Original Article

Clinicohistologic Characteristics of
Breast Cancer in Ghanaian Patients

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ABSTRACT

Background: Breast cancer is the leading cause of cancer morbidity and mortality worldwide. The management and prognosis of breast cancer depend heavily on the different histologic and molecular biologic features of the tumour. The different histologic types describe the distinct growth patterns and cytological features of the tumour.

Methodology: This is a retrospective study of archival breast cancer excision and mastectomy specimen at KBTH from 2012-2016. 729 cases were retrieved over the period and examined by two pathologists independently. Demography of the cases, tumour size, grade, histologic type, stage, mitosis, site of lesion etc. were entered into SPSS and analysed with chi-square done with P-value set at $P < 0.05$.

Results and Conclusion: The mean age of presentation is 52.45 ± 12.75 years. The commonest histologic type of breast cancer is invasive carcinoma (NOS) forming (87%). Only 1.2% of male presented with breast cancer with the other percentage in females. Most (88%) of the tumours were greater than 5cm at the time of surgery. The tumours are of high grade (II and III) forming 88%. Seventy-eight percent of cases presented with late stage of the disease ($\geq$ stage IIB). There was association between histologic type and vascular invasion ($P < 0.000$) and lymph node involvement ($P = 0.010$). Moreover, tumour size showed an association with tumour grade ($P < 0.05$).

This study has shown that breast cancer among Ghanaian patients has a worse histologic type with poor tumour characteristics giving it poor prognosis.

Keywords: Breast Cancer, Invasive Carcinoma

Introduction

Breast cancer is the leading cause of cancer morbidity and mortality worldwide. The management and prognosis of breast cancer depend heavily on the different histologic type and molecular biologic features of the tumour [1] . The different histologic type of breast cancer and its variant has already been established[2]. The histological types describe the distinct growth patterns and cytological features of the tumour. They comprise different epidemiology, clinical and prognosis. Breast cancer can broadly be classified as in-situ carcinoma and invasive carcinoma. The in-situ carcinoma is the preinvasive carcinomas they grow from the terminal ductal-lobular normal cells and are therefore referred to as lobular carcinoma in-situ and ductal carcinoma in-situ[3]. Like the premalignant class, the invasive carcinomas fall under the invasive ductal carcinoma and lobular carcinoma broadly. Within these broad categorizations are different variants. Breast cancer can be categorized under 21 different histological categories based on architecture patterns, cell morphology and growth as per WHO classification[2, 4, 5]. Invasive carcinoma no special type (NST) has over the period been known to be the commonest breast cancer.

The features are varying to fit in any of the special types. The special type of breast cancer which comprises of classical lobular and invasive carcinoma forms about 25% of all breast cancer[4, 6]. These varying classifications have prognostic value [4, 6].

Systemic therapy has been determined to be effective in patients with early-stage breast cancer, the three main determining factors are lymph nodes status, tumour size and histologic grade as having been used in routine practice[1].

The Nottingham grading system which is a modification if Bloom Richardson grading system is recognised by most international professional bodies in grading of breast cancer is prognostically relevance was demonstrated in the early part of 1991[1, 5, 7] and has also been validated by multiple independent studies. NGS has been combined with lymph node stage and tumour size to form the prognostic index due to the fact that NGS has independent and equally powerful prognostic value. These prognostic indices are referred to as Nottingham Prognostic Index, NPI [1, 8].

The histological grading is the means of identifying the extent of differentiation of a tumour. Although its well

known that the histological type of a tumour has prognostic value, most tumours are invasive carcinoma no special type [1, 8]. The semi-quantitative approach of determining morphological differentiation of a tumour is quite simple and depends on an examination of haematoxylin and eosin stained slide by a well-trained pathologist. This is based on three morphological features; a) degree of tubule or glandular formation, b) nuclear pleomorphism, c) mitotic count [1, 9].

Several independent studies have shown that the prognostic value of histological grading is equivalent to lymph node involvement and higher than tumour size

Materials and Methods

Study area: The source of the data was from the Department of Pathology Korle-Bu Teaching Hospital which is the premier and largest teaching hospital in Ghana. It is located in Ghana's capital city, Accra and receives cases from all over the country especially the southern half of Ghana.

Data Collection: This was a retrospective study of archival tissue blocks and slides of breast cancer cases from the Department of Pathology, KBTH. All excision specimen including wide local excision and mastectomy specimen blocks and haematoxylin and eosin stained slides between the periods 2012 to 2016 were retrieved. The request forms were also retrieved for these cases. Demography such as age, sex, site of lesion, the location of the tumour in the breast and size of the tumour were retrieved from the request forms.

New slides were prepared for broken and faded slides from the formalin fixed paraffin embedded blocks. New slides were stained with haematoxylin and eosin stain.

Each case was examined by two independent pathologists. Discordant cases were reviewed by a third pathologist and in some case a fourth pathologist. The pathologists were given strict guidelines as to the histological type, grading, staging and margins of tumours.

Histological Type: Each pathologist was given strict guidelines as pertain to WHO breast cancer classification guidelines. The cases were classified using the WHO breast cancer typing.

Histological Grading: The tumour was graded using the Nottingham grading system which is a modification of the Bloom-Richardson grading system. This grading system is based on three parameters; Tubule or glandular formation, Pleomorphism of the tumour cells, Mitotic figures present the tumour. The field diameter of the microscope used in assessing the mitotic figure was 0.59.

Staging : The staging was done using revised American joint committee on Cancer (AJCC) 8th edition recommended

TNM staging criteria with T representing tumour size, N lymph node involvement and M as distant metastasis.

Data Analysis: The data were entered into SPSS version 22.0 and analysis were done. Descriptive statistics were done for the parameters with tables, graphs and figures drawn. Univariate and multivariate analysis was done for some of the parameters using a Pearson correlation at 95% confidence intervals.

Results

From **table 2.1**. A total number of 726 age of cases were retrieved over the five year period (2012-2016) with a mean and SD of 52.45±12.75. Of the age of cases, the number of lymph nodes retrieved and involved in the study was 520 for each with a mean and standard deviation of 10.79±5.36 and 3.83±4.74

With regards to the age group of cases **(table 2.2)** with breast cancer, participants from 50-59years recorded the highest frequency (218) representing 30% of the participants whereas participants <20 had the least frequency (4) representing 0.6%

From **table 2.3**, males represented 1.2% while females represented 98% of the participants. Patients who have undergone mastectomy were 68% while those with excision were 32%. Tumours located at the right recorded the highest (49.7%) of laterality of tumour location and tumours with solitary were 94%. However, tumour with size >5 had 88.6% with grade II tumour recording 54.9%. With regards to the margin of excision, the complete excision was 80%.the mitotic figures of tumour <10 were 47.6% and tumours located within the outer quadrant of the breast was 57%.

Table 2.4 shows distribution on the various histological subtypes. Among these various histological subtypes, invasive ductal carcinoma (NOS) had the highest frequency (640) with a mean age and standard deviation of 52.67±12.73 yearsfollowed by DCIS with a frequency of (19) with mean±SD of 46.63±10.39 and invasive lobular carcinoma (17) with mean±SD of 52.76±12.24

From **table 2.5**, out of 640 samples with Invasive Ductal carcinoma (NOS), 635 were females and 5 were males. However, there was a significant association between gender and invasive ductal carcinoma since p-value = 0.004. Furthermore, there was no male recorded with Invasive ductal carcinoma (Papillary) although a frequency of one female was recorded. There was however a significant association between gender and Invasive ductal carcinoma (Papillary) since p value<0.05. There was no significant association between other histological subtypes and gender.

From **table 2.6**, a cross-tabulation between histological types and age group indicated that the histological type Invasive Ductal carcinoma (NOS) recorded the highest (638) with age≥50 being the age group with predominant(371) Invasive Ductal carcinoma (NOS). There was a significant association between age group and histological subtype Malignant phyllodes with a p-value = 0.004 while there was no significant association between the other histological subtypes and age.

Table 2.7 shows the staging of tumours using the Tnm Staging Method. The peak stage case was was 28% of stage IIIA tumours, followed by 20.5% Stage IIB tumours, 17.1%Stage IIIB, 12.6%Stage IIA, 11.8%Stage IIIC, 5.9%Stage 1, 3.4%Stage II and 0.5% stage O tumours respectively.

A univariate analysis was done on various histological features as seen in **table 2.8.** The Pearson product moment correlation coefficient (r) between the size of tumor and tumor grade, tumor stage, and vascular invasive was recorded as, (r= 0.096, p= 0.029), (r=0.086, p= 0.039) and (r= -0.086, p=0.039) respectively.

Further, a correlation coefficient of less than 0.5 (r<0.5) was documented for the analysis between tumor grade and tumor stage (r=0.153, p=0.05) and tumor grade vs number of lymph nodes involved (r=0.133, p= 0.10). From **table 2.8b** above shows the test of between-subjects effects and it indicates there was significance between staging and the following:tumour grade,size of tumour,vascular invasive and number of LN involved with p value of 0.002,0.002,0.000,0.000 respectively.

Table 2.1: Descriptive Statistics of The Cases.

Variable	frequency(N)	Minimum	maximum	Mean±SD
Age of Cases	726	14	104	52.45±12.75
Number of LN retrieved	520	1	42.00	10.79±5.36
Number of LN involved	520	.00	42.00	3.8305±4.74

Table 2.2: Age Groupings of Cases with Breast Cancer.

Age Group	Frequency	Percent (%)
<20	4	.6
20-29	17	2.3
30-39	94	12.9
40-49	193	26.6
50-59	218	30.0
60-69	132	18.2
70-79	50	6.9
≥80	18	2.5
Total	**726**	**100.0**

Table 2.3: Breast Cancer Distributions with Various Clinicopathologic Features.

Sex Distribution Of Cases				
	Males	**Females**	**Total**	
Percent (%)	1.2	98.8	100	
Type Of Surgery Undergone				
	Excision	Mastectomy	Total	
Percent(%)	32	68	100	
Laterality of Tumour Location				
	Right	Left	Bilateral	Total
Percent(%)	49.7	49	1.3	100
Multiplicity of Tumor				
	Solitary	Multiple	Total	
Percent(%)	94	6	100	

Tumour Size Range			
	≤2	≥2 - ≤5	>5	Total
Percent(%)	2.2	9.2	88.6	100
Grade of Tumour			
	I	II	III	Total
Percent(%)	11.8	54.9	33.3	100
Margins of Excision With or Without Tumour			
	Complete Excision	Incomplete excision	Total	
Percent(%)	80	20	100	
Mitotic Figures Per Tumour			
	<10	11 – 20	>20	Total
Frequency	188	121	86	395
Percent(%)	47.6	30.6	21.8	100
Tumour Locations Within the Breast			
	Outer Quadrant	Inner Quadrant	Central	Total
Percent(%)	57	44.4	18.6	100

Table 2.4: Histological Subtypes of Tumour with Their Frequencies and Mean Age of Each Type.

Histological type	Frequency	Percent	Mean
Invasive Ductal carcinoma (NOS)	640	87.8	52.67±12.73
Invasive mucinous carcinoma (colloid carcinoma)	17	2.3	56.35±15.01
Invasive Papillary carcinoma	1	0.1	59
invasive lobular carcinoma	17	2.3	52.76±12.24
Medullary carcinoma	9	1.2	51.33±15.75
Intraductal papillary carcinoma	7	1.0	63.00±5.94
spindle cell carcinoma	1	0.1	56.00
DCIS	19	2.6	46.63±10.393
Invasive Adenoid cystic carcinoma	1	0.1	51.00
Malignant phyllodes	7	1.0	35±11.045
Comedo carcinoma	1	0.1	43
Squamous Cell Carcinoma	1	0.1	44
Mixed Lobular and Ductal carcinoma	2	0.3	44±4.243
Lymphocytic Lymphoma	1	0.1	47
Malignant myoepithelioma	1	0.1	14
Metaplastic Carcinoma (spindle cell)	1	0.1	35
Invasive cribriform carcinoma	1	0.1	51
NHL follicular small cleaved cell	1	0.1	61
Invasive ductal carcinoma (mucinous + NOS)	1	0.1	63
Total	**729**	**100.0**	

Table 2.5: Association Between Gender Differences and Histological Subtypes of Tumours.

Histologic Type and Gender				P-Value
Histologic type		Sex	Total	
	Male (%)	Female (%)		
Invasive Ductal carcinoma (NOS)	5(0.8)	635(99.2)	640	0.004*
Invasive ductal carcinoma (mucinous)	0(0.0)	17(100.0)	17	0.662
Invasive ductal carcinoma (Papillary)	0(0.0)	1(100.0)	1	0.000*
invasive lobular carcinoma	0(0.0)	17(100.0)	17	0.662
Medullary carcinoma	0(0.0)	9(100.0)	9	0.736
Intraductal papillary carcinoma	2(28.6)	5(71.4)	7	0.823
spindle cell carcinoma	0(0.0)	1(100.0)	1	0.911
DCIS	1(5.3)	18(94.7)	19	0.093
Invasive Adenoid cystic carcinoma	0(0.0)	1(100.0)	1	0.911
Malignant phyllodes	0(0.0)	7(100.0)	7	0.784
comedo carcinoma	0(0.0)	1(100.0)	1	0.911
Squamous Cell Carcinoma	0(0.0)	1(100.0)	1	0.911
Mixed Lobular and Ductal carcinoma	0(0.0)	2(100.0)	2	0.875
Lymphocytic Lymphoma	0(0.0)	1(100.0)	1	0.911
Malignant myoepithelioma	0(0.0)	1(100.0)	1	0.911
Metaplastic Carcinoma (spindle cell)	0(0.0)	1(100.0)	1	0.911
Invasive cribriform carcinoma	0(0.0)	1(100.0)	1	0.911
NHL follicular small cleaved cell	1(100.0)	0(0.0)	1	0.911
Invasive ductal carcinoma (mucinous + NOS)	0(0.0)	1(100.0)	1	0.911
Total	9(1.2)	720(98.8)	729	

Table 2.6: Histological Subtypes of Tumour Between <50Year And ≥50 Years.

Histologic type * Age group Crosstabulation				
Count				P-Value
Histologic type	Age group		Total	
	<50(%)	≥50(%)		
Invasive Ductal carcinoma (NOS)	267(41.8)	371(58.2)	638	0.083
Invasive ductal carcinoma (mucinous)	6(35.3)	11(64.7)	17	0.479
invasive lobular carcinoma	7(41.2)	10(58.8)	17	0.857
Medullary carcinoma	3(33.3)	6(66.7)	9	0.585
Intraductal papillary carcinoma	0(0.0)	7(100.0)	7	0.086
spindle cell carcinoma	0(0.0)	1(100.0)	1	0.911
DCIS	11(57.9)	8(42.1)	19	0.249
Invasive Adenoid cystic carcinoma	0(0.0)	1(100.0)	1	0.392
Malignant phyllodes	6(85.7)	1(14.3)	7	0.004*
comedo carcinoma	1(100.0)	0(0.0)	1	0.911
Squamous Cell Carcinoma	1(100.0)	0(0.0)	1	0.911
Mixed Lobular and Ductal carcinoma	2(100.0)	0(0.0)	2	0.188
Lymphocytic Lymphoma	1(100.0)	0(0.0)	1	0.911

Histologic type * Age group Crosstabulation				P-Value
Count				
Histologic type	Age group		Total	
	<50(%)	≥50(%)		
Malignant myoepithelioma	1(100.0)	0(0.0)	1	0.911
Metaplastic Carcinoma (spindle cell)	1(100.0)	0(0.0)	1	0.911
Invasive cribriform carcinoma	0(0.0)	1(100.0)	1	0.911
NHL follicular small cleaved cell	0(0.0)	1(100.0)	1	0.911
Invasive ductal carcinoma (mucinous + NOS)	0(0.0)	1(100.0)	1	0.911
Total	**307(42.3)**	**419(57.7)**	**726**	

Table 2.7: Staging of Tumour Using TNM Staging Method.

Tumour Stage	Frequency	Percent	Stages
Tis	2	0.5	**0.5%** Stage 0
T1N0Mx	25	5.7	**5.9%** Stage 1
R1N0Mx	1	0.2	
T1N1Mx	15	3.4	**3.4%** Stage II
T2N0Mx	45	10.3	**12.6%** Stage IIA
R1N1Mx	7	1.6	
R2N0Mx	3	0.7	
T2N1Mx	56	12.8	**20.5%** Stage IIB
T3N0Mx	30	6.8	
R2N1Mx	4	0.9	
T1N2Mx	7	1.6	28.3% Stage IIIA
T2N2Mx	37	8.4	
T3N1Mx	36	8.2	
T3N2Mx	42	9.6	
R1N2Mx	2	0.5	
T4N0Mx	11	2.5	**17.1%** Stage IIIB
T4N1Mx	30	6.8	
T4N2Mx	32	7.3	
T4NxMx	2	0.5	
T3N3Mx	22	5	**11.8%** Stage IIIC
T4N3Mx	16	3.6	
T2N3Mx	11	2.5	
R2N3Mx	3	0.7	
Total	**439**	**100**	

TABLE 2.8 Univariate Analysis of Histologic Features against Each Other.

		Size of Tumour	Tumour Grade	Tumour Stage	Vascular invasive	Number of LN involved	Histologic type
		Correlations					
Size of Tumour	Pearson Correlation	1	.096	.154	-.086	.073	-.066
	Sig. (2-tailed)		.029	.001	.039	095	.078
Tumour Grade	Pearson Correlation	096	1	.153	-.059	.133	-.060
	Sig. (2-tailed)	029		005	.226	.010	.168
Tumour Stage	Pearson Correlation	.154	.153	1	-.312	.389	-.061
	Sig. (2-tailed	001	.005		.000	.000	.202
Vascular invasive	Pearson Correlation	-.086	-.059	-.312	1	-.495	.164
	Sig. (2-tailed	039	.226	.000		.000	.000
Number of LN involved	Pearson Correlation	.073	.133	.389	-.495	1	-.112
	Sig. (2-tailed	095	.010	.000	.000		.010
Histologic type	Pearson Correlation	-.066	-.060	-.061	.164	-.112	1
	Sig. (2-tailed	078	.168	.202	.000	.010	

Table 2.8 b: Tests of Between-Subjects Effects.

Variable	Mean sqaure	Sum of squares	F value	P value	Adjusted R squared	Modified R squared
Tumour grade	0.682	14.981	2.171	0.002**	0.075	0.139
Size of tumour	49.915	1098.125	2.144	0.002**	0.073	0.137
Vascular invasive	2.163	47.576	47.889	P <0.001**	0.764	0.780
Number of LN involved	276.338	6079.434	29.310	P <0.001**	0.661	0.685
Histologic type	2.588	56.939	0.905	0.5888	-0.007	0.063

Discussion

The mean age of this study is 52.45±12.75 years which is contrary to some of the researches done within the subregion. In a study done by Ngwogu, Offiah [10], the mean age was reported as 46.5±5.4 years. In that same study, 79.1% of the cases were within 21-50years. Other studies show similar findings which are different from this study with 42.4% less than 50years [10, 11].

The mean age is consistent with similar studies done in Ghana [12, 13]. The peak incidence age of breast cancer by Ohene-Yeboah and Adjei [13] was 40-49year while in this study it was noted to be 50-59years. The percentage of male to female was consistent with other researchers [10, 13].

Histologic subtypes of breast cancer have over the years been shown as one of the established factors upon which treatment is based on. The histologic diversity of breast adenocarcinoma has different morphological and cytological patterns that have been associated with distinctive clinical presentation and/or outcomes.

In this current study the commonest histologic type of breast cancer is invasive ductal carcinoma no special type (NST) as described by literature [5, 10, 13, 14].

This was followed by DCIS, mucinous carcinoma and invasive lobular as seen in the study by Edmund et al [14]. There is no appreciable difference between tumours in the left versus right breast as seen by Ngwogu, Offiah [10]. Most of the tumours were located in the upper outer quadrants.

In this study, malignant phyllodes were the commonest sarcoma with 7cases forming 1% of all the malignant cases with an average age of 35±11.04 years. This value is consistent with the literature that put the incidence of malignant phyllodes at less than 1% with peak age incidence of 35 and 55 years. Few cases have been reported in men [15-17]. There was no case reported in men. There was a significant case of malignant phyllodes before age 50years (p=0.004).

The commonest grade of the tumour was identified as grade 2 followed by grade 3 and grade 1 was the least identified. This phenomenon was similar to most of the studies done in Ghana and other parts of Africa [10, 13, 14, 18, 19]. This study has shown that there is a relationship between tumour grade and tumour size (p=0.029), tumour stage (p=0.005) and number of lymph nodes involvement (p=0.010) but no association between the grade and histologic type. This is so because of the aggressive nature of the malignant tumours. Certain studies have shown that the 5year survival rate of high-grade tumours [14, 20, 21] and this may be so because of the association that exists between tumour grade and these factors.

The number of lymph nodes retrieved from our study ranges from 1 – 42 lymph nodes with a mean of 10.79±5.364 with mean lymph nodes involvement of 3.86±4.744. These findings support that of Edmund, Naaeder [14]. We also identified an association between histologic type of tumour (p=0.010), and tumour grade (p=0.010) and tumour stage (p<0.001). These associations indicate treatment failure, high recurrence and survival rate of patients.

Staging is one of the most important factors in determining the survival of patients with the disease. This study reports a higher stage disease of breast cancer of stage III and above accounting for 57.2% of the cases consistent with the findings of other researchers in Ghana, Nigeria and other parts of Africa [10, 11, 13, 14, 19, 22]. We also report of an increasing percentage of early disease probably due to the effectiveness of breast cancer education, self-breast examination and increasing numbers of patients reporting early to the hospital.

The high stage of the disease was also identified to be associated with tumour size (p=0.001). Most of the tumours measure more than 5cm. Tumour size has been shown to be a prognostic indicator; the larger the size the poorer the survival rate [23, 24]. It can, therefore, be said that our patients with larger tumour size have a low survival rate. There is no association between tumour size and histologic grade.

Vascular invasion in breast cancer has shown to be an important prognostic factor. We had 70.6% of our cases with vascular invasion as opposed to 5.1% by Edmund, Naaeder [14] this figure stresses the fact that breast cancer in Ghanaian patients has a poor prognosis. Our study also demonstrated an association between vascular invasion and nodal involvement (p<0.001), histologic type (p<0.001) and tumour stage (p<0.001); none of the previous studies done in Ghana has ever shown any associations between vascular invasion and any of these factors.

A multivariate analysis of tumour stage against tumour size, grade, vascular invasion and histologic type has shown positive correlation indicating that breast cancer in Ghanaian woman is generally poor using staging as the prognostic indicator.

Conclusion
It can be deduced from the study that, the frequent histological subtype of breast cancer is invasive ductal carcinoma(NOS) and breast cancer in Ghanaian woman is generally poor using staging as the prognostic indicator.

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Conflict of Interest
None

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