Breast cancer survival in rural sub-Saharan Africa

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Abstract
INTRODUCTION: Five-year overall survival rate of breast cancer in low-income countries (LICs) is significantly lower than in high-resource countries. In this study, we explored clinical and pathological factors influencing mortality in a rural community setting in sub-Saharan Africa. METHODS: We performed a retrospective medical review of patients undergoing surgery and chemotherapy for breast cancer at a regional hospital in Ghana from January 2014 through January 2017. Descriptive and survival analysis was done. RESULTS: One hundred and twenty-nine patients were included in the study. The median age at presentation was 51 years. 60.0% of patients presented with poorly differential histological grade III. The most common histological type was invasive ductal carcinoma (83%). Based on assessment of stage using only tumor size and lymph node status, 60% presented at stage 3. Only 25% were tested for hormone receptor proteins and HER2 status. Of these, 57% had triple-negative breast cancer (TNBC). The 3-year overall survival rate was only 52%. A significant proportion of the patients (46%) were lost to follow-up. CONCLUSIONS: The cumulative 3-year survival was 52 %. Despite success in the reduction of cancer mortality in southern and northern Africa, survival in the rural communities of sub-Saharan Africa remains poor. A significantly higher percentage of GIII and TNBC is found in breast cancers seen in Ghana. Late-stage presentation, when combined with limited capacity for accurate diagnosis, cancer subtype analysis, adequate therapy and follow-up, leads to poor outcomes. Future studies should emphasize identification of barriers to care and opportunities for cost-effective and sustainable improvements in the diagnosis and treatment of breast cancer in LICs.

Introduction
Breast cancer (BC) mortality rates are significantly higher in low-and-middle-income countries (LMICs), such as those in sub-Saharan Africa, than in high-income countries (HICs).[1, 2] Breast cancer is well studied in HICs and issues of access to healthcare in rural or underserved areas have been studied in this demographic as well. However, the epidemiology of BC is not well studied in low and middle-income countries (LMICs), especially in the underserved/rural areas. Delayed clinical presentation, limited access to treatment, geographical location[3], stage of the disease[4], tumor
biology[5] and access to care[6] all contribute to the high mortality rates in LMIC[7]. Breast cancer outcomes, especially mortality rates, need to be studied in order to define the scope of the issue, which will establish the need for protocols for exploring risk factors and opportunities for intervention. Eastern Ghana represents a rural district of sub-Saharan Africa where the results of treatment have not been well studied. The prevailing hypothesis in such settings is that late presentation accounts for poor long-term outcomes. The main objective of this study was to investigate the 3-year overall survival of breast cancer patients treated at the Eastern Regional Hospital of Ghana. While Koforidua is an urban setting, the Eastern Regional Hospital is a referral hospital which serves the population of the rural eastern region where many patients must travel hours to obtain medical care. We sought to characterize the regional epidemiology of breast cancer by assessing age at onset, tumor grade and biology.

Methods

**Sampling of study participants**

We conducted a prospective cohort study with a consecutive sampling of all women who presented with diagnosis of breast cancer from January 2014 to January 2017. The study was conducted at Eastern Regional Hospital of Koforidua (ERHK), a referral hospital of the eastern region of Ghana, serving approximately 3 million people. It is the referral hospital of 26 district hospitals and has a 364-bed capacity. All patients received breast cancer surgeries by one surgeon, 80% chemotherapy, 20% anti-hormonal therapy and about 20% radiotherapy (patients all had to travel to Accra for treatment).

Formalin-fixed and paraffin-embedded blocks for the participants were prospectively analyzed by an offsite staff pathologist for the histopathological classification. Pathology is not covered by the National Health Insurance. The specimens must be transported by the patient or their family to St. Joseph’s hospital located two miles away and analysis requires an out of pocket cost which often leads to delays and in some cases the specimen is discarded – cases with no available pathology were not included in this analysis. The time of specimen fixation is about 24 hours. The average time for final anatomic pathology report to be released is between 30 -60 days. Immunohistochemistry
analysis incurs an extra charge. When performed, during the study period, the slides were either sent to a pathologist in England with the results taking an average of 9 months before completion. Currently slides for immunohistochemistry are sent to Kumasi with an average 1 month turn around. Patients were followed for 1.5 to 4.5 years, starting from January 1, 2014 through June 2018. During the follow-up period, patients were followed or contacted periodically, either through outpatient clinic visits, at chemotherapy appointments or through phone calls. If we could not reach patients, we contacted their caretakers to ascertain death/survival. The index date for the survival calculation was determined to be the first date of the histologically confirmed diagnosis of breast cancer. Death was the event outcome. Patients who were alive by the closing date of June 2018 and those who were lost to follow-up were censored. The study was approved by the Pennsylvania State College of Medicine institutional review board and ethical review board of Mount Crest University and Eastern Regional Hospital.

Treatment algorithms

All of patients underwent breast cancer surgery and approximately 80% also received chemotherapy secondary to locally advanced disease. Surgical treatment included mastectomy with axillary dissection for resectable disease. With late stage presentation, which is common in the LMIC population, mastectomies were performed for palliation, when possible (technically feasible). The Eastern region of Ghana has no combined multidisciplinary clinic for the treatment of breast cancer. The Eastern Regional Hospital in Koforidua, Ghana houses the only chemotherapy treatment facility in the region. Chemotherapy cost is not covered by the National Health Insurance Scheme (NHIS). In Koforidua, the JEAD foundation – a breast cancer charitable foundation that funds community outreach and unreimbursed treatment expenses which was established by a local breast cancer survivor, covers the cost of chemotherapy for many of the patients who cannot afford to pay for their treatment. Those on chemotherapy received an average of 6 cycles of combination chemotherapy, which most often include cyclophosphamide, adriamycin and 5-fluorouracil (CAF). Estrogen receptor (ER), progesterone receptor (PR)-positive patients and some of those whose hormone receptor status was not known received tamoxifen or anastrazole anti-estrogen targeted treatment (AET) generally
for 5 years. The chemotherapy and AET were prescribed by the surgeon in this cohort. The nearest oncological center is located in Accra more than a 2 hour drive away from Eastern Regional Hospital. When radiotherapy was recommended and utilized, patients had to travel to the nearest radiotherapy center, also located in Accra, Ghana’s capital city.

**Statistical analysis**

The Cox regression model was used to estimate survival probabilities while controlling for clinically relevant confounders such as age and smoking status. The survival analysis was also stratified by the grade and histological type of cancer. Survival analysis was not stratified by hormone receptor status because data was available in only a small portion of the study group. The survival probabilities were calculated using the nonparametric approach, Kaplan-Meier method of estimating survival. Survival rate was taken as the proportion of people diagnosed with a disease who live for a specific period of time. Log-rank test was used to compare survival curves with the assumption that the censoring patterns were the same for the two cohorts being compared, and the hazard functions for the cohorts being compared are proportional. Therefore, 3-year cancer survival rate was defined as the ratio of cancer patients who were still alive (regardless of cancer status) over the total number of patients diagnosed with cancer. All data were analyzed using SAS version 9.4 and R statistical software. A P-value of <0.05 was considered to denote statistical significance.

**Results**

This study included a cohort of 129 women diagnosed with breast cancer at Eastern Regional Hospital between 2014 and 2017. The median age at presentation was 51 (interquartile range 30-75). Approximately 76% of patients were between 30 and 60 years old at the time of diagnosis, and less than 1% were either younger than 25 or older than 90. (Figure 1).

All of the patients had completed at least one previous pregnancy and had one living child. The average number of pregnancies was 4, with 3 living children. Among the patients for whom we could ascertain a breastfeeding history, all except one reported having breastfed for a duration of one year or longer. Approximately 32% of patients had a known family history of breast cancer. Co-morbidities included hypertension in 24% and diabetes in 13%. No patients reported drinking alcohol or smoking.
Based on histological analysis, less than 5% of patients had grade I cancer, whereas the rest of patients had either grade II or III breast cancers (Figure 2). The most common histologic type of breast cancer was invasive ductal carcinoma (83%). Unfortunately, only 25% of patients had hormone receptor protein testing on the cancer performed. Among these patients, 57% had a triple-negative breast cancer (Figure 3). All of the patients who were tested and found to have hormone receptor-positive tumors were prescribed tamoxifen. However, no data on patient compliance with AET was available. The overall 3-year survival rate was only 52% (Figure 4). Survival was higher in patients with grade I disease compared to grade II and III (Hazard ratio=1.5 95% CI (0.5-2.0), p=0.35. This association of low histologic grade and prognosis, however, did not reach statistical significance. The overall median (IQR) survival was 50 months (range 20-60 months). Unfortunately, 46% percent of the treated patients were lost to follow-up, despite the staff and investigators making significant efforts to reach them or their relatives.
Table 1: Demographics of study participants

Discussion

This study is the first to explore breast cancer mortality rates for patients treated in a regional
hospital serving a majority rural population in Ghana. The data primarily highlights three critical issues. First, the survival rates in rural Ghana are substantially lower than in HICs and also significantly lower than documented in studies of survival in other regions of Africa. Second, patients in this cohort presented more often with advanced stage disease and at a younger age. Finally, the proportion of grade III and triple negative breast cancers (TNBCs) is substantially higher when compared to breast cancers diagnosed in HICs, such as the US, or in other regions of Africa[5]. The calculated 3-year survival rate in this study was only 52%. Despite recent success in the reduction of breast cancer mortality in regions of southern and northern Africa, the survival in Ghana and other sub-Saharan countries is especially poor. The poor survival has been attributed primarily to breast cancer that is locally advanced at time of presentation (7, 10). The substantiated drivers of low breast cancer survival in LMICs include: multifactorial delayed individual health-seeking behavior, low socio-economic circumstances, multifaceted limits of access to the health system, and a lack of resource prioritization for treatment of non-communicable diseases[8-10]. Specifically, there is a lack of infrastructure and capacity for early breast cancer detection, significant social stigma is still associated with a cancer diagnosis and as well as there is a lack of access to diagnostic and treatment facilities that all contribute to the poor outcomes. These disparities are even more pronounced in the rural regions of sub-Saharan Africa when compared to its urban counterparts. This may explain the difference in 3-year survival rate between this study (52%) and that reported in studies of southern Africa (72%)[3]. Also, this survival rate is lower than in studies which were performed in urban settings such as Accra and Kumasi, major cities in Ghana. For example, for this studies’ patient population, the nearest oncologic center with medical oncologists or access to radiation is more than 2 hours away in Accra. Of note, patients must hand-deliver their own specimen to the pathologist and pay out of pocket for the analysis. The time until complete pathologic assessment was available in this study was up to 9 months causing delays in critical systemic treatments or forcing the treatment to be given without knowledge of the biological subtype, decreasing the likelihood of therapeutic response. In addition, non-standardized and delayed histological preparation can degrade gene and protein expression patterns of the surgical specimen,
falsely underestimating the cancer’s ER, PR, HER2 expression.[11] College of American Pathologists (CAP) guidelines recommend a fixation time of less than 72 hours, optimally less than 24 hours, for estrogen and progesterone receptors and <48 hours for HER2 receptor evaluation.[12]

With high medicals costs in addition to the significant burden for most patients of finding and paying for transportation, delays in treatment and diagnosis seem inevitable. Basic insurance under the National Health Insurance Scheme (NHIS) in Ghana costs about 25 Cedis (approximately 5 USD) for enrollment, with yearly renewal ranging between 6 – 8 Cedis / year. The daily minimum wage in Ghana is 12 Cedis. Not all hospitals accept the National Health Insurance. In Ghana 57% of the population has NHIS benefits. In the Eastern Region of Ghana, the rate of NHIS coverage is 72% and at Eastern Regional Hospital. Likely because it accepts HHIS, 90% of patients are covered. As of September 2016, the Ghanaian NHIS began to cover breast cancer treatment (http://www.nhis.gov.gh/News/nhis-covers-cervical-and-breast-cancers-%E2%80%93-nhia-4093).. However, this coverage while covering surgery and inpatient care does not include the cost of pathology review, chemotherapy, anti-hormonal targeted therapy or radiation treatments. During the time of this review, comprehensive breast cancer treatment required either that the patient have a supplemental insurance plan or incur out-of-pocket expenses. Currently there is proposed legislation in Ghana that would expand coverage for cancer treatment to include pathology, chemotherapy and radiation. Many patients who had to pay for adjuvant treatment out-of-pocket failed to complete the prescribed number of cycles of chemotherapy or had a longer than recommended time intervals between treatments. Though radiation was indicated based on the advanced cancer stage, due to the high cost and distance to treatment facilities, radiotherapy was only utilized in 20% of cases. Future studies can be performed to demonstrate that if such treatment modalities were included under the basic medical insurance coverage, it would not only decrease the individual economic impact, but also the national economic burden by improving survival in this young demographic allowing them to care for their families and participate in the work force.

Limited education, a fear of Western medicine and the observed adverse effects of breast cancer treatment including amputation of the breast and potential side effects such as post axillary
dissection lymphedema lead to the preference of the majority of especially the rural population to seek care first from spiritual healers. All of these factors continue to be known barriers to the introduction and adoption of evidence-based medicine in Ghana[13]. In fact, these also explain one of our study's major limitations - the high attrition rate of approximately half the treated patient population. Tackling such issues will require not only education of the civilian population but also working together with the traditional and spiritual healers of Ghana to ensure women are encouraged to screen themselves for symptoms of breast cancer and then seek early medical treatment. Acknowledging the importance of Ghanaian health beliefs and traditions is critical and can only help in reinforcing a sustainable health care system for those who develop breast cancer and other non-communicable diseases.

Half of the women in our study were diagnosed at the age of 40 or younger, two decades younger than the median age at diagnosis in HICs, such as the United States (US). [14] Patients in this rural region of Ghana presented at a younger age, with late stage disease, and with a higher rate of the most aggressive cancer biology, which predicted the substantially higher mortality rates observed. In the US, black women are more likely than whites to be diagnosed with breast cancer under the age of 40 and also have twice the incidence of TNBC.[5] Black women are also more likely to present with advanced disease when compared with white patients.[14-17] It is not well understood whether these differences in age of onset and tumor biology are caused by specific genetic differences between blacks and whites. However, this study does reinforce the established empirical evidence and support the premise that black women need to be educated about the signs of breast cancer and offered screening for breast cancer beginning at a younger age than Caucasians, Hispanics or Asians.

Despite only a quarter of our patient population having received comprehensive pathologic assessment including immunohistochemistry, the 57% rate of triple negative (TNBC) disease is consistent with prior peer-reviewed studies where over one-half of patients were diagnosed with TNBC, suggesting a hereditary risk factor for this most aggressive variant of breast cancer[13]. The TNBC phenotype has been shown to be more prevalent among people of African descent when compared with Caucasian populations[18]. In a comparative analysis by Jiagge E et al, among
patients younger than 50 years of age, prevalence of TNBC was highest among Ghanaians (50.8%) and African Americans (34.4%) compared with White Americans and Ethiopians (16% each)[19]. Interestingly, while the populations in both Northern Africa and South Africa include a substantial percentage of non-blacks, including whites and Asians, the population in Ghana is mostly black.

Breast cancer survival rates were similar between Caucasians and African Americans in the United States until the 1970s, which was when tamoxifen – the first hormone receptor targeted treatment was discovered and began to be used. It has been postulated that the divergence in survival between the two racial groups was because African Americans benefited less from adjuvant anti-endocrine therapy secondary to the two-fold higher frequency of estrogen receptor-negative breast cancers[20, 21]. Oncologic anthropology studies suggest that the high incidence of hormone receptor-negative breast cancer (and younger age of diagnosis) in West Africa mirrors age and racial TNBC discrepancy of related black populations in HICs[22]. This may be a long-term effect of transatlantic slave trade when most of the African slaves originated from West Africa, with many coming directly from ports in Ghana. Future studies of TNBCs may assess the cancers found in both populations of African descent in HICs and Africans in sub-Saharan Africa to look for common genomes that may allow the development of better targeted therapies.

Despite elucidating the shared ancestry between West Africans and HIC populations of African descent, it is essential to note that no pathological, genetic, and prognostic differences in TNBC tumors between those of African descent and Caucasians populations have been identified to date. [18] This intrinsic similarity, regardless of race, is important to acknowledge as risk reduction strategies and targeted therapy continue to be improved and shared for the TNBCs that occur both in HICs and in LICs, like Ghana. Our study was not powered to calculate the survival probabilities by tumor phenotype. However, 50% of the patients who were documented to have died also had had immunohistochemistry demonstrating TNBC, suggests an association with the high mortality rate seen in our study. Due to the availability of inexpensive tamoxifen, those patients who had known hormone receptor-positive tumors were prescribed anti-estrogen therapy though we have no data on compliance or duration. For HER2+ cancers, very effective targeted therapies have been developed
and are routinely used in HICs with marked improvement in survival of women with HER2 positive cancers. However, due to fiscal constraints, trastuzumab and other HER2 targeted agents are not available to patients in rural Ghana.[23]

As discussed, Ghana’s low breast cancer survival rate has a multifactorial etiology. Hence, given the limited health resources, the challenge lies with efficiently innovating and sustaining detection and treatment strategies to optimize survival for a disease that is multidisciplinary in nature. In 2008, Breast Health Global Initiatives (BHGI) created a four-tiered breast cancer diagnosis resource allocation system, recommending a tiered approach to what resources should be available. BHGI addressed the role of clinical examination, imaging & laboratory tests, pathology diagnosis, and delineated metrics for success based on the resource level of the community (basic, limited, enhanced, maximal)[24-26]. For areas with only a basic level of resources, the diagnosis of breast cancer is made on the basis of clinical breast examination, and the pathologic diagnosis is made by any available sampling procedure, especially when imaging services for guidance of percutaneous biopsies are unavailable. In the next level, communities with limited-resources, ultrasound is recommended for diagnostic evaluation and also allows the use of image guided fine needle aspiration biopsy for diagnosis. It is also recommended that limited-level resource communities should have access to basic lab work (e.g. blood chemistry panel, complete blood count) in preparation for chemotherapy and to sentinel lymph node biopsy (SLNB) performed using blue dye. Pathology in limited level resource communities should be able to determine at least the estrogen receptor status via immunohistochemistry and provide SLN analysis. At this level, despite it being nonstandard and not necessarily efficient, it is recommended that the use of endocrine therapy can be based on clinical judgement and eventual clinical response. Regions with enhanced and maximal level of resources are essentially HICs that offer full access. [24]. With the standardized approach of prioritization proposed by BHGI, early detection has been shown to increase, which dramatically improved outcomes including mortality and morbidity of breast cancer[27, 28].

Eastern Regional Hospital’s resources at the time of this review fell between the limited and basic level of BHGI. A modified radical mastectomy was the first course of therapy for all resectable breast
cancers. Afterwards, obtaining biologic subtype and hormone receptor status was inconsistent and their results were substantially delayed as they required analysis by a remotely located pathologist. Without knowing the biologic subtype to tailor treatment, the surgeon often prescribed chemotherapy which was indicated in most cases due to advanced stage lymph node positive disease and adjuvant endocrine therapy often before the final pathology results were known. Neoadjuvant treatment with chemotherapy was only used in cases of unresectable disease. At this level, performing SLNB which substantially decreases the risk of lymphedema for assessment the axillary lymph nodes is a BHGI recommendation. Diagnosis by FNA or core biopsy is also recommended to establish the diagnosis and allow tailoring of treatment including neoadjuvant systemic treatment to shrink advanced cancers. However, for this to become part of standard practice prompt access to pathology would need to have been available. Recently a pathologist has begun working at St. Joseph’s Hospital in Koforidua so percutaneous core biopsy is being used to confirm diagnosis before reviewing treatment options. Unfortunately, the breast specimens still need to be sent to Kumasi or Accra for immunohistochemistry analysis. This study focused on one regional hospital serving a rural catchment area over seventy miles away from Accra. Our hope is that as breast cancer awareness rises, additional data will be collected for in-depth analysis on additional rural settings, especially in sub-Saharan Africa, where breast cancer mortality rates are among the highest in the world. Future studies should continue to evaluate barriers to care, genetic risk factors, pathogenesis of TNBC, and opportunities for cost-effective & sustainable improvements in communities with only basic or limited resources.

**Study limitations and strengths**

With this being the first analysis of breast cancer in a predominantly rural setting, it may be difficult to extrapolate the results to other rural areas of either Ghana or other in sub-Saharan Africa. In addition, 46% of our patients were lost to follow-up and therefore censored. This could have over or under estimated the cumulative survival in this study. Lastly, sub-analysis of survival by biologic subtype could not done be due to a lack of statistical power in the analysis of the results from the limited number of patients who had complete immunochemistry analysis available. However, the
major strength of our study is being the first study of outcomes in Ghana that reflects the breast
cancer survival rate in a rural population of sub-Saharan Africa. In addition, this data adds to the
growing body of literature showing extraordinarily high rates of the most aggressive breast cancer
subtype -TNBC in the black population of Ghana

Conclusions
Despite success in the reduction of cancer mortality in southern and northern Africa, survival in the
rural communities of sub-Saharan Africa remains poor. Under the Breast Health Global Initiative
guidelines, Eastern Region Hospital’s resources fall between that of limited to basic level. Advanced
disease presentation combined with sub-standard capacity for accurate diagnosis, cancer subtype
analysis, adequate therapy and follow-up play a role in the poor outcomes. Future studies should
emphasize identification of barriers to care, genetic risk factors and opportunities for cost-effective
and sustainable improvements in LICs.

Abbreviations

**LIC:**
Low-income country

**LMIC:**
Low-middle- income countries

**HIC:**
High-income countries

**IHC:**
Immunohistochemistry

**BSE:**
Breast self-examination

**TNBC:**
Triple-negative breast cancer

Declarations

**Ethics approval and consent to participate**

This study was approved by the Pennsylvania State University Institutional Review Board and by the
ethics board in Ghana Eastern Regional Hospital. All patients in this study consented to participate in the study.

**Consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

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**Authors’ contributions**

PS, FA, JSO originated the concept, and designed experiments.

FA, XC and ABS collected data.

PS performed the data analysis and drafted the manuscript.

FA, JSO, AES, WW, DGD performed critical reviews of the manuscript.

All authors approved the final manuscript.

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**Availability of data and materials**

The dataset used and analyzed during the current study are not publicly available due to patient confidentiality, but are available from the corresponding author on reasonable request.

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Figures

Figure 1

Age of patients presenting with breast cancer. Approximately 76% of Patients were between 30 and 60.
Figure 2

Percent of patients presenting with each grade type. Approximately 60% of patients presented with grade three tumors.
Figure 3

Histological type of Breast Cancer. Triple-Negative Breast Cancer (TNBC) accounted for approximately 57% of cases.
Survival stratified by grade type. Three-year survival was approximately 50%.

Figure 4