Original Article

Histopathological and Immunohistochemical Characteristics of Breast Carcinomas in Uyo, Subtropical Region of Africa

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ABSTRACT

Background: There is a relative dearth of data for immunohistochemical characteristics of breast carcinomas in cancer registries of Nigeria and some parts of Africa. A descriptive hospital based study, done over a year, involving three hospitals in Uyo rendering breast cancer care.

Objective: To determine the immunohisto chemical-expression pattern of oestrogen receptor, progesterone receptor, and human epidermal receptor 2 and their relationship with histopathological features of invasive breast carcinomas in Uyo, Akwa Ibom State.

Materials and methods: Each specimen with an accompanying completely filled coded proforma form containing clinical characteristics of patients with breast cancer was received at the Histopathology Department for subsequent histopathological and immunohistochemical analysis.

Results: The age range for patients with breast carcinoma was 23 -70 years with a mean age at presentation of43.07 ± 11.19 years. Invasive ductal carcinoma was the commonest histological type accounting for 86.9 % of all breast cancer. Positivity for oestrogen receptors, progesterone receptors and Her-2 were seen in 18.0 %, 14.8 % and 32.8 % of breast carcinomas respectively. Majority of breast carcinomas were triple negative phenotype (62.3 %).

Conclusion: Majority of the invasive breast carcinomas in our environment were triple negative phenotype (62.3 %).

INTRODUCTION

Breast carcinoma is the commonest site-specific malignancy among females globally, and the leading cause of cancer deaths in females accounting for over 300,000 deaths in 2008; most arising from metastasis.[1] Immunohistochemical markers are invaluable for diagnosis, prognosis and clinical decision making in managing of breast carcinoma.[2,3] Receptor status determines the hormonal and cytotoxic therapies for breast cancers with over-expression of Her-2 protein showing better response to Herceptin.[2,4]

Breast carcinomas are often painless, and frequently involve the upper outer quadrant of the left breast owing to the fact that this anatomic site has abundant breast tissue when compared to its counterpart right breast.[2,3] Generally, invasive ductal carcinoma is the commonest type of breast cancer.[4,5]

Activated Her-2 protein has been said to enhance tumour invasion and metastases, accounting for the association of Her-2 over-expressed tumours with

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intermediate to high grade tumours as well as large tumours.[6]

There is a relative dearth of data for immunohistochemical characteristics of breast carcinomas in cancer registries of Nigeria and some parts of Africa.[7,8] The aim of this study, therefore, is to determine patterns of breast carcinomas in Uyo, with a view to assessing their pathological and immunohistochemical characteristics.

MATERIALS AND METHODS

Study design:

A descriptive hospital based study was carried out in 2015 involving the University of Uyo Teaching Hospital, St. Luke's Hospital and selected private hospitals in Uyo rendering breast cancer care.

Target population:

All consenting patients between the ages of 20 and 99 years, irrespective of gender with diagnosis of breast cancer and attending the surgical outpatient clinics of respective hospitals were recruited into the study.

Selection of the Cases:

Total sampling method was used by including all consecutive sixty-one (61) patients available within the period of one year in 2015.

Inclusion criteria:

Patients with clinically and histological diagnosis of breast cancer having complete clinical information whose samples have been fixed in 10 % neutral buffered formalin not exceeding 48 hours.

Exclusion criteria:

Patients with breast cancer without incomplete clinical information; whose samples have been fixed in 10 % neutral buffered formalin exceeding 48 hours; taking Herceptin chemotherapy; and samples with histological diagnosis of carcinoma-in-situ.

Ethical consideration:

The study was approved by the Ethical and Research Committee of University of Uyo Teaching Hospital (UUTH) and managements of other public and private hospitals.

General Assessment of Subjects:

The case notes of all consenting patients with breast cancer were retrieved and data recorded in the proforma questionnaire with coded registration research number. Biodata, findings of physical examinations, operation findings and drug history were recorded.

Data Collection Tool and Procedure for processing breast tissues

Samples comprise core biopsy, excision biopsy, incision biopsy and mastectomy with an accompanying completely filled coded proforma form was received at the Histopathology Department for routine histological andimmunohistochemical studies using monoclonal (ER and PR) or polyclonal (Her-2) Dako Denmark branded antibodies by indirect immunoenzymatic method.[9-11]Appropriate positive and negative controls were used for each staining batch.Using the Allred scoring guideline for ER/PR pharmDx™, a total score of ≥ 3 was considered positive.[10] For the HER-2 evaluation, sections with scores of +2 and +3 were considered positive while those with scores of 0 and +1 were considered negative.

Data analysis: Statistical analysis of data was performed using SPSS Software version 20 (IBM, SPSS Inc., Chicago, IL, USA).Comparisons of discrete data were done using Chi-square test, with levels of significance being set at $p \leq 0.05$. The results were presented in tables, figures and photomicrographs.

RESULTS

A total of sixty-one (61) cases of breast carcinomas were recruited and analysed.

Socio-demographic Characteristics of Breast Carcinoma:

The age of patients with invasive breast carcinomas ranged from 23.0 to 70.0 years with a peak age incidence in the 30-39 years age group (32.8 %) and a mean age at presentation of 43.07 ± 11.19 years. Majority (59.0 %) of the patients were aged 40.0 years or older while the remaining 41.0 % were aged 40 years or younger. (Table 1)

Table 1 : Showed frequency distribution of Breast Carcinoma by Age

Age groups	Frequency	Percentage (%)
20-29	5.0	8.2
30-39	20.0	32.8
40-49	17.0	27.9
50-59	13.0	21.3
60-69	5.0	8.2
70-79	1.0	1.6
Total	61.0	100.0

Invasive breast carcinomas were diagnosed commonly in females accounting for 60 cases (98.4 %) while only 1 (1.6 %) case was seen in a male patient giving a female to male ratio of 60:1.

Clinicopathological Characteristics of Breast Carcinoma:

The left and right breasts were involved in 65.6 % and 31.1 % of breast carcinomas respectively. Two (3.3 %) cases of bilateral carcinomas were observed. Most of the breast carcinomas were painless in 48 (78.7 %) cases while painful breast cancers were observed in 13 (21.3 %) cases. Most high grade breast carcinomas were painless (41.4 %).

Majority of breast carcinomas had tumour size of 2-5 cm in 30 (49.2 %) cases. Twenty-nine (47.5 %) patients presented with tumour size of more than 5 cm while 3.3 % had a tumour size of less than 2 cm.

Invasive ductal carcinoma was the commonest histological subtype of breast cancers accounting for 53 (86.9 %) cases. Secretory, invasive papillary and medullary carcinomas were other histological subtypes; responsible for 3.3 % cases each. Invasive lobular and metaplastic carcinomas were the least subtype and each accounted for 1.6 % of the tumours.

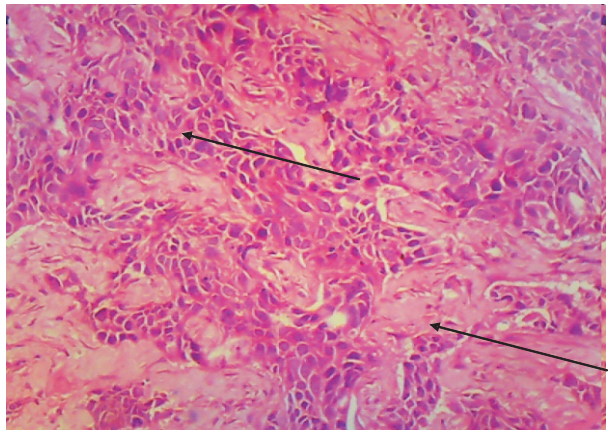

Figure 1: Histologic section showed pleomorphic epithelial tumour cells disposed in cords, clusters, irregular sheets and anastomosing trabeculae infiltrating desmoplastic stroma of the breast, H & E X 40.

Grade II breast carcinoma was the commonest, accounting for 42.7 % of all breast carcinomas. Grade I and III breast carcinomas were seen in 27.8 % and 29.5 % of cases respectively. (Table 2) Although there was no significant association between age group and histological grade (p value = 0.22), a significant correlation was observed between histological grade and tumour size (p value = 0.006) as larger tumour size greater than 5 cm had higher proportions of high histological grade.

Table 2: Tumour Grade against Histological Type of Breast Carcinoma

Histological Type	Grade I	Grade II	Grade III	Total (%)
Invasive Ductal Carcinoma	15.0	21.0	17.0	53.0 (86.9)
Medullary Carcinoma	-	1.0	1.0	2.0 (3.3)
Papillary Carcinoma	1.0	1.0	-	2.0 (3.3)
Secretory Carcinoma	1.0	1.0	-	2.0 (3.3)
Invasive Lobular Carcinoma	-	1.0	-	1.0 (1.6)
Metaplastic Carcinoma	-	1.0	-	1.0 (1.6)
Total (%)	17.0 (27.8)	26.0 (42.7)	18.0 (29.5)	61.0 (100)

Immunohistochemical Characteristics of Breast Carcinoma:

Positive estrogen receptors (ER) were seen in 18.0 % of breast carcinomas while positive progesterone receptors (PR) were observed in 14.8 % cases. (Figure 2) Her-2 positivity was observed in 32.8 % of breast carcinomas. (Table 3 and Figure 3) Majority of breast carcinomas were triple negative phenotype in 62.3 % of cases, frequently seen in the 41-60 years age group (31.1 %) and patients older than 40.0 years (60.5 %); less frequently observed in patients aged 40 years or younger (39.5 %). (Table 4)Majority of triple negative breast carcinomas had tumour size greater than 5 cm (39.9 %), grade 3 (26.2%) and invasive ductal carcinoma histologic subtype (52.5%).

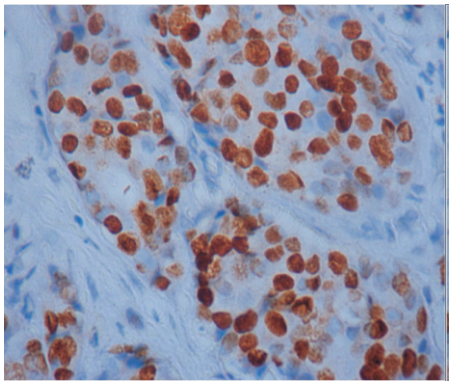

Figure 2: Immunohistochemical section showed strong nuclear staining indicative of positive ER over-expression of breast carcinoma, Immunohistochemistry X 40.

Table 3: Expression of ER, PR and HER-2 receptor status in Breast Carcinoma

MARKER Cases	POSITIVE Frequency (%)	NEGATIVE Frequency (%)	SUBTOTAL Frequency (%)
ER	11.0 (18.0)	50.0 (82.0)	61.0 (100.0)
PR	9.0 (14.8)	52.0 (85.2)	61.0 (100.0)
Her-2/neu	20.0 (32.8)	41.0 (67.2)	61.0 (100.0)

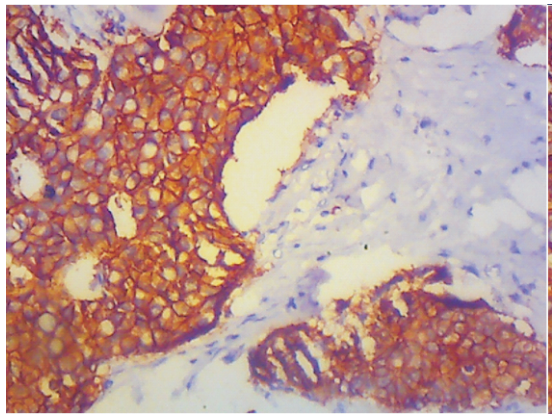

Figure 3: Immunochemical section showed strong circumferential membrane staining indicative of HER-2 over-expression of breast carcinoma, Immunohistochemistry X 40.

Variables	Groups	Non Triple Negative	Triple Negative
Age	<30	3 (4.9)	2(3.3)
	31-40	12 (19.6)	13(21.3)
	41-60	6 (9.8)	19(31.1)
	>60	2 (3.3)	4(6.6)
	Total	23 (37.7)	38(62.3)
Tumour size	<2	1(1.6)	1(1.6)
	2 – 5	17(27.9)	13(21.3)
	>5	5(8.2)	24(39.9)
	Total	23(37.7)	38(62.3)
Histological grade	Low	9(14.7)	8 (13.1)
	Intermediate	12(19.8)	14(22.9)
	High	2(3.3)	16(26.2)
	Total	23 (37.7)	38(62.3)
Histological type	invasive ductal carcinoma	21(34.4)	32(52.5)
	Invasive lobular carcinoma	0(0)	1(1.6)
	Medullary carcinoma	1(1.6)	1(1.6)
	Papillary carcinoma	0(0)	2(3.3)
	Secretory carcinoma	0(0)	2(3.3)
	Metaplastic carcinoma	1(1.6)	0(0)
	Total	23 (37.7)	38(62.3)

DISCUSSION

Immunohistochemistry based classification of breast carcinoma is known to providing indispensable therapeutic and prognostic information.[1-4] ; though this is not always done in resource poor setting of developing countries.[8,9]

The mean age of patients in this study was 43.07 ± 11.19 years and a peak age incidence in the 30 - 39 years age group (32.8 %). This is similar to mean ages of 42.6 and 49.1 years reported in Ibadan, Nigeria and Ghana respectively, but differs slightly from a study in the United States where a bimodal mean age of 44 and 73 years was observed.[9-11]The median age at the time of diagnosis for breast carcinoma was 44.6 years, 46 years and 52 years in North India, Morocco and Eastern Algeria respectively.[12-14]Thepa et al in Nepal recorded a mean age of 34.6 ± 5.0 years among younger patients compared to 54.1 ± 9.9 for those ≥ 40 years.[15] In addition, two independent studies in Benin, Nigeria recorded a mean age of 45.7 years and 46 years for breast carcinoma.[16,17] Reports have shown that the mean age at presentation for breast carcinoma varies from region to region[18] ; however, mean age of 48 years was recorded in Africa with approximately two-thirds being premenopausal in contrast to preponderance among postmenopausal women in Europe.[19,20-23]

In the index study, breast carcinoma in the older patients (≥40 years) slightly outnumbered those in younger patients (≤40 years) in frequencies of 51 % to 41 %. This finding in younger population in our study is however higher than 33.1 % and 27.9 % recorded in North India and Nepal respectively.[12,15] This observation in younger population could be adduced to the fact that breast tissue in them has immature proliferating mammary epithelial cells enriched with luminal progenitors, mammary stem cells, expression of c-kit and receptor activator of nuclear factor κ-B ligand and growth factor signaling promoting uncontrolled to autonomous proliferation which may promote carcinogenesis.[24,25]Furthermore, it has been reported that the occurrence of germline mutations in highly penetrant genes, such as BRCA1 or BRCA2, culminating in development of breast cancer at a younger age.[24]The roles of interaction between breast cancer genes (BRCA 1 and 2) and their variants and environmental carcinogens in the aetiopathogenesis of breast cancer cannot be overemphasized, as both factors may modulate the risk of developing breast cancer.[26,27]

A female to male ratio was 60:1 which is similar to findings from Zaria, Benin and Osogbo, Nigeria.[28-30] These findings are further corroborated by a study in Thailand wherein majority (99.3 %) of breast cancer were seen in females.[31]

Left sided breast carcinoma predominated (65.6 %) which compares relatively with a report in Benin, Nigeria where left sided breast carcinoma accounted for 50.6 % to 53.3 % of cases.[16,17]The propensity of left sided breast carcinoma has been ascribed to abundance of glandular breast tissue in the left breast as compared to the right counterpart.

Invasive ductal carcinoma was the commonest histological type of breast carcinoma in the index study (86.9 %) with similar frequency in Africa, Europe, North America and Asia ranging from 75 % to 96.1 %.[13-16.22,28,31- 35] Furthermore, in the index study, lobular, medullary, and papillary carcinoma accounted for 1.6 %, 3.3 % and 3.3 % of histological type respectively. This is however slightly different from corresponding values of 3.6 %, 1.3 % and 0.6 % recorded for lobular, medullary and papillary carcinoma respectively in Benin, Nigeria.[28]Ngadda et al in Maiduguri, Nigeria reported a lobular carcinoma rate of 6.6 % while a study in United States reported a high rate of 15 % for lobular carcinoma.[33,34]Rais et al in Morocco recorded medullary carcinoma to be representing 9.0 % of all breast carcinomas[13] while papillary carcinoma was the least common among subtypes of breast carcinomas (2.7 %) in Benin, Nigeria.[16]

In the index study, majority (49.2 %) of breast carcinomas had tumour size of 2-5 cm; this is closely followed by tumour size of greater than 5 cm in 47.5

%. This finding concurs with a report in Lagos, Nigeria[32] but differs from findings of a study in Eastern Algeria where 70.1 % of the tumours were greater than 5.0 cm.[14] Studies have shown positive correlation between outcome and tumour size wherein larger tumour size above 5.0 cm is commonly associated with poor prognostic indices including local spread to surrounding lymph nodes and distant metastasis.[12,15] Furthermore, Thepa et al in Nepal has reported that the mean tumour diameter was significantly larger in young women (5.0 ± 2.5) than older women (4.5 ± 2.4 cm), thus overemphasizing the aggressive behaviour of breast cancer in the younger population.[15]

The most common tumour grade seen in this study was intermediate grade II accounting for 42.7 % of cases with age group between 46-60 years being most commonly affected. Grade I and III breast carcinomas accounted for 27.8 % and 29.5 % of all cases respectively. This finding compares relatively with a report apportioning 48 % as the frequency of intermediate grade breast cancer by Makanjuola et al in Lagos, Nigeria but differ greatly from a record of 23.5 % in another study by Gukes et al in Jos, Nigeria.[32,36]In the index study, majority (62.3%) of breast carcinomas were triple negative. This is however lower than the rate of 87 % reported in Lagos, South-Western Nigeria but higher than that of 11 %, 15.7 %, 21.6 % and 27.0 % reported in India, Senegal, Eastern Algeria and United States respectively.[14,31,32,37,38] Most breast carcinomas with triple negative phenotypes were seen in the 41-60 years age group (31.1 %) with majority being older than 40 years (60.5 %). This compares relatively with a study in North India where triple negative breast cancer occurred in patient older than 40 years in 46.6 %.[12] This finding is further corroborated by a study in Eastern Algeria in which 21.6 % of patients with triple negative breast cancer (TNBC) had a median age of 52 years.[14]In addition, triple negative breast cancer (TNBC) is commonly associated with poor prognosis which could be substantiated by the fact that majority of triple negative breast cancers have tumour size greater than 5.0 cm (39.9 %) and are of high grade (26.2 %) as documented in the index study.

ER and PR positive breast carcinomas accounted for 18.0 % and 14.8 % of cases respectively in the index study. This is similar to rates of 24 % and 20 % for ER and PR positivity respectively reported in Senegal but much higher than the rates of 7 % and 2.1 % reported in Lagos, South Western Nigeria.[37,38] Kinsella et al in United States however reported ER and PR positivity of 45.0 % and 37.0 % respectively.[39]Deepti Sharma et al recorded oestrogen receptor (ER) positivity of 39.8% and 55.2% in younger and older population respectively while progesterone receptors (PR) positivity of 38.5 % versus 44.8 % in younger and older population respectively.[12]

Moreover, this index study showed that 32.8 % of breast carcinomas over-expressed Her-2 epidermal growth factor. This is however higher than the rates of 3.9 %, 4.0 %, 7.0 %, 15.0 %, 20.4 %, 26.0 % and 32.0 % reported in Lagos, Ibadan, Nigeria, Senegal, Ghana, South Africa and United States respectively.[10,32,39-41] In addition, the presence of Her-2/neu gene amplification in breast carcinoma has been linked with poor prognosis, lower response to hormonal therapy and chemotherapy.[9,42] Her-2 over-expressed breast carcinoma however predicts response to anti-Her-2 antibody therapy (herceptin).[42]

Activated Her-2 epidermal growth factor have been said to enhance tumour invasion and metastases, accounting for the association of Her-2 over-expressed breast cancers with intermediate to high grade tumours as well as large sized tumours.[6] In addition to being a prognostic indicator, Her-2 over expression is important in determining treatment strategies, survival and response to treatment.

CONCLUSION

Majority of the invasive breast carcinomas in our environment were triple negative phenotype (62.3 %).

CONFLICT OF INTEREST

There is no conflict of interest declared.

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