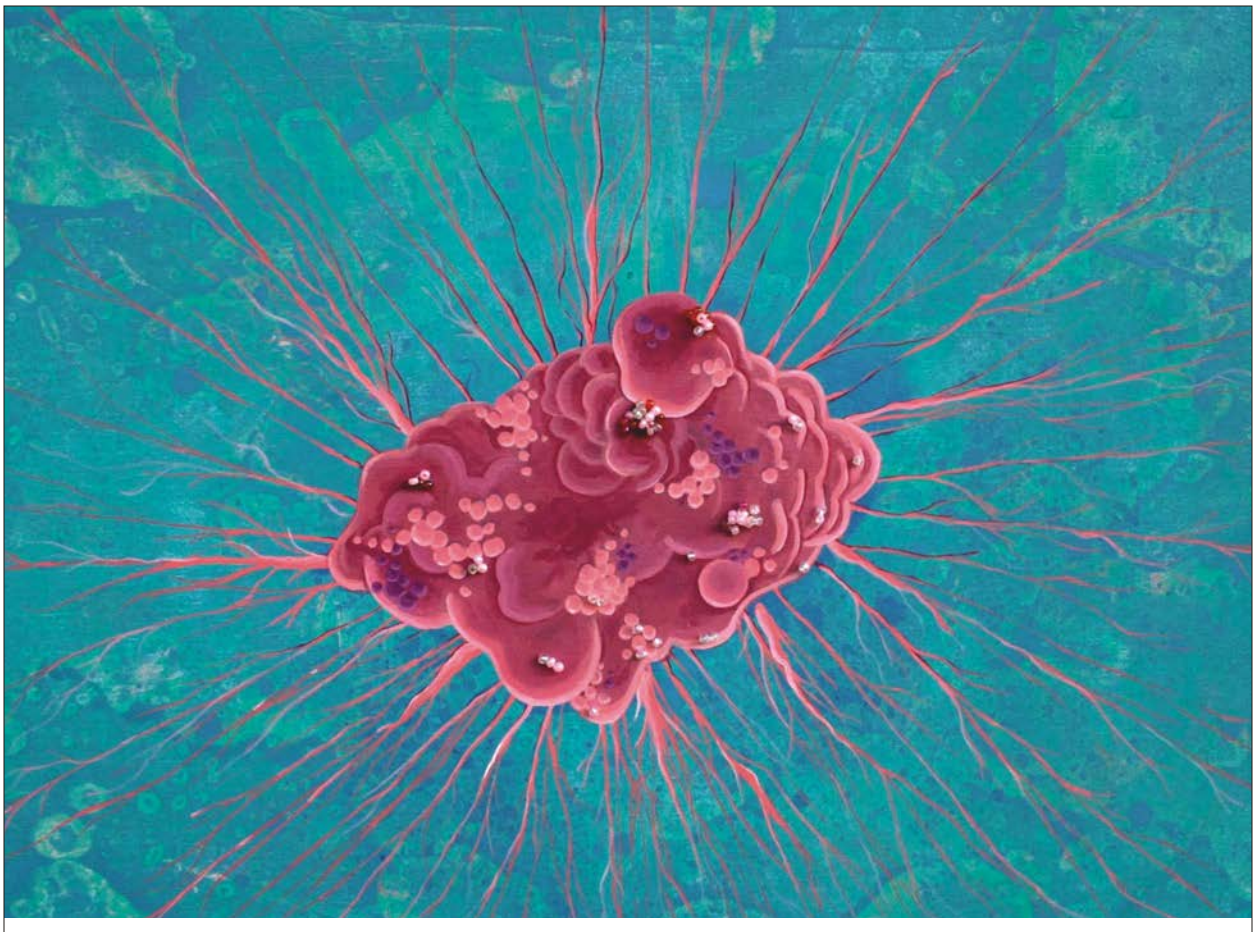

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Clinicopathologic Features of Female Breast Cancer in Kumasi, Ghana

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Abstract: The aim of this study is to investigate the clinicopathologic features of breast cancers in African women. The incidence of breast carcinoma is increasing in the African countries. It is presumed that the cancer is more aggressive and occurs in younger age, similar to that seen in the African-American (AA) women in US. In this study, twenty-one consecutive breast carcinoma specimens received in Komofo Anokye Teaching Hospital (KATH) in Kumasi, Ghana during a two-month period and compared the clinicopathological and immunohistochemical features with Caucasian (White) and African American (AA) women as described in the literature. It is found that approximately 35.2% (24 out of 68) of the presenting palpable breast masses to be malignant. There is a preponderance of the usual ductal type (23 out of 24, 95.8%), mostly (90%) showing high grade (2 and 3). Fifty five percent of patients had axillary metastasis, 33% showed skin involvement and 16% had chest wall invasion. The mean tumor size was 4.6 cm and the mean age of patients was 42 years (median age 47.5 years). Immunohistochemical profiles of 8 cases showed majority (5 out of 8) with triple (ER, PR, HER-2) negative pattern, but did not show the basal phenotype. Basal cytokeratin 5/6 was negative in 7 out of 8 cases and both EGFR and HER-2 were negative in all cases. The tumors showed higher rate of p53 mutation. In summary, the carcinomas in African women occurred in younger age and were of higher grade and stage. Majority were triple negative, ductal type but not of luminal or basal cell types. These findings are different from the Caucasian Americans but somewhat similar to the African Americans.

Key words: Breast, cancer, Ghana, Africa, histology, immunopathology, African-American

INTRODUCTION

Carcinoma of breast is the second most common cancer in African women (Mbonde *et al*., 1998). Although, it is not as prevalent as in the western developed countries, the incidence rate of breast cancer is increasing in Africa, with aggressive behavior and appearance at younger age than that seen in the developed countries (Mbonde *et al*., 1998; Wabinga *et al*., 1993). Age adjusted incidence rates are quite variable throughout the continent. In Western Africa the incidence rate is 24.8 per 100,000 population (Fregene and Newman, 2005). Early age at childbirth and prolonged breastfeeding do not seem to provide the protection as seen in the white women. Similar trend is also seen in the breast cancers affecting African American (AA) women who have ethnic roots in the western African countries.

To date, few studies have compared the pathologic and immunohistologic features of these cancers in African and African-American women.

Ghana is situated along West Africa, coastline and was one of the primary sources of slave trade to the America from 16th to 18th century A.D (Fregene and Newman, 2005). Kumasi is Ghanas second largest city, situated inland, in Ashanti tribal region, North from the coastal capital Accra. The 1000 bed Komofo Anokye Teaching Hospital (KATH) is the main hospital in town and draws patients from the entire Northern half of the country. In spite of the high volume, there is no cancer registry and appropriate pathologic examination is absent in many cases due to lack of adequate resources. Cervix, prostate and breast cancer are the three most commonly diagnosed malignancies in daily practice. Most patients with breast cancers present in advanced stage with large, palpable breast masses (Bewtra, 2009). The pathologic features of the breast cancers in African women are described in literature but prognostic markers by immunostains are mostly unavailable.

The My objective was to study the histologic and immunohistologic features of these tumors and compare them with those seen in white and AA women as quoted in literature.

MATERIALS AND METHODS

Sixty eight consecutive breast specimens (including needle biopsies, excisions and mastectomies) obtained in one month of July, 2007 were examined. Benign fibroadenomas were found to be the commonest lesion, making up 45.5% (31 out of 68) of all the cases. Twenty four cases were malignant (35.2%). The remaining 13 cases (9.3%) were fibrocystic changes, breast abscesses and other miscellaneous benign lesions.

These 24 consecutive malignant cases, obtained in one month, constitute the basis of this study. Criteria for selection included availability of all the clinicopathologic data needed for the study. Complete gross and microscopic pathologic examination with routine H and E stains and light microscopy were performed on each case. The following clinicopathologic factors were noted. The patients ages, gross size of the tumors, histological types and grades, evidence of lymph node and other extramammary involvements. Permissions were granted for 8 cases to be further evaluated in USA (Creighton University Medical Center). Criteria for selection of these 8 cases included availability of the tissue blocks, adequate amount of properly fixed tissue and permission from the Pathology laboratory. Tissue immunoperoxidase stains for estrogen (ER), progesterone (PR) and androgen (AR) receptors, c-erb2 oncogene (HER2), basal cytokeratin 5/6, epidermal growth factor receptor (EGFR or HER1), p53 mutation and e-cadherin (E-CAD) molecules were performed on these cases. The immunostaining was graded semi quantitatively from 0 to 4. (0: completely negative; 1: Weak, focal positive; 2: Weak, diffuse positive; 3: Strong focal positive; 4: Strong, diffuse positive). Commercially prepared antigens and reagents were used. Appropriate positive and negative controls were included.

Authorization was obtained from the Pathology Department to study the above cases and conduct immunostains. In all cases, identifying names and accession numbers were obliterated to protect anonymity and privacy of the patients.

RESULTS

The mean age at initial diagnosis of cancer was 42 years (range 25-92) and median age was 47.5 years. 29% (7 out of 24) of the patients were at or below age 44.

The mean tumor size was 4.6 cm. 23 out of 24 cases were Infiltrating Ductal Carcinoma (IDS), usual type. Two cases showed areas of comedo pattern, one case each showed mucinous and squamous foci as minor components. One case had Pagets disease of the

Table 1: Immunoperoxidase staining of breast carcinomas

Case No.	ER	PR	HER-2NEU	AR	CK5/6	EGFR	p53	E-cad
8	--	--	--	--	--	--	1+	2+
12	--	--	--	3+	--	--	3+	3+
14	--	--	--	1+	--	--	3+	3+_
15	--	--	--	--	--	--	2+	2+
16	4+	2+	--	2+	--	--	--/+	3+
22	2+	2+	--	2+	--	--	1+	2+
23	--	--	--	--	2+	--	1+	3+
24	--	--	--	3+	--	--	--/+	2+

+ Positive stain graded semi-quantitatively 1-4

nipple and one case had inflammatory type skin involvement. There was only one case of lobular carcinoma. The histologic grading of the 23 IDS cases showed only 2 cases (8.6%) of grade 1 tumors. Ten cases (43.4%) were grade II and 11 cases (47%) were grade III.

Most of the tumors presented in advanced stages. Out of 18 cases with clinical information available, only one case (5.5%) was lymph node negative, localized in breast only (stage I). Ten (55%) had axillary involvement, 6 cases (33%) had skin involvement and 3 (16%) showed chest wall invasion. One case had pleural involvement and two cases had bilateral breast involvements.

Table 1 shows the immunoperoxidase staining results of the 8 selected cases. Six out of 8 cases (75%) were Triple Negative (negative ER, PR and HER2). None of the cases stained positive for HER2 or HER1 (EGFR). However, the triple negative cases were mostly (5 out of 6) basal cytokeratin (CK) 5/6 negative also. Thus they were not of basal phenotype (triple negative, CK5/6 and EGFR positive). All cases were variably positive for p53 mutation and E-CAD, confirming ductal phenotype. Androgen Receptor (AR), also was found in basal type tumors, was positive in 5 out of 8 (62%) cases.

Table 2 compares the above data with those found in the literature for Caucasian and AA women (Ries *et al*., 2002; Middleton *et al*., 2003; Hassan *et al*., 1999; Kovi *et al*., 1989; Elmore *et al*., 1998; Isola *et al*., 2005; Rakha *et al*., 2007; Morris *et al*., 2007; Oka *et al*., 1993; Carey *et al*., 2006). Prevalence of malignancy in palpable breast lump was 41.8% in my series, compared to 37% in AA women (Kovi *et al*., 1989) and 51.8% (Howat *et al*., 2007) in white women.

Mean age of the patients at initial diagnosis showed a racial trend of significant decrease from white women (61 years) (Ries *et al*., 2002) to AA women (57 years) (Middleton *et al*., 2003) to African women in my series (42 years). Concomitant increase was found in the proportion of younger women (below 54 and 44 years) in my series, with AA women falling in the middle of white and African women as depicted in Table 2.

The tumors appeared more aggressive (higher grade and stage, larger size) in the African women compared to the whites. This may be due to innate nature of the tumors or lack of screening and early detection in the AA and African groups. IDS appears to be the predominant histologic type in all 3 groups. Similar findings were noted in other studies on African women (Mbonde *et al*., 1998). An excess of medullary carcinoma seen by one study (Middleton *et al*., 2003) was not noted in my series.

The immunomarker findings showed the tumors in African women to be much less positive with ER, PR and HER2 and much more positive with p53 and E-CAD, compared to the white women (Isola *et al*., 2005; Rakha *et al*., 2007; Morris *et al*., 2007; Oka *et al*., 1993; Carey *et al*., 2006; Amend *et al*., 2006; Klijn *et al*., 1992). Prevalence of triple negative tumor is considerably higher in my series of African women (75 vs. 16.3%) than whites with AA women showing intermediate numbers (Bauer *et al*., 2007).

Table 2: Comparison of breast carcinomas in different races

Features	General population (Caucasian/American)	African-American	African (Sub Sahara, West) (cb*)
Prevalence (in palpable breast masses) %	51.8 (Kovi *et al*., 1989)	30 (Kovi *et al*., 1989)	35.2
Mean age (year)	61, Range 26-89 years (Ries *et al*., 2002)	50 Range 31-90 year (Elmore *et al*., 1998)	42 (25-92)
Median age (year)	64 (Ries *et al*., 2002; Middleton *et al*., 2003)	57 (Middleton *et al*., 2003)	47.5
% cases at or below 54 years	53 (Middleton *et al*., 2003)	68 (Middleton *et al*., 2003)	62
% Cases at or below 44 years	12 (Ries *et al*., 2002)	--	29
Tumor<2cm	3.4 (Elmore *et al*., 1998)	6.8	0
Tumor=/>2cm	47	65 (Elmore *et al*., 1998)	100
Invasive Ductal (usual) carcinoma %	82 (Ries *et al*., 2002)	77 (Ries *et al*., 2002)	87.5
Special tumor type %	2.7 medullary (Middleton *et al*., 2003)	6.8 medullary	0
Grades 3 (%)	41 (Ries *et al*., 2002)	57 (Amend *et al*., 2006)	47.8
PR+(%)	68 (Ries *et al*., 2002)	54 (Amend *et al*., 2006)	25
ER+(%)	77 (Ries *et al*., 2002)	61(Amend *et al*., 2006)	25
Androgen receptor AR+	79% (Isola *et al*., 2005)	--	62.5%
HER-1 (EGFR)+(%)	48 (Klijn *et al*., 1992)	--	0
HER-2+(%)	30 (Ries *et al*., 2002)	30 (Amend *et al*., 2006)	0
Basal Cyto-Keratin+(%)	9 (Rakha *et al*., 2007)	--	12.5
P53 mutation+ (%)	19.4 (Morris *et al*., 2007)	13.1 (Morris *et al*., 2007)	87.5
E-cadherin positive %	47 (Oka *et al*., 1993)	--	100
Triple negative phenotype %	10.8 (Rakha *et al*., 2007; Bauer *et al*., 2007)	24.6 (Carey *et al*., 2006)	75
Basal-like subtype % (ER-,PR-,HER2-.CK+)	15-16 (Carey *et al*., 2006; Tischkowitz *et al*., 2007)	26.5 (Carey *et al*., 2006)	12.5
Luminal A subtype % (ER+,PR+,HER2-)	81 (Carey *et al*., 2006)	47 (Carey *et al*., 2006)	25
Luminal B subtype % (ER+,PR+,HER2+)	17 (Carey *et al*., 2006)	25 (Carey *et al*., 2006)	0

References in Parenthesis

The recently described immunosubtypes of breast cancers into Luminal A and Luminal B also shows decreasing numbers from white women to AA and Africans. However the basal subtype shows more variability. 12.5% in my series is similar to the whites (Tischkowski *et al*., 2007) but less than AA women (Carey *et al*., 2006).

DISCUSSION

In United States and other developed countries, breast cancer is the commonest malignancy in women (Ries *et al*., 2002). Age adjusted detection rate in these countries average 95-100/100,000. In Africa, comparable values are much lower. Some study (Fregene and Newman, 2005) quotes a detection rate of 24.8/100,000. Yet other studies (Mbonde *et al*., 1998; Wabinga *et al*., 1993) show a rise in breast cancer rates in sub Saharan African countries up to twice the rate seen a few decades ago. It is noticed that breast cancer to be second only to cervix cancer in the women in Ghana. This may appear unusual, as the African women do not share the usual risk factors of breast cancer. Unlike their counterparts in western countries, the women in sub Saharan Africa tend to have late menarche, early and multiple childbirths and prolonged lactation periods. The reason for recent increase in breast cancer remains unknown.

Previous reports (Fregene and Newman, 2005) have described some notable features of breast cancers in Africa, which are confirmed in my series. The mean presenting age in my series is 42 years, markedly low compared to 61 years in the American women as published

by the SEER data (Ries *et al*., 2002). The breast cancer in African women also appears more aggressive, i.e., present as a larger mass with higher grade and extramammary spread. This may partly be the result of late diagnosis due to lack of availability and access to adequate medical care and poor socioeconomic and educational status of the women in these countries. However other innate genetic factors involving the tumor biology cannot be ruled out.

Relatively little data are available regarding the hormone receptors and other immunomarkers of breast carcinomas in African women. My series is small but it shows some notable differences from the tumors in American women as published in the literature cited previously.

The more aggressive triple negative phenotype (ER, PR and HER2 negative) occurs more frequently (73%) in African women than the white American (16.3%) women (Rakha *et al*., 2007). The African tumors appear to be more often p53 and E-CAD positive (87.5 and 100%, respectively) compared to the American counterparts (23.1 and 47%) (Morris *et al*., 2007; Oka *et al*., 1993). Also, none of the tumors in my series were positive for the amplification of the HER oncogene group (EGFR and HER2), whereas these were found in 48 and 30% of American women respectively (Klijn *et al*., 1992). Significance of these findings needs further studies with larger groups of patients. However ER/PR negative tumors are usually more aggressive and this may explain some of the clinical findings of the breast caners in African women.

African-American (AA) women in the United States share genetic roots with the women in the western sub-Saharan countries like Ghana, which were the original source of the infamous slave trade to the Americas. Thus it is not surprising that the breast cancers in AA women would differ from the white women and resemble the tumors seen in the African women.

Compared to the cancers in white women, several studies describe breast cancers of the AA women to show lower incidence (Carey *et al*., 2006), lower prevalence of malignancy in palpable breast mases (Kovi *et al*., 1989), lower presenting age, more aggressive, larger in size, more poorly differentiated and more often ER/PR negative (Elmore *et al*., 1998; Amend *et al*., 2006). Some researchers (Weiss *et al*., 1995) dispute these data by showing no significant differences in ER, PR, HER-2 and EGFR values and explain the higher stage and grade in AA women due to late diagnosis because of poor access to medical care. They also mention obesity as one of the possible contributing factor. However, most studies favor true racial differences in the tumors. The Carolina breast cancer study (Carey *et al*., 2006) summarizes these findings very well.

Interestingly, the findings of the AA women fall in between those of the white women and the women in Africa (Table 2). The prevalence rate, mean age, tumor size and ER/PR negativity are all in between the comparative numbers in the white and the African patients. The Triple Negative tumors that are considered more aggressive are found more commonly in AA and African women. However, unlike both the white and AA women, the tumors in African women were more often HER-2 and EGFR negative. Recently described three immunophenotypes (Carey *et al*., 2006) of breast carcinomas (basal, luminalA and B) also showed different rates in the three populations. Recent studies have also reported significant inter-ethnic differences in prevalence of BRCA1 and 2 mutations in women of Western-European and African ancestry (Hall *et al*., 2009; Olopade *et al*., 2002). So, far, relatively few AA or African women have been systemically studied for these genetic mutations. The psychosocial implications of such studies are not known.

There are some deficiencies in present study. The number of patients in my series is too small for any statistical analysis. Also, due to logistical reasons appropriate data, I could not

obtain regarding family cancer history, childbearing and menstrual histories, hormonal usage, obesity, response to treatment and overall follow up and survival data. Additionally, no genetic analysis was performed on the African women regarding the BRCA 1 and 2 mutation analysis. Recently, some researchers (Gukas *et al*., 2009) have noted an excess of BRCA-1 mutation young AA women with breast carcinoma. Lastly, race and ethnicity are politically and emotionally charged words with little scientific validation. The division of African-Americans from whites (non AA) is poorly defined in terms of genetic and biologic differences. Additionally, the women of Africa too are of heterogenous groups with possible significant genetic differences. Majority of women in the Kumasi region belong to the Ashanti tribe, but many other tribes coexist in the community. Tribal, ethnic and racial factors may have complex interplay with genetic and environmental risk factors of breast carcinoma (Gukas *et al*., 2009). More culturally sensitive studies are needed to clarify these issues.

CONCLUSION

This study is a preliminary study describing the clinicopathologic features of breast carcinoma in the women in sub-Saharan Western African country of Ghana. Contrary to the expectations, the breast cancer rate is rising in these countries and breast cancer in the second most common cancer in women in Africa. Compared to the breast cancers seen in white women in the western developed countries, the tumors in Africa seem to occur in younger age, higher histologic grade and are more often triple negative, non-basal immunophenotype with high p53 mutation rate. The comparative findings in the African American women are in between these two populations. As a preliminary study, the number of cases in this study is quite small. Further studies with larger number of patients are needed to draw definitive conclusions.

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