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ABSTRACT

Objective: **To determine the relationship between the age at diagnosis and established prognostic factors of breast cancers in Calabar, Nigeria. Attempts made to assess the prognostic value of age at presentation.**

Design: **Retrospective study of invasive breast cancer seen in Calabar over a seventeen-year period. Pearson's correlation, univariate and multivariate Cox's regression were used.**

Setting: **University of Calabar Teaching Hospital, Calabar, Nigeria, a referral and teaching hospital.**

Subjects: **Three hundred cases of invasive breast cancer diagnosed between 1983 and 1999 in Calabar, Nigeria. The necessary follow-up data was available for 129 patients.**

Results: **The mean age at diagnosis of breast cancer in Nigeria was 42.7 years (SD 12.2, range 18-85 years). Patients less than 40 years accounted for 39.8% of the total number of patients with infiltrating breast carcinoma. In the whole material (n=300), there was a positive association between age and tumour size (r=0.44, p=<0.0001), stage (r=0.47, p=<0.0001), the degree of necrosis (r=0.21, p=0.0002), histological grade (r=0.11, p=0.0476), MAI (mitotic activity index, r=0.12, p=0.0338), and MNA (mean nuclear area, r=0.17, p=0.0033). The correlation between age and SMI (standardized mitotic index), AI (apoptotic index), SMI/AI ratio, and FTD (fraction of fields showing tubular differentiation) were not statistically significant. The optimal decisive prognostic cut point for age was 33 years (p=0.0064). Age was also a significant prognosticator when used as a continuous variable (p=0.0240). Survival was better in the younger patients. However, in the Cox's multivariate analysis involving SMI, tumour size and age (both as a continuous variable and using the determined cut point of 33 years), the age at diagnosis lacked an independent prognostic value.**

Conclusion: **The more advanced nature of breast cancers and the possible more aggressive tumours (reflected by the higher MNA values) in the older patients may explain the poorer survival seen in patients diagnosed at 40 years or above. It is also probable that the lifestyle differences between the two studied age groups may influence the early detection and prompt commencement of therapy. Screening and treatment approaches between the two age groups may differ in view of the differences.**

INTRODUCTION

The relationship between the age at diagnosis and prognosis in patients with breast cancer remains controversial. A widely held perception is an unfavourable prognosis in young women(1-4). The difference in survival is not solely a reflection of more advanced disease but may reflect differences in tumour biology.

Unlike breast cancer patients in Western countries, those in Africa, and indeed developing countries, are predominantly premenopausal at diagnosis(5-8). This group of patients may require a different therapeutic approach. In this study, an analysis is performed to clarify the relationship of age at diagnosis to the pathological and morphometric characteristics of breast cancer in the Nigerian women, paying emphasis on patients less than 40 years. The prognostic value of age in Nigerian breast cancer is also determined.

MATERIALS AND METHODS

The studied population were female patients, with histologically confirmed invasive breast carcinoma, seen at the Department of Pathology of the University of Calabar Teaching Hospital, Nigeria between January 1983 and December 1999. The age at presentation was extracted from

the patients' medical records. The surgery notes yielded the tumour size, presence or absence of histological evidence of tumour in lymph nodes and metastases (picked up clinically or using laboratory, radiological or histological methods).

The clinical staging at the time of diagnosis was according to the guidelines of AJCC(9). All were treated with either simple or radical mastectomy with axillary dissection, with no prior preoperative radiotherapy or adjuvant treatment using a uniform treatment regimen. Chemotherapy was given after surgery to 85(65.9%) patients. Twenty(15.5%) had endocrine therapy while 19(6.3%) had both chemotherapy and endocrine therapy. Twenty-four(18.6%) had additional radiotherapy to the surgery. Follow-up information, obtained from the hospital medical records, was available for 129 patients. The follow-up period ranged from 2 to 60 months (mean 25.9, median 24.0).

This patient material was stratified into subgroups, according to tumour size and axillary lymph node involvement. The causes of death were collected from hospital data, death certificates, and autopsy reports. The end point of the follow-up was the survival status, which keenly followed the pattern of disease recurrence. Deaths from other causes than cancer were recorded when information was available, and only cancer-associated survival was evaluated as end point in the survival analysis.

Histological examination: Though the tumours had been previously graded for diagnostic purposes, this was repeated for all samples as proposed by Bloom and Richardson(10). Histologic typing was as recommended in the WHO classification of breast tumours(11). Inflammatory carcinoma and atypical medullary carcinoma were all grouped together with IDC-Nos (Infiltrating ductal carcinoma-not otherwise specified). Paget's disease was defined as breast cancer showing the typical skin lesion as the first symptom; such cases were excluded. But when the symptom was associated with a definite lump with histologically proven invasive ductal carcinoma, the disease was classified as infiltrating ductal carcinoma. Other carcinoma types not listed in the WHO classifications like the comedo, scirrhous, inflammatory and anaplastic carcinomas were all grouped as invasive ductal carcinoma.

Necrosis was identified as contiguous field of homogenous granular material with loss of nuclear staining and cell outlines. The degree of necrosis, expressed as the area in percentage of section covered by necrotic tissue, was stratified as follows: mild (tumour necrosis evident in 0-29% of tumour fields), moderate (tumour recrosis evident in 30-59% of tumour fields), and extensive (tumour necrosis evident in over 60% of tumour fields in the examined haematoxylin and eosin (H&E) slide).

Counting of mitotic figures and apoptotic bodies: Counting was carried out using a standard light microscope (objective: x 40, numeric aperture: 0.75; field diameter: 420μm). The criteria used in identifying mitotic figures were those described by Baak and Oort(12). Apoptotic counts were counted using a protocol earlier described(13). Counting of mitotic figures and apoptotic bodies was carried out in the most cellular region at the tumour periphery, avoiding areas of necrosis, inflammation, calcification and in situ carcinoma. If several areas met these criteria, the area with most mitotic figures, assessed subjectively, was chosen.

The number of mitotic figures in 10 consecutive fields from the most cellular area of the sample was the mitotic activity index (MAI). The volume fraction corrected mitotic index or standardised mitotic index (SMI), expressed per mm^2, gives the mitotic count as the number of mitotic figures by the area of the neoplastic tissue in the microscopic fields. This was the number of mitoses in 10 consecutive fields corrected for the volume fraction and field size. In this method, the area fraction (as estimate of volume fraction) of neoplastic tissue in the microscopic field was evaluated simultaneously with the mitotic count(14).

The total of apoptotic cells counted in 10 consecutive fields over the most proliferating area at the periphery of the tumour was the apoptotic index (AI), expressed per mm^2, calculated in a similar fashion as mitotic bodies were counted for SMI. Efforts were made to count both AI and the proliferative indices from the same area.

Fraction of tubular differentiation (FTD): This was expressed as a percentage, represents the fraction of fields showing tubular differentiation and this was determined after assessing the whole of the tumour area. Tubules were counted following strictly an earlier described protocol(15).

Nuclear morphometry: The nuclear profiles(16) of the cancer cells in the samples were measured using a digitising interactive image overlay system run by the Prodit morphometry program (Prodit 3.1, Promis Inc, Almere, The Netherlands). The system included a microscope, a personal computer (MultiSync 3D) Colour Monitor; NEC, Japan), a video camera (JVC TK-870U; JVC Japan) and a digitizer board (PIP-512B video digitizer board; Matrox Electronic Systems, Dorval, Quebec, Canada). Digitised images of the nuclear profile were outlined on the monitor screen using a computer mouse. The instrument was calibrated with a micrometer slide before each measurement. Measurements were carried out using a 2500 magnification on the monitor screen (x40 objective magnification, x10-video ocular and x2 internal magnification) on the most cellular area, usually at the periphery of the tumour while avoiding necrotic and inflammatory areas. An average of 8-15 microscopic fields were screened and 50 consecutive tumour cells with clear nuclear borders were outlined with the computer mouse. At the end of each measurement, the computer automatically produced the basic statistics of the variables.

Statistical analysis: SAS®System for Windows release 8.1; SAS Institute, Cary, North Carolina, USA was used for statistical evaluations. The significance of the associations was determined using the chi-square test, Fisher's exact probability test, correlation analysis and two-tailed t-test.

The possible cut-points for age were tested for optimal thresholds predicting disease free survival. Kaplan-Meier survival curves (patients with age below or above the cut-points) were drawn for each cut-point. The curves were tested for statistical significance using the log-rank test. The cut-point with the most significant difference in survival, between groups above and below the cut-point, was considered the best for separating cases with different prognosis. Cox's regression(17) was used to assess the prognostic significance of age at presentation in univariate and multivariate modes. Ratios indicating relative risk (RR) of breast cancer recurrence or death and the corresponding 95% confidence intervals were used to evaluate associations between different prognostic factors and outcome.

RESULTS

In the whole material (n=300), there was a positive association between the age of the patients and tumour size (r=0.44, p=<0.0001), stage (r=0.47, p=<0.0001), the degree of necrosis (r=0.21, p=0.0002), histological grade (r=0.11, p=0.0476), MAI (r=0.12, p=0.0338), and MNA (r=0.17, p=0.0033). The correlations between age and SMI, AI, SMI/AI ratio, and FTD were not statistically significant.

Patients less than 40 years accounted for 39.8% of the total number of patients with infiltrating breast carcinoma. The tumours in this younger group were less advanced than in the older patients. In those less than 40 years, 19.4% of the tumours were of stage 3 and stage 4 (vs. 75.3% in those over 40 years).

In both groups, the differences in the histological grades (p=0.4513) and types (p=0.4132) were not statistically significant. However, the older group displayed a more extensive necrosis (p=0.0003). The mean values of SMI, MAI and FTD in the younger population were 42.6±29.1, 29.1±25.6, and 16.6±17.5%. respectively. The differences with the values observed in the older subgroup were not statistically significant. In those aged less than 40 years, the mean AI and SMI/AI values of 10.7±20.0 and 9.8±17.2, respectively, were higher than observed in those older, but the difference was not statistically significant (AI p=0.3056, SMI/AI p=0.5000). On the other hand, MNA values were significantly higher in the older subgroup of patients (p=0.0016). Table 1 compares the characteristics of patients and their tumours in those younger than 40 years and among 40 years and above.

Table 1

Characteristics of patients with invasive breast cancer and their tumours in Nigeria

Characteristic	Age under 40 years (n = 118)	Age 40 years or above (n = 182)	p-value for differences between age groups
Mean age (SD) in years	31.2±5.5	50.2±9.0	
Mean tumour size in cm	3.4±2.2	5.7±2.0	0.0001
Lymph node status (%)			0.0001
Lymph node negative	54(45.8)	11(6.0)	
Lymph node positive	64(54.2)	171(94.0)	
Clinical stages (%)			0.0001
Stage 1	54(45.8)	11(6.0)	
Stage 2	41 (34.8)	34(18.7)	
Stage 3	16(13.6)	82(45.1)	
Stage 4	7 (5.9)	55(30.2)	
Histological types(%)			n.s
Invasive ductal	96(81.4)	146(80.2)	
Lobular	6(5.1)	4(2.2)	
Tubular	5(4.2)	12(6.6)	
Medullary	4(3.4)	4(2.2)	
Mucinous	3(2.5)	2(1.1)	
Papillary	0	4(2.2)	
Epidermoid	2(1.7)	4(2.2)	
Others	2(1.7)	6(3.3)	
Prominent intraductal component (n=83)	59(71.3)	24(28.7)	
Histological grade (%)			0.4513
Grade 1	20(17.0)	24(13.1)	
Grade 2	49(41.5)	70(38.5)	
Grade 3	49(41.5)	88(48.4)	
Degree of necrosis (%)			0.0003
Mild	92(78.0)	101(55.5)	
Moderate	22(18.6)	71 (39.0)	
Severe	4 (3.4)	10(5.5)	
Morphometric indices			
SMI	42.6±29.1	42.7±26.5	0.9755
MAI	29.1±25.6	31.5±24.8	0.4195
AI	10.7±20.0	89±10.2	0.3056
SM1/Al	9.8±17.2	8.8±8.2	0.5000
MNA	81.5±31.5	94.1±34.7	0.0016
FTD	16.6±17.5	16.7±20.4	0.9651

In patients less than 40 years, the subgroup with lymph node-negative tumours were clearly younger (28.2±5.0 vs. 33.7±4.5 years) than the lymph node-positive subgroup and presented with smaller tumours at diagnosis (p=0.0001). Proliferative and apoptotic activities were higher in the lymph node-positive subgroup (SMI p=0.0061, MAI p=0.0257, AI p=0.1520, SMI/AI p=0.1685), though statistical significance was demonstrated in only the proliferative indices.

The fraction of fields showing tubular differentiation (FTD) was higher in the LN- tumours than in LN+ tumours (19.2±19.6 vs. 14.5±15.3%, p=0.1465). The mean values of MNA, on the hand, were almost equal. Table 2 shows the differences in tumour size, histological grade and morphometric indices in LN- and LN+ tumours.

Increasing tumour size was significantly associated with extent of necrosis (p=0.0033), proliferative activity (SMI p=0.0042, MAI p=0.0131) and apoptosis (0.0165). The FTD declined gradually with increasing tumour size (Table 3).

Table 2

Pathological and morphometric characteristics of breast cancers in Nigerian females aged less than 40 years divided according to lymph node status

Characteristic between	LN-negative n = 54	LN+positive n = 64	p-value for differences LN status
Mean age (SD) in years	28.2±5.0	33.7±4.5	
Mean tumour size in cm	1.6±0.8	4.9±1.9	0.0001
Histological types(%)			0.0197
Invasive ductal	39(72.2)	57(89.1)	
Others	15(27.8)	7(10.9)	
Histological grade(%)			0.0993
Grade 1	13(24.1)	7(10.9)	
Grade 2	23(42.6)	26(40.6)	
Grade 3	18(33.3)	31(48.4)	
Degree of necrosis(%)			0.0189
Mild	48(88.9)	44(68.8)	
Moderate	6(11.1)	16(25.0)	
Severe	0	4 (6.2)	
Morphometric indices			
SMI	34.6±26.7	49.2±29.6	0.0061
MAI	23.4±22.6	33.9±27.1	0.0257
AI	7.9±11.1	13.2±25.0	0.1520
SMI/AI	7.4±4.8	11.8±22.9	0.1685
MNA	82.0±33.6	81.1±29.8	0.8777
FTD	19.2±19.6	14.5±15.3	0.1464

Table 3

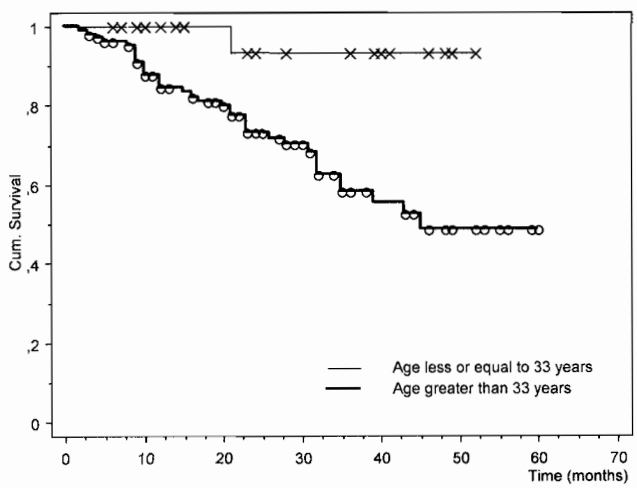
Pathological and morphometric characteristics of breast cancers in Nigerian females aged less than 40 years divided according to tumour size

Characteristic classes	Tumour size (cm) <2.5 (n = 53)	2.5-5 (n = 37)	≥5 (n = 28)	p-value for differences between size
Histological grade (%)				0.0742
Grade 1	14(26.4)	3 (8.1)	3(10.7)	
Grade 2	23(43.4)	16(43.2)	10(35.7)	
Grade 3	16(30.2)	18(48.7)	15(53.6)	
Degree of necrosis (%)				
Mild	48(90.6)	28(75.7)	16(57.1)	0.0033
Moderate	5(9.4)	6(16.2)	11(39.3)	
Severe	0	3(8.1)	1(3.6)	
Morphometric indices				
SMI	32.9±26.1	49.2±31.4	51.9±26.8	0.0042
MAI	21.9±21.8	32.5±26.5	38.3±27.8	0.0131
AI	7.7±11.3	9.7±9.4	17.8±24.5	0.0165
SMI/AI	9.8±18.1	8.4±6.4	11.6±36.0	0.8393
MNA	80.7±34.2	84.3±31.6	79.4±26.1	0.8001
FTD	19.6±19.6	15.0±14.0	13.2±16.9	0.2316

In univariate analysis, the threshold for age in years, with the optimal significance, capable of dividing patients according to outcome was 33 years (p=0.0064). Age was also a significant prognosticator when used as a continuous variable (p=0.0240) in the whole material. However, in the multivariate analysis involving SMI, tumour size and age (both as a continuous variable and using the determined cut-point of 33 years), the age at diagnosis lacked all independent prognostic value. Figure 1 shows the age associated survival curves (cut-point at the age of 33 years) in the Nigerian material with invasive ductal carcinoma of stages 1-4.

Figure 1

Survival curves in the whole material (n=129) of patients with invasive ductal carcinoma divided into two age groups using a cut-point of 33 years. This cut point is capable of dividing patients into those with favourable and unfavourable outcome (p= 0.0064)



The upper curve shows the survival in patients less than or equal to 33 years (1 dead, 27 alive).
The lower curve shows the survival in patients with an age over 33 years (35 dead, 66 alive).

Table 4

Prognostic multivariate analysis on Nigerian breast cancer patients utilising the SMI (cut-points of >92), tumour size(>5cm) and age (either with the cut-point 33 years or as a continous variable)

Variable	p-value	RR	CI
Whole material (129)			
SMI	<0.0001	11.9	4.9-28.7
Tumour size	0.0001	8.1	2.8-23.2
Age (cut-point 33)	0.5036	-	-
SMI	<0.0001	11.9	4.9-28.7
Tumour size	0.0001	8.1	2.8-23.2
Age (continuous variable)	0.0743	-	-
Premenopausal			
SMI	<0.0001	33.4	7.9-145.1
Tumour size	0.0003	10.0	2.9-34.2
Age (continuous variable)	0.1081	-	-
Postmenopausal			
SMI	0.0395	5.2	1.1-25.5
Tumour size	0.4106	-	-
Age (continuous variable)	0.3595	-	-

DISCUSSION

Generally accepted prognostic factors in patients with breast cancer are distant metastases, lymph node involvement, tumour size, histological grade, patients age, and markers of proliferation(18). In this study we evaluated the relationship of young age at diagnosis to the pathological features of the tumour and prognosis in patients with infiltrating breast cancer in Nigerian material. In patients less than 40 years, 80.6% presented with tumours of either stage 1 or 2; in contrast to 24.7% in those aged 40 years and over.

It is probable that the higher educational and social status, psychosocial differences and better accessibility to health-care facilities in the younger age group may influence this observation(25,26). Though the differences in the histological type, histological grade, proliferative and apoptotic indices were not statistically different, the higher degree of necrosis, larger tumour size at presentation and higher values of MNA of tumour cells noted in the older group may reflect not only a progression but actual biological differences between breast cancers in the two populations.

Boon *et al's* classification of DNA patterns(19) of breast carcinomas correlates positively with the mean nuclear area of cancer cells. The higher MNA observed in the older group may suggest high frequency of DNA hyperploidy and aneuploidy. With advancement or tumour progression, there is increasing probability of genome instability mutations associated with altered proliferative and apoptotic activities.

Of the 83 tumours that showed evidence of prominent intraductal component, 59(71.3%) occurred in the patients whose age was less than 40 years. This observation buttresses the hypothesis of tumour progression initiated in the younger patients. In the material of the younger studied group (aged less than 40 years), the mean tumour size, extent of necrosis and proliferative activities were significantly higher in the LN+ subgroup than in the LN- tumours (Table 3). These suggest that at the early phase of tumour progression the immunological response to tumour cells is able to check the proliferative processes. Breast tumours are often frequently associated with a predominantly lymphocytic infiltrate, which constitutes an immune response against the tumour. This is often inefficient and the tumour is able to evade the immunological surveillance. Proliferation related mechanisms are more important than apoptosis in the early phase of tumour progression. In contrast, in poorly differentiated and advanced tumours, apoptosis, or lack of apoptosis, seems to be of increasing importance in carcinogenesis and progression(20,21).

The optimal threshold capable of dividing patients into groups of favourable and unfavourable prognosis was 33 years of age. This implies that being a patient younger than 33 years at the time of diagnosis indicates a favourable prognosis. The contrary is the observation in several previous reports(1-4) where young breast cancer patients have a decreased survival rate and young age was also shown to be independent predictor of adverse prognosis.

The more advanced nature of breast cancers and the possible more aggressive tumour (reflected by the higher MNA values) in the older patients may explain the poorer survival seen in patients diagnosed at 40 years or above. It is also probable that the lifestyle differences between the two studied age groups may influence the early detection and prompt commencement of therapy(25,26). These require further investigation. The age at presentation could not, however, be demonstrated to be an independent prognosticator in the Nigerian material. The lack of independence may be due to the fact that proliferation, tumour size and age at presentation are interdependent factors. Proliferation and tumour size have a stronger prognostic power and this cancels the value of age in the multivariate analysis. Different screening and treatment approaches between the two age groups should be considered in view of the differences observed in this study.

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