Receptor Status and Associated Clinico-Histopathological Characteristics among Women with Breast Cancer in a Ugandan Tertiary Hospital

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Abstract

Background: The breast cancer landscape in Uganda is characterized by late disease and poor outcomes. Even though receptor status is an important prognostic factor, it is not routinely conducted in the country. This study was set to describe the oestrogen receptors (ER) status and associated clinico-histopathological features of breast cancer among women in Uganda. **Method:** A cross sectional descriptive study, carried out among women with histologically confirmed breast cancer, recruited at the Mulago Hospital breast clinic and determined their receptor status determined by immunohistochemistry (IHC), which was preceded by H&E staining. **Results:** In total 114 women were enrolled over a 5 months period. Mean age was 47years (13-87), half (50%) of the women had advanced disease (T_4 tumours), 48/114 (42%) presented more than 12 months after onset of symptoms and most had poorly differentiated (grade III) invasive ductal carcinomas, 61/114 (53%) and 50/114 (44%) were ER^- negative tumours. **Conclusion:** Breast cancer is common among young African premenopausal women, it presents mostly as T_4 tumours and close to half are ER negative. This is an over representation of ER negative tumours.

Key Words: Breast cancer, Advanced stage, Hormonal receptor status, Triple negative breast cancer

Introduction

Globally, breast cancer is the most frequently diagnosed life threatening cancer and leading cause of cancer death among women (1). In Uganda, breast cancer is the third most commonly diagnosed cancer after Kaposi's sarcoma and cancer of the cervix with a peak age of 30-39 years (2). It is increasing rapidly at a rate of 4.5% per year tripling from 11:100,000 to 31:100,000 in four decades (3). Breast cancer prevalence is known to vary with age, race, and ethnicity being more common in the Western world than in the African populations and has a strong relation to age with only 5% of all breast cancer occurring in women under 40 years in the developed nations (3). In Uganda and other African countries patients are more likely to be premenopausal with a peak age of onset a decade or so earlier than in the Western world (1, 5, 6, 7).

Black women have a lower incidence rate of breast cancer compared to white women, but they have poorer survival outcomes (8). Considering that socioeconomic factors lead to later stage at diagnosis and that limited access to health care contributes substantially to this disparity, differences in outcome are still observed between black and white women after accounting for stage, socioeconomic status, and age (9-10). Although receptor status is a pivotal prognostic factor in light of treatment and has been found to vary among patients of different age groups, it is not routinely done in most resource constrained countries. Even though some studies in Africa suggest disparities of ER positive tumours between Africans and Caucasians, not enough has been documented about the subject to form the basis of change in the way breast cancer is treated (11,12,13). For example most patients with breast cancer are given tamoxifen routinely under the assumption that the majority are ER positive.

The aim of this study therefore was to determine the ER status and describe the associated clinico-histopathological characteristics among women with breast cancer at a tertiary hospital in Uganda.

Methods

This was a cross sectional descriptive study carried out in the Breast unit of Mulago Hospital from January 2012 - May 2012. Mulago Hospital is a national referral hospital and the teaching hospital for the Makerere University College of Health Sciences, Uganda. About 200 incident cases of breast cancer are received per year from all over the country. All consenting non pregnant women with histologically confirmed breast cancer were included.

An experienced consultant pathologist reviewed all the slides and the tumours were classified according to Nottingham modification of the Scorff Bloom Richardson criteria.

Triple Negative Breast Cancer (TNBC) was defined as all ER, PR and HER2 receptors staining negative. HER2 positives were ER and PR negative and the HER2 positive staining. Luminal A was either ER or PR positive with a negative HER2. Luminal B was either ER positive /negative and or PR positive with a positive HER2. Antibodies used were: ER (clone SP-I), ASR PR (clone Y85), ASR and HER2/neu (c-erbB-2), clone CB-11 (Cell marquee corporation, Rocklin, CA). ER/PR scoring system staining of <5% of tumour cell nuclei was considered negative. Both border line and overtly positive stains were considered positive.

Her2/neu; negative was considered when no staining was observed or membrane staining was <10% of the tumour cells.

We used the quality assurance guidelines of the College of American Pathologists (CAP). The laboratory control tissue had a proven positive slide for each of the antibodies. A section of the positive and negative controls were used at every run of the day. Paraffin block specimens were cut into four sections and mounted on positively charged slides. The slides were paraffinized and rehydrated in xylene followed by graded alcohols, then washed in Tris buffered saline. The immunochemistry assays were performed using an immunostainer with antibodies and antigen unmasking.

Appropriate negative controls for the immuno-staining were prepared by omitting the primary antibody step. The results were scored semi quantitatively using Reiner's four point scale based on intensity and percentage of IHC reaction, HER2 staining were evaluated according to manufacturer's instructions.

Variables collected for the study included; age, duration of symptoms, age at menarche, age at menopause, family history of breast cancer, parity, age at first child birth, lactation history, history contraceptive use, history of benign breast disease, clinical stage of the disease (only T and N), histological type and grade, oestrogen receptor, progesterone receptor and Her2 receptor status. The relationship between the receptor status and the various clinico-pathological factors listed above was determined by sub-analysis.

The data were collected using a structured questionnaire and entered into EpiData computer software version 3.1, and exported to SPSS version 17 for analysis. Frequency tables and cross tabulations were used to summarize the categorical variables. Means and Standard deviations were used to summarize the continuous variables.Odds ratios and P-values were used to test for associations.

Ethical approval was granted by the institutional ethics committee.

Results

A total of 114 women were consecutively enrolled.

Basic characteristics of study participants are shown in Table 1

Table 1: Baseline characteristics of all study participants

Characteristics	Number =114	Percentage %
Age category		
<30	8	7
30-39	23	20
40-49	39	34
50-59	21	18
>60	23	20
Menopausal status at diagnosis		
Pre-menopausal	70	61
Post-menopausal	44	39
Duration of symptoms		
< 6months	23	20
7-12 months	43	38
13-18	20	18
19-24	20	18
>25	8	7
Oral contraceptive use		
Yes	47	41
No	67	59
Family history†		
Cancer breast	25	22
Cancer ovary	1	1
*Other cancers	13	11
Parity		
Nulliparous	7	6
<6	75	66
>6	32	28

*Other cancers included cancer cervix (5) cancer oesophagus (4) hepatocellular cancer (2) cancer colon (2)

†missing values 75

Sixty one per cent (61%) of participants were premenopausal, 80% had duration of symptoms exceeding 6 months and 41% had used contraceptives.

Table 2: Table showing clinical features of all the study participants

Clinical feature	Numbers n=114	Percentage %
Skin ulceration		
Yes	62	54
No	52	46
Lump		
Yes	113	99
No	1	1
Nipple discharge		
Yes	14	12
No	100	88
Clinical- T stage		
T1	3	3
T2-T3	55	48
T4	56	49
Clinical stage		
N0	26	23
N1	48	42
N2-N4	40	35
Histological type		
Invasive ductal carcinoma	98	86
Invasive lobular carcinoma	7	6
Others	9	8
Histological grade		
I	11	10
II	42	37
III	61	54
†Receptor status		
ER+PR-HER2+ (luminal B)	6	5
ER+PR+HER2+ (luminal B)	15	13
ER+PR+HER2- (luminal A)	33	29
ER+PR-HER2- (luminal A)	10	9
ER-PR-HER2- (Triple negative)	23	20
ER-PR-HER2+ (HER2+)	27	24

† Luminal A 43/114 (38%), Luminal B 21/114 (18%), TNBC 23/114 (20%), HER2 27/114 (24%)

T1=< 2cm, T2 = 2-5cm, T3 > 5 cm T4- any size of tumour with skin changes

N1= Mobile axillary nodes N2=Fixed matted axillary nodes N3=Supraclavicular or infraclavicular nodes, N4=Distant nodes

Majority of patients had skin ulceration (54 %), lump (99%) and no nipple discharge (88%).

Most of the patients were of clinical stage -T4 N1. The commonest histological subtype was invasive ductal carcinoma in 86% of the patients.

Other types of breast cancer included Ductal carcinoma in situ, lobular carcinoma in situ medullary carcinoma, Tubular carcinoma, mucinous carcinoma and cribriform carcinoma.

ER negative tumors contributed 44% (50/114), ER+ were 56%, Triple negative tumors were 20% (23/114).

Table 3: Distribution of clinical- histopathological characteristics associated with triple negative breast cancer

Clinico-histopathological Characteristics	Triple negative n=23	%
Patient Age category		
≤50 years	18	78
>50 years	5	22
Menarche		
≤ 12 years	3	13
>12 years	20	87
Menopausal status		
Premenopausal	17	74
Postmenopausal	6	27
Family history of breast Cancer		
yes	9	39
no	14	61
Histology type		
Invasive Ductal carcinoma	22	96
Others	1	4
Grade		
I and II	2	9
III	21	91
T STAGE		
T1-T3	10	44
T4	13	56
N STAGE		
N0/N1/N2	19	83
N3/N4	4	17

Table 4: Association of triple negative breast cancer with patient characteristics

Characteristics	Presence of triple negative N=114		OR 95% (CI)	P-Value
	Positive	Negative		
Patient Age category				
≤50	18	58	2.1	0.187
>50	5	33	(0.7-6.0)	
Menarche				0.139
≤ 12	3	11		
>12	20	80		
Menopausal status				
Premenopausal	17	53	2.0	0.230
Postmenopausal	6	38	(0.7-5.6)	
Oral contraceptive use				
Yes	12	35	1.7	0.246
No	11	56	(0.7-4.4)	
Family history of breast cancer	9	16		0.026
Grade				
I/II	2	51		0.001
III	21	40		
T Stage				
T1-T3	10	48		
T4	13	43		0.423
N stage				
N0/N1/N2	19	83		0.230
N3/N4	4	8		

Discussion

In this study we set out to determine the ER status and describe the clinicopathological characteristics of breast cancer among women presenting at a tertiary hospital in sub-Saharan Africa. ER status established by IHC staining techniques is not routinely done in clinical practice in Uganda due to resource constraints. We found that breast cancer was occurring mostly among young premenopausal women, with T4 tumours and more than half were ER negative similar to what previous accounts from Uganda, Mali and Nigeria (7, 11 -14). We therefore concluded that there was over representation of ER negative tumours. The reasons for this scenario are not clear and ought to be investigated.

Risk Factors

Premenopausal women were the majority (61%) as other various studies in African women have reported (4-7). This in part can be explained by the relatively young population structure in Uganda. Majority (59%) had no prior history of oral contraceptive use which is a risk factor for development of cancer of the breast (15). Few women were nulliparous, women who give birth to ≥ 5 children have half the risk of women who have not given birth (16).

Only 22% had a positive history of breast cancer. A woman's risk of breast cancer is higher if her first degree relative had breast cancer, and the risk becomes significant if at least two close relatives had breast or ovarian cancer and also if the family member got breast cancer before age 40 (17).

A significant proportion (42%) presented more than 12 months after onset of symptom-a reflection of delay in presenting for breast cancer care. The reasons were not elicited in this study. Clearly, most patients presented with locally advanced disease characterized by skin ulceration in (54%), breast masses > 2cm in size (48%) and T4 tumours in (49%) and N1 nodal status among (42%) of participants.

Studies in the region (1,7) show that majority of patients with breast cancer present with locally advanced disease with skin involvement (including ulceration) or chest wall fixation.

We found patients with invasive ductal carcinoma in 86% of the cases and this was followed by lobular carcinoma (6%) other types of breast cancer contributed 8%. Most of these tumours were poorly

differentiated (54%) and this is an indication of the tumour's aggressive nature among these women

Hormonal Status

The most frequent tumour subtype based on IHC was (luminal A) (29%) followed by HER2+ in 24%. TNBC had a prevalence of 20%. This figure is comparable to that in some studies done among African American women though most post higher values (18, 23).

TNBC was mostly found in young women {≤ 50years (78%), premenopausal (74%)}. The odds ratio of having TNBC among women less than 50 years was 2. This was not statistically significant; neither was contraceptive use (OR=1.7, P=0.246).

TNBC presented earlier and at an advanced stage (T ≥ 5cm (87%), nodal involvement (52%) and less than a year of symptomatology in 65%). Over a third (39%) of these patients had a positive family history.

Triple-negative breast cancer, characterized by tumours that do not express oestrogen receptor (ER), progesterone receptor (PR), or HER-2 genes, represent an important clinical challenge because these cancers do not respond to endocrine therapy or other available targeted agents. The metastatic potential in triple-negative breast cancer is similar to that of other breast cancer subtypes, but these tumours are associated with a shorter median time to relapse and death.

The presence of receptors in breast cancer is associated with a good response to hormonal therapy and is also important in predicting likelihood of response to hormonal therapy in metastatic breast cancer (19-22).

In addition HER2 + tumours have a poor prognosis, however drugs like monoclonal antibodies have been able to improve its prognosis significantly.

A number of studies-have suggested that after menopause the rates of ER positive tumours increase with increasing age whereas rate of ER negative tumours do not (17).

Study Limitations

Whereas, this was a single site hospital based study and therefore with limited generalizability, the results are consistent with the emerging picture of breast cancer patterns among African women with breast cancer. This evidence adds the data that characterizes breast cancer disease in the African woman. The duration of onset of symptoms is subject to recall bias and may not reflect when the tumour truly started however, it gives some sense of how long it takes to present to where appropriate care is

Conclusion

Breast cancer is common among young African premenopausal women, it presents mostly as T4 tumours and close to half are ER negative. This is an over representation of ER negative tumours.

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