

Histological classification, grading, staging, and prognostic indexing of female breast cancer in an African population: A 10-year retrospective study

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ABSTRACT

Background: Breast cancer (BC) is a heterogeneous disease characterized with diverse genetic and ethnic/racial variations that may influence tumor characteristics and prognosis. We studied different histological types of BC and their prognostic indicators in part of Southwestern Nigeria.

Materials and Methods: A 10-year retrospective study of archival tissue-paraffin blocks and records of surgical cases (documented as BCs) between January 2005 and December 2014 was done. Tumor classification was made after the World Health Organization guidelines. Modified Bloom-Richardson score and TNM staging system were used in grading and staging the tumors. Nottingham prognostic index was employed in scoring the prognosis.

Results: The mean age was 49.7 years (20–89 years). The age group from 50 to 59 years was most affected. Out of 343 total cases, the most common histological type was invasive ductal carcinoma of no special type (88.9%). The majority (51.9%) had tumor sizes ranging 2–5 cm (pT2) and some (39.1%) with >5 cm (pT3) were all at palpable stages. The tumors were mostly Grades II and III types. Observation for lymph node metastasis confirmed that 261 (76.1%) were pN0 (negative), 77 (22.4%) were pN1, and 5 (1.5%) were pN2. Prediction of a chance of survival showed moderate prognosis in the majority (48.7%) of the cases.

Conclusion: Although early detection of BC in this region was considerably poor, there was a better outcome compared with some other black populations. Clinical presentation, histological type, and prognostic indices varied from existing reports in many ethnic/racial groups. Indexing of BC pattern on a regional standpoint may serve a new direction toward better management considering the associated geographic disparity.

Keywords: Breast cancer, Nottingham prognostic index, TNM staging system, tumor classification, tumor grading

Introduction

Breast cancer (BC) remains one of the most common female cancers globally. In Nigeria, different histological types of BC have been reported across the country.^[1,2] BC is a heterogeneous disease with geographic disparity.^[3] In other words, it is characterized by diverse genetic, geographic, racial, and ethnic variations which may, in turn, influence tumor characteristics and prognosis.^[4] In addition, the report shows that there is a considerable difference in tumor stage at diagnosis by race/ethnicity and birthplace.^[5] Of recent, report on clinical and pathological profiles of BC between two different races corroborates significant geographic disparities and therefore calls for swift intensification of regional cancer control plan to improve management.^[6]

Moreover, apart from geographic consideration, better management of BC in guiding decision-making (especially from various alternatives of therapeutic options) involves the availability of robust clinical and pathological information. Pathological investigation requires histologic and prognostic parameters. Presently, the three established prognostic indicators in clinical and pathological investigation involve; degree of axillary lymph node involvement, primary tumor size, and histological grade.^[7] Lymph node status is a key factor among prognostic indicators designed for predicting spread or overall survival for operable BC. It is incorporated in both the TNM staging system and Nottingham grading system.^[8] Most times, the more positive lymph nodes involved, the higher the risk for recurrence of a BC.^[9] Likewise, tumor size is an important factor in prognosticating BC and it is independent

of lymph node metastasis.^[8] There is consistent evidence that size of a tumor forms part of the basis for traditional prognostic classification developed by the Union for International Cancer Control (UICC).^[10] The report shows a decline in prognosis or chance of survival with an increase in the size of the primary tumor.^[9] In the same way, the histologic grade is used to determine the aggressiveness of a tumor. It provides prognostic information in many tumors, including BC.^[7]

Application of these tools in investigations of incidence and trend of BCs with regard to clinical presentation, histological classification, tumor staging and their predictive outcome in every individual ethnic group may impact more to the knowledge of BC. Our aim was to study clinical presentation, histological pattern, and survival outcome of BC in part of Southwestern Nigeria.

Materials and Methods

Study design

This is a hospital-based retrospective study. The study involved retrieval of archival records and tissue-paraffin blocks of surgical cases histologically documented as BC between January 2005 and December 2014. A total number of 343 cases ($n = 343$) were reviewed.

Stud location

This study was carried out at the Histopathology Departments, Ladoke Akintola University Teaching of Technology Hospitals (LAUTECH) situated in Osogbo (Osun State) and Ogbomosho (Oyo State), located in the Southwest of Nigeria. These two hospitals, by geographic location, also serve many urban, semi-urban, and rural communities of neighboring states (Ekiti and Kwara States). The population in this region are dominated by the Yoruba. Yoruba are one of the most urbanized natives in Africa and makeup 21% of the Nigerians' population according to CIA World Factbook.^[11]

Ethical approval and consent

Ethical approval was obtained from the Research and Ethics Committee of LAUTECH Teaching Hospital Ogbomosho, Oyo state. The permission of the Heads of Histopathology Departments of the two hospitals was sought and the departmental rules were duly followed. This study posed no risk to the patients, their relatives or the community as it was carried out on archival tissue blocks and patients' clinical records. Data generated during the course of this study were accessible to the investigators only. All information was coded by number and no name was recorded. All data were transferred to a password-protected personal computer.

Exclusion and inclusion criteria

Tissue blocks with incomplete information or records without tissue blocks were equally excluded.

Data acquisition

The original request cards were retrieved and studied. Furthermore, essential clinical details which included the age and macroscopic descriptions (including size and nodal involvement) of BC were recorded.

Slide preparation

Tissue blocks were retrieved and fresh thin sections about 3–5 μm were cut using rotary microtome from formalin-fixed paraffin-embedded blocks. The slides were de-waxed in the oven under 70°C for 2 h and stained using hematoxylin and eosin staining technique for histologic analyses. The stained slides were finally observed under the microscope and reported by a consultant pathologist.

Tumor classification

Histological classification of the tumor was done according to the World Health Organization guidelines. Tumor grading was accomplished using the Nottingham modification of the Scarff-Bloom-Richardson grading system. Tumor staging was reported using the TNM system adopted by UICC and the American Joint Committee on Cancer and End Results Reporting. In addition, Nottingham prognostic index (NPI) was applied to score the prognosis for the possible outcome.

Statistical analysis

Data obtained were reported in percentage (frequency) and proportion using descriptive statistics.

Results

A total number of 343 cases ($n = 343$) suitably registered in the recording system with complete information were histologically identified with various types of female BC between January 2005 and December 2014, at Ladoke Akintola University Teaching Hospitals (Osogbo and Ogbomosho units).

Age distribution

The age of the patients ranged between 20 and 89 years (mean = 49.70 years). The peak incidence age was the 6th decade (50–59 years). Majority of the cases occurred between the 4th and 7th decades (30–69 years).

Histological type

The most common histological variant of female BC recorded was infiltrating ductal carcinoma (IDC) (305 cases; 88.9%). Other less common types were invasive lobular carcinoma (ILC) (16 cases; 4.7%), medullary carcinoma (6 cases; 1.7%), and mucinous carcinoma (4 cases; 1.2%). The uncommon types recorded were three cases (0.9%) each of carcinosarcoma and metaplastic carcinoma, two

Table 1: Frequency distribution and comparison of histologic phenotypes of female breast cancer across Nigeria

Histologic type versus Region	Freq. in present study (%)	Abeokuta-Shagamu, Southwest ^[13] (%)	Zaria, Northwest ^[14] (%)	Maiduguri, Northeast ^[15] (%)	Warri, South-south ^[16] (%)	Aba, Southeast ^[1] (%)
Invasive ductal carcinoma	305 (88.9)	94.9	82.5	82.6	70.0	53.0
Invasive lobular carcinoma	16 (4.7)	NS	4.9	6.6	7.2	18.0
Medullary carcinoma	6 (1.7)	1.8	5.8	4.3	1.5	NS
Mucinous carcinoma	4 (1.2)	0.3	1.0	1.7	1.9	NS
Carcinosarcoma	3 (0.9)	NS	NS	NS	0.8 (combined)	NS
Metaplastic carcinoma	3 (0.9)	NS	NS	NS		NS
Malignant phyllodes tumor	2 (0.6)	NS	NS	NS	1.9	NS
Poorly differentiated carcinoma	2 (0.6)	NS	NS	NS	NS	NS
Apocrine carcinoma	1 (0.3)	NS	NS	NS	0.8	NS
Tubular carcinoma	1 (0.3)	NS	NS	NS	0.4	NS
Others (unrelated histological types)	-	3.0	5.8	4.8	15.5	29.0
Total	343 (100)	100	100	100	100	100

*NS: Not seen (not recorded)

cases (0.6%) each of malignant phyllodes tumor and poorly differentiated carcinoma and one case (0.3%) each of apocrine and tubular carcinoma, respectively [Table 1 and Figures 1-5].

Tumor grade

Out of 343 cases, 24 cases (7%) showed Grade I of Nottingham modification of Bloom Richardson system. Two hundred forty-four cases (71%) showed Grade II, while 75 (22%) showed Grade III, respectively [Table 2].

Tumor size

All the 343 BC cases had specified tumor sizes. The tumor size ranged from 1 to 22 centimeters in the widest diameter (mean = 6.2 cm). Thirty-one (31 cases; 9.0%) cases had tumor size ≤ 2 cm and were classified as tumor size Stage 1 (pT1), 178 cases (51.9%) had tumor size of 2–5 cm and were classified as tumor size Stage 2 (pT2), while 134 cases (39.1%) had tumor size < 5 cm and were classified as Stage 3 (pT3), correspondingly [Table 2].

Lymph node metastasis

Table 2 also illustrates the degree of lymph node involvement. Lymph node biopsy was reviewed in the record for a possible note on metastasis of individual cases. Two hundred and sixty-one cases (76.1%) were negative for the malignancy (pN0), while 82 cases (23.9%) showed nodal metastases. Of a total number of lymph node involved or positivity, 77 cases (22.4%) comprising three groups of 67 cases (19.5%), 3 cases (0.9%), and 7 cases (2.0%) correspondingly had 1, 2, and 3 positive lymph nodes (all classified as pN1). Five cases (1.5%) had

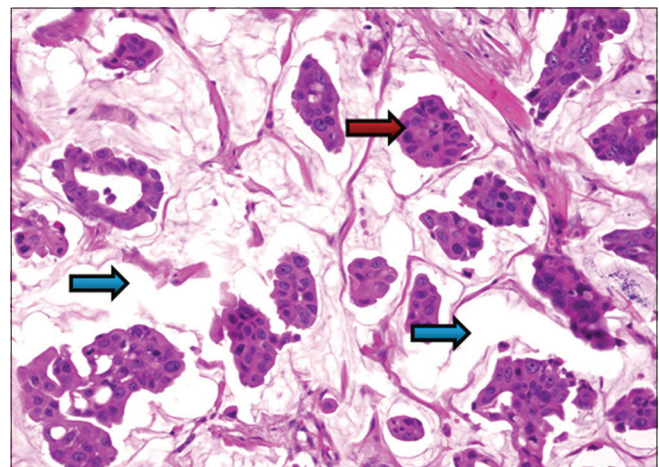


Figure 1: Mucinous carcinoma (hematoxylin and eosin, $\times 40$). Red arrow indicates the clusters of malignant cells; blue arrows indicate the pools of extracellular mucin

6 positive lymph nodes (lymph node positivity of > 3 ; pN2) [Table 2].

NPI

The NPI conventionally combines nodal status, tumor size, and histological grade for assessment of possible survival outcome. Table 3 shows how NPI was used to predict the probabilities of the patients surviving from BC using a recent prognostic scoring, namely NPI-I (excellent) ≤ 2.4 ; NPI-II (good) > 2.4 but ≤ 3.4 ; NPI-III (moderate) > 3.4 but ≤ 5.4 ; and NPI-IV (poor) > 5.4 .^[12] Out of 343 cases, 105 cases (30.6%) showed good prognosis, 167 cases (48.7%) showed moderate prognosis, while 71 cases (20.7%) showed poor prognosis [Table 3].

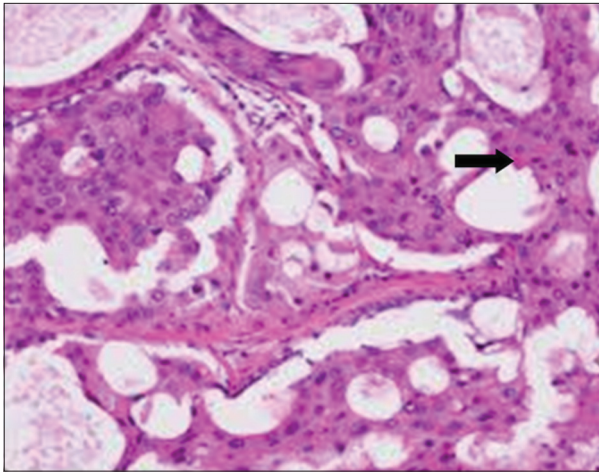


Figure 2: Apocrine carcinoma (hematoxylin and eosin $\times 40$). Blue arrows indicate the presence of tubules lined by tumor cells that exhibit apocrine metaplasia

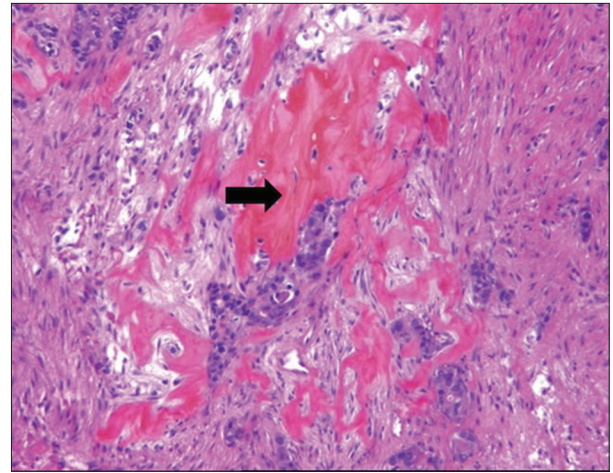


Figure 4: Metaplastic carcinoma (hematoxylin and eosin $\times 40$). Black arrow indicates the presence of a matrix-producing tumor. Blue arrow indicates squamous cell carcinoma

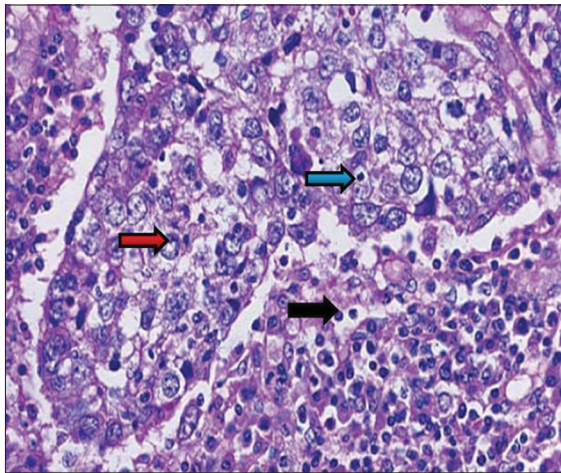


Figure 3: Medullary carcinoma (hematoxylin and eosin $\times 40$). Red arrow indicates the presence of solid, syncytial-like sheets of large cells with vesicular, pleomorphic nuclei with prominent nucleoli. Blue arrow depicts a mitotic figure. Black arrow depicts moderate to marked lymphoplasmacytic infiltrate surrounding the tumor

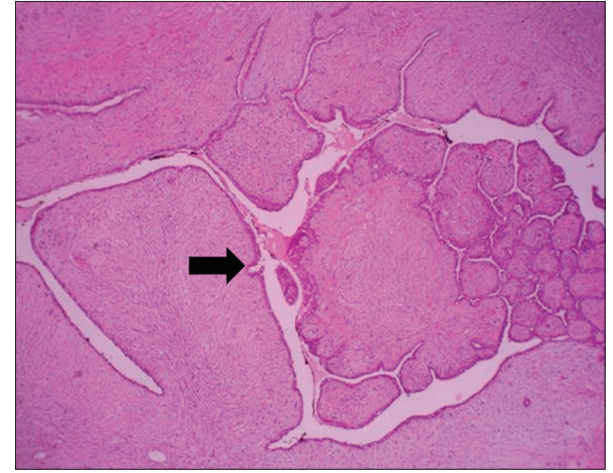


Figure 5: Malignant phyllodes (hematoxylin and eosin $\times 40$). Black arrow shows the presence of nodules of proliferating stroma covered by epithelium. The tumor has infiltrative borders

Discussion

In this study, we observed various histological forms of BC, but there was a predominance of invasive ductal carcinoma of no special type (IDC) compared with other phenotypes. This was more than in the majority of other centers in Nigeria, such as Zaria (Northwest), Maiduguri (Northeast), Warri (South-south), and Aba (Southeast) with 82.5%, 82.6%, 70%, and 53%, respectively.^[1,14-16] On the other hand, the prevalence in our study was less than figures reported in Abeokuta and Shagamu, Ogun state and Ibadan, Oyo state (within the same neighborhood of our study region) where 94.9% and 95% were reported, respectively.^[13,17] The findings of this study in agreement with Titiloye *et al.*^[2] suggest that individuals in Southwestern Nigeria may be at higher risk of developing IDC than other parts of the country. Although the reason behind

this is yet unknown, there may be a connection with increased western lifestyle in this zone.

In contrast, the prevalence of ILC in the present study was lower than the reported figures in many other parts of Nigeria, including Kaduna State (Northwest),^[14] Sokoto and Borno states (Northeast)^[15,18] as well as Delta state (South-south).^[16] Even though the previous study in Ile-Ife, our neighboring town, previously reported the absence of ILC.^[13] This shows that southwest residents may be at lower risk of developing ILC compared with many other regions in Nigeria where more cases of ILC had been reported.^[1,14-16] Furthermore, the prevalence of ILC in this study was lower compared with the reported figures for both Iraqi and British individuals^[6] indicating both ethnic and racial differences.

Moreover, our study recorded a low prevalence of medullary carcinoma compared with many other centers across the

Table 2: Frequency distribution of histologic grade, tumor size, and lymph node positivity in female breast cancers

Nottingham prognostic index (NPI)	Tumor index	Frequency (%)
Tumor grade ^a	I (Low)	24 (7)
	II (Intermediate)	244 (71)
	III (High)	75 (22)
Tumor size ^b	pT1	31 (9.0)
	pT2	178 (51.9)
	pT3	134 (39.1)
Lymph node status ^c	pN0	261 (76.1)
	pN1	77 (22.4)
	pN2	5 (1.5)

^a is the grade of tumor (Nottingham grade): Grade 1=I, Grade 2=II, Grade 3=III. ^b is the size of the index lesion (cm): pT1= \leq 2 cm, pT2=2–5 cm, pT3= $>$ 5 cm. ^c is the node status (node positivity): pN0=0 nodes, pN1=1–3 nodes, pN2= $>$ 3 nodes

Table 3: NPI score: Prediction of breast cancer survival against BC-specific 10-year figures^[12]

*NPI score	Frequency (%)	Interpretation	10-year BC-specific survival figures (%)
<2.4–3.4	105 (30.6)	Good prognosis	93
>3.4–5.4	167 (48.7)	Moderate prognosis	78
>5.4	71 (20.7)	Poor prognosis	44

NPI: Nottingham prognostic index. *NPI=tumor size (cm) \times 0.2+histological grade (I–III) + number of positive lymph nodes (1=0 nodes; 2=1–3 nodes; 3= $>$ 3 nodes). BC: Breast cancer

Northern belt of Nigeria^[14,15] but more than that recorded in part of southern sub-region (South-south).^[16] This is in agreement with the previous study.^[2] It showed that medullary carcinoma phenotype followed geographic disparity across Nigeria divide. Mucinous carcinoma is a mucin-producing BC phenotype bounded by tumor cells. It has been documented to have a better prognosis than IDC.^[19] Although the associated positive prognostic effect had not been noted in any region, in this study, we recorded the higher prevalence of mucinous carcinoma compared with that reported in some states across Nigeria, including a neighboring southwestern state (Ogun state) in our region^[13] and Maiduguri, Bornu state (Northeast).^[20] In contrast, a considerably higher prevalence had been reported in a nearby town.^[2] This suggests that the risk of individuals developing mucinous carcinoma may be higher in our study areas. Of note, the pattern of spread showed inexplicable geographic disparity, including intra-regional distribution.

In addition, low prevalence of carcinosarcoma, metaplastic carcinoma, malignant phyllodes tumor, poorly differentiated carcinoma, apocrine, and tubular carcinomas were recorded in our study. However, these were rarely or less reported in many other studies across Nigeria.^[14,15] Even though carcinosarcoma and metaplastic carcinoma were reported in Warri (South-south) and Sokoto (Northwest), Nigeria, there was still lower prevalence compared with the present study.^[16,20] Likewise, Agbo *et al.*^[18] reported a lower prevalence of malignant phyllodes tumor (MPT) compared with what we recorded in

the present study. Meanwhile, MPT is rarely seen or recorded across Nigeria at large. It is categorized as a rare fibroepithelial malignancy representing approximately 0.3–0.9% of all BC subtypes but has great potential to reappear locally and metastasize following a treatment.^[21]

Furthermore, the present study showed that BC presentation is more prevalent among the age range of 50–59 years. This is in agreement with the previous study by Okoye *et al.*^[13] in Ile-Ife, a neighboring town. However, this was notably higher compared with many reports in various other regions across Nigeria, including Zaria in Northwest,^[14] Bayelsa, South-south,^[22] Abia, Southeast^[1] and Abuja, and Northcentral.^[23] Likewise, the mean age (49.70 years) of BC presentation in this study was relatively similar with that reported in a separate study in our study region^[13] but higher than other geopolitical zones across Nigeria, including Southeast,^[1] South-south,^[16] Northwest,^[14,18] and Northeast.^[20] This suggests that patients with BC in Southwestern Nigeria had late presentation compared to other regions. On the contrary, the mean presentation age is about 12 years earlier than the reported mean age (61.70 years) in their British counterparts.^[6] The report shows that the average age of cancer presentation is a factor of racial and ethnic backgrounds.^[4] The previous report shows dissimilarity in BC regarding the age at presentation and histological variation between Nigerians and the Finnish counterparts.^[24] More so, a recent study demonstrates that Black women are more diagnosed with BC at a younger age than the white counterparts with an estimated median age of 50 years against 62 years.^[25] Meanwhile, diagnosis of BC at younger and reproductive age has been linked to the increased mortality rate in spite of a proportional rise in the incidence with age.^[25,26]

However, a large body of research implies that the racial differences between the Black and White are due to combined effects of a complex interaction of biologic and non-biologic factors. These factors are thus suggested to have plausible influences on the histologic stage of diagnosis, tumor characteristics, tumor type and size, lymph node metastasis, obesity, and other health-related factors.^[26] We characterized patients with BCs using histologic grade, tumor size, lymph node metastasis, and prognosis to see a pathological pattern and outcome of BC in our region as a result of higher age at presentation than in other regions. Meanwhile, the report shows that histological grading has good reproducibility and useful as an important independent prognostic factor for predicting outcome in patients with BCs. It further states that a combination of histological grading with tumor size, lymph node involvement, and the NPI offers best and remarkable stratification for management of these patients.^[7] Our observation on overall grading of female BC showed that majority of the patients presented their case when the tumor was already at Grade 2 while some of the patients presented at Grade 3. In other words, there was a preponderance of Grades 2 and 3 (93%) of BCs when combined, in the same

trend with previous reports, namely 95.5% by Titiloye *et al.*^[2] in our study area (Southwest) and 99% by Agbo *et al.*^[18] in Sokoto (Northwest) Nigeria. However, studies involving Nepalese^[8] and Americans show a predominance of lower grade proportions without any advanced tumor grade documented, constituting 64.5% and 64.5–82.7%, respectively.^[27] Meanwhile, a separate report corroborates that Black population have a tendency to have higher grade and node-positive tumors compared with White.^[25]

Furthermore, our study showed that very few among the patients had tumor size of 2 cm or less. We observed that the majority of the cases in these areas had tumor sizes within Stages 2 and 3 with overall average tumor size of 6.2 cm. This is in agreement with a previous study^[28] from our study area. This means that patients in this region tend to evade early detection of BC. The reasons for this may be partly linked with consequential poor awareness, poverty, socio-cultural behavior, and lack of instituted screening program using ancillary investigative tools.^[26] Meanwhile, most tumors <2 cm would require ancillary investigations such as mammogram and breast ultrasound before they could be detected. Our centers currently lack these ancillary methods, and our screening method has been mass education on self-breast examination.

In addition, previous studies in Nigeria only looked at the lymph node in the context of either positive or negative for malignancy without actually specify the number of positive lymph nodes for staging. Likewise, many studies often ignore the report of lymph node status during the investigation. This has precluded further study in this area related to survival rate using NPIs for predicting the outcome. The present study thus looked at the number of lymph node biopsied and the number that were positive. Alternatively, we could not estimate absolute survival rate of individual patients, partly due to lack of follow-up report on a timely basis and lack of adequate cancer-specific death record. However, we stratified the patients according to prognostic scores using NPI index^[12] considering the number of positive lymph nodes, among other factors. We observed that the majority of the patients showed moderate prognosis. Our findings are in tandem with a previous study in a sub-Saharan African (Ghanaian) population^[29] but worse than that reported in the Libyan population (in the Northern African region).^[30] Nevertheless, our report, in conformity with an earlier study in Nigerian population^[14] showed poorer outcome compared with the Finnish population (in Europe).^[30]

Conclusion

The pathological features of primary epithelial breast malignancies seen in some parts of southwestern Nigeria showed high proportion characteristic with considerable large tumor sizes, intermediate-high histological grades, and presence of lymph node metastasis on occasions. This shows that early detection of BC in these areas was poor. On the

contrary, the chance of survival was better compared with other Black populations documented with advanced cancers of the breast. Ethnic/racial variations observed in this group of patients against other reports in different populations may be primarily associated with genetic factor involving varying gene mutation, degree of penetrance, and expressivity, among others. Further studies are therefore encouraged to involve molecular and biological characterizations. This may serve as a critical step for better-improving management of BC considering the diverse geographic heterogeneity with different ethnic/racial backgrounds.

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