google Maps data base(28).

Patients were classified by the extent of disease at diagnosis as local, if there was no evidence of distant spread, or metastatic, when there was distant spread at time of diagnosis. Data on stage at diagnosis based on the widely used TNM Tumor, Nodes, Metastasis) system were not available, because during this period the registries were using an international standard to code the extent of disease (29). Follow-up for vital status was passive, by linking each woman's tumour registration with the national mortality database (*Sistema de Informações de Mortalidade*, SIM). Women whose registration was not linked to a death record in the SIM database were considered to be alive on 31 December 2014, the closing date for follow-up. Survival time was calculated as the interval between the date of diagnosis and the date of death from any cause.

Survival times of more than 10 years were censored at that point. Net survival was estimated by modelling the excess mortality hazard (21) from the relationship between observed survival among the women with breast cancer and expected survival in the general population. Expected survival was obtained from life tables of all-cause mortality for women in the municipalities of Aracaju and Curitiba by single year of age and single calendar year (27). The life tables were standardized by SES using data for the population of the United Kingdom, accessible on the website of the Office for National Statistics (30).

Estimates of the effects of SES, race/skin colour, extent of disease, age and year of diagnosis on the excess mortality hazard were obtained from multivariate parametric regression models with flexible functions (31), using cubic b-splines with knots at 1 and 5 years. A final model for each municipality was reached by an iterative process, starting from a "full" model in which the EMH was allowed to vary as a function of SES, race/skin colour, extent of disease, age and year of diagnosis, including effects that were non-linear or non-proportional over time. The non-linear effect of age was modelled using a squared spline function with one knot at 70 years. The non-linear effect of year of diagnosis was modelled using a squared spline function with one knot at the year 2005.

At each stage of the iterative process, the models were simplified by excluding associations that were not statistically significant, using the likelihood ratio test at a 0.05 level of significance, until obtaining an optimal model fit by the Akaike Information Criterion (32). Lastly, the inclusion of level of aggregation (statistical ward) yielded the final, multi-level model, including both the individual level and a level of aggregation by statistical ward. From that final multivariate model, the estimates of excess mortality hazard associated with a diagnosis of breast cancer were made.

The excess hazard ratio and its 95% confidence interval were estimated whenever the effects retained in the final model were linear and proportional over time. For discrete variables, a reference category (the one with the least hazard) was specified as the basis to compare excess mortality *hazards*. For continuous variables, the hazard ratio expresses the effect on the EMH of a unit change in the value of the explanatory variable. When the effects were time-dependent, i.e. non-proportional over time since diagnosis, the variable was retained in the model and the results are shown as graphs of the EMH at different follow-up times.

To include cases with missing data on race/skin colour and/or place of residence, a multiple imputation procedure was applied, assuming that the data were missing at random (33). Five imputed datasets were generated by multinomial logistic regression, taking as predictors the other variables present in the original dataset. The five datasets were analysed separately and the estimates were combined according to Rubin's rule, to account for the variance within and between each set of data, and to enable the confidence interval around the pooled estimate to be produced (34,35).

To facilitate comparisons between Aracaju and Curitiba of the survival estimates for all ages combined, the survival estimates were standardized by age with the International Cancer Survival Standard (ICSS) weights (36). Confidence intervals for the age-standardized survival estimates were derived by the normal approximation (37).

The study was approved by the Research Ethics Committees of the Instituto de Medicina Social from Rio de Janeiro State University (Universidade do Estado do Rio de Janeiro – UERJ) , the Municipal Health Department of Curitiba and by the Aracaju Cancer Registry.

3. Results

After the exclusion of duplicate records, and of those that failed to meet inclusion criteria, 2,208 women from Aracaju and 7,969 from Curitiba were initially selected. Data for both area of residence and race/skin colour were available for 1,488 of the women in Aracaju (67.4% of those eligible) and 6,670 (83.7%) in Curitiba, and we included these women in a complete case analysis. After multiple imputation of missing data for race/skin colour and place of residence, it was possible to include 2,045 women in Aracaju (92.6% of those eligible) and 7,872 (98.8%) in Curitiba in the final analyses.

In Aracaju, black and brown women comprised 42.2% of the study population, whereas white women represented 78.6% of the population in Curitiba. In both locations the fifth quintile of SES (most affluent) showed the highest percentage of cases: 39.8% in Aracaju and 33.4% in Curitiba. The characteristics of the study population from Aracaju and Curitiba, including all cases and cases with complete data on race/skin colour and place of residence are summarized in Table 1.

Table 1 - Distribution of epidemiological and clinical characteristics of women with breast cancer. All cases and complete case population (socioeconimic status and race/skin colour), Aracaju and Curitiba, 1996 to 2012.

	Aracaju				Curitiba			
	All Cases		Complete Cases*		All Cases		Complete Cases*	
	N	%	N	%	N	%	N	%
Total	2208	100	1488	100	7969	100	6670	100
Age (years)								
18 to 19	0	-	0	-	3	<0.01	3	<0.01
20 to 29	42	1.9	30	2.0	121	1.5	101	1.5
30 to 39	254	11.5	176	11.8	894	11.2	755	11.3
40 to 49	594	26.9	408	27.4	2039	25.6	1693	25.4
50 to 59	529	24.0	352	23.7	2113	26.5	1750	26.2
60 to 69	407	18.4	263	17.7	1564	19.6	1354	20.3
70 to 79	292	13.2	202	13.6	1015	12.7	839	12.6
80 to 89	90	4.1	57	3.8	220	2.8	175	2.6
Region of birth								
Other	276	12.5	199	13.4	1389	17.4	1257	18.8
PBCR**	821	37.2	649	43.6	3143	39.4	2888	43.3
Missing	1111	50.3	640	43.0	3437	43.1	2525	37.9
Race-skin colour								
Yellow	0	-	0	-	96	1.2	96	1.4
White	681	30.8	615	41.3	6260	78.6	6221	93.3
Indigenous	0	-	0	-	8	0.1	8	0.1
Brown	846	38.3	791	53.2	231	2.9	226	3.4
Black	86	3.9	82	5.5	120	1.5	119	1.8
Missing	595	26.9	-	-	1254	15.7	-	-
Socioeconomic Status* **								
Q1 (lowest status)	182	8.2	132	8.9	798	10.0	735	11.0
Q2	243	11.0	188	12.6	1143	14.3	1019	15.3
Q3	315	14.3	215	14.4	1454	18.2	1285	19.3
Q4	443	20.1	321	21.6	1843	23.1	1575	23.6
Q5 (highest status)	878	39.8	632	42.5	2665	33.4	2056	30.8
Missing	147	6.7	-	-	66	0.8	-	-
Marital status								
Married	673	30.5	540	36.3	3499	43.9	3014	45.2
Separated	106	4.8	90	6.0	484	6.1	425	6.4
Single	347	15.7	282	19.0	1106	13.9	996	14.9
Civil union	12	0.5	10	0.7	254	3.2	228	3.4
Widow	187	8.5	147	9.9	1234	15.5	1075	16.1
Missing	883	40.0	419	28.2	1392	17.5	932	14.0
Disease extension								
Localized	1346	61.0	837	56.2	5282	66.3	4292	64.3
Metastatic	862	39.0	651	43.8	2687	33.7	2378	35.7
Year of diagnosis								
1998 to 2005	1054	47.7	818	55.0	3974	49.9	3374	50.6
2006 to 2012	1154	52.3	670	45.0	3995	50.1	3296	49.4
Vital status								
Dead	919	41.6	745	50.1	2442	30.6	2291	34.3
Alive	1289	58.4	743	49.9	5527	69.4	4379	65.7
Cause of death* ***								
Cancer related	767	83.5	637	85.5	1802	73.8	1714	74.8
Non-cancer related	122	13.3	88	11.8	314	12.9	269	11.7
Missing	30	3.3	20	2.7	326	13.3	308	13.4

Legend: first socioeconomic status quintile (Q1); second quintile (Q2); third quintile (Q3); fourth quintile (Q4); fifth quintile (Q5); Population based cancer registry (PBCR).

* Composed by the population without missing information on socioeconomic status and race/skin colour.

** State of Paraná for Curitiba Cases and State of Sergipe for Aracaju cases.

*** Estimated using income and educational level data relative to the area of residence.

**** Including only cases for which vital status was registerd as dead.

3.1 Excess mortality hazard

Among women with complete data on race/skin colour and place of residence, the excess mortality hazard increased in linear fashion across the five SES groups in both cities, to about 1.4-fold in Aracaju and 1.8-fold in Curitiba for women in the most deprived category (group 1) (Table 2). Excess mortality was more than two-fold higher among women with metastatic disease than among those with localised disease. Compared with white women, excess mortality was between 1.4-fold and 1.6-fold higher for brown and black women in Curitiba, whereas the excess hazard ratios of 1.2 to 1.4-fold for black and brown women in Aracaju were of borderline significance. The excess hazard ratio declined slightly with each year of diagnosis in Curitiba. The relationship between the EMH and age was not linear (Table 2).

After imputation of missing values for race/skin colour and residence, the socio-economic gradient in excess mortality persisted in Curitiba, reaching 1.93-fold (95%CI 1.63-2.28) for the most deprived women (group 1). In Aracaju, the socio-economic gradient in excess mortality was smaller than in Curitiba. Excess hazard related to race/skin colour in Curitiba was 1.49 fold among brown and 1.35 fold for black women, when compared to white women. In Aracaju, this effect reached marginal significance for brown and black women. (Table 2).

Table 2. Mortality hazard ratios associated to breast cancer diagnosis, by socio-economic level. Results derived from the multilevel spline regression model, adjusted by age, year of diagnosis, extension of the disease and race/skin colour, Aracaju and Curitiba, 1996 to 2012

	Complete cases*		Multiple imputation**	
	Aracaju HR (95% CI)	Curitba HR (95% CI)	Aracaju HR (95% CI)	Curitba HR (95% CI)
Q5 (Higest SES)	1	1	1	1
Q4	1.12 (0.92 - 1.36)	1.10 (0.96 - 1.25)	1.30 (0.90 - 1.88)	1.17 (1.02 - 1.36)
Q3	0.89 (0.70 - 1.13)	1.47 (1.28 - 1.67)	1.06 (0.72 - 1.57)	1.59 (1.37 - 1.84)
Q2	1.19 (0.94 - 1.51)	1.74 (1.52 - 2.00)	1.61 (1.09 - 2.40)	1.92 (1.65 - 2.37)
Q1 (Lowest SES)	1.41 (1.10 - 1.81)	1.77 (1.51 - 2.06)	1.38 (0.94 - 2.03)	1.93 (1.63 - 2.28)
Age	TD	TD	TD	TD
Year of diagnosis	TD	0.97 (0.95 - 0.98)	TD	0.97 (0.92 - 1.02)
Local	1	1	1	1
Metastatic	2.43 (2.10 - 2.83)	2.50 (2.30 - 2.71)	2.40 (2.09 - 2.74)	2.63 (2.43 - 2.85)
White	1	1	1	1
Brown	1.16 (0.99 - 1,36)	1.35 (1.09 - 1.67)	1.27 (0.98 - 1.65)	1.49 (1.14 - 1.92)
Black	1.36 (1.01 - 1.83)	1.57 (1.20 - 2.04)	1.10 (0.95 - 1.27)	1.35 (1.09 - 1.66)

Legend: socio-economic status (SES); time-dependent effects (TD) when the effects varied with calendar time.

Note: The effects of age for both municipalities and year of diagnosis for Aracaju are shown in **Figures 2 and 3.**

* Only cases with complete records for socio-economic status and race/skin colour (N Curitiba = 1488 and Aracaju = 6670).

** Including cases after multiple imputation for socio-economic status and race/skin colour (N Curitiba = 2045 and Aracaju = 7872)

Mortality hazard by age at diagnosis, against a reference age of 70 years, was greater at highest and lowest ages in both municipalities. The effect was greater in Aracaju at 1 year and 8 years of follow-up. In Curitiba, HR was higher only under 30 years of age and at 1 and 5 years of follow-up. At 8 years' follow-up, the effect lost magnitude, while the HR increased considerably at ages above 70 years (Figure 1). Mortality hazard by year of diagnosis in Aracaju, presented two distinct patterns. Hazard of death within one year of diagnosis was greater between 2000 and 2005. Hazard of later mortality, at up to 5 years' follow-up, was slightly higher in the years prior to 2005 and later stabilized (Figure 2).

3.2 Net survival

After multiple imputation for race/skin colour and residence (SES), age-adjusted five-year net survival in Aracaju ranged from 55.7% among women in the most deprived group to 67.2% among the most affluent, an absolute difference of almost 12%. Eight years after diagnosis, the gradient in net survival was similarly wide, from 48.3% to 61.0% (Table 3).

In Curitiba, age-standardised five-year net survival was higher than in Aracaju in all SES groups, but the socio-economic gradient is even more marked, from 63.8% in the poorest regions of the city to 79.1% in the most affluent districts, an absolute difference of 15%. At eight years, the gradient is even wider, from 55.1% to 73.2% (Table 3).

Table 3. Net survival* (%) with 95% confidence intervals (CI) at 5 and 8 years for women diagnosed with breast cancer in Aracaju and Curitiba, 1996 to 2012, by socio-economic status.

Location	Net survival	Q1 %(CI95%) Lowest SES	Q2 %(CI95%)	Q3 %(CI95%)	Q4 %(CI95%)	Q5 %(CI95%) Highest SES
Aracaju	**5 years**	**55.7** (52.1-59.5)	**56.9** (53.3-60.8)	**69.4** (64.9-74.1)	**63.6** (59.6-68.0)	**67.2** (62.9-71.8)
	8 years	**48.3** (45.2-51.6)	**49.7** (46.5-53.1)	**63.4** (59.4-67.8)	**57.0** (53.3-60.9)	**61.0** (57.1-65.1)
Curitiba	**5 years**	**63.8** (61.3-66.4)	**64.2** (61.7-66,8)	**68.6** (65.9-71.3)	**75.1** (72.1-78.1)	**79.1** (76.0-82.3)
	8 years	**55.1** (52.9-57.3)	**55.5** (53.3-57.7)	**60.5** (58.2-63.0)	**68.2** (65.6-71.0)	**73.1** (70.3-76.1)

Legend: 5 years (5a); 8 years (8a); 95% confidence interval (95%CI).
Note: Total of 7872 cases in Curitiba and 2045 cases on Aracaju.
***Age-standardized net survival.

4. Discussion

The results presented here show that between 1996 and 2012, in two state capitals in Brazil, Curitiba and Aracaju, black and brown women had higher excess mortality from breast cancer than white women, while in both cities, women with lower socio-economic status had higher excess mortality than women with higher socio-economic status.

Net survival was higher among women in Curitiba than in Aracaju in each socio-economic group. The difference in 8-year survival was about 7% for the lowest SES groups and 12% for the highest SES groups. In Curitiba, the socio-economic gap in net survival was about 15% at five years after diagnosis and 18% at eight years. The socio-economic gap in survival in Aracaju was 12% at five and 13% at eight years after diagnosis.

The association between ethnic and racial traits or socio-economic status and breast cancer survival is well described (38,39). Comparisons between 5-year survival for breast cancer in high-income and low- and middle-income countries (40) is compatible to those observed in this study using data from two cities located in different socio-economic regions of Brazil. Evidence from studies in screening-age population in the United Kingdom indicate that survival differentials relating to socio-economic deprivation are smaller or even non-existent when cancer is diagnosed at early stages, suggesting that access to screening may play an important role in the relationship between SES and breast cancer survival (6,41).

A high prevalence of late-stage breast cancer among black and brown women in Brazil has been described (15,42), but we are not aware of population-based studies of net survival for breast cancer by race or skin colour in Brazil. Although no information on screening history was available, our findings for both Aracaju and Curitiba show that even after adjusting for extent of disease, the effect of socio-economic status on EMH remained significant. These results, however, should be interpreted with caution because the cancer registries could not provide more detailed data on stage at diagnosis other than whether it was metastatic. It is thus possible that the survival differentials observed here would be smaller if analyses could have been restricted to women with early disease (e.g., with tumours smaller than 5 centimetres, without skin or axillary involvement). Further studies with more complete information on stage at diagnosis are needed to elucidate this issue.

Black and brown women had higher excess mortality than white women, even after adjustment for age, year of diagnosis, extent of disease and SES. These findings, especially in Curitiba, are consistent with studies in other countries (38). This fact may be related both to different biological characteristics of breast cancer within the diverse ethnic groups (43,44) and to inequalities in access to treatment due to social and racial related conditions (45). There is evidence that black women in the United States tend to receive different cancer treatment from that offered to white women, even in the same socio-economic status (46–48).

Evidence in the literature also suggests that black women tend to present similar prognosis when treated similarly to white women (49,50). Yet, improvement in breast cancer survival has occurred at a faster pace for white women than for black women in the US (51). In our study, the survival differentials between white and non-white women were significant, even after adjustment for extent of disease and socio-economic status. The fact that this difference loses statistical significance after imputation of missing data in Aracaju, may be related to the low proportion of women classified as black in the data from that city. This fact could be related with selective losses of black women, shifting the results toward the null hypothesis (due to overrepresentation of white and brown women). Additionally, inaccuracy of the registered data on race/skin colour may play a role: misclassification of race/skin colour, especially between the black and brown categories, cannot be ruled out. The point estimates, however, are consistent with other studies of other health conditions in Brazil(52), showing a clear excess mortality hazard for black women when compared to white or brown women.

The effect of age at diagnosis on breast cancer prognosis is well established. Young women tend to present with biologically more aggressive forms of the disease (53). In addition, high breast density, usual among pre-menopausal women, makes non-palpable lesions more difficult to detect by mammography, reducing the impact of screening on that age group (54). The findings of this study are compatible with these concepts. In Aracaju, excess mortality was higher among women aged less than 50 years at one, five and eight years after diagnosis, especially at follow-up of one year; this probably reflects high rates of early relapse, common in aggressive types of breast cancer. In Curitiba, a similar pattern was found for younger women at one and five years, but at 8 years' follow-up, excess mortality became greater than at one year only from 70 years of age onwards. It can be inferred that tumours diagnosed at a very advanced stage, with early relapse, occurred with similar frequency in Aracaju and Curitiba, leading to high early mortality. At longer follow-up times, however, the excess mortality hazard was lower in women from Curitiba, possibly due to differences between the two municipalities in the delivery of cancer treatment, leading to a lower risk of late mortality for women in Curitiba, a more affluent municipality than Aracaju.

In the year chosen as reference (2005), a ministerial order was published regulating national cancer care policy (55), which set out rules for access to cancer diagnosis and treatment in Brazil. In Curitiba, excess mortality from breast cancer declined slowly but steadily over time, and it was not possible to identify any change in that trend after 2005. In Aracaju, however, excess mortality seems to have decreased sharply in the period immediately after 2005, particularly at 1 year after diagnosis, becoming stable afterwards. This may reflect reduction in the differences between the two municipalities, but will require confirmation by further studies that include women diagnosed after 2012.

This study has some limitations. Information on income and educational level used in our study, derived from census data, was matched to the individuals by the address at diagnosis. Such use of ecological measures tends to underestimate, rather than overestimate, any underlying socio-economic gradient in health outcomes. Also, the ideal territorial unit for specifying the SES index should consider that contiguous areas with different levels of schooling and income should belong to different divisions. The census statistical wards used here meet that criterion only partly: their purpose in the census is related mainly to the territorial distribution of the population. That tends to mitigate differences between the SES strata, forcing the results towards the null hypothesis. The life tables stratified by SES, used in the analysis, were constructed assuming that the socio-economic gradient in mortality by age in Brazilian women is similar to the corresponding gradient in the United Kingdom each year.

Given the possible differences in the distribution of mortality among the two populations, assumptions concerning socio-economic gradients in survival for

Brazilian women must still be considered with caution. The availability of all-cause mortality rates by age, sex and socio-economic status would enable construction of life tables by SES, to evaluate this pattern more accurately. Other prognostic factors, such as expression of hormone receptors, HER-2, proliferation markers and histological type, data for which were unavailable at the registries at the time this study was conducted, if distributed unequally between the groups could lead to inaccurate interpretations of the risk associated with the study variables. That is unlikely, however, given that prevalence of prognostic factors is associated more with age and genetic factors than with geographic location (56). Use of passive follow-up, despite the high level of coverage by the National Mortality Information System (SIM) (57), may affect the survival time estimates, given the possibility that some deaths may not be included in the SIM or flaws in linkage with the registry data. Finally, the possibility of missing data not completely at random could have affected specially race-skin colour variable. In that case, it is possible that the imputed data may have led to over-representation of categories with better prognosis. This would have reduced the magnitude of the race effect on survival for black women.

5. Conclusion

The findings on breast cancer survival presented here are important for two major reasons. First, contrasting results from Aracaju and Curitiba suggest regional inequalities in access to health care, consistent with the levels of human development in Brazil's Northeast and South regions. Second, inequality within each municipality, where excess mortality and net survival differ by socio-economic status and race/skin colour, underline the need to strengthen the national health system to improve equity. Early detection, early diagnosis and timely access to specialized treatment must be prioritized as measures to reduce racial and social inequalities in breast cancer survival among Brazilian women.

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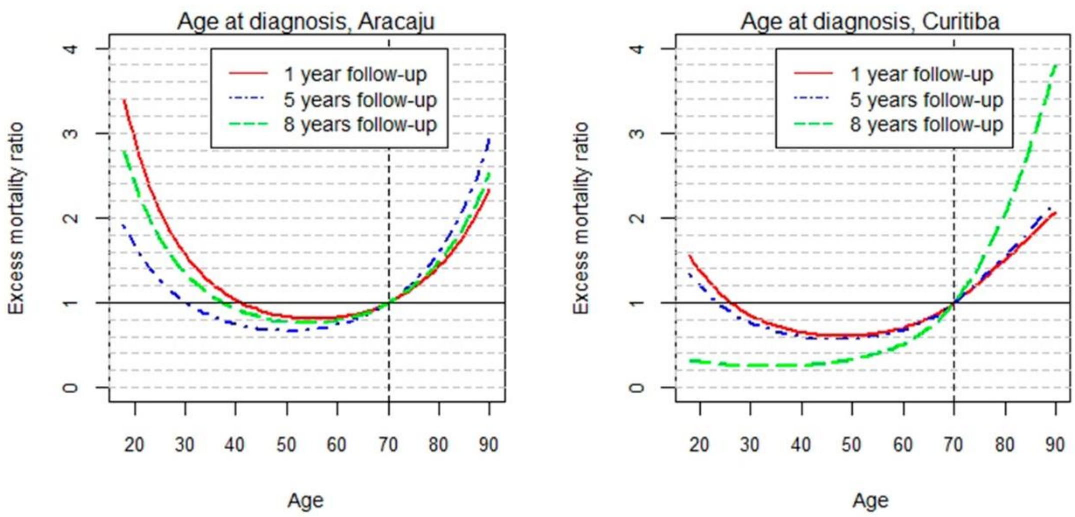
Figure 1. Excess mortality hazard for women with breast cancer in the municipalities of Aracaju and Curitiba at one, five and eight years of follow-up, 1996 to 2012, by age at diagnosis.



Note: Results from multi-level spline regression, adjusted for socio-economic status, age (reference 70 years of age), single calendar year of diagnosis, stage of disease and race/skin colour.

Figure 2. Effect of year of diagnosis on excess mortality hazard from breast cancer in Aracaju at 1 and 5 years after diagnosis. Results derived from the multilevel spline regression model, adjusted by socio-economic level, age, year of diagnosis, extension of the disease and race-skin colour.