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Epidemiology of Breast Cancer Presentation in Botswana, South Africa, and the United States

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Abstract

Introduction: This study sought to compare the clinicopathologic features of women with breast cancer presenting in South Africa, Botswana, and the United States (US).

Methods: Breast cancer samples from Botswana ($n = 384$, 2011–2015), South Africa ($n = 475$, 2016–2017), and the US ($n = 361{,}353$, 2011–2012) were retrospectively reviewed.

Results: The median age of sub-Saharan African women presenting with breast cancer (age 54 in Botswana and South Africa) was younger than that of those in the US (age 61) ($P < 0.001$). Sub-Saharan women were more likely to present with advanced stage disease than US counterparts (64.7% in Botswana, 63.3% in South Africa, 13% in the US, $P < 0.001$). Triple negative disease was highest in Botswana (21.3%) compared to South Africa (11.4%) and the US (12.94%) ($P < 0.001$). Differences in receptor status at presentation among the three cohorts ($P < 0.001$) were not observed when the cohorts were stratified by ethnicity. Black/multiracial patients in Botswana and the US were the most likely subsets to present with the adverse characteristic of triple negative disease (21.3% and 23.2%, respectively). No correlation was found between HIV and receptor status in the Botswana ($P = 0.513$) or South African ($P = 0.352$) cohorts.

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Author Contributions

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Disclosure

None declared.

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Conclusions: Here we report receptor status patterns at presentation in Botswana and South Africa. This study reveals important similarities and differences which may inform policy and provide context for future epidemiologic trends of breast cancer in low- and-middle-income countries particularly in sub-Saharan Africa.

Keywords

Botswana; Breast cancer; Clinicopathology; Low-and-middle-income countries; South Africa

Background

Worldwide, breast cancer is the most common cancer among females with an estimation of 2.3 million new cases and 684,996 deaths in 2020.[1] The effects of breast cancer are unequally distributed across high-income countries (HICs) and low and-middle-income countries (LMICs).[2] For example, incidence in North America, Northern Europe, and Australia ranges from 95 to 100 cases per 100,000 persons compared to 13.5–39 per 100,000 women in sub-Saharan Africa.[3,4] Though limited data are available, breast cancer incidence for sub-Saharan Africa per 100,000 women is estimated at 38.9 in Southern Africa, 38.6 in Western Africa, 30.4 in Eastern Africa, and 26.8 in Central Africa.[3,4] Despite a higher incidence of breast cancer in HICs compared to LMICs, breast cancer mortality is higher in LMICs.[5] Moreover, while breast cancer incidence rates have increased worldwide, this rate has accelerated more rapidly in LMICs[5]; it is estimated that in Africa, breast cancer incidence will be doubled by 2050.[3] A registry of rural Eastern Cape, South Africa reported an annual increase in breast cancer of 4.3% from 1998 to 2012.[6]

Considerable strides have been made in cancer centers of sub-Saharan Africa however several challenges remain. For example, screening mammography is neither widely implemented nor recommended in LMICs due to cost and competing healthcare needs.[7] South African public hospitals found significant delays in adjuvant chemotherapy, radiotherapy, and endocrine therapy which was exacerbated for women living >20 km from the hospital or who were non-English speaking.[8] Lack of awareness and access to screening resources may, in some settings, be exacerbated by social and cultural stigma regarding breast cancer[9] and limited resource availability (e.g., low numbers of screening centers clustered in urban areas). At the same time, recent advances in Human immunodeficiency virus (HIV) control has improved life expectancy and increased the burden of non-communicable diseases.[10] Limited data suggests that HIV-positive patients may present at a younger age and later stage due to confounding factors.[11] Management and presentation of HIV with breast cancer is an emerging area of interest with important implications in sub-Saharan Africa.

A large barrier to closing the breast cancer gap among HICs and LMICs is a lack of data quantifying the problem. For example, age, stage of presentation and clinicopathological features of breast cancer in Botswana and South Africa have been difficult to obtain with limited national cancer registries and non-standardized descriptive pathology reports. One meta-analysis of hormone receptor status in Africa found significant heterogeneity in estimates of estrogen receptor positivity (ER+) among 26 studies from sub-Saharan Africa,

ranging from 20% to 70%.[12] Challenges to hormone receptor testing included lack of standardized procedures and methodological quality.[12] Currently, policy is often driven by data generated from HICs which is then applied to LMICs.[7] Understanding the differences in breast cancer presentation would allow more effective strategy. This study sought to compare the clinicopathological features of women with breast cancer presenting in South Africa and Botswana to those in the United States (US).

Methods

This study was reviewed and approved by the Institutional Review Board of the University of Botswana, Health Research and Development Committee of Ministry of Health and Wellness, the Institutional Review Board of Diagnofirm Medical Laboratory (DML), Gaborone, Botswana, and the Institutional Review Board of the University of Witwatersrand, Johannesburg, South Africa; informed consent was waived for retrospective review of the data registries.

Setting

Republic of Botswana—Botswana, located in southern Africa, had a population of approximately 2.3 million in 2017.[13] The country is described as a middle income, emerging economy with a recent gross national income per capita of US $16,420 in 2017.[13] Despite a relatively high standard of living among sub-Saharan African countries, Botswana has the third highest prevalence of HIV in the world.[13,14] In 2017 there were 380,000 people living with HIV in Botswana and the prevalence among individuals age 15–49 was 27.4%.[15] As HIV/AIDs (acquired immunodeficiency syndrome) treatment and control improves and life expectancy increases, cancer incidence has increased.[16] Breast cancer is the second most common cancer diagnosed in women after cervical cancer, with an age adjusted incidence of 20 per 100,000 women.[1] Public health care is accessible to 90% of the population, however screening mammography is rare.[16] Oncology treatment occurs primarily at Princess Marina Hospital in Gaborone and Nyangabgwe Referral Hospital in Francistown where surgery and chemotherapy are offered. Radiotherapy is currently available in the private sector only at Gaborone Private Hospital.

South Africa—South Africa has a population of approximately 56 million and the second largest economy in Africa with a recent gross domestic product per capita of US $5274.55.[17] In 2017, there were approximately, 7.2 million individuals living with HIV in South Africa, the largest population in the world.[17,18] The prevalence of HIV among individuals age 15–49 was 18.8% and more than half of infected individuals were female.[7,18] South Africa maintains a National Cancer Registry collecting information from all pathology laboratories in the country which was established in 1986.[19] Breast cancer is the most prevalent cancer in the country, now with an age adjusted incidence of 31.4 per 100,000.[7] Approximately, 84% of the population utilizes public healthcare though access to breast cancer screening is similarly limited in South Africa.[7] Oncology care is available via a network of public and private hospitals and care centers dispersed throughout the country.[20] Access to all treatment modalities, medical, surgical, and radiation is available in both the public and private sectors.

United States of America—The population of the US is approximately, 325 million with a gross domestic product per capita of $57,638.16.[21] Approximately, 1.2 million in the US are infected with HIV.[14,21] The age adjusted incidence of breast cancer in the US is 126 per 100,000 women per year.[22] Cancer care is delivered through both public and privately funded health networks and access to breast cancer screening is commonly utilized in the US. Access to all treatment modalities, medical, surgical, and radiation, is available in the both the public and private sectors.

Data collection

This retrospective review compared clinicopathology results of breast cancer presenting in Botswana, South Africa, and the US. Modern cohorts of different time periods based on availability were collected in each center and all available cases were reviewed. In Botswana and South Africa, all patients with a diagnosis of breast cancer who had available tissue sampling underwent hormone receptor testing. There was no additional cost to patients for hormone receptor testing. However, if the laboratory was unable to access reagents at the time of cancer diagnosis due to resource or supply chain limitations, administrative challenges, or equipment failure, receptor testing was not performed. Breast cancer sample data in Botswana were retrospectively reviewed from two centers, the National Health Laboratory (NHL) and DML from January 1, 2011 to December 31, 2015. Both centers are located in Gaborone, Botswana. The NHL is the largest public referral laboratory for southern Botswana which reviews samples from hospitals in 14 of Botswana's 17 districts. DML is a network of eight private pathology laboratories which serve all parts of Botswana. Data regarding age, gender, pathologic staging, tumor laterality, tumor grade, tumor size, nodal status, patient demographic data, and HIV status were manually extracted from NHL and DML electronic records of pathology reports wherever available. Surgical samples were used for receptor testing. Stage IV was not reported in Botswana due to the use of pathologic staging on specimens sent to the laboratory. Data collection in South Africa was conducted January 2016 to February 2017 at the Helen Joseph Breast Clinic. Data from 2011 to 2015 was unavailable in South Africa. Helen Joseph Breast Clinic is an open-access, walk-in public, government hospital located in Johannesburg South Africa which accepts all patients in South Africa though it predominantly serves the local region. Pathology from core biopsy or surgery was reviewed at the National Health Laboratory Systems in the Department of Anatomic Pathology, University of Witwatersrand per protocols previously described.[23] Clinical stage at the time of diagnosis was reported. The National Cancer Database (NCDB) of the US was used for comparison including all patients with a diagnosis of breast cancer from January 1, 2011 to December 31, 2012. The NCDB is a comprehensive registry of patients receiving oncology care at over 1500 centers affiliated with the Commission on Cancer of the American Cancer Society. The database encompasses 70% of all newly diagnosed cancers in the US. The NCDB does not provide HIV status.

Statistical analysis

All data were collected in a Research Electronic Data Capture database (Vanderbilt University, Nashville, TN). Demographic data was calculated using mean, median, and range comparisons. For comparison of data sets, information was entered into the STATA software (StataCorp LP, College Station, Texas, Stata/IC 14.1). Comparison of categorical

variables was made using the chi-square test, whereas, continuous variables were assessed for normal distribution using histograms and compared with the Student *t*-test. A two-sided *P* value of <0.05 was used as the criterion for statistical significance.

Results

Demographic patterns of presentation in breast cancer

Clinicopathologic variables were recorded from pathologically confirmed breast cancer samples in Botswana ($n = 384$) and South Africa ($n = 475$). These samples were compared to NCDB data of breast cancer samples ($n = 361,353$). Here, advanced stage was defined as stage III or IV disease in this study. Table 1 demonstrates the demographic data, HIV status, receptor status, and stage of samples. Notably, the median age of sub-Saharan African women presenting with breast cancer (age 54 in both Botswana and South Africa) was younger than that of those in the US (age 61) ($P < 0.0001$). HIV status was largely unreported in both Botswana and South Africa (70% and 42%, respectively). Among those reporting HIV status, the prevalence was higher in Botswana (12.76% infected and 16.83% uninfected) compared to South Africa (10.52% infected and 47.16% uninfected).

Prevalence of receptor positivity

The distribution of receptor status by regions shows significant variance with estrogen-receptor (ER) positivity highest in South Africa (80.0%) and the US (80.8%) followed by Botswana (67.9%). Triple negative disease was highest in Botswana (21.33%) compared to South Africa (11.36%) and the US (12.94%) (Table 1). In Table 2, we assessed the prevalence of receptor positivity by ethnicity in each country to determine pathological trends in disease presentation. Because the Botswana cohort consisted entirely of Black/multiracial patients, we could not assess differences among ethnicities. There was no significant difference in receptor status at presentation among the South African cohort with all ethnicities most likely to present with ER and/or progesterone positive, human epidermal growth factor receptor 2 negative disease (73% among whites, 64.8% among Blacks/multiracial, 82.5% among other, $P = 0.098$). In the US, there was a statistically significant difference in the distribution of receptor status among ethnicities with Black/multiracial patients almost twice as likely as Whites or others to present with triple negative disease. The increased rate of triple negative disease in the US was similar to the rates among the Black/multiracial cohorts of Botswana and South Africa. Correlation of HIV status with receptor status did not find statistically significant differences in the Botswana ($P = 0.513$) or South African ($P = 0.352$) cohorts.

Variance of stage at presentation

Amongst patients sub-divided by country, we found a statistically significant difference in stage at presentation when stratifying by ethnicity (Table 3). In sub-Saharan countries, Black/multiracial patients were more likely to present with advanced stage disease (64.7% in Botswana and 63.3% in South Africa) than with early stage disease (35.3% and 36.7%, respectively). In the US, Black/multiracial patients were more likely to present with early stage disease (87%) than advanced disease (13%). In both South African and US cohorts however, White patients were more likely to present with early stage disease compared to

advanced stage disease (53.4% *versus* 46.6% in South Africa, $P = 0.003$ and 92.3% *versus* 7.7% in the US, $P < 0.001$). Finally, though HIV status was largely un-reported in the cohort, we did not identify a statistically significant difference in stage at presentation between HIV-infected and–uninfected patients in the Botswana or South African cohorts ($P = 0.764$ and $P = 0.087$, respectively) (Table 3).

Discussion

Epidemiology of breast cancer in sub-Saharan Africa

This study provides new assessment of the clinicopathological presentation of breast cancer in Botswana and South Africa with comparison to the US. It has previously been shown that patients in LMICs are more likely to present with advanced stage disease. For example, Vanderpuye *et al.* found the incidence of advanced stage breast cancer in South Africa to be 50%–55%.[3,4] Our study supports these findings, demonstrating an incidence of advanced stage disease of 64.7% and 57.1% in Botswana and South Africa, respectively. The limited resources available for and access to preventative care such as clinical breast exams and screening imaging (ultrasound or mammography) are felt to influence these patterns.[24] Importantly, when stratified by ethnicity, White patients in South Africa and the US are more likely to present with early rather than advanced disease while Black/multiracial patients in all countries were more likely to present with advanced disease. Though differences between LMICs and HICs are often highlighted, these findings demonstrate parallels in disease presentation when patients are stratified by ethnicity. Prior work has shown rising rates of breast cancer incidence among Blacks/multiracial and Asian minorities in South Africa while incidence among whites decreased between 1994–2009 similar to trends observed in HICs.[20]

In addition, epidemiologic trends in sub-Saharan Africa may increase the similarities to the US. Previously, the relatively low incidence of breast cancer in sub-Saharan Africa had been attributed to factors such as late menarche, early age at first pregnancy, high parity, and prolonged lactation.[6] Changing fertility patterns (declining fertility, later age of first birth, increased use of oral contraception) as well as lifestyle changes (increased obesity, change in diet, decreased physical activity, increased alcohol consumption) may contribute similarly to the acceleration of breast cancer incidence in the region.[6,25,26] As these changes unfold, the observed differences in between sub-Saharan Africa and the US may further diminish.

Our findings suggest that average age at presentation in sub-Saharan African breast cancer patients is younger than their US counterparts. In part, this finding reflects the age distribution in sub-Saharan Africa with the young population constituting a larger proportion than in Western nations.[25] Notably, since fertility and lifestyle changes mentioned previously are present more commonly in younger generations of sub-Saharan African women, the younger age distribution may reflect evolving changes in risk factor prevalence. Conversely, aggressive disease (such as triple negative breast cancer) which presents at younger age was more common in Botswana compared to South Africa or the US, which may point to a true difference in clinicopathology of breast cancer in this population. Previous report of a higher incidence of triple negative breast cancer in

black females in the US age <45 y than in white females may support the difference in clinicopathology as explanation for the differing presentations.[26–28]

Ultimately, though differences between sub-Saharan and US cohorts have previously been documented, here we report similarities in presentation characteristics such as stage when stratified by ethnicity. Evolving epidemiologic factors may further shrink these differences and continued surveillance is merited.

Receptor status in sub-Saharan Africa

Previously, McCormack *et al.* has found high variability in the reported prevalence of receptor status in sub-Saharan Africa with ER negative reporting ranging from 30% to 40% or >70%.[29] Here we report receptor status in populations of Botswana and South Africa. We found that triple negative disease was more common in Botswana than in either South Africa or the US. When each country was stratified by ethnicity, the US Black/multiracial population was most similar to the sub-Saharan African cohorts.[28] Risk factors for triple negative disease (young age, high parity, short/absent breastfeeding, obesity, BRCA1 mutations) differ from those of breast cancer overall and may contribute more strongly in the sub-Saharan African cohorts.[25] Notably, prior studies have shown the influence of tissue processing and sample quality on rates of receptor positivity in African nations. Studies using standardized collection and processing of tumors may report lower rates of triple negative cancers.[29,30] The methodologies used by the laboratories of these studies has been previously reported to validate the accuracy of these data.[23,31] The distribution of receptor status however merits further investigation. There is a movement toward increasing access to targeted therapies in sub-Saharan Africa. Currently, the majority of patients treated in Botswana and South Africa undergo local therapy with surgery and radiation or systemic cytotoxic chemotherapy; there is a limited access to receptor-based targeted therapy such as anti-Her2 therapy. These cohorts highlight the need for further studies of receptor status in sub-Saharan Africa to best understand and address this need. Increased access to pathology facilities and increased reliability of immunohistochemistry may be required.[26]

HIV status and breast cancer in sub-Saharan Africa

Previous studies have shown the increasing incidence of breast cancer among HIV positive women as HIV treatment improves and life expectancy lengthens.[32,33] Our analysis did not find a detected difference in age, stage, or receptor status at presentation between HIV infected and uninfected patients. These results are limited by the underreporting of HIV status in both sub-Saharan African cohorts however we hope to highlight the importance of the relationship and contribute to future study. Our study findings differ from previous reports which found that HIV positive patients were more likely to present at a younger age,[33] with more advanced stage disease,[32] and higher cancer-specific mortality.[33] Additional studies with more comprehensive reporting and outcomes assessment are needed to further characterize the differences, if any, between breast cancer in HIV positive and negative patients. Overall, since HIV is often a competing risk among breast cancer patients, region specific screening, and treatment guidelines ought to take into consideration the specific clinicopathology of HIV-positive breast cancer patients.

Limitations

Data collection, particularly pertaining to receptor status, is limited in both Botswana and South Africa and therefore reportable cohort sizes are small, especially relative to the US cohort. Data collection was conducted over different time periods for the cohorts which reflects the available data based on receptor status testing. As cancer registries are established in LMICs such as Botswana and South Africa, gaps in clinical and pathologic information have been identified and are apparent in these cohorts, for example in patient staging with pathologic staging in Botswana and clinical staging in South Africa. Further, correlation of pathology to treatment such as neoadjuvant chemotherapy was unavailable and may influence pathologic staging. This work highlights the limitations of descriptive pathology reports in sub-Saharan Africa with an eye toward future awareness for synoptic reporting, minimizing subjectivity, and emphasizing the minimal variables required for optimum patient care. In addition, given that both African hospitals are public, the population served is predominantly lower income. Given the breadth of patients treated however these cohorts are still felt to be representative. Larger cohort studies, though difficult to implement, may further validate this data. Similarly, the implications of HIV findings in this study are limited by the small response rate recorded in Botswana and South Africa however preliminary review points to the need for further study. In addition, self-reporting of HIV status may cause under-reporting of true HIV rates in the described cohorts. Finally, the large size of the US cohort (n = 361,353) increases the probability of reaching statistical significance. Any differences observed in this study should be interpreted in the context of their effect size and clinical significance.

Conclusions

Here we highlight similarities and differences in presentation of breast cancer in LMICs such as Botswana and South Africa to HICs such as the US. Factors such as age, ethnicity, and receptor status should inform targeted guidelines for LMICs. More work is required to understand how HIV prevalence in alters the clinicopathology of breast cancer in LMICs. Further studies are merited to explore specific screening and treatment guidelines for this sub-population.

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Table 1 –

Population demographics–features of patients in three cohorts at presentation.

Demographic	Botswana(*n* = 384)	South Africa(*n* = 475)	United States(*n* = 361,353)	*P*-value
Median age (IQR)	54 (44–65)	54 (44–66)	61 (51–70)	<0.0001
Gender				
Female (%)	378 (98.44%)	468 (98.53%)	358,367 (99.17%)	
Male (%)	6 (1.56%)	7 (1.47%)	2986 (0.83%)	
HIV				
HIV-Infected (%)	49 (12.76%)	50 (10.52%)	N/A	<0.0001 *
HIV-Uninfected (%)	65 (16.93%)	224 (47.16%)	N/A	
HIV-Unknown (%)	270 (70.31%)	201 (42.32%)	N/A	
Ethnicity				
White	0 (0%)	124 (26.11%)	300,671 (83.20%)	<0.0001
Black/multiracial	384 (100%)	276 (58.11%)	41,365 (11.45%)	
Other	0 (0%)	75 (15.79%)	19,317 (5.35%)	
Receptor status				
ER+ and/or PR+, HER2−	132 (62.56%)	276 (69.70%)	180,604 (73.96%)	<0.001
ER+ and/or PR+, HER2+	19 (9.00%)	49 (12.37%)	21,987 (9.00%)	
ER−/PR−/HER2+	15 (7.11%)	26 (6.57%)	9999 (4.09%)	
ER−/PR−/HER2−	45 (21.33%)	45 (11.36%)	31,592 (12.94%)	
Stage †				
Early Stage	18 (35.29%)	190 (42.89%)	261,414 (91.62%)	<0.001 ‡
Stage I	4 (7.84%)	54 (12.19%)	174,294 (61.09%)	
Stage II	14 (27.45%)	136 (30.70%)	87,120 (30.53%)	
Advanced Stage	33 (64.71%)	253 (57.11%)	23,903 (8.38%)	
Stage III	33 (64.71%)	216 (48.76%)	20,274 (7.11%)	
Stage IV	0 (0.00%) §	37 (8.35%)	3629 (1.27%)	

* Comparison of Botswana and South Africa only.

† Stage at diagnosis (pathologic stage in Botswana and clinical stage in South Africa and the United States).

‡Comparison of early *versus* advanced stage by country.

§Stage IV unreported in Botswana due to use of pathologic staging.

Table 2 –

Correlation of ethnicity with receptor status.

Ethnicity	ER+ and/or PR+, HER2−	ER+ and/or PR+, HER2+	ER− and PR−, HER2−	ER− and PR−, HER2+	*P*-value
Botswana					NA
White	0	0	0	0	
Black/multiracial	132 (62.6%)	19 (9.0%)	45 (21.3%)	15 (7.1%)	
Other	0	0	0	0	
South Africa					0.098
White	73 (73.0%)	12 (12.0%)	11 (11.0%)	4 (4.0%)	
Black/multiracial	151 (64.8%)	33 (14.2%)	28 (12.0%)	21 (9.0%)	
Other	52 (82.5%)	4 (6.3%)	6 (9.5%)	1 (1.6%)	
United States					0.001
White	153,500 (75.8%)	17,887 (8.8%)	23,344 (11.5%)	7817 (3.9%)	
Black/multiracial	17,771 (62.1%)	2778 (9.7%)	6651 (23.2%)	1421 (5.0%)	
Other	9333 (71.7%)	1322 (10.2%)	1597 (12.3%)	761 (5.8%)	

Table 3 –

Correlation of stage with ethnicity, age, HIV status.

Ethnicity	Botswana			South Africa			United States		
	Early	Advanced	*P*-value	Early	Advanced	*P*-value	Early	Advanced	*P*-value
Ethnicity			NA			0.003			$P < 0.001$
White	0	0		63 (53.4%)	55 (46.6%)		220,125 (92.3%)	18,347 (7.7%)	
Black/multiracial	18 (35.3%)	33 (64.7%)		95 (36.7%)	164 (63.3%)		28,052 (87.0%)	4208 (13.0%)	
Other	0	0		34 (50.0%)	34 (50.0%)		13,237 (90.8%)	1348 (9.2%)	
Age			0.229			0.104			$P < 0.001$
Median (IQ range)	51 (42–65)	54 (44–64)		55.5 (44–65)	54 (43–67)		62 (52–71)	57 (48–67)	
HIV status			0.764			0.087	Unavailable		
HIV-Infected	1 (25.0%)	3 (75.0%)		14 (28.6%)	35 (71.4%)				
HIV-Uninfected	3 (33.3%)	6 (66.7%)		87 (41.8%)	121 (58.2%)				

Early stage was defined as stage I or II.

Advanced stage was defined as stage III or IV.