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Survival in HIV+ and HIV− women with breast cancer treated at the National Cancer Institute in the city of Rio de Janeiro, Brazil, between 2000 and 2014

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ABSTRACT

Background: The goal was to assess the survival of HIV+ women and HIV- women for breast cancer at a referral center for cancer treatment in Brazil.

Methods: A retrospective cohort study was performed. A total of 136 women patients with breast cancer were included, being 36 HIV+ women and 100 HIV- women. Controls (HIV-) were selected according to HIV status, matched by date of cancer diagnosis, clinical stage, breast cancer treatment, and date of birth. Sociodemographic and cancer treatment data, as well as clinical HIV data, were extracted from physical and electronic medical records and secondary Instituto Nacional of cancer databases. To estimate survival, the Kaplan-Meier method was used. To determine the factors associated with mortality, Cox regression were used.

Results: The mean age of patients at diagnosis of cancer was 52 years. Regarding marital status, HIV+ patients had a higher frequency of single status). There were 44.1% deaths that occurred during the study period. Among HIV+ patients, there were 16 deaths, 15 of which were due to cancer. In HIV- patients there were 44 deaths (44%), with 32 cancer as the cause of death and 12 due to other causes. For the analysis of Overall. Differences were found in overall survival at 60 months (p=0.026), 55% and 69% respectively. The increased risk of death at 60 months among HIV+ women was observed also, after adjusting for schooling and molecular subtype (HR=1.95; 95% CI 1.03 – 3.70; p=0.041).

Conclusion: HIV infection influenced a worse prognosis for women with breast cancer regardless of tumor factors.

1. Introduction

Breast cancer is the most common type of cancer among women worldwide and the leading cause of cancer death in the female population [1]. A total of 66,280 new cases are estimated per year for the 2020–2022 triennium in Brazil [2].

Cancer has been associated with HIV infection since the beginning of the HIV/AIDS epidemic. With the development of highly active antiretroviral therapy (HAART), available in 1996, increased life expectancies for people living with HIV and decreased mortality from opportunistic infections and AIDS-defining cancers are noted. In turn, the cancer incidence rates in these individuals have altered considerably due to increased life expectancies [2]. In this context, breast cancer has emerged as an important non-AIDS-defining cancer in the HIV+ female population [2,3].

Some studies have demonstrated an increased risk for the development of breast cancer in the HIV+ population [4–8], as well as prognosis worsening. In this context, this study aimed to assess the overall survival of HIV+ and HIV- breast cancer patients at a referral cancer treatment center in Brazil.

2. Methodology

This study comprises a retrospective cohort study on breast cancer

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patients treated at the National Cancer Institute (INCA) in Rio de Janeiro, Brazil. Patients with a confirmed diagnosis of breast cancer were initially selected, presenting three different histological types according to the International Code of Diseases for Oncology (ICD-O), namely infiltrating ductal carcinoma (8500/3), infiltrating lobular carcinoma (8520/3) and mucinous carcinoma (8482/3), enrolled and treated at the INCA from January 1, 2000 to December 31, 2014 and aged over 18 years old. Patients were defined as HIV-positive when HIV diagnosis was performed at the Institution, and they had to have at least two tests (diagnosis + confirmatory test or additional HIV viral load positive tests). HIV diagnosis was also confirmed in the physical record. Women diagnosed with HIV infection after the cancer diagnosis were excluded from the analyses.

Controls (HIV-) were selected matched according to HIV+ status (1:3) by date of breast cancer diagnosis, clinical stage, primary breast cancer treatment, and date of birth (±5 years).

A total of 136 women with breast cancer were included in the study following these inclusion criteria, comprising 36 HIV+ and 100 HIV- patients. The study was approved by the INCA Research Ethics Committee (CAAE number: 25445414.7.0000.5274).

Sociodemographic, cancer staging and treatment data, as well as HIV clinical data, were extracted from physical and electronic medical records and from INCA's secondary databases and plotted an Excel spreadsheet. Descriptive statistics were applied to describe the analyzed cohort characteristics. A frequency distribution assessment was applied for categorical variables and central tendency and dispersion measures for continuous variables. Differences between groups were evaluated by Pearson's chi-square test and results presenting $p < 0.05$ were considered statistically significant.

The Kaplan-Meier method was used to estimate survival, and statistically significant differences between groups were calculated using the Log-Rank test. The overall survival analysis considered time from the breast cancer diagnosis to death from any cause (event). Patients without an event at the end of the 60-month follow-up were censored, and follow-up losses were censored on the date of the last hospital visit.

Both univariate and multiple Cox regressions were used to determine mortality-associated factors, applying the Hazard Ratio (HR) and a 95% confidence interval. Variables presenting p-value < 0.20 in the univariate analysis or with high clinical relevance were included in the multiple Cox analysis. Variables presenting $p < 0.05$ were retained in the model. All analyses were performed using the Statistical Package for Social Sciences (SPSS Inc, Chicago, IL, USA), version 18.0.

3. Results

Forty-one HIV+ patients were identified, while three matched controls for each case in five circumstances could not be identified. Of the 41 HIV+ patients, 36 were matched to three HIV- patients, four to two HIV- patients and one HIV+ patient was matched to one HIV- patient. Five HIV+ patients were excluded due to HIV+ diagnosis after breast cancer diagnosis. Therefore, a total of 36 HIV+ patients and 100 HIV- patients were analyzed (Fig. 1).

The mean age of patients at diagnosis of breast cancer was 52 years (±10). Matching variables (breast cancer diagnosis, date clinical stage, primary breast cancer treatment, histological cancer type and date of birth) were not analyzed due to similarities between both study two groups. No statistically significant differences were observed for most of the demographic variables when comparing the groups according to the presence or absence of HIV, with most HIV+ patients comprising white (61.1%), non-tobacco use (74, 2%) and non-alcohol use (80%) individuals. Regarding marital status, HIV+ patients were mostly single (80% p-value = 0.005) (Table 1).

Table 2 presents patient tumor characteristics according to HIV diagnosis. Most HIV+ patients exhibited infiltrating ductal carcinomas at clinical stage III B (25%) of the luminal molecular subtype (83.9%). No statistically significant difference was observed between groups (Table 2).

Regarding cancer treatment, 37% of HIV+ patients underwent neoadjuvant treatment. Surgical treatment was the main applied treatment (80.5%), with mastectomy as the most frequent type of surgery (58.3%). Most of the lymph nodes in the histopathological evaluation were negative (60.0%) (Table 2).

Patients who underwent radical or conservative surgery were considered in the disease-free survival (DFS) analysis. Of the 30 HIV+ women and 87 HIV− women included in this analysis, 10 HIV+ and 21 HIV− women relapsed within five years. However, no survival rate differences were detected when comparing HIV+ and HIV− patients ($p = 0.121$), with mean times to death of 38 months and 45 months, respectively (Fig. 2).

A total of 60 (44.1%) deaths took place during the study period, 16 (44.4%) among HIV+ patients, 15 of which were specifically due to cancer, and 44 deaths (44%) among HIV− patients, 32 specifically due to cancer and 12 from other causes. No patient presented AIDS as the cause of death.

The patients were followed up from the breast cancer diagnosis up to 60 months for the Overall Survival (OS) analysis. Differences in OS at 60 months were observed ($p = 0.026$), of 55% and 69% respectively. Follow-up time was shorter for HIV+ patients when compared to HIV− patients (51 months versus 89 months) (Fig. 3).

Concerning the univariate Cox regression, a 1.95-fold higher risk of death was observed for HIV+ patients during the 60-month follow-up (HR = 1.95; 95% CI 1.06–3.57; $p = 0.030$) (Table 3). The same higher

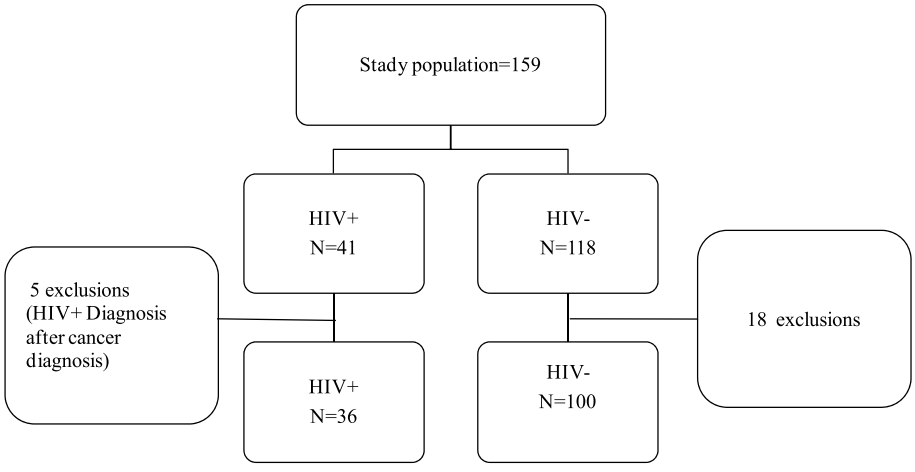

Fig. 1. Study population identification flowchart.

Table 1
Sociodemographic and clinical INCAbreast cancer patient characteristics from 2000 to 2014.

	HIV positive		HIV negative		*p*-value
	N°	%	N°	%	
Total	36		100		
Age (mean - SD)[a]	52 (9.9)	–	52 (10.8)	–	0.999
Year of diagnosis[a]					0.157
2000–2004	10	27.8	34	32.0	
2005–2009	10	27.8	39	39.0	
2010–2014	16	44.4	27	27.0	
Ethnicity					0.315
White	22	61.1	54	54.5	
Non-white	14	38.9	45	44.5	
No information	–	–	1	–	
Schooling					
< 8 years	20	58.8	70	70.0	0.162
≥ 8 years	14	41.2	30	30.0	
_No information[b]	2	–	–	–	
Marital status					**0.005**
Without a partner	28	80.0	54	54.0	
With a partner	7	20.0	46	46.0	
Tobacco use					0.184
Yes	8	25.8	36	36.7	
No	23	74.2	62	63.3	
No information[b]	5	–	2	–	
Alcohol use					0.384
Yes	6	20.0	24	25.0	
No	24	80.0	72	75.0	
No information[b]	6	–	4	–	
Family history of breast cancer					0.640
Yes	3	8.8	9	9.0	
No	31	91.2	89	91.0	
No information[b]	2	–	2	–	
BMI					0.677
<25	5	29.4	29	39.2	
25 to 29	5	29.4	22	29.7	
>30	7	41.2	23	31.1	
No information[b]	13	–	27	–	

Note: N, Total number of cases; BMI, body mass index.
[a] Pairing variable.
[b] Variables with no information were not included in the percentage calculations or in the p-values and chi-square test. Statistically significant values are displayed in bold.

risk of death at 60 months among HIV+ women was observed after adjusting for schooling and molecular subtype (HR = 1.95; 95% CI 1.03–3.70; p = 0.041) (Table 4).

Patients were followed from the breast cancer diagnosis until specific death by cancer in the Specific Survival (SS) analysis. No differences in 60-month survival rates were observed when comparing HIV+ and HIV− patients (69% and 73%; p = 0.252), and the mean times to death were 45 months and 52 months, respectively (Fig. 4).

The Cox model was employed to assess factors associated with cancer-specific survival. No association was detected between HIV infection and cancer-specific survival at 60 months (HR 1.50 CI = 0.74–3.03; p = 0.256). (Table 5) in the univariate analysis.

3.1. Clinical HIV+ infection data in breast cancer patients

Of the 36 HIV-infected women, 24 (66.7%) exhibited $CD4^+$ cell count data close to the cancer diagnosis, with an average $CD4^+$ cell count close to diagnosis of 565 cells/ml (interquartile range 122–1347). The median HIV viral load was 4500 copies/ml (interquartile range <34–230,122). Twenty-one HIV+ women (58.3%) were undergoing antiretroviral therapy at the INCA close to the cancer diagnosis. One patient with $CD4^+$ results was diagnosed with AIDS. Among the 36 HIV+ women, only two presented co-infectiondata, both co-infected with the Herpes virus type C (HCV) (Table 6).

Table 2
Tumor and treatment characteristics of INCA HIV+ and HIV− breast cancer patients during the study period.

	HIV positive		HIV negative		*p*- value
	N°	%	N°	%	
Total	36	100	100	100	
Histological type					0.579
Infiltratingductal carcinoma	33	91.7	96	96	
Infiltrating lobular carcinoma	2	5.6	3	3.0	
Mucinous carcinoma	1	2.8	1	1.0	
Clinical staging*					0.994
I	7	19.4	23	20.2	
IIA	5	13.9	14	12.3	
IIB	8	22.2	22	19.3	
IIIA	3	8.3	11	9.6	
IIIB	9	25	27	23.7	
IIIC	1	2.8	5	4.4	
IV	3	8.3	12	10.2	
Molecular subtype					0.530
Luminal	26	83.9	82	91.1	
HER2 positive	2	6.5	3	3.3	
Triple negative	3	9.7	5	5.6	
No information[a]	5	–	10	–	
Neoadjuvant treatment					0.487
Yes	13	37.1	35	35.0	
No	22	62.9	65	65.0	
Surgical treatment					0.780
Yes	30	83.3	85	85.1	
No	6	16.7	15	14.9	
Type of surgery					0.240
Conservative surgery	8	22.2	13	13.0	
Mastectomy	21	58.3	73	73.0	
Not performed	7	19.4	14	14.0	
Positive lymph node					0.597
Yes	14	40.0	45	45.0	
No	21	60.0	55	55.0	
No information[a]	1	1	–	–	

Note: N, Total number of cases.
[a] Variables with no information were not included in the percentage calculations or in the p-values and chi-square test.

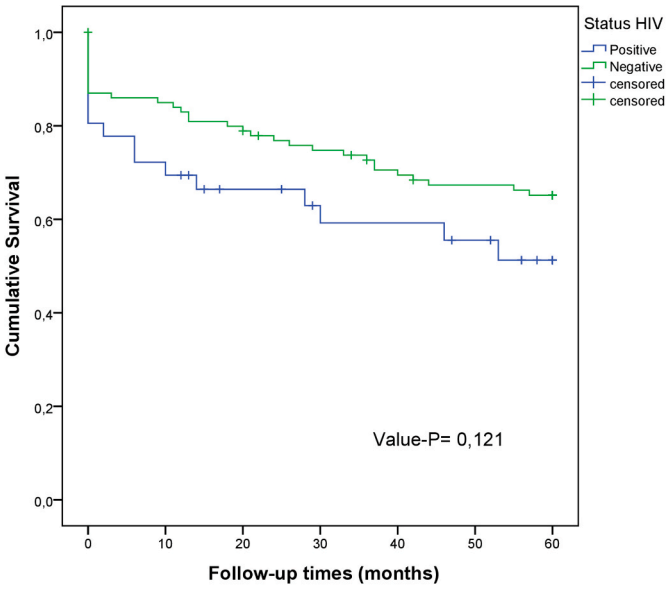

Fig. 2. Kaplan-Meier analysis of disease-free survival among INCA HIV+ and HIV- breast cancer patients.

4. Discussion

Breast cancer is the most common cancer among women worldwide and the most common type of non-AIDS-defining cancer in HIV+

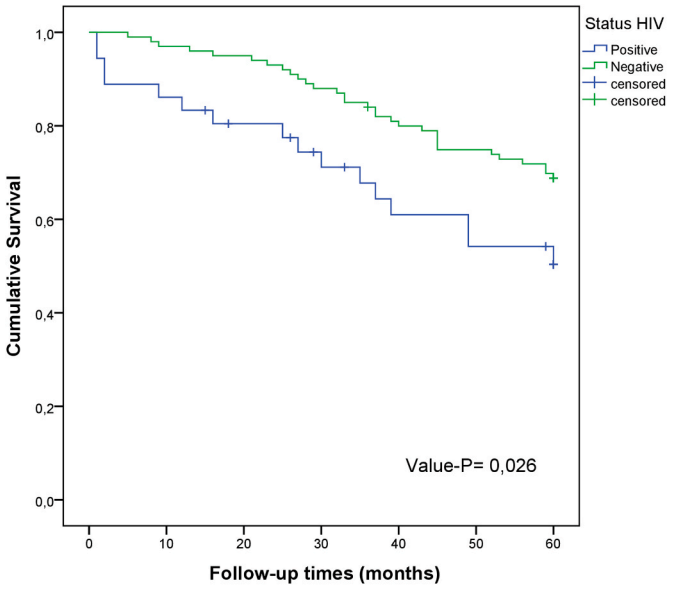

Fig. 3. Kaplan-Meier analysis of overall survival among INCA HIV+ and HIV− breast cancer patients.

Table 3
Univariate analysis of factors associated with overall survival of INCA breast cancer patients 2000 to 2014.

	Overall survival (60 months)		
	Mean time	HR (CI)	P-value
HIVstatus			
HIV+	43	1.95(1.06–3.57)	**0.030**
HIV−	54	Reference	
Age			
<65	49	Reference	
>65	55	0.44(0.13–1.42)	0.170
Ethnicity			
White	50	0.95(0.53–1.42)	0.863
Non-white	48	Reference	
Schooling			
<8 years	51	0.61(0.34–1.10)	0.104
>8 years	47	Reference	
Marital status			
With a partner	49	Reference	
Without a partner	51	1.30(0.70–2.38)	0.394
Tobacco use			
Yes	45	0.58(0.29–1.14)	0.259
No	52	Reference	
Alcohol use			
Yes	50	1.14(0.57–2.27)	0.704
No	51	Reference	
Histological subtype			
ICD	49	3.21(0.44–23.2)	0.249
Other	60	Reference	
Clinical staging			
I - IIA	57	Reference	
IIB - IV	46	4.2(1.78–9.90)	**0.001**
Subtype Molecular			
Luminal	52	0.42(0.21–0.82)	**0.012**
Other	41	Reference	
Neoadjuvant treatment			
Yes	48	1.09(0.60–1.99)	0.760
No	50	Reference	
Surgical treatment			
Yes	54	Reference	
No	23	9.82(5.34–18)	**<0.001**
Positive lymph node			
Yes	51	1.02(0.57–1.82)	0.931
No	48	Reference	

HR= Hazard Ratio, CI= Confidence interval,ICD= International Code of Diseases. Statistically significant values are presented in bold.

Table 4
Multivariate analysis of the impact of HIV+ status on overall INCA breast cancer patient survival from 2000 to 2014.

	Overall survival (60 months)[a]	
	HR (CI)	HR (CI)
HIVstatus		
HIV+	1.95(1.03–3.70)	**0.041**
HIV−	Reference	

[a] Analysis adjusted for schooling and molecular subtype. HR= Hazard Ratio; CI= Confidence interval. Statistically significant values are presented in bold.

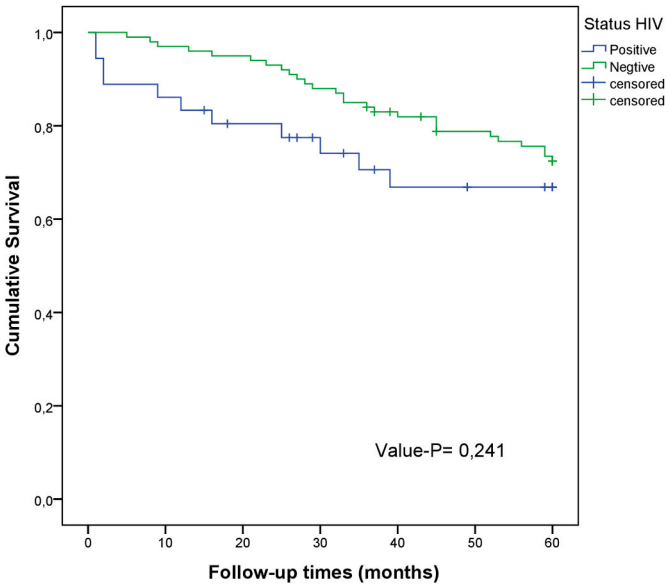

Fig. 4. Kaplan-Meier analysis of specific survival among INCA HIV+ and HIV− breast cancer patients.

women. This was the first study to assess breast cancer survival in HIV+ women at a cancer treatment reference institution in Brazil. Most HIV+ patients were diagnosed with stage II and III breast cancer, over 80% were estrogen receptor positive and underwent surgery as the main type of treatment, associated or not with neoadjuvant, adjuvant either/or neoadjuvant chemotherapyand radiotherapy. Regarding clinical staging, our findings were similar between HIV+ and HIV− patients, as the patients were matched by this variable in order to better conduct data comparisons. However, several studies have demonstrated that HIV+ breast cancer patients exhibit more advanced cancer staging compared to HIV− patients, negatively impacting cancer prognoses for these patients [9–11,13]. With respect tobacco use and alcohol use, no difference in the distribution of users and non-users was found for these variables in relation to HIV status. However, several studies show that there is a higher frequency of tobacco and alcohol use in HIV-positive individuals. In addition, they show an increase risk of developing several diseases in this population, impacting on mortality in HIV-positive patients [14–17].

Patient treatment was based on clinical staging for both groups, and it is important to highlight that the treatment protocols for HIV+ and HIV− breast cancer patients at INCA are the same. Thus, treatment was applied as an adjustment variable. Regarding deaths, most HIV+ patients died of breast cancer, few died from other causes and no deaths due to AIDS were observed. Regarding outcomes, the overall (OS), specific (SE) and disease-free (DFS) survival ratesin 60 months were evaluated. No association was detected for SE and DFS. However, our results indicate a worse overal survival for HIV+ breast cancer patients at 60 months, even after adjusting for clinical staging, histological type, molecular subtype, and schooling (HR 1.95; 95% CI 1.03–3.70). Worse

Table 5
Univariate analysis of factors associated with specific survival in INCA breast cancer patients from 2000 to 2014.

	Specific survival(60 months)		
	Mean time	HR (95% CI)	P-value
HIVstatus			
HIV+	45	1.50(074–3.03)	0.256
HIV−	52	Reference	
Age			
<65	49	1.72(0.76–3.92)	0.191
>65	56	Reference	
Ethnicity			
White	51	0.87(0.48–1.66)	0.690
Non-white	50	Reference	
Schooling			
<8 years	50	0.57(0.29–1.10)	0.094
>8 years	53	Reference	
Marital status			
With partner	50	1.01(0.52–1.95)	0.973
Without partner	51	Reference	
Tobacco use			0.294
Yes	53	0.67(0.32–1.40)	
No	50	Reference	
Alcohol use			0.702
Yes	50	1.16(0.54–2.48)	
No	51	Reference	
Histological type			
ICD	50	22.2(0.6–71.0)	0.292
Other	49	Reference	
Clinical staging			
I – IIA	56	Reference	
IIB – IV	44	3.76(1.86–7.60)	**0.0001**
Molecular subtype			
Luminal	53	0.50(0.27–0.95)	**0.035**
Other	43	Reference	
Treatment Neoadjuvant			
Yes	50	0.99(0.50–1.94)	0.983
No	51	Reference	
Surgical treatment			
Yes	55	0.07(0.03–0.14)	**0.0001**
No	23	Reference	
Positive lymph node			
Yes	52	0.91(0.48–1.74)	0.791
No	49	Reference	

HR= Hazard Ratio; CI= Confidence interval. ICD= International Code of Diseases. Statistically significant values are presented in bold.

Table 6
Clinical data on HIV+ infection in INCA breast cancer patients during the study period.

Variables	N (%)
On antiretroviral treatment[a]	21(58)
Median $CD4^+$ T cell count (Cells/mm^3) close to cancer diagnosis (QI)[b]	513 (122–1193)
Median HIV viral load (copies/ml) close to cancer diagnosis (QI)[c]	4.500 (34–203.122)
TCD4+ count (Cells/mm^3)	
<200	1 (4.3)
≥200	21 (95.7)
Viral load count (copies/ml)	
>1000	2 (9.1)
¬≤1000	4(18.2)
Undetectable	16(72.7)

[a] 15 patients with no information.
[b] Based on 24 patients.
[c] Based on 22 patients. IQ = Quotient Index.

survival has also been reported for HIV+ patients in other countries [9,12]. Cancer outcomes and prognosis have been investigated in this population in other studies. Several factors are known to influence breast cancer prognosis in the general population, such as younger age at diagnosis, late cancer diagnosis and poorer response to chemotherapy [13,19]. Here in, these variables were used as matching variables, allowing for a more accurate analysis of potential associations between HIV infection and breast cancer patient survival. A study published by Youngblood and colleagues in 2020 evaluated breast cancer prognoses in HIV+ women, reporting a strong association between HIV infection, advanced stagingand molecular subtype and a worse breast cancer prognosis [18]. A meta-analysis published by Brandão and colleagues evaluated 18 studies, comparing tumor characteristics (stage and/or subtypes) and/or overall survival of HIV-positive women *versus* HIV-negative women with breast cancer. The results showed that HIV-positive women presented more advanced stages of cancer and worse overall survival compared to HIV-negative women [20].

An important limitation of our study comprises lack of information on $CD4^+$ cell counts in medical records to assess potential relationships between immunosuppression level and cancer outcomes in breast cancer patients. Based on limited data, we noted that most breast cancer patients were on antiretroviral treatment, displaying a median TCD4 lymphocyte count of 513 cells/mm^3, and that most presented therapeutic success, due to undetectable viral loads. In Brazil, people infected with HIV are eligible for free HIV treatment through the Unified Health System (*SistemaÚnico de Saúde*- SUS). Access to HAART treatment in Brazil follows international standards. Although the HIV+ women included in the present study were eligible for HIV treatment under a national policy, the use of antiretroviral drugs was probably incompletely recorded at the Ministry of Health HIV database (data not shown) and in medical INCA records. Another limitation of our study was the definition of the molecular subtype for breast cancer, since the Ki-67 antigen analysis (necessary for distinguishing luminal types) was not available for most of our population, as it only began to be evaluated at our institution in 2010.

One of our studies strengths is the matching of HIV+ and HIV− patients for most important breast cancer prognosis characteristics. Patients were treated at a single institution and received oncologic assessment and care following international cancer care guidelines. Finally, most deaths were verified through standard clinical follow-up at INCA, allowing for higher data reliability regarding cause of death.

In conclusion, we demonstrate here in that HIV+ patients exhibit worse overall survival when compared to HIV− patients, regardless of cancer-related factors. This study further highlights the need for future research of breast cancer in HIV-positive patients to better understand HIV infection contributions to breast cancer outcomes. Beside to help guide preventive care guidelines for screening and diagnosis of breast cancer in this population. Is important to emphasize that cancer patients should undergo appropriate HAART regimens.

Ethical

This study was approved by the INCA Research Ethics Committee, under no. 25445414.7.0000.5274.

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