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Real-world data on metastatic breast cancer in Goiânia, Brazil: a 17-year analysis (1995–2011)

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ABSTRACT

Introduction: Most of the data on metastatic breast cancer (MBC) originate from hospital-based studies or controlled trials involving specific populations and controlled treatments. In this respect, few population-based studies have analyzed the profile of MBC in low- and middle-income countries. **Objective:** To describe the epidemiological profile of women with de novo MBC using data from a population-based cancer registry (PBCR). **Methods:** An ecological study conducted in a PBCR in Goiânia, Brazil, for the 1995–2011 period. Women with MBC at diagnosis were included and the standardized incidence rate and annual percent change (APC) over the period were calculated. The women's clinical and demographic characteristics and data on diagnosis and treatment were analyzed. **Results:** Overall, 5,289 cases of breast cancer were registered in the Goiânia PBCR, 277 (5.2%) at metastatic stage. The adjusted incidence was 8.9/100,000 in 1995 and 6.04/100,000 in 2011 (APC: 1.1; p=0.6). Most of the patients (70.3%) were receiving care within the public healthcare system and the mean age at diagnosis was 54.7±14.5 years. Additional data for a subpopulation of 156 patients were identified at the city's two main treatment centers. According to immunohistochemistry, 53 women (67.1%) had hormone receptor-positive cancer. Of these, 14.0% (6/43) received endocrine therapy as first-line systemic treatment and 48.5% (17/35) as second-line treatment. A comparison of clinical data between the 1995–2003 and 2004–2011 periods revealed no significant differences in age, histological grade, locoregional staging, the presence of symptoms at diagnosis, or in treatment. **Conclusion:** This study population of women with MBC consisted predominantly of locally advanced tumors and the luminal-like subtype. The incidence rate of MBC in Goiânia did not change over the 17-year period. Most cases received chemotherapy as first-line systemic treatment irrespective of the tumor phenotype.

KEYWORDS: breast neoplasms; neoplasm metastasis; incidence; epidemiology.

INTRODUCTION

Breast cancer is a heterogenous pathology involving different patterns of tumor biology that are reflected in individualized clinical behavior and response to treatment[1-4]. As a result of population screening, there has been an increase in the number of incident cases diagnosed at the initial stages in various countries[5-7]; however, no reduction has been seen in the number of women diagnosed with de novo metastatic carcinoma[4,6,7].

Patients with metastatic breast cancer (MBC) receive a continuous regime of palliative treatment, resulting in elevated financial costs due to the high cost of the medications and the need to frequently undergo tests and hospitalization for clinical support[8,9]. The median 5-year survival of these women, however, remains poor, ranging from 15% to 35%[10-12].

In recent years, increased knowledge of tumor biology, advances in disease diagnosis, and access to new therapeutic agents have increased the overall survival of patients with MBC[13,14]. Although these advances have resulted in more personalized management of the metastatic disease, they have also introduced new challenges associated with controlling adverse events[8,15]. Therefore, epidemiological and population-based evaluations of women with MBC can contribute towards elaborating and implementing measures for more effective management of these patients.

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Currently, most of the data on MBC originate from retrospective hospital-based studies or controlled trials involving specific populations and controlled treatments[13,14,16]. In this respect, few population-based studies have analyzed the profile of MBC in low- and middle-income countries[10-12,16-18].

Since population-based cancer registries record incident cases of cancer in a defined population over a period of time, their use in real-world studies allows a wider exploratory analysis to be conducted and confers the possibility of external validation. Therefore, the objective of this study was to describe the patient profiles and patterns of care in MBC in the city of Goiânia, Brazil.

METHODS

An ecological, population-based clinical study was conducted with women with MBC in the city of Goiânia, Brazil. The cases were extracted from the Goiânia population-based cancer registry database for the period between 1995 and 2011[10].

Goiânia cancer registry, Goiás

The Goiânia population-based cancer registry was created in 1986 and has been recording all new cases of cancer in residents of the city of Goiânia uninterruptedly since its creation to the present day[4,10,19].

Criteria for the selection of cases

All incident cases for which the variable "extent of the disease" was described as "metastatic" or "unknown" were potentially eligible for inclusion in the study.

Cases

The cases registered as metastatic at diagnosis were classified as de novo metastatic disease. This classification is based on the clinical report, imaging tests, and/or a histology report showing the presence of metastatic disease at sites other than the breast and axillae[8,15].

All the cases of breast cancer for which the variable "extent of the disease" was registered as "unknown" in the cancer registry were reviewed by performing an active search in the patient's medical records at the Araújo Jorge Hospital of the Association for the Combat of Cancer in Goiás and at the Universidade Federal de Goiás Teaching Hospital, two reference centers for cancer treatment in the city of Goiânia. The medical records of patients with a diagnosis of metastatic disease were then reviewed and constituted the subsample of the population-based registry.

Cases of breast carcinoma in situ were excluded from the study, as were those without histological confirmation and cases in which diagnosis had only been recorded on the death certificate.

Variables selected for analysis

The demographic variables *age at diagnosis*, *age at menarche*, *family history of breast or ovarian cancer*, and *type of access to treatment* (public or private healthcare system) were retrieved from the medical records at the city's treatment centers.

The site and morphology of the tumor were coded in accordance with the International Classification of Diseases for Oncology, third edition (ICD-O-3). The cases included the morphological codes 8500/3, 8520/3, and 8521/3[20,21]. Sarcomas (8800/3) and other morphological types (anaplastic carcinoma and spindle-cell neoplasms) were classified as "other subtypes".

Histological grade was classified as G1, G2, or G3 according to the Bloom-Richardson grading system[22]. Locoregional staging was classified according to the tumor-node-metastasis (TNM) staging system, as defined in the American Joint Committee on Cancer's (AJCC) cancer staging manual, 8th edition[23,24].

Immunohistochemical estrogen and progesterone receptor expression was considered positive or negative according to the report from each laboratory. Human Epidermal growth factor Receptor-type 2 (HER2) expression was considered positive when reported as three crosses (3+) or when amplification was confirmed by immunofluorescence. Tumor phenotype classification was determined following the recommendations of the 2017 St. Gallen International Expert Consensus Conference[25].

Data on the site of metastasis were collected from the medical records at the two participating institutes. The site of metastatic lesions and the presence of associated clinical symptoms were evaluated, as well as whether aspiration and/or biopsy of the lesions had been performed. Treatment data were collected on the type of surgery performed for the primary tumor and/or for metastasis and any systemic treatments given.

Statistical analysis

The database was constructed using Microsoft Office Excel®, version 2003 (Microsoft Corporation, Redmond, WA, USA). The frequency of all the variables was established and a central tendency analysis was conducted to determine the mean age.

The crude incidence rate was defined as the ratio between the number of new cases of MBC diagnosed annually and the number of women exposed to the risk of developing the disease at the mean point of the respective year, with the result being expressed as a coefficient per 100,000 women[26]. The number of women exposed to the risk of cancer was defined as the female population of the city of Goiânia in the respective year according to the census population count for the years 2000 and 2010 and the intercensal population counts for the other years[27].

The standardized incidence rate was calculated based on Segi's world standard population and expressed per 100,000 inhabitants[28,29]. Due to the rarity of this event, the rates were smoothed to a three-year mean.

The temporal analysis of the clinical and therapeutic characteristics was performed by comparing the 1995–2003 period with the 2004–2011 period. Statistical analysis was performed using MedCalc for Windows (MedCalc Software, Ostend, Belgium), version 18.11. The chi-square test was used to compare two proportions (of independent samples), expressed as a percentage. P-values <0.05 were considered statistically significant.

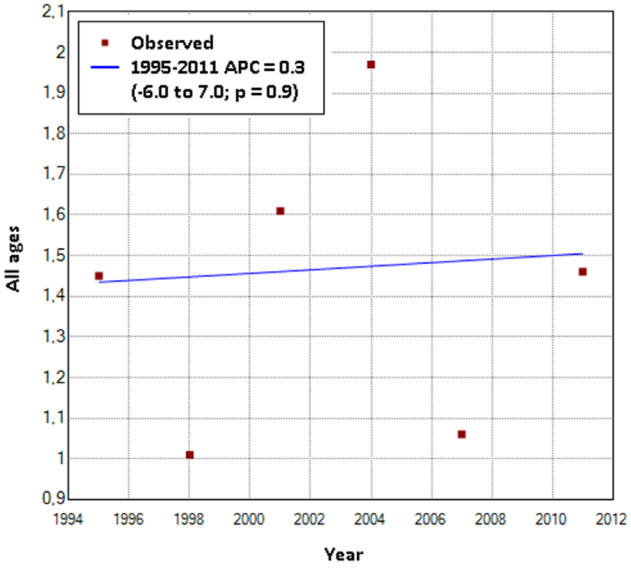
The annual percent change (APC) and the average APC (AAPC) in the rate of MBC were calculated for the total sample and according to the age group (<50, 50–69, and ≥70 years), with age being the only variable for which data were available in all cases. The relevant 95% confidence intervals (95%CI) were calculated, with p-values <0.05 being considered statistically significant. The Poisson regression model was used for these calculations and the software program used was JoinPoint Regression, version 4.7.0.0, of February 2019 (National Cancer Institute, USA)[30].

Ethical aspects

The Internal Review Board at the Araújo Jorge Hospital of the Goiás Association for the Combat of Cancer approved the study protocol under CAAE No. 61987716.0.0000.0031. All the recommendations for good clinical practice outlined in the Brazilian National Health Council's resolution 466/2012 and the Helsinki Declaration were followed.

RESULTS

Between 1995 and 2011, 5,289 cases of breast cancer were registered in Goiânia and 277 (5.2%) were diagnosed as de novo metastatic disease. The adjusted incidence rate was 8.9/100,000 in 1995 and 6.04/100,000 in 2011 (Figure 1). There was no difference in the proportion of metastatic cases between the 1995–2003 period (n=129; 46.6%) and the 2004–2011 period (n=148; 53.4%; p=0.2) or in the trend during the periods (APC: -1.1; -5.2–3.2; p=0.06).



*Average APC (AAPC) 0.3; -6.0 to 7.0; p=0.9.

Figure 1. Trend in the standardized incidence rate of metastatic breast cancer in the city of Goiânia, Brazil, between 1995 and 2011, adjusted for age.

In the subsample of 156 cases identified in the two treatment centers, the majority (70.3%) were patients receiving care in the public healthcare system. The mean age was 54.7±14.5 years (mean±standard deviation [SD]). Eighty-eight women (88/129; 68.2%) had a single metastatic lesion and 65 (65/129; 50.4%) had a visceral disease at diagnosis (Table 1).

Ten patients were subjected to resection of the metastatic lesion (10/108; 9.2%). Four of these patients had lesions in the brain and three in distant lymph nodes (mediastinal, cervical, and contralateral axillary lymph nodes). A further twenty women were subjected to percutaneous biopsy (20/108; 18.5%) for confirmation by cytology or histology. Of the 50 women subjected to breast surgery, 40 underwent radical mastectomy and 10 conservative breast surgery.

Endocrine therapy was prescribed as first-line treatment for 14.0% (6/43) of the patients with hormone receptor-positive cancer, and for 48.5% (17/35) of the patients, as second-line therapy. Of the 24 women with HER2-positive breast cancer, three were given trastuzumab as first-line treatment (3/24; 12.5%) and two as second-line treatment for the metastatic disease (Tables 2 and 3).

There was no change in the distribution pattern of cases of MBC in the time periods analyzed here concerning histological grade, locoregional staging, the presence of symptoms at diagnosis, or the type of oncological treatment given. Between 2004 and 2011, there was a decrease in the number of luminal-HER2-positive cases and a reduction in the percentage of patients using the private healthcare system compared to the 1995-2003 period (Table 4). There was a reduction in the APC in women over 70 years of age (APC: -4.8; -9.3–-0.1; p<0.001); however, there was no statistically significant difference for any of the other age groups. There were no statistically significant differences in the AAPC as a function of the age group (Figure 2).

DISCUSSION

This population-based study describes the profile of MBC in the city of Goiânia, Brazil. Around 5.0% of breast cancer cases were metastatic at diagnosis, a finding that is similar to that of other hospital-based studies conducted both in Brazil[3,31] and in countries with population-based mammography screening, including the United States, Denmark, and the Netherlands[2,6,7,32]. Therefore, genetic factors or exposure to risks may have made these women more susceptible to diagnosis at an advanced stage, not being detected through the screening policy adopted in Brazil[5]. Nevertheless, it was impossible to establish whether these women had undergone mammography screening. Likewise,

Table 1. Sociodemographic and clinical characteristics of 277 women with metastatic breast cancer between 1995 and 2011.

Characteristics	Cases (n)	%	Characteristics	Cases (n)	%
Age at diagnosis (years)			Total n*	89	100.0
≤49	103	37.2	Estrogen receptor status		
50–59	75	27.1	Positive	53	67.1
≥60	99	35.7	Negative	26	32.9
Total n*	277	100.0	Total n*	79	100.0
Skin color/ethnicity			Progesterone receptor status		
White	98	55.4	Positive	42	55.3
Brown	69	39.0	Negative	34	44.7
Black	5	2.8	Total n*	76	100.0
Others	5	2.8	C-erb-B status		
Total n*	177	100.0	Positive	24	33.8
Age at menarche (years)			Negative	47	66.2
<11	10	21.8	Total n*	71	100.0
12–13	18	39.1	Tumor phenotype		
>13	18	39.1	Luminal	34	47.9
Total n*	46	100.0	Luminal-HER2	16	22.5
Family history			Pure HER2	8	11.3
Breast cancer, first-degree relatives	9	13.7	Triple-negative	13	18.3
Breast cancer, second-degree relatives	6	9.1	Total n*	71	100.0
Ovarian cancer, first-degree relatives	3	4.5	Staging (T)		
None	48	72.7	T0	3	2.3
Total n*	66	100.0	T1	12	9.3
Presence of symptoms			T2	22	17.1
Yes	103	81.8	T3	25	19.4
No	23	18.2	T4	67	51.9
Total n*	126	100.0	Total n*	129	100.0
Histological type			Staging (N)		
Carcinoma, not otherwise specified	19	14.0	N0	31	25.2
Ductal carcinoma	107	78.6	N1	40	32.5
Lobular carcinoma	6	4.4	N2	37	30.1
Sarcoma and others	4	3.0	N3	15	12.2
Total n*	136	100.0	Total n*	123	100.0
Histological grade			Type of healthcare		
G1	11	12.3	Public	90	70.3
G2	51	57.3	Private	38	29.7
G3	27	30.4	Total n*	128	100.0

*The number of individuals for whom data were available.

a more in-depth analysis of the respective risk factors could not be performed.

Over the 17-year period analyzed (1995–2011), no trend was found towards any changes in the incidence of MBC. This finding showed that the opportunistic screening carried out in the city of Goiânia has not been successful in reducing the incidence of advanced breast cancer. This fact is even more evident when comparing data with those of other Brazilian populations, for example, comparing data from the Goiânia population-based cancer registry with data from the city of Barretos and surrounding region where there is population-based mammography screening[33]. In the area covered by screening, there were significantly

Table 2. Anatomical site of metastasis and treatment given to women with metastatic breast cancer at diagnosis in Goiânia, Brazil (n=277).

	Cases (n)	%
Number of metastatic sites*		
1	88	68.2
2	31	24.0
≥3	10	7.8
Total n†	129	100.0
Site of metastasis		
Bone	36	27.9
Visceral	41	31.8
Visceral+bone	24	18.6
Central nervous system	11	8.5
Skin, subcutaneous tissue cells or distant lymph nodes	17	13.2
Total n†	129	100.0
First-line systemic treatment		
Chemotherapy (≥2 drugs)	94	86.2
Chemotherapy (1 drug)	6	5.5
Endocrine therapy	9	8.3
Total n†	109	100.0
Surgery for resection of the primary tumor		
Yes	50	40.6
No	73	59.4
Total n†	123	100.0
Surgery for resection of metastases		
Yes	10	9.2
No	98	90.8
Total n†	108	100.0

*At the time of initial diagnosis; †Number of individuals for whom data were available.

fewer cases detected at stage III compared to Goiânia. However, for cases with a metastatic disease already at diagnosis, the incidence was similar[33].

The subsample analyzed revealed a predominance of large tumors at diagnosis, with skin involvement and clinically compromised lymph nodes, reflecting difficulty to access disease diagnosis. This fact could probably be explained by the predominance of users of the public healthcare system in this study, since there are limitations to access within this system that are not found in the private healthcare system[17,34,35]. Nevertheless, the other clinical and demographic characteristics of the sample analyzed here were similar to those of the population with non-metastatic disease[36].

Palliative endocrine therapy is the systemic treatment of choice for women with metastatic disease and hormone-positive tumors in the absence of visceral crisis[8,15,25]. In itself, this is a more accessible and less expensive treatment than chemotherapy, a fact that is particularly important bearing in mind the progressive increase in the costs of cancer treatment[9]. In addition, endocrine therapy is associated with lower rates of adverse events and better quality of life, with no negative effect on progression-free survival or overall survival[37,38]. Therefore, the underutilization of endocrine therapy found in this study may reflect an inappropriate approach to treatment according to current recommendations and even according to the standard clinical practice within the time period studied[8,15,37].

In the subgroup of women with HER2-positive tumors, the small number of patients who received anti-HER2 therapy is noteworthy. This finding could be explained by the predominance of patients receiving care within the public healthcare system where trastuzumab only became available for the treatment of metastatic HER2-positive breast cancer in 2017[34,39]. In years to come, with increased access to targeted therapy, a reduction should be seen in the rates of chemotherapy alone, with the introduction of CDK 4/6 inhibitors and anti-HER therapy[8,14].

Data on the extent and the site of the metastatic lesions are crucial for planning treatment and evaluating individual prognosis[12,40]. In this study, despite the predominance of lesions at a single anatomical site, there was a high prevalence of visceral lesions and symptomatic disease at diagnosis. These data may partially explain the choice of chemotherapy as a first-line systemic treatment, even in cases of luminal tumors[8,25].

Subjecting women with metastatic disease to breast surgery remains controversial and is usually reserved for selected cases[8,41,42]. However, scientific evidence at the time evaluated by this study was limited to retrospective, non-controlled studies showing better overall survival in patients subjected to breast surgery[41]. In this study, around 40% of the patients had been subjected to some type of breast surgery, a finding that could also be explained by the better local control that was achieved[42]. A population-based study conducted in the United States also found a similar rate of breast surgery in this population[43]. However, in the context of public health in low- and medium-income countries, the possibility of inadequate systemic staging at diagnosis and confirmation of the metastatic disease in the first months following breast surgery deserves special emphasis[8,35,44].

The temporal analysis performed in this study failed to reveal any significant changes in the clinical characteristics or in the treatment provided despite the advances in diagnosis and treatment that have occurred in recent years[8]. This fact is probably due to the predominance of users of the public healthcare system in this study population. Nevertheless, a hospital-based study conducted in São Paulo included metastatic patients who received similar cancer treatment irrespective of whether they were clients of the private or public healthcare sector. In that series too, no statistically significant changes were found in the

Table 3. Description of the systemic treatment given as first- or second-line treatment according to the immunohistochemical characterization of tumor subtype.

	Systemic treatment	Anthracyclines	Taxanes	Tamoxifen	Aromatase inhibitors
	Tumor subtype	n (%)	n (%)	n (%)	n (%)
First-line	HR(+)/HER2(-) (n=34)*	25 (73.5)	16 (47.0)	3 (8.8)	3 (8.8)
	HR(+)/HER2(+) (n=9)*	7 (77.8)	4 (44.4)	-	1 (11.1)
	HR(-)/HER2(+) (n=7)*	7 (100.0)	4 (57.1)	-	-
	HR(-)/HER2(-) (n=11)*	10 (90.9)	7 (63.6)	-	-
2nd line	HR(+)/HER2(-) (n=29)*	3 (10.3)	1 (3.4)	12 (41.4)	5 (17.2)
	HR(+)/HER2(+) (n=6)*	1 (16.6)	1 (16.6)	2 (33.3)	-
	HR(-)/HER2(+) (n=4)*	-	-	-	-
	HR(-)/HER2(-) (n=5)*	-	-	-	-

	CMF	Platinum-based	Capecitabine	Gemcitabine	Vinorelbine	Trastuzumab
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
First-line	1 (3.0)	-	-			-
	1 (11.1)	-	-			1 (11.1)
	-	1 (14.3)	-			2 (28.5)
	1 (9.1)	-	-			-
2nd line	-	4 (13.8)	3 (10.3)	4 (13.8)	1 (3.4)	-
	-	1 (16.6)	1 (16.6)	1 (16.6)	-	1 (16.6)
	-	2 (50.0)	1 (25.0)	2 (50.0)	1 (25.0)	1 (25.0)
	-	4 (80.0)	1 (20.0)	3 (60.0)	1 (20.0)	-

*Total number of individuals for whom data were available for the respective line of systemic treatment. Each patient could have received more than one drug per line of treatment. CMF: Cyclophosphamide, methotrexate, 5-fluorouracil; HR: hormone receptor.

frequency distribution of the treatments carried out between 2000 and 2012[45]. Taken together, these data may reflect the progress of breast cancer treatment in the period, with a qualitative improvement in treatments already in use rather than the implementation of new treatment modalities.

Over the 17 years of analysis, a statistically significant alteration was found in only two variables. The reduction in the luminal-HER2 cases identified in immunohistochemistry is due to the small sample size. On the other hand, the increase in the proportion of public healthcare system users probably reflects the local socio-economic conditions[17,35]. Nevertheless, despite the difficulties of the Brazilian healthcare model[10,16,34], the data found in this series are in agreement with international population samples and reinforce the concept of cancer treatment globalization[11-14,16].

Limitations of this study include data missing from the population-based cancer registry database and from the medical records. These limitations are inherent to retrospective studies and do not affect the credibility or relevance of the results obtained[46]. The intersection of the population-based data made it possible to increase the robustness of this study by adding information on clinical, pathological, and treatment variables in patients with MBC. In theory, this real-world study, conducted in a city located in Brazil's Midwest, may reflect several other populations in low- and middle-income countries.

CONCLUSIONS

Around 5% of the women with breast cancer in Goiânia between 1995 and 2011 had MBC, of which the most common subtype was luminal breast cancer. There was no change in the incidence trends over the 17 years of the study. Almost 90% of the patients received chemotherapy as first-line treatment and, of the patients with hormone receptor-positive tumors, only 14% received endocrine therapy as first-line treatment. The use of anti-HER2 treatment was also remarkably low. Therefore, further studies are required to identify the biomarkers that could anticipate the diagnosis of

Table 4. Temporal distribution of clinical and therapeutic variables in the 1995–2003 and 2004–2011 periods in women with metastatic breast cancer at diagnosis in the city of Goiânia, Brazil.

	1995–2003 (n=129)		2004–2011 (n=148)		Absolute difference (%)	95%CI (%)	p-value†
	Cases (n)	%	Cases (n)	%			
Age at diagnosis (years)							
≤49	50	38.8	53	35.8	3.0	-8.2 to 14.2	0.6
50–59	37	28.7	38	25.7	3.0	-7.4 to 13.4	0.5
≥60	42	32.5	57	38.5	6.0	-5.3 to 16.9	0.2
Total n*	129	100.0	148	100.0			
Presence of symptoms							
Yes	40	75.5	63	86.3	10.8	-2.85 to 25.19	0.1
No	13	24.5	10	13.7	‡	‡	‡
Total n*	53	100.0	73	100.0			
Histological grade							
G1/G2	31	72.1	31	67.4	4.7	-14.18 to 22.94	0.6
G3	12	27.9	15	32.6	‡	‡	‡
Total n*	43	100.0	46	100.0			
Tumor phenotype							
Luminal	10	41.6	24	51.1	9.5	-14.41 to 31.45	0.4
Luminal-HER2	9	37.5	7	14.9	22.6	1.85 to 43.76	0.03
Pure HER2	2	8.4	6	12.7	4.3	-14.49 to 18.09	0.5
Triple-negative	3	12.5	10	21.3	8.8	-11.91 to 24.68	0.3
Total n*	24	100.0	47	100.0			
Staging (T)							
T0–2	19	31.7	18	26.1	5.6	-9.83 to 21	0.4
T3–4	41	68.3	51	73.9	‡	‡	‡
Total n*	60	100.0	69	100.0			
Staging (N)							
N0	19	32.8	12	18.5	14.3	-1.1 to 29.19	0.06
N1	19	32.8	21	32.3	0.5	-15.62 to 16.82	0.9
N2–3	20	34.4	32	49.2	14.8	-2.62 to 30.91	0.09
Total n*	58	100.0	65	100.0			
Access to treatment							
Public healthcare	32	60.4	58	77.3	16.9	0.82 to 32.54	0.04
Private healthcare	21	39.6	17	22.7	‡	‡	‡
Total n*	53	100.0	75	100.0			
First-line systemic treatment							
Chemotherapy (≥2 drugs)	41	89.1	53	84.2	4.9	-9.14 to 17.44	0.4
Chemotherapy (1 drug)	1	2.2	5	7.9	5.7	-4.51 to 15.2	0.1
Endocrine therapy	4	8.7	5	7.9	0.8	-9.91 to 13.26	0.8
Total n*	46	100.0	63	100.0			
Surgery for primary tumor							
Yes	22	44.0	28	38.3	5.7	-11.52 to 22.84	0.5
No	28	56.0	45	61.7	‡	‡	‡
Total n*	50	100.0	73	100.0			
Surgery for metastasis							
Yes	2	4.5	8	12.5	8.0	-4.17 to 18.78	0.1
No	42	95.5	56	87.5	‡	‡	‡
Total n*	44	100.0	64	100.0			

*Number of individuals for whom data were available for each variable. †Chi-square test. ‡For the dichotomous variables, the same proportion of difference and the same significance level values were maintained.

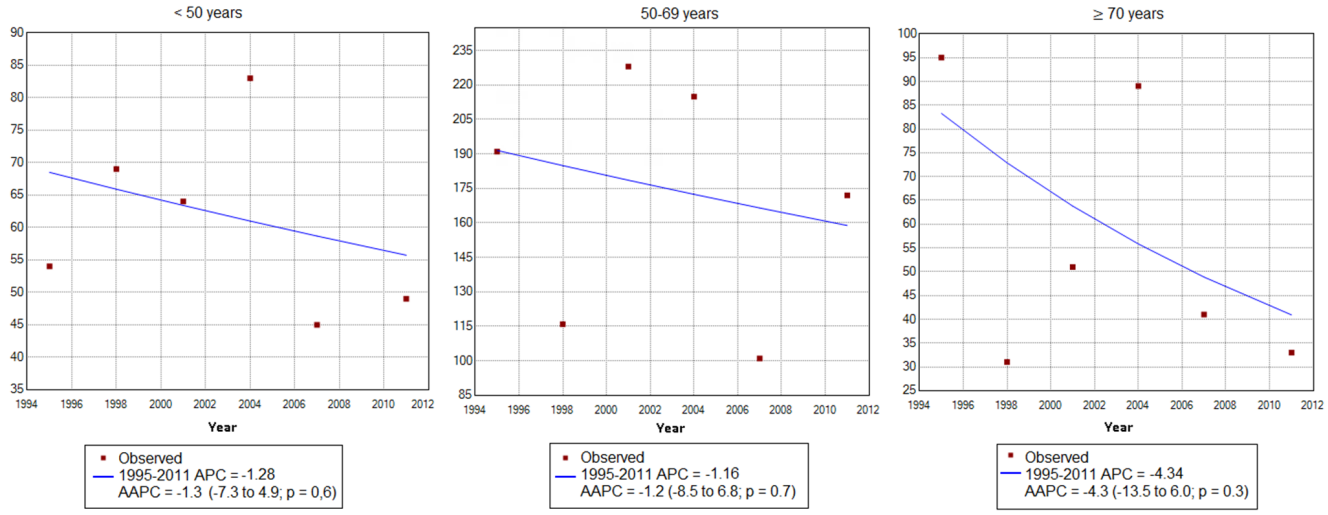


Figure 2. Trend in the standardized incidence rate of metastatic breast cancer in the city of Goiânia, Brazil, between 1995 and 2011, by age group.

breast cancer before it becomes metastatic. Finally, appropriate health policies need to be implemented to ensure the availability of new agents for use in systemic rescue therapy, including anti-HER2 agents and cyclin-dependent kinase inhibitors.

AUTHORS' CONTRIBUTION

LRS: Conceptualization, Data curation, Formal analysis, Resources, Writing – original draft, Writing – review & editing. RFJ: Conceptualization, Methodology, Supervision, Writing – original draft, Writing – review & editing. RDN: Conceptualization, Methodology, Validation, Writing – original draft, Writing – review & editing. EM: Conceptualization, Data curation, Formal analysis, Investigation, Validation, Visualization, Writing – review & editing. JCO: Conceptualization, Methodology, Validation, Writing – original draft, Writing – review & editing. MPC: Conceptualization, Methodology, Supervision, Validation, Writing – original draft, Writing – review & editing.

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