RESEARCH ARTICLE

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Lack of Impact of Race Alone on Cervical Cancer Survival in Brazil

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Abstract

Objective: To analyze differences in survival between black and non-black women diagnosed with cervical cancer and treated at the National Cancer Institute in Brazil. **Methods:** This retrospective cohort study was conducted using medical records of patients who were treated for cervical cancer between 2006 and 2009 at the Brazilian National Cancer Institute - Rio de Janeiro - Brazil. The clinical and epidemiological characteristics of black and non-black patients were compared using the chi-square test. Survival functions over five years were calculated using the Kaplan-Meier estimator and compared using the log-rank test. Associations between race and mortality risk were analyzed using the Cox proportional hazards model. P-values <0.05 were considered statistically significant. **Results:** The study included 1,482 women, of whom 188 (12.7%) were black, 1,209 (81.6%) were non-black and 85 (5.7%) were of unspecified race. The age at diagnosis of the patients ranged from 19 to 84 years (mean 50.1 years; SD±13.2). Hemoglobin <12 g/dL at the time of diagnosis (p=0.008) and absence of surgery as primary treatment (p = 0.005) were more frequent among black women. Cox analysis adjusted for these two factors showed no statistically significant difference in the mortality risk associated with cervical cancer among black and non-black women (HR=1.1 95% CI 0.9-1.5; p=0.27). **Conclusion:** After adjusting for hemoglobin levels and surgery, race alone was not shown to be a prognostic factor for patients with cervical cancer.

Keywords: Cervical neoplasms- race or ethnicity- prognosis- Brazil

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Introduction

Cervical cancer is currently an important public health issue worldwide. According to the Brazilian National Cancer Institute (INCA in Portuguese), in the year 2017, 16,340 new cases are expected to occur in Brazil, with an estimated risk of 15.85 cases per 100,000 women. It is the third most frequent tumor in the female population and the fourth cause of death by cancer among Brazilian women. Worldwide estimates consider that this disease was responsible for the death of 265,000 women in 2012 (Siegel et al., 2014; Brasil, 2015).

Cervical cancer screening by cervical cytology (Pap smear exam) has been shown to be effective in the detection of precursor lesions. Studies have shown that the introduction of screening tests has caused a decline in the incidence and mortality of cervical cancer in developed countries. Although this decline has occurred in all ethnic and racial groups, some differences have been found regarding incidence and mortality among black and white women (McCarthy et al., 2010). These racial differences have been associated with several factors, including tumor behavior, access to screening exams, advanced tumor stage at diagnosis and treatment. Black women tend to be diagnosed with tumors in more advanced stages and receive less aggressive treatments than white women (Adams et al., 2009; McCarthy et al., 2010; Rauh-Hain et al., 2013).

However, several authors suggest that, when socioeconomic factors and comorbidities are balanced across racial groups in data analysis, mortality due to cervical cancer is similar between strata (Movva et al., 2008; Fleming et al., 2014). The lack of consensus in the scientific literature and the lack of cohorts from developing countries such as Brazil, where part of the population is black, reflect the need for new studies to clarify the association between the race and cervical cancer prognosis. The objective of the present study was

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to compare survival rates between black and non-black women with cervical cancer treated at the INCA, through the evaluation of the epidemiological and clinical characteristics of both populations.

Materials and Methods

After submission, evaluation and subsequent approval by the Research Ethics Committee of the INCA, located in the City of Rio de Janeiro, Brazil, a retrospective cohort study was carried out by analysis of the medical records of 1,482 women diagnosed with cervical cancer and treated between January 1, 2006 and December 31, 2009. Cases of squamous cell carcinoma, adenocarcinoma, adenosquamous carcinoma, and other carcinomas were included in this study.

The following data were collected directly from the medical records: initials and patient ID, date of diagnosis or biopsy examination, date of last contact or hospital visit included, age at diagnosis and/or biopsy examination, race/skin color, self-reported race (classified according to the Brazilian Institute of Geography and Statistics –IBGE in Portuguese - as white, brown or black), marital status (single, married, widow, others), occupation (housewife,works outside), smoking status (yes, no, ex-smoker), alcohol consumption, (yes, no, ex-consumer), comorbidity (yes, no), hemoglobin levels at the beginning of the treatment (stratified as <12 g/dL or ≥12 g/dL), performance status according to the scale of the Eastern Cooperative Oncology Group (PS ECOG), histological tumor type (squamous cell carcinoma, adenocarcinoma, adenosquamous carcinoma and other carcinomas), degree of differentiation (well differentiated [G1], moderately differentiated [G2], slightly differentiated [G3] and undifferentiated [G4]), clinical staging according to the International Federation of Gynecology and Obstetrics (FIGO) (localized disease, locally advanced disease and distant metastasis), status at last contact (dead or alive), and treatments received. The treatment to which the patient was allocated primarily was considered as the primary treatment, which included surgery (trachelectomy, types I to V hysterectomies, according to the classification of Piver and Rutledge, or not determined), chemotherapy, external radiotherapy, brachytherapy or associations among these treatments. Secondary treatments included chemotherapy and radiotherapy, alone or in combination.

For analysis purpose, patients were classified as black or non-black (white or brown). Clinical and epidemiological characteristics were compared using the chi-square test. Overall survival was calculated using the interval between the diagnosis and/or biopsy examination and the death. For patients that were alive on the time of the last follow-up, the time was censored at the last contact or visit to the hospital, or December 31, 2013, depending on the case. Survival curves in 5 years were estimated using the Kaplan-Meier method, whereas the analysis of difference between the groups was performed using the log-rank test. A Cox proportional risk model was developed to adjust mortality risk according to the clinical and epidemiological characteristics that were statistically significant. We also investigated the collinearity between variables and included in the final model variables that showed an association with mortality risk ($p < 0.05$). When two or more variables presented collinearity, only the one with the most likely clinical significance was included in the final model. P-values <0.05 were considered statistically significant. Data were analyzed using the statistical software SPSS version 20.0 (IBM Corp., Armonk, USA).

Results

The study included 1,482 women diagnosed with cervical cancer. Of these, 188 (12.7%) patients were black, 1,209 (81.6%) were non-black, and 84 (5.7%) did not have a specified race. The age at diagnosis of the patients ranged from 19 to 84 years, with a mean age of 50.1 years (SD ± 13.2), with 51.0 years (SD ± 13.3) for black women and 49.9 years (SD ± 13.2) for non-black women ($p = 0.266$). There was no statistically significant difference between the groups regarding marital status, occupation, smoking and alcoholism, comorbidities, PS ECOG and histological type. In the staging analysis, 75.3% of non-black patients and 81.3% of black women had locally advanced disease at diagnosis, respectively ($p = 0.156$). The moderately differentiated degree (G2) was the most frequently found in both groups, corresponding to 55.0% of the total number of patients ($p = 0.449$). However, hemoglobin levels below 12g/dL at diagnosis were more frequently observed among black women (56.5% versus 45.8%, $p = 0.008$) (Table 1).

Also, black women were less frequently submitted to primary surgery (18.1% versus 28.3%, $p = 0.005$) and lymphadenectomy (10.6% versus 18.5%, $p = 0.027$). There was no statistically significant difference in the use of primary chemotherapy (black 54.8% versus 55.2% non-black, $p = 0.564$), primary radiotherapy (69.7% among black women versus 63.2% among non-black women, $p = 0.063$) and brachytherapy (57.4% among black women versus 56.9% among non-black women, $p = 0.632$). Adjuvant treatments (radiotherapy and chemotherapy), as well as the use of more chemotherapy lines, were infrequent in both races (Table2).

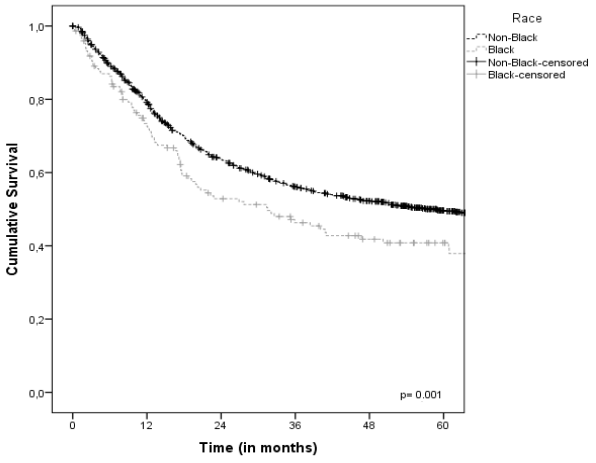

Figure1. Global Survival–black Women Versus Non-black Women

Table 1. Socio- Demographic and Clinical Characteristics

Variables	Black	Non-Black	Total	p-value
Age at diagnosis				
< 60 years	139 (73.9%)	920 (76.1%)	1059 (75.8%)	0.520
≥ 60 years	49 (26.1%)	289 (23.9%)	338 (24.2%)	
Marital status				
Single	81 (43.1%)	425 (35.2%)	506 (36.2%)	
Married	48 (25.5%)	365 (30.2%)	413 (29.6%)	
Widow	27 (14.4%)	176 (14.6%)	203 (14.5%)	0.226
Others	17 (9.0%)	151 (12.5%)	168 (12.0%)	
Unknown	15 (8.0%)	92 (7.6%)	107 (7.7%)	
Occupation				
Works outside	32 (17.0%)	301 (24.9%)	333 (23.8%)	
Housewife	127 (67.6%)	741 (61.3%)	868 (62.1%)	0.062
Unknown	29 (15.4%)	167 (13.8%)	196 (14.0%)	
Smoking				
Yes	41 (21.8%)	252 (20.8%)	293 (21.0%)	
No	91 (48.4%)	598 (49.5%)	689 (49.3%)	
Ex-smoker	32 (17.0%)	235 (19.4%)	267 (19.1%)	0.665
Unknown	24 (12.8%)	124 (10.3%)	148 (10.6%)	
Alcohol consumption				
Yes	32 (17.0%)	135 (11.2%)	167 (12.0%)	
No	124 (66.0%)	901 (74.5%)	1025 (73.4%)	0.068
Ex-consumer	7 (3.7%)	40 (3.3%)	47 (3.4%)	
Unknown	25 (13.3%)	133 (11.0%)	158 (11.3%)	
Comorbidities				
Yes	99 (52.7%)	553 (45.7%)	652 (46.7%)	
No	68 (36.2%)	503 (41.6%)	571 (40.9%)	0.209
Unknown	21 (11.2%)	153 (12.7%)	174 (12.5%)	
Hemoglobin levels (g/dL)				
<12	96 (56.5%)	493 (45.6%)	589 (47.0%)	0.008
≥12	74 (43.5%)	589 (54.4%)	663 (53.0%)	
Performance status				
0-1	124 (86.7%)	903 (90.6%)	1027 (90.1%)	0.149
2-4	19 (13.3%)	94 (9.4%)	113 (9.9%)	
Histological type				
Squamouscell carcinoma	148 (78.7%)	954 (78.9%)	1102 (78.9%)	
Adenocarcinoma	30 (16.0%)	185 (15.3%)	215 (15.4%)	0.910
Adenosquamous carcinoma	4 (2.1%)	36 (3.0%)	40 (2.9%)	
Others carcinomas/Unknown	6 (3.2%)	34 (2.8%)	40 (2.9%)	
Staging				
Localized disease	31 (17.0%)	272 (23.4%)	303 (22.5%)	
Locally advanced disease	148 (81.3%)	876 (75.3%)	1024 (76.1%)	0.156
Distant metastasis	3 (1.6%)	15 (1.3%)	18 (1.3%)	
Differentiation degree				
G1	16 (8.5%)	118 (9.8%)	134 (9.6%)	
G2	115 (61.2%)	654 (54.1%)	769 (55.0%)	
G3	27 (14.4%)	218 (18.0%)	245 (17.5%)	0.449
G4	1 (0.5%)	4 (0.3%)	5 (0.4%)	
Unknown	29 (15.4%)	215 (17.8%)	244 (17.5%)	

Table 2. Treatments Received

Variables	Black	Non-Black	Total	p-value
Primary treatments:				
Surgery				
Yes	34 (18.1%)	342 (28.3%)	376 (26.9%)	
No	148 (78.7%)	849 (70.2%)	997 (71.4%)	0.005
Unknown	6 (3.2%)	18 (1.5%)	24 (1.7%)	
Lymphadenectomy				
Yes	20 (10.6%)	224 (18.5%)	244 (17.5%)	
No	151 (80.3%)	895 (74.0%)	1046 (74.9%)	0.027
Unknown	17 (9.0%)	90 (7.4%)	107 (7.7%)	
Chemotherapy				
Yes	103 (54.8%)	667 (55.2%)	770 (55.1%)	
No	80 (42.6%)	523 (43.3%)	603 (43.2%)	0.564
Unknown	5 (2.7%)	19 (1.6%)	24 (1.7%)	
External radiotherapy				
Yes	131 (69.7%)	764 (63.2%)	895 (64.1%)	
No	52 (27.7%)	428 (35.4%)	480 (34.4%)	0.063
Unknown	5 (2.7%)	17 (1.4%)	22 (1.6%)	
Brachytherapy				
Yes	108 (57.4%)	688 (56.9%)	796 (57.0%)	
No	71 (37.8%)	479 (39.6)	550 (39.4%)	0.632
Unknown	9 (4.8%)	42 (3.5%)	51 (3.7%)	
AdjuvantTreatments:				
Radiation				
Yes	16 (8.5%)	138 (11.4%)	154 (11.0%)	
No	166 (88.3%)	1039 (85.9%)	1205 (86.3%)	0.466
Unknown	6 (3.2%)	32 (2.6%)	38 (2.7%)	
Chemotherapy				
Yes	17 (9.0%)	152 (12.6%)	169 (12.1%)	
No	165 (88.8%)	1025 (84.8%)	1190 (85.2%)	0.364
Unknown	6 (3.2%)	32 (2.6%)	38 (2.7%)	
Second or more lines of chemotherapy				
Yes	10 (5.3%)	98 (8.1%)	108 (7.7%)	
No	171 (91.0%)	1069 (88.4%)	1240 (88.8%)	0.410
Unknown	7 (3.7%)	42 (3.5%)	49 (3.5%)	

The mean follow-up time was 40.2 months (SD ± 27.6). A higher percentage of black women experienced disease progression or relapse compared to non-black women (60.0% versus 50.0%, p = 0.019). At the end of the study, 40.2% of the women had died, and this percentage was higher among black women (48.9% versus 38.7%, p = 0.008).

Regarding survival, 57.3% of the women were alive after five years of follow-up - 47.5% of patients in the group of black women and 59.1% of patients in the group of non-black women. Median survival time was 40.8 months (95% CI: 16.8-64.9) for black women and was not achieved by non-black women (p = 0.001) (Figure 1).

In the univariate analysis using the Cox regression, black women presented a 50% higher mortality risk over a period of 5 years compared to non-black women (HR = 1.5 95% CI 1.2-1.8, p = 0.001). These differences remained statistically significant in women with localized disease (p = 0.032) and in women with locally advanced disease (p = 0.016). However, there was no difference in survival time between patients with distant metastasis (p = 0.880).

In the multiple analysis, after adjusting for hemoglobin levels and surgery (there was a correlation between the variables surgery and lymphadenectomy, and only the first one was included in the model), Cox regression showed no statistically significant difference in the mortality risk associated with cervical cancer between black and non-black women (HR = 1.1 95% CI 0.9-1.5, p = 0.27).

Discussion

In the present analysis, the association between race

and poor survival was not confirmed when adjusted for hemoglobin level and type of treatment, which are factors with demonstrated prognostic impact on cervical cancer. Previous studies have shown that the incidence of cervical cancer and mortality rates vary considerably among racial and ethnic groups. In addition, black women have been shown to have poor survival rates in some studies, but the reasons for these results are still unclear (Samelson et al., 1994; Morgan et al., 1996; Howell et al., 1999; Hicks et al., 2006; Adams et al., 2009; Coker et al., 2009; McCarthy et al., 2010; Rauh-Hain et al., 2013). In a huge study conducted by Rauh-Hain et al., (2013) with 12,170 cases of cervical cancer diagnosed between 1985 and 2009 in the United States black women had poorer survival rates compared to non-black women, even after adjusting the analysis for marital status, disease stage, age, treatment, degree of differentiation and histology of the tumor. The authors concluded that the difference in survival is likely to be a result of multiple complex factors, including access to screening exams and health care, diagnosis staging, quality of health services, treatment disparities, as well as other cultural and social issues. In a different way, similarly to our results, some studies have not identified race as an independent predictor of poor survival (Farley et al., 2001; Movva et al., 2008).

In this cohort, squamous cell carcinoma was the most common histology in both races, followed by adenocarcinoma. These results are in line with previous studies in which this histological type was also the most common in both racial groups (Movva et al., 2008; Adams et al., 2009; Coker et al., 2009).

In the staging assessment, we observed that the majority of patients of both races had locally advanced disease at diagnosis. In most of the studies analyzed, advanced stages were predominant among black women. The scientific literature shows that the strongest predictor of mortality associated with cervical cancer is staging at the time of diagnosis (Chen et al., 1994; Morgan et al., 1996; Howell et al., 1999; Coker et al., 2009; Movva et al., 2008; Adams et al., 2009; Rauh-Hain et al., 2013). After 5 years of follow-up, 57.3% of the women were alive, but a higher percentage of black women experienced disease progression or relapse compared to non-black patients, similar to results reported in most previously published studies (Samelson et al., 1994; Rauh-Hain et al., 2013). We may speculate that our findings are justified by the inclusion of a homogeneous population of women with cervical cancer, all users of the public health service.

In the present study, there were no statistically significant differences between black and non-black patients regarding the number of comorbidities ($p = 0.209$) or performance status at diagnosis ($p = 0.149$). Studies that analyzed treatment differences between black and non-black patients showed that black patients are less frequently submitted to surgical procedures (as in the present study) and radiotherapy, and that radiotherapy is associated with better survival rates compared to no therapy. When differences in primary radiotherapy were evaluated, it was shown that lower levels of hemoglobin at presentation and during treatment are associated with poorer outcome (Howell et al., 1999; Winter et al., 2004; Hicks et al., 2006; Movva et al., 2008; Coker et al., 2009).

However, in this study, hemoglobin levels <12 g/dL at the time of diagnosis were more frequently observed among black women. Only a few studies have analyzed the levels of pre-treatment hemoglobin as a factor associated with survival, which makes a comparison with the results of the present study difficult. Also, most of the analyzed studies were based on cohorts from developed countries, with populations that have different social and demographic characteristics from those reported in developing and underdeveloped countries, where most cases of cervical cancer currently occur and where the present study was carried out. These differences should be considered for data interpretation.

Although in our study the results of the univariate analysis indicated poorer survival in black women when compared to non-black women, black women had lower levels of hemoglobin at the beginning of treatment and were less frequently submitted to surgery and lymphadenectomy as primary treatments, which can explain the results obtained. After adjustment for hemoglobin levels and surgery in the multiple analysis, the association between race and survival ceased to exist, which corroborates previous studies reporting that race alone was not a predictive factor for mortality (Farley et al., 2001; Movva et al., 2008).

Several limitations should be considered when interpreting the findings from this study. First, all data were collected from hospital records and were only as complete or accurate as the original record. Second, racial classification for individuals who participated in this research was registry-reported, being susceptible to miscategorization. Third, we used overall survival as an outcome rather than cancer-specific survival, because the cause of death variable derived from the registry in the hospital records can be prone to misclassification. Another potential problem is that we do not assess data regarding screening behaviors or socioeconomic predictors of survival as the patient's socioeconomic status and income that could have an impact on the outcome analyzed. Finally, a selection bias should be considered once this study includes only patients referred to a highly specialized clinical service. Race may have influenced the access to health care facilities. Other Brazilian studies have shown that black women were significantly less likely to have had a Pap-smear than white women and that black skin color was a determinant of late stage (≥IIB) diagnosis of cervical cancer (OR=1.2; 95%CI 1.1-1.4) (Bairros et al., 2011; Thuler et al., 2014). The strengths of our study include the large population size, the long period of follow-up, and the access to variables potentially related to cervical cancer survival as comorbid conditions and level of pretreatment hemoglobin. In addition, in our Hospital, during the study period, there was no structural improvement or changes in the medical staff.

Regardless, this study presents relevant data for subjects treated in the Brazilian Public Health System (Sistema Único de Saúde - SUS, in Portuguese). Black and non-black women are similar in relation to comorbidities, performance status, histological type,

staging and differentiation degree. However, black women have been less frequently submitted to primary surgery and lymphadenectomy, and had lower pretreatment hemoglobin levels than non-black women. In conclusion, the multivariate analysis revealed that race alone was not shown to be a prognostic factor for patients with cervical cancer. Though, more studies are necessary to evaluate the differences in disease characteristics, treatments and survival among black patients, to improve care and quality of life of these patients.

Conflict of interest

The authors declare no potential conflicts of interest.

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