Original Article

Pattern of Molecular Phenotypes of Breast Carcinomas using Immunohistochemistry in a District Hospital in Nigeria

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Abstract

Background: Cancer of the breast is the most common organ-specific cancer, affecting women worldwide with disproportionately higher mortality seen among women of Africa ancestry. Molecular phenotyping is crucial for tailored treatment of such patients. **Aim:** The aim of the study is to describe the molecular phenotypes of carcinomas of the breast based on their oestrogen, progesterone, and HER-2/Neu receptors status in our centre. **Design:** This was a retrospective analysis of 136 histologically diagnosed breast carcinomas, for which oestrogen, progesterone, and HER2 receptors status data were available at the Pathology Unit in a Nigerian District Hospital. **Materials and Methods:** Relevant biodata and pathology and molecular information of all patients with histologically diagnosed breast cancer (BC) were extracted from patients' forms and reports archived in the department. Immunohistochemistry was performed on formalin-fixed, paraffin-embedded tissue blocks of 136 (54.4%) cases of the BCs utilizing the avidin-biotin complex technique. **Results:** The ages of the patients ranged from 17 to 74 years, and the mean age was 47.3 ± 11.7 at diagnosis. All affected patients were females except for a male teenager. oestrogen, progesterone, and HER-2/Neu receptor-positive breast carcinomas were 43.4% (59), 39% (53), and 27.2% (37), respectively. Triple-negative breast carcinoma (39%, 53/136) was the most prevalent phenotype, followed by Luminal A (33.8%, 46/136) and Luminal B (14.7%, 20/136), while HER2-enriched (12.5%, 17/136) was the least common molecular subtype in our series. **Conclusion:** Breast carcinomas are predominantly of the triple-negative molecular phenotype in our setting and commonly affected young women.

Keywords: Breast carcinoma, immunohistochemistry, molecular phenotype, triple-negative

Introduction

Primary cancer of the breast is the most prevalent site-specific cancer seen in women in Nigeria and globally, beside nonmelanoma skin malignancy.[1-8] Data from most Nigerian cancer registries suggest increasing occurrence of breast cancer (BC), with more than a threefold increase in its incidence in a decade (1992–2001) reported in Ibadan.[1-7,9] BC-related mortality is second only to that of lung cancer globally.

The now-known disparate nature of BC in its histology, molecular biology, clinical behavior, and outcomes informs the need for personalized treatment of both the local and systemic disease by global best practice guidelines.[10-13] This individualized management approach espouses local and systemic management of BC by appropriate combination of surgery and/or irradiation, as well as chemotherapy regimens with or without hormonal therapy or targeted monoclonal antibody.[10-13] Molecular typing of BC is crucial to achieving this tailored treatment.[11-13] Breast carcinomas are categorized into four molecular phenotypes: triple negative breast cancer (TNBC), luminal A, luminal B, and HER-2/Neu-enriched. This is based on the pattern of expression of progesterone receptor (PR), oestrogen receptor (ER), and Human epidermal growth factor receptor 2/Neu (HER-2/Neu) determined using either molecular techniques such as *in situ* hybridization (ISH), fluorescence ISH (FISH), and polymerase chain reaction, or surrogate immunohistochemical methods.[11-14]

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These molecular phenotypes have peculiar clinicopathologic features, differing sensitivity to chemotherapeutic, hormonal, and targeted monoclonal antibody agents, and overall survival outcomes.[10-16]

Hence, molecular subtyping is pivotal for selection of systemic drug combinations, prediction of response, prognostication, genetic counselling, and planning of screening programs.[10-14] Molecular phenotyping using immunohistochemical procedure which is the relatively cheaper and easier to set-up method for routine clinical use is the preferred surrogate approach to molecular subclassification of breast carcinoma. We described the molecular phenotypes of breast carcinomas in the Pathology Unit, Asokoro District Hospital, Abuja, Nigeria, based on their ER, PR, and HER-2/Neu receptor status and compared our results with studies from Nigeria and Africa.

Materials and Methods

This was a retrospective review of 136 histopathologically diagnosed breast carcinomas for which biodata and pathology and molecular (ER, PR, and HER2) data were available in the Pathology Unit of Asokoro District Hospital, Abuja, Nigeria, from January 1, 2012, to December 31, 2019. For each case of cancer of the breast, we extracted clinicopathological data - patients' age and sex, tumor laterality, histological subtypes, histological grades and the immunohistochemical results of ER, PR, and HER-2/Neu status of the breast carcinoma from patients' request forms and histopathology reports archived in the Unit during the period under review. The histology slides of each case of BC had been reviewed to confirm the diagnoses and grading. The cancers were classified in accordance with the 2012 WHO International Classification of breast Tumours[15] and graded according to the Nottingham grading system.[16] Breast carcinomas with missing immunohistochemical profiles of ER, PR, and HER2 in the archive were excluded from the study. The avidin-biotin complex method with ABCAM (Cambridge, MA, USA) monoclonal antibodies was used for the immunostainig procedure.

Receptors status were scored, and molecular subtypes allocated utilizing the Joint American Society of Clinical Oncology/College of American Pathologists and the St. Gallen International Expert Consensus (2013) guidelines and recommendations bar utilizing FISH to ascertain the HER2 status when it is equivocal on immunohistochemistry (2+).[11-13] According to the guideline, brown nuclear immunostain of ≥10% of neoplastic cells at light microscopy was adjudged as positive for ER (ER^+) and PR (PR^+) expression, while score 3+ brown membrane immunostaining of >10% of neoplastic cells was adjudged as immunopositive for HER2 expression ($HER2^+$). Lack of brown nuclear immunostaining of BC cells was considered negative for ER (ER^-) and PR (PR^-) while staining of scores 0, 1+, and 2+ was deemed negative for Her2 ($Her2^-$) since facility for FISH (equivocal 2+) is absent in our centre (two cases of 2 + where seen in our study). Based on the immunostaining profile, the molecular phenotypes were classified as luminal A cancers (PR^+/ER^+, $HER2^-$ or PR^-/ER^+, $HER2^-$ or PR^+/ER^-, $HER2^-$), luminal B cancers (PR^+/ER^+, $HER2^+$ or PR^-/ER^+, $HER2^+$ or PR^+/ER^-, $HER2^+$), triple-negative BCs (PR^-/ER^-, $HER2,^-$) and HER2-enriched cancers (PR^-/ER^-, $HER2^+$). The resultant data were managed using Microsoft Excel software program (Microsoft Corporation 2016, New York, USA) and displayed using tables and chart.

Results

Eight hundred and thirty-eight surgical breast lesions were diagnosed during the period of the study. Primary BCs constituted 30.3% (254/838) of all the breast lesions, with carcinomas making up 98.4% (250/254). Immunohistochemical data (ER, PR, and HER2) were available for 136 (54.4%) of these carcinomas. The age of the patients ranged from 17 to 74 years and the mean age was 47.3 ± 11.7 at diagnosis with about 60% (81/136) of the patients aged ≤50 years. All the affected patients were females, except for one male teenager. The most prevalent histological subtype of breast carcinoma was invasive carcinoma, no special type (NST) (94.12%, 128/136), followed in the distant by mucinous carcinoma (2.94%). A case (0.74%) each of invasive lobular, invasive cribriform, invasive papillary, and medullary carcinomas was seen during the period of the study. Grade II (59.5%, 81/136) tumors were the most common tumor grade encountered. Grade I and Grade III tumors constituted 1.5% (2) and 24.3% (33), respectively. The results of the immunohistochemical staining showed that ER-, PR-, and HER-2/Neu-positive cases were 43.4% (59/136), 39% (53/136), and 27.2% (37/136), respectively, of the breast. Conversely, the number of breast carcinomas that immunostained negatively for ER, PR, and HER2 was 56.6% (77/136), 61% (83/136), and 72.8% (99/136), respectively [Table 1].

Triple-negative breast carcinoma (39%, 53/136) was the most common molecular phenotype, followed by luminal A (33.8%, 46/136) and luminal B (14.7%, 20/136), while HER2-enriched (12.5%, 17/136) was the least common molecular subtype in our series [Figure 1]. Photomicrographs of positive immunostains are shown in Figures 2-4, while those of negative immunostains are shown in Figures 5-7.

The mean age of patients with triple-negative BC (TNBC) was 46.1 ± 12.6 (range of 17–74 years). TNBC peaked in the fourth decade and became relatively rare after the sixth decade. Almost 42% (22/53) of the patients with TNBC were young women (≤40 years) and women ≤50 years make up 64% (34/53) of all the TNBC patients [Table 2].

Discussion

At diagnosis, the average age of our patients was 47.3 years, with almost 60% of the affected patients being ≤ 50 years old, and this is congruent with the reported mean age for women with breast cancers in Nigeria and Africa.[7,9,17-38] The peak

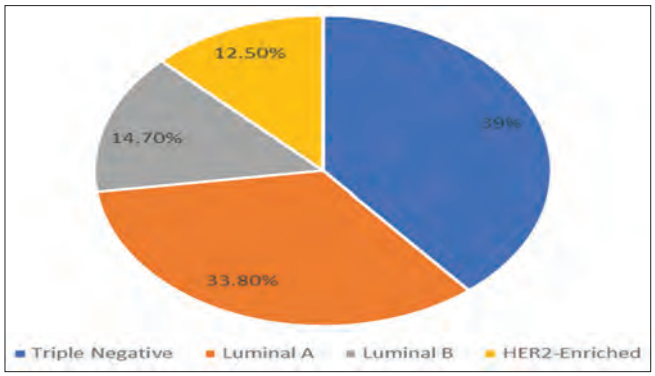

Figure 1: Pie chart showing the frequency distribution of the molecular phenotypes of breast carcinoma

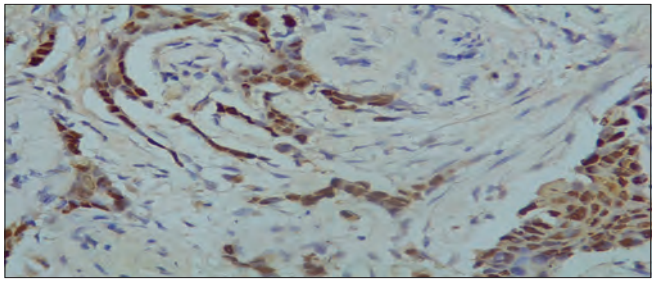

Figure 3: Photomicrograph of breast carcinoma immunostained positively for progesterone receptor positive; 5 + 3 strong diffuse nuclear staining of invasive breast carcinoma cells (Immunohistochemistry, ×40)

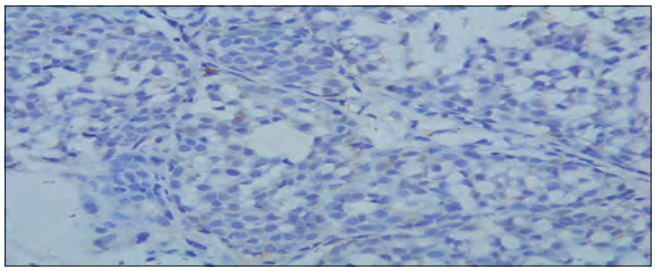

Figure 5: Photomicrograph of breast carcinoma immunostained negatively for estrogen receptor showing complete absence of nuclear staining of invasive breast carcinoma cells (Immunohistochemistry, ×40)

age range of the index study (31–40 years) is the same as the ones documented in Jos[19] and Uyo,[29] but it is a decade earlier than those recorded in Kano,[17] Lagos,[22] and Nnewi.[27] While differences in sample sizes and study designs may explain this disparity, our finding authenticates the documented fact that BC occurs earlier in the women of African ancestry compared to their Caucasian counterparts, attributed to aggressive biogenetic factors, changing carcinogenic environmental factors, and shorter life expectancy.[39-41,43]

Invasive carcinoma, NST was the most prevalent histologic subtype of BC in our study, like all series from Nigeria and Africa.[17-36] However, while our reported relative frequency (94.12%) of invasive carcinoma, NST is in consonant with those recorded in Lagos,[22,23] Nnewi,[27] Angola,[32] and Eritrea,[33] it is higher than most studies in Nigerian and African

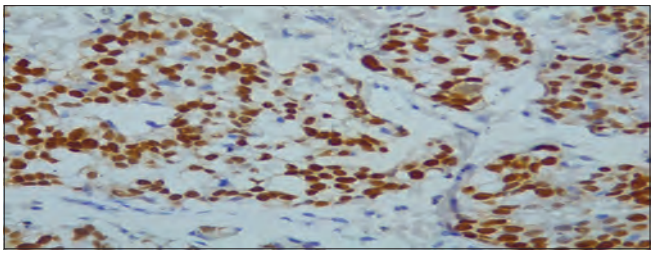

Figure 2: Photomicrograph of breast carcinoma immunostained positively for estrogen receptor showing strong diffuse nuclear staining of invasive breast carcinoma cells (Immunohistochemistry, ×40)

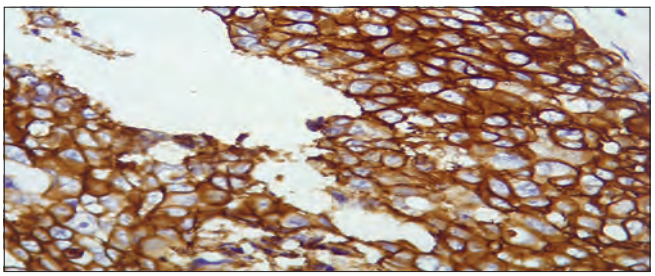

Figure 4: Photomicrograph of breast carcinoma immunostained positively for HER2; 3+ showing diffuse intense membrane staining of invasive breast carcinoma cells (Immunohistochemistry, ×40)

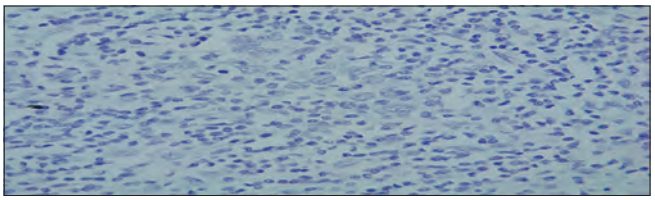

Figure 6: Photomicrograph of breast carcinoma immunostained negatively for progesterone receptor showing complete absence of nuclear staining of invasive breast carcinoma cells (Immunohistochemistry, ×40)

with a reported range of 73.2%–88%.[17-21,24-26,28-31,33-35] This is likely due to the varying small sample sizes of the mainly hospital-based studies across the continent.

The predominant grade of tumors in this work is Grade II (59.5%) in conformity with most Nigerian[22,23,27,29] and African series.[32,33,36,37] It is, however, in contrast to findings from other Nigerian[17,18,25,30] and African[34,35] studies which reported a preponderance of Grade III BCs. All the previous studies though reported an overwhelming majority of higher Grade (II and III) tumors, typical of BCs in women of African extraction.[40,41] We, thus, agree with Chowdhoury *et al*.[42] that the discrepancy in findings of higher tumor grades in the literature reviewed may have been influenced by intra- and inter-observer variability in BC grading.

Our study revealed that most carcinomas did not express hormonal receptors (ER^- - 56.6%, PR^- - 61%) [Figures 5-7]. This parallels the nonexpression of ER^- (57.7%) and PR^- (62.6%), ER^- (75.0%) and PR^- (62.2%), ER^- (61.6%) and PR^- (70.0%), ER^- (85.9%) and PR^- (90.1%), and ER^- (93.0%) and PR^- (97.9%) documented in Nnewi,[27]

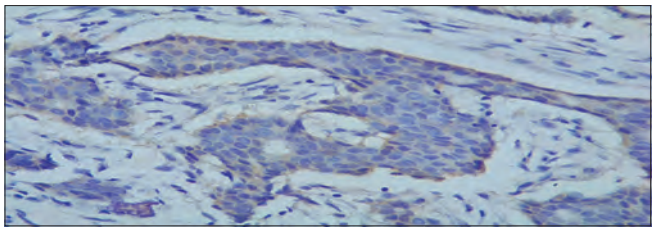

Figure 7: Photomicrograph of breast carcinoma immunostained negatively for HER2; 1+ showing sparse incomplete membrane staining of invasive breast carcinoma cells, (Immunohistochemistry, ×40)

Table 1: Baseline Clinicopathological and Molecular features of Breast Carcinomas

Variables	*n* (%)
Laterality;	
Left breast	70 (51.47%)
Right breast	58 (42.65%)
Bilateral breasts	01 (0.74%)
Unstated	07 (5.15%)
Histological subtypes;	
Invasive carcinoma (NST)	128 (94.12%)
Mucinous carcinoma	004 (2.94%)
Invasive lobular carcinoma	001 (0.74%)
Invasive cribriform carcinoma	001 (0.74%)
Invasive papillary carcinoma	001 (0.74%)
Medullary carcinoma	001 (0.74%)
Nottingham Histologic Grades;	
Grade I	02 (1.5%)
Grade II	81 (59.5%)
Grade III	33 (24.3%)
Unstated	20 (14.7%)
Estrogen receptor;	
Positive (ER+)	59 (43.4%)
Negative (ER-)	77 (56.6%)
Progesterone receptor;	
Positive (ER+)	53 (39%)
Negative (ER-)	83 (61%)
Her 2/Neu overexpression;	
Positive (Her 2+)	37 (27.2%)
Negative (Her 2-)	99 (72.8%)

Jos,[20] Ile-Ife,[25] Benin,[30] and Lagos,[23] respectively, in Nigeria as well in Ghana[37] and Angola[32] with non-expression rates of ER^- (67.9%) and PR^- (64.4%) and ER^- (86.5%) and PR^- (90.8%), respectively. In contrast, higher hormonal receptor positivity was reported in Ibadan[24] (ER^+ - 65.1%, PR^+ - 54.7%), a private facility in Lagos[21] (ER^+ - 54.2%, PR^+ - 50%) and Morocco[36] (ER^+ - 64.2%, PR^+ - 66.9%). We are unsure if these differences in the hormonal expression pattern within the country and continent with a tendency toward non-expression of hormonal receptors are truly reflective of the intrinsic biologic characteristics of the carcinomas. Eng *et al*.,[41] in their review of receptor-defined subtypes of BC in Indigenous African Populations, reported significant disparity in the documented frequencies of hormonal receptor profile of BCs in the continent. They posited that the heterogeneity may be due to differences in the tumor pathologic characteristics, differences in the prevalence of risk factors for specific subtype, and differences in the quality control of preanalytic and analytical handling of tumor specimens.

Triple-negative breast carcinomas (TNBCs) were the most frequent molecular phenotype of the cases reviewed in our study, affecting 42% of young women aged ≤40 years. In a similar vein, researchers in virtually all geopolitical regions in Nigeria[17-19,22,23,25-27,29] as does Seshie *et al*.[37] in Ghana reported relative predominance of the triple-negative BC in their series. The index 39% relative frequency of TNBC is similar to the 40.7% recorded by Ukah *et al*.[27] in Nnewi and 41.3% documented by Emmanuel *et al*.[19] in Jos, but it is lower than values cited by previous works with reported relative frequency range of 42.1%–87%.[17,18,22,23,25,26,29] Like these studies, our value is higher than the documented figures from the United States and United Kingdom (15%–25%).[40,43] While we cannot adduce a definite explanation for the extensive range of proportions reported within the country for TNBC, we hypothesize that variable small sample sizes (range 20–235), differential level of quality control of preanalytical and analytic factors, and variability in immunohistochemical processes may play a role. The implication, however, of the predominant TNBC is that most of our young women were affected by a BC molecular subtype with limited response to platinum-based chemotherapy and intractable to targeted endocrine and monoclonal antibody therapies. This provides the biomolecular basis which in part explains the dire outcome noted for Nigerian BC patients.[9,38,43] The work by Agboola *et al*.,[43] which compared Nigerian and the UK grade-matched BC patients, showed that Nigerian patients have a fourfold likelihood to have TNBC with basal phenotype than White UK women with significantly poorer survival statistics.

Luminal A and luminal B together represented the largest group with luminal A molecular phenotype representing the second predominant specific subtype in our study. Luminal A phenotype accounted for 33.8% of all the phenotypes, and 54.3% of the cases seen affected women aged ≤50-year-old. Luminal A was the most common phenotype reported by Adebamowo *et al*.[24] in Ibadan (77.6%), Omoruyi *et al*.[28] in Calabar (52.4%), Oboma *et al*.[31] in Bayelsa (54.1%), and Nwafor and Keshinro[21] in a private setting (39.6%) in Nigeria as well in Eritrea (55.6%),[33] Angola (45%),[32] Morocco (42%),[36] Ethiopia (40%),[34] and Guinea (34.5%).[35] While ethnic comparative studies have shown that Luminal A BCs are predominant in Caucasian women compared to African and American Black women, reproductive factors and age at diagnosis have also been shown to affect the incidence of ER-positive cancers and could explain the differential distribution within Nigeria and the continent.[10,39,43]

Luminal B cancers were seen in 20 (14.7%) patients and represented the third most frequent phenotype. This rate is similar to findings in Maiduguri (13.2%)[18] and Calabar (12.93%)[28] but higher than values reported in

Table 2: Age distribution of patients with different molecular subtypes of breast carcinoma (*n*=136)

	Molecular phenotypes				
Mean age	**Luminal A 48 ± 11.9**	**Luminal B 45.5 ± 9.7**	**Her-2/Neu 51 ± 10**	**TNBC 46.1 ± 12.6**	**Total 47.3 ± 11.7**
Age group	*n*	*n*	*n*	*n*	*n*
11-20	0	0	0	1	1 (0.7%)
21-30	1	1	0	3	5 (3.7%)
31-40	14	5	3	18	40 (29.4%)
41-50	10	8	5	12	35 (25.7%)
51-60	13	5	6	13	37 (27.2%)
61-70	3	1	2	3	9 (6.6%)
70-80	5	0	1	3	9 (6.6%)
Total	46	20	17	53	136 (100%)

Kano (6.7%)[17] and Nnewi (4.9%).[27] ER-positive cancers are sensitive to the endocrine agent tamoxifen with variable chemosensitivity and have a better overall prognosis relative to TNBC and HER2/Neu-enriched cancers.[10,13,39,43]

HER2/Neu-enriched carcinomas were the least common molecular type in our series, accounting for 12.5%. This finding is in keeping with the high non over-expression of HER-2/Neu pattern across Nigeria[19-21,23-25,27,43] and Africa,[32-38] with reported proportion ranges from 68.8% to 96.2% and 60.7% to 77%, respectively. HER2/Neu-enriched carcinomas exhibit HER2/Neu gene overexpression, an independent poor prognostic factor which effect is mitigated by trastuzumab, anti-HER2/Neu monoclonal antibody agent.[11-13]

Conclusion

We conclude that in our setting like most others in Nigeria and Africa, high-grade invasive carcinoma, NST of the breast commonly affects young women and is predominantly of the triple-negative molecular phenotype. Thus, we recommend that as much as possible, immunophenotyping to stratify patients and provide rational basis for tailored treatment should be pursued.

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Conflicts of interest

There are no conflicts of interest.

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