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Triple-Negative Breast Cancer in Ghanaian Women: The Korle Bu Teaching Hospital Experience

Edmund M. Der, MB ChB,* Richard K. Gyasi, MB ChB,* Yao Tettey, MB ChB,* Lawrence Edusei, MB ChB,* Marcel T. Bayor, PhD,† Evelyn Jiagge, MB ChB,‡ Mawuli Gyakobo, MB ChB,§ Sofia D. Merajver, MD, PhD,‡,¶ and Lisa A. Newman, MD, MPH, FACS‡,¶

**University of Ghana Medical School and Korle-Bu Teaching Hospital, Accra, Ghana; †Kwame Nkrumah University of Science and Technology, Kumasi, Ghana; ‡University of Michigan Medical School, Ann Arbor, Michigan; §Ghana Health Service, Accra, Ghana; ¶Center for Global Health, University of Michigan, Ann Arbor, Michigan*

■ **Abstract:** Breast cancers that have negative or extremely low expression of estrogen receptor and progesterone receptor and non-amplification of human epidermal growth factor receptor-2 (HER2)/*neu* are termed triple-negative breast cancer (TNBC). The majority of TNBC tumors belong to the biologically aggressive basal subtype, and they cannot be managed with targeted endocrine or anti-HER2/*neu* agents. In western, high resource environments, risk factors for TNBC include younger age at diagnosis and hereditary susceptibility. Women of African ancestry in the United States and in continental Africa have higher frequencies of TNBC, prompting speculation that this risk may have an inherited basis and may at least partially explain breast cancer survival disparities related to racial/ethnic identity. Efforts to document and confirm the breast cancer burden of continental Africa have been hampered by the limited availability of registry and immunohistochemistry resources. Our goal was to evaluate the breast cancers diagnosed in one of the largest health care facilities in western Africa, and to compare the frequencies as well as risk factors for TNBC versus non-TNBC in this large referral tertiary hospital. The Korle Bu Teaching Hospital is affiliated with the University of Ghana and is located in Accra, the capital of Ghana. We conducted an institutional, Department of Pathology-based review of the breast cancer cases seen at this facility for the 2010 calendar year, and for which histopathologic specimens were available. The overall study population of 223 breast cancer cases had a median age of 52.4 years, and most had palpable tumors larger than 5 cm in diameter. More than half were TNBC (130; 58.3%). We observed similar age-specific frequencies, distribution of stage at diagnosis and tumor grade among cases of TNBC compared to cases of non-TNBC. Ghanaian breast cancer patients tend to have an advanced stage distribution and relatively younger age at diagnosis compared to Caucasian Americans and African Americans. The triple-negative molecular marker pattern was the most common subtype of breast cancer seen among this sample of Ghanaian women, regardless of age, tumor grade, or stage of diagnosis. Research into the molecular pathogenesis of TNBC may help elucidate the reasons for its increased prevalence among women with African ancestry. ■

Key Words: Ghana, high grade, immunohistochemistry, triple-negative breast cancer, young

Breast cancer is estimated to be the second most common cause of cancer mortality among women in Ghana (1), motivating a call for increased breast health awareness in the country. Low- and middle-income countries, however, have limited financial resources to solely support population-based tumor registries. Although estimates of population-based cancer incidence and mortality rates exist, they are frequently based on data from other countries that possess population-based registries (such as Uganda) or data from single institutions. In spite of these limitations, undertaking studies at major teaching hospitals help establish better Ghanaian-based estimates of the burden of breast cancer.

Breast cancers are categorized as invasive tumors with or without a non-invasive (in situ) component. Advances in the technologies associated with whole-genome profiling for invasive breast cancer have led to improved understanding regarding the spectrum of tumor subtypes associated with varying degrees of

Address correspondence and reprint requests to: Lisa A. Newman, MD, MPH, FACS, Professor of Surgery, Director, Breast care Center, University of Michigan, 1500 East medical Center Drive, Ann Arbor, MI 48167, USA, or e-mail: lanewman@umich.edu

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malignant aggressiveness, with the basal subtype having the most inherently aggressive behavior. In clinical practice, immunohistochemistry (IHC) is a reliable method to detect patterns of expression for three molecular markers that help map the therapeutic options for newly diagnosed patients. Tumors that are negative for the estrogen receptor (ER), the progesterone receptor (PR), and human epidermal growth factor receptor-2 (Her2/*neu*) are termed triple-negative breast cancer (TNBC). Triple-negative status is an adverse prognostic feature because of the close correlation with the basal subtype, and because the micrometastatic potential of these tumors cannot be controlled effectively with either endocrine therapy or anti-HER2/neu therapy. In high resource countries and among women of white/European American and European background which are part of high incidence populations, TNBC accounts for 10–20% of all breast cancers (1–4). TNBC is more prevalent among breast cancer patients that are diagnosed at young ages, patients with hereditary susceptibility derived from BRCA-1 mutations, and African-American patients (4,5). The frequency of TNBC is approximately twofold higher for African American compared to white American and European breast cancer patients, and recent studies (6–8) have demonstrated that one-third to more than half of sub-Saharan African breast cancer patients have triple-negative disease. The higher proportion of TNBC among African American and African women has prompted speculation that shared African ancestry may be associated with a heritable marker of TNBC risk. Robust data on the breast cancer burden in Africa are lacking, however, because the limited health care workforce and pathology infrastructure in most facilities precludes routine IHC testing as well as epidemiologic studies. These limitations make it difficult to ascertain whether the higher frequency of TNBC reported in African-American populations is a phenomenon related to some intrinsic, inherited susceptibility of the African provenance. The goal of this study was to evaluate the clinicopathologic patterns of breast cancer observed in one of the largest tertiary care hospitals in sub-Saharan Africa.

MATERIAL AND METHODS

The Korle Bu Teaching Hospital (KBTH) is affiliated with the University of Ghana and is located in Accra, the capital of Ghana. Accra is a city of approximately 2.3 million people. KBTH is a major referral center for cancer care in Ghana, and a site that participates in the Ghanaian national health program. We retrospectively reviewed all cases of histologically confirmed breast cancers for which IHC analyses of ER, PR, and HER2/*neu* were conducted in the Korle Bu department of pathology during the calendar year 2010. IHC for molecular markers were evaluated and interpreted by the lead author (EMD), who generated the data for this manuscript while participating in a 4-month research program at the University of Michigan through the sponsorship of the Center for Global Health and under the supervision of senior authors (SDM and LAN). We compiled and recorded clinicopathologic features (patient age; presentation; stage; histology; and molecular marker profile) of breast cancer for each patient. IHC was performed on sections from formalin-fixed, paraffin-embedded specimens using Novolink Detection system (Novocastra TM, manufactured by Leica Microsystems GmbH, Wetzlar, Germany). Cases were scored as being ER or PR positive if at least 10% nuclear staining was observed. They were scored as being HER2/*neu* positive if complete membranous staining was observed in 10% or more cells. These data were entered into SPSS software (version 19; SPSS, Chicago, IL and SPSS/IBM, Armonk, NY), and analyzed. Histologic grade of tumors was based on the architectural and cytologic features of the tumor; the grade was according to the modified Scarff–Bloom–Richardson grading system and the TNM staging was that used by the American Joint Committee on Cancer (AJCC).

RESULTS

A total of 223 histologically confirmed breast cancer cases were identified during calendar year 2010. Clinicopathologic characteristics of this study sample are shown in Table 1. The ages ranged from 25 through 90 years with a mean of 52.4 years (SD = 13.6). The majority of cases (61%) presented with palpable breast masses associated with skin changes/involvement. Mean tumor size was 4.5 cm, with a range of 0.5–14 cm. Information on duration of breast symptoms/palpable disease prior to biopsy was available for 67 patients, and the mean time of 35 weeks (range 1–53 weeks).

Histopathologic characteristics and IHC were assessed from core needle biopsy specimens in 95 cases (42.6%) versus lumpectomy and mastectomy specimens in 19.3% and 34.6% of cases, respectively.

Table 1. Clinical Characteristics of Breast Cancers from Korle Bu Teaching Hospital 2010, Total Sample (223 Cases)*

	Freq (%)
Age/years	
Mean	52.4 (SD = 13.6)
Lowest thru 39	41 (18.4)
40–49	56 (25.1)
50–59	56 (25.1)
60–69	38 (17.0)
70+	32 (14.4)
Total	223 (100.0)
Size of breast lump (cm)	
Mean	4.5
2.0	22 (25.6)
2.5–5.0	38 (44.2)
Highest thru 5.5	26 (30.2)
Total	86 (100.0)
Other associated symptoms	
Skin involvement	22 (61.1)
Chest wall	2 (5.6)
Nipple discharge	4 (11.1)
Others	8 (22.3)
Total	36 (100.0)
Duration of breast lump or symptoms (weeks)	
Mean	35
Lowest thru 16	33 (49.3)
17–32	12 (17.9)
33–52	13 (19.4)
>52	9 (13.4)
Total	67 (100.0)
Type of surgical specimen analyzed	
Trucut needle biopsy	95 (42.6)
Mastectomy	68 (30.5)
Lumpectomy	52 (23.3)
Incisions biopsy	8 (3.6)
Total	223 (100.0)

*Total number of cases do not add up to 223 for all categories because of missing data on selected patients.

Table 2. Histologic Characteristics of Breast Cancers from Korle Bu Teaching Hospital 2010, Total Sample (223 Cases)*

	N (%)
Histologic type	
NOS	169 (75.8)
Lobular	12 (5.4)
Mucinous	9 (4.0)
Cribriform	7 (3.1)
Micropapillary	6 (2.7)
Medullary	4 (1.8)
DCIS	7 (3.1)
Others	9 (4.0)
Total	223 (100.0)
Histologic grade	
Grade I	20 (17.2)
Grade II	46 (39.7)
Grade III	50 (43.1)
Total	116 (100.0)
Nodal positive	
Single	8 (25.8)
Multiple	23 (74.2)
Total	31 (100.0)
TNM stage	
Stage I–II	11 (44.0)
Stage III–IV	14 (66.0)
Total	25 (100.0)
Immunohistochemistry profile	
TNBC	130 (58.3)
HR−/HER2+	52 (23.3)
HR+/HER2−	18 (8.1)
HR+/HER2+	23 (10.3)
Total	223 (100.0)

*Total number of cases do not add up to 223 for all categories because of missing data on selected patients.

As shown in Table 2, the majority of cancers (169, 75.8%) were invasive ductal histology and 12 (5.4%) were invasive lobular; 7 (3.1%) were DCIS; and the remaining 12% were various unusual breast cancer patterns (e.g., mucinous, micropapillary, and neuroendocrine). Nearly half of the 113 cases for which tumor grade was available (50 cases, 43.1%) were grade 3 lesions. Complete clinicopathologic staging was available for only 25 cases and of these, two-thirds (14 cases, 66%) were stage III or IV disease.

Regional nodal staging information was only available for the 68 patients who underwent mastectomy, and of these cases, there was unfortunately further limited documentation regarding the anatomic extent of the axillary dissection. However, of these cases, 31 (45.6%) were node-positive, and the majority of these node-positive cases (23/31, 74%) had multiple metastatic nodes, with a mean of five positive nodes (range 1–28).

One hundred and thirty (58.3%) of the 223 cases were TNBC and another one-quarter (52, 23.3%) were negative for ER and PR but positive for HER2/*neu*. Only 41 (18%) were positive for ER and/or PR, and among these hormone receptor-positive tumors more than half (23/41, 56%) were HER2/*neu*-positive.

Age range for the 130 TNBC cases was 25–90 years, with a mean of 51.7 (SD 13.3); range for the 93 non-TNBC cases was 25–84 years, with mean age 52.9 (SD 14.2). Mean size for the TNBC tumors was 5.1 cm (range 1–14 cm), and patients reported the presence of a palpable mass that was present for 1–156 weeks (mean 37 weeks). Comparison of the TNBC and non-TNBC tumors is shown in Table 3. No significant differences were observed between these subsets in distribution of age, histology, stage, or tumor grade.

Table 3. Comparison of Triple-Negative and Non-Triple-Negative Breast Cancers

Feature	TNBC ($N = 130$), N (%)	Non-TNBC ($N = 93$), N (%)	p-value (comparing proportion of TNBC expressing the selected feature with the proportion of non-TNBC cases expressing the selected feature)
Age <40 years*	23 (17.1)	18 (19.4)	0.774
Age 40–49 years	34 (26.2)	22 (23.7)	0.369
Age ≥50 years	73 (56.1)	35 (56.9)	0.513
Tumor ≤2 cm*	8 (16.3)	14 (37.8)	0.327
Tumor >2 cm, ≤5 cm	22 (44.9)	16 (43.2)	0.324
Tumor >5 cm	19 (38.8)	7 (19.0)	0.153
Skin involvement*	11 (61.1)	10 (61.1)	0.500
Grade III histology*	33 (47.1)	17 (37.0)	0.142
AJCC stage 1	1 (6.2)	0 (0.0)	0.398
AJCC stage 2	5 (31.2)	6 (60.0)	0.478
AJCC stage 3	3 (18.8)	1 (10.0)	0.358
AJCC stage 4	7 (43.8)	3 (30.0)	0.320
AJCC stage 1–2	6 (37.5)	6 (60.0)	0.500
AJCC stage 3–4	10 (62.5)	4 (40.0)	0.334
Invasive ductal histology*	89 (87.1)	62 (86.1)	0.476
Invasive lobular histology	2 (1.9)	6 (8.3)	0.144
Node positive*	20 (44.4)	11 (47.8)	0.730

*Total number of TNBC and non-TNBC cases do not add up to 223 because of missing data on selected patients.

DISCUSSION

Breast cancer is known to have a lower incidence, but higher mortality in low and middle resource countries of Asia and Africa compared to western, industrialized areas of the world such as North America and Europe. Financial resources to support accurate and updated registries are limited, but recent estimates of incidence rates indicate rates of 15–53 per 100,000 women in western, sub-Saharan Africa (9). By comparison, population-based incidence rates in the United States are 125 and 116 per 100,000 white American and African-American women, respectively (10). Historically, this difference in breast cancer burden has largely been attributed to the variation in reproductive history risk factors, such as age at first live birth and number of pregnancies. Women in developing countries typically begin childbearing at relatively young ages and they have multiple pregnancies, which would account for a lower population-based breast cancer burden.

Trying to understand the basis for differences in the distribution of markers between high and low resource settings, hereditary factors have been entertained as potential culprits. At least two lines of evidence have generated speculation that hereditary factors may also be contributing to the patterns of breast cancer observed in women from the developing countries of western, sub-Saharan Africa:

1. Similarities in the breast cancer burden of western, sub-Saharan Africans and African Americans, who would be expected to have a significant degree of shared ancestry dating back to the colonial slave trade. Both of these populations have a lower lifetime risk of female breast cancer, yet they face a higher risk of early onset disease, and an increased risk of male breast cancer. These same patterns are characteristically seen in families with documented hereditary susceptibility for BRCA1 mutation-associated breast cancer.

2. Advances in the understanding of breast cancer subtypes have led to an appreciation for particular disease patterns that have different risk factors as well as inherent aggressiveness. TNBC (tumors that lack expression of ER, PR, and HER2/*neu*) are biologically more prone to give rise to metastatic lesions, presumably largely because they are resistant to targeted endocrine and anti-HER2/neu therapies, and also because they are more likely to belong to the biologically more aggressive basal breast cancer subtype. TNBC is now considered to be a hallmark of inherited susceptibility for breast cancer especially from deleterious mutations in the BRCA1 gene, prompting a genetic counseling referral when detected in women up to age 50 years (11). TNBC is more common in African American compared to white American women, and as shown in Table 4, frequency of triple-negative breast cancer is also higher in women of

Table 4. Selected Studies Reporting Frequency of Triple-Negative Breast Cancer in African Nations Compared to Other Developing Countries

Study	Country	Region of the world	Frequency of TNBC
Trinkaus et al. (21)	Kenya	East Africa	32%
Gakinya et al. (22)	Kenya	East Africa	23%
Bird et al. (7)	Kenya	East Africa	44%
Roy et al. (8)	Uganda	Southern, sub-Saharan Africa	36%
Huo et al. (13)	Nigeria and Senegal	Western, sub-Saharan Africa	27% (proportion of cases that were TNBC and cytokeratin-positive)
Stark et al. (6)	Ghana	Western, sub-Saharan Africa	82%
Awadelkarim et al. (23)	Sudan	Northern Africa	15.9%
Abdelkrim et al. (24)	Tunisia	Northern Africa	18%
Ambroise et al. (25)	India	South Asia	25%
Teoh et al. (26)	Malaysia	Southeast Asia	15%
Tan et al. (27)	Malaysia	Southeast Asia	17.6%
Ghosh et al. (28)	India	South Asia	29.8%
Ng et al. (29)	Indonesia	Southeast Asia	21%

western, sub-Saharan Africa compared to those of other developing countries, suggesting that African ancestry may be the common denominator link to TNBC risk.

Although parallels in the breast cancer burden of African American and African women are provocative and suggestive of heritable risk, the paucity of tumor registry and molecular marker information in Africa makes it difficult to draw definitive conclusions. Additional data characterizing the breast cancer burden of African women are therefore necessary.

The American Society of Clinical Oncology/College of American Pathologists (12) currently recommends quantified percentage staining to document level of hormone receptor expression. Widespread dissemination of these guidelines (which were published in July 2010) occurred after IHC analysis of the cases included in this report. The specimens included in this study were therefore evaluated in terms of hormone receptor positivity using the cut-point of ≥10%, which was the pre-existing convention for our institution. Finding more than 80% of our cases to be hormone receptor negative using this cut-point, however, is still higher than historic data reported by other, western institutions using the now-outdated cut-point of ≥10%(12). Furthermore, due to the economic realities of the Ghanaian resources, fluorescence in situ hybridization testing was not available. The HER2/neu staining was therefore reported in the binary negative/positive fashion as described in the manuscript. Although these issues may have resulted in misclassification of a minority of our cases, the finding of a majority of breast cancers from this institution to be triple-negative nonetheless represents a notable difference in comparison to white American/European populations and is consistent with data from other sub-Saharan African countries, as demonstrated in Table 4.

The scarcity of financial resources to support maintenance of basic pathology services and IHC facilities for routine molecular marker assessment in Ghana prompts the question of whether the absence of ER, PR, and HER2 staining might simply reflect suboptimal tissue processing with universal antigen decay. However, other studies have demonstrated increased expression of other molecular markers in African populations, suggest as cytokeratins (which are associated with the inherently aggressive basal-TNBC subtype) (13,14), and aldehyde dehydrogenase 1 (a mammary stem cell marker) (15).

It is now known that the triple-negative phenotype is a marker of risk for harboring a mutation in the BRCA1 gene (11,16,17). Unfortunately, genetic counseling and testing was not available for our patients and we therefore cannot comment on the frequency of our cases having hereditary susceptibility for breast cancer. The global experience with BRCA mutation testing and the limited information on BRCA mutation status in African countries is reviewed by Karami and Mehdipour (18).

Ghana is located in western, sub-Saharan Africa. Accra is the capital of Ghana, and its KBTH, affiliated with the University of Ghana, is one of the few facilities where breast cancer specimens are routinely referred for IHC to assess ER, PR, and HER2/neu expression. In this study of 223 breast cancer cases that had IHC for hormone receptor and human epidermal growth factor (ER, PR and Her2-neu), the

majority of cases (58.3%), were triple-negative tumors. Although studies of TNBC in North America and Europe have consistently demonstrated an association between TNBC and young age at breast cancer diagnosis (3,4,19), our study revealed a similar prevalence of TNBC among Ghanaian breast cancer patients in all age categories. Similarly, at least one population-based study from California has demonstrated an increased risk of TNBC among African American compared to white American women in the fourth, fifth, sixth, and seventh decades of age (20). These observations suggest that African ancestry may be associated with some heritable pattern of mammary tissue that is more susceptible to the development of TNBC in both the pre- and postmenopausal age categories.

Triple-negative breast cancer is the common pattern of invasive breast cancer seen among Ghanaian women, based upon our retrospective review of cases evaluated at one of the largest hospitals in western Africa during a recent 1-year period. Presentation for all breast cancers from this region tends to be delayed and thus at late stages, with most cases characterized by large/palpable, node-positive, and high grade tumors. Increased breast health awareness and improved access to health care in Africa may strengthen early detection efforts. However, the increased prevalence of TNBC among Ghanaian breast cancer patients of all ages suggests that research regarding the genetics of breast cancer related to African ancestry warrants further study.

CONCLUSION

Our study of TNBC accounting for more than half of the Ghanaian breast cancers diagnosed in the year 2010 is hypothesis-generating, Additional studies using the more rigorous ASCO/CAP guidelines for quantified hormone receptor expression in additional African datasets is necessary. Also, given the known correlation between the triple-negative phenotype and breast cancer hereditary susceptibility syndromes, availability of genetic counseling and testing programs in Africa should be considered.

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