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Immunohistochemical Expression of p53 Protein, in Relation to the Histological Type and Grade in Invasive Breast Carcinomas

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Original Research Article

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ABSTRACT

Background: Breast cancer remains the commonest cause of cancer-related deaths in women. This study aims to determine the proportion of p53 expression in breast cancer cases in OAUTHC Ile-Ife and relate this to histological grades and types.
Methods: Eighty-five histologically diagnosed breast cancer cases seen within a 2-year (2018-2019) period were retrieved. The tumours were graded using Nottingham grading system and the histological types were stated. Immunohistochemistry for p53 was performed on retrieved representative tissue blocks and its level of expression was scored as positive or negative. The association of p53 expression and the histological types and grades were sorted using the chi-square statistical test to compare variables and p-value < 0.05.
Results: The Invasive Ductal Carcinoma-Not Otherwise Specified (IDC-NOS) was the commonest histological type (92.9%). The histological grades 2 and 3 predominated accounting for 48.2% each. Of all the breast carcinoma cases analysed, grades 2 and 3 constituted 93.1%. The median age of 50.6 years was observed in p53 positive and 49.4 years in p53 negative. Even though most high-grade tumours were p53 positive, no significant association between p53 positivity and histological grades or histological types.
Conclusion: Conclusion: Many of our cases show expression of p53 and high grade tumours bare a high level of p53 expression. This finding though not statistically significant may suggest aggressive behaviour of tumours.

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1. INTRODUCTION

The incidence of cancer is rising worldwide, putting a huge burden on the existing health resources. The incidence of breast cancer had remained constant for many years but has gradually increased in the last decade [1]. A cancer database released by the Descriptive Epidemiology Group of the International Agency for Research on Cancer (GLOBOCAN 2018) put the incidence of breast cancer in West Africa at 37.3/100,000 females [2]. The incidence seems to be rising in developing countries such as Nigeria, Ghana and South Africa [2,3]. In Nigeria, the latest incidence rate of new cases of breast cancer in females is 26,310 (37%) [2]. The rising incidence has been attributed to improved diagnosis, access to good health care and lifestyle changes [3].

Tumour size, grade, lymphovascular invasion, number of axillary lymph nodes involved, hormone receptors status and Her-2 status are predictive and prognostic indicators of breast cancers. Studies have shown that mutation in p53 is more common in patients of African descent irrespective of where they live and it's over expression has also been identified as a poor prognostic marker in breast cancer [4,5]. Similarly, p53 is closely related to clinicopathological findings such as lymph node metastasis, high histological grade and Her2 overexpression [6,7]. The clinical course of breast carcinoma varies greatly and these depend on many factors [7]. The identification and documentation of specific protein molecules in a cohort of breast cancer cases may suggest the biological behaviour and clinical characteristics of breast cancer [8,9]. This biological behaviour associated with documented specific proteins may also be responsible for the poorer prognosis of breast cancer as observed in Nigerian patients compared to their counterparts in developed countries [9].

Evaluation of molecular markers in breast cancers may be a valuable tool in prognosticating the outcome of the disease. The tumour suppressor gene plays an indispensable role in many cellular pathways controlling cell proliferation and cell survival. It reacts to various forms of cellular stresses to mediate anti-proliferative processes. Disrupting its function promotes checkpoint defects and inappropriate survival leading to the uncontrolled proliferation of damaged cells [10]. In fact, their importance lies more as predictors of response to therapy. Moreover, the presence of TP53 mutation could be one of the underlying causes of drug resistance, which is the major cause of treatment failure.

However, it is not clear how p53 expression might accurately correlate with the histological grade or types of breast carcinomas It is therefore imperative to explore the immunohistochemistry of p53 in the cases of breast cancer in our patients.

2. METHODOLOGY

Eighty-five cases of histologically diagnosed breast cancer from the Department of Morbid Anatomy and Forensic Medicine Obafemi Awolowo University Teaching Hospitals Complex (OAUTHC), Ile-Ife, Osun State within 2 years (2018- 2019).

The inclusion criteria are breast carcinoma from biopsy, lumpectomy or mastectomy specimens. Exclusion criteria are Non-epithelial tumours of the breast, all cases in which the tissue blocks could not be retrieved and any lumpectomy or mastectomy case which had a previous biopsy diagnosis of breast carcinoma to prevent double accession were excluded.

The age, gender, nature of the specimen and other relevant clinical information were obtained from the medical report. Representative sections from Formalin-Fixed Paraffin-Embedded (FFPE) tissues blocks were obtained for Haematoxylin and Eosin (H&E) stain and immunohistochemistry. The slides were reviewed and graded using the Modified Bloom and Richardson grading system.

Immunohistochemical staining for p53 was done on the cases using mouse monoclonal antibody by DAKO. An indirect immunoperoxidase method was used according to standard laboratory protocol. Tonsilar tissue was used as p53 positive control while negative control was obtained by replacing the primary antibody with non-immune serum.

P53 was considered positive where there was ≥ 5% positive nuclear staining regardless of the intensity [11].

The overall expression was further evaluated and graded according to Evaluation of IHC for p53 as follows: (0-5% of p53 staining are scored as negative and graded 0 while 6-25%, 26-50%, 51-75%, 76-100% staining are evaluated as positive and graded 1+, 2+, 3+ and 4+ respectively.)

The data generated were analysed using SPSS version 20.

Chi-square test statistics were used to determine the association between p53 expression, the patients' clinicopathological data and histopathological features. The significance was set at $P<0.05$.

3. RESULTS

3.1 Demography of Patients with Breast Carcinoma

The total number of cases was eighty-five. The age range of patients was 32 to 76 (mean age = 50.07 $\pm$ 9.79 years, modal age = 47 years, median age = 50 years). The majority of the cases (70.6%) were within the (41-50) age group while 10.6% of the cases were above sixty years (Table 1).

3.2 Histological Types and Grades of Breast Carcinoma

The histological types of breast carcinoma seen were Invasive Ductal Carcinoma 79 (92.9%), Metaplastic carcinoma 5 (5.9%) and Lobular carcinoma 1(1.2%). The photomicrograph of the histological types is depicted in Figs. 1.

The histological grade 1 is 3(3.5%) grades 2 and 3, accounting for 41(48.2%) each of the total number of cases.

3.3 Immunohistochemistry Expression of p53 in Breast Carcinoma

Among the cohort of breast carcinoma, forty-five cases showed positive expression of p53 while forty cases did not express p53 (Table 2).

In p53 positive breast carcinoma cases, based on the percentages of cells positive for p53, 17 (20.0%), 10(11.8%), 6(7.1%) and 12 (14.1%) of the cases were scored (+1), (+2), (+3) and (+4) respectively. (Table 3) The photomicrographs in figure 2 (A, B, C, and D) demonstrate invasive ductal carcinoma with no nuclear expression of p53 protein (score 0), invasive ductal carcinoma score 1+, invasive ductal carcinoma score4+ and lobular carcinoma score 3+ respectively.

3.4 Comparison of p53 Protein Expression with Histologic Types and Grade of Breast Carcinoma

The p53 expression in these histological variants were 88.9%, 8.9% and 2.2% for the Invasive Ductal Carcinoma, Metaplastic carcinoma and Lobular carcinoma. histological types respectively.

Table 1. Showing Age group distribution of the Breast Carcinoma cases

s	Frequency	Percentage (%)
31-40	16	18.8
41-50	30	35.3
51-60	30	35.3
61-70	5	5.9
71-80	4	4.7
Total	85	100

Table 2. Showing Age Distribution of Positive and Negative expression of p53

	P53 positive Freq (%)	P53 Negative Freq (%)
31-40	6 (13.3)	9 (22.5)
41-50	18 (40)	13 (32.5)
51-60	16 (35.6)	14 (35.0)
61-70	3 (6.7)	2 (5.0)
71-80	2 (4.4)	2 (5.0)
Total	45 (100)	40 (100)

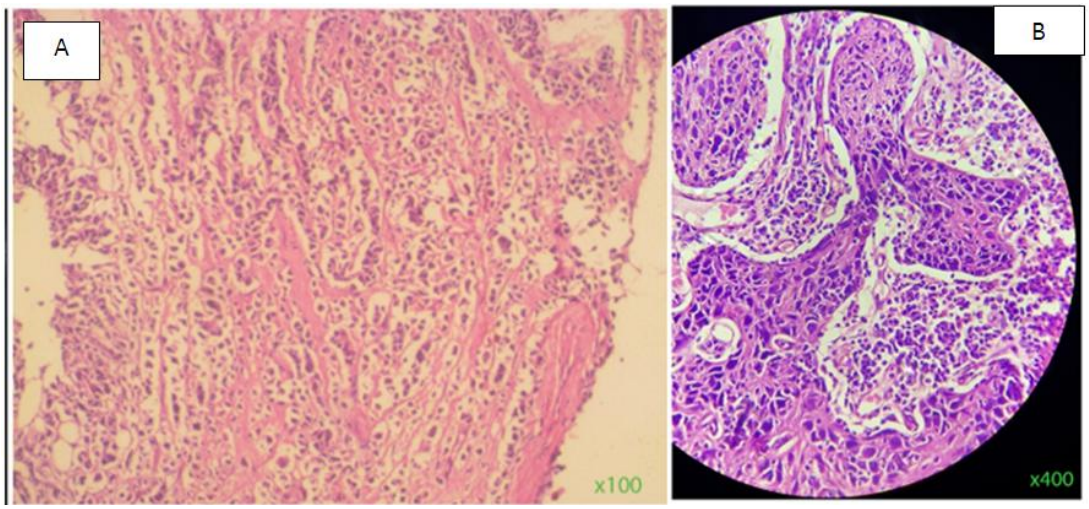

Fig. 1. A: Lobular carcinoma B: Metastatic carcinoma (Hematoxylin and Eosin stain)

Table 3. shows the percentage of positive and negative expressions of p53 in breast carcinoma

P53 scores	Freq (%)
0	40(47.10)
1+	17(20.00)
2+	10(11.80)
3+	6(7.10)
4+	12(14.10)
Total	85(100)

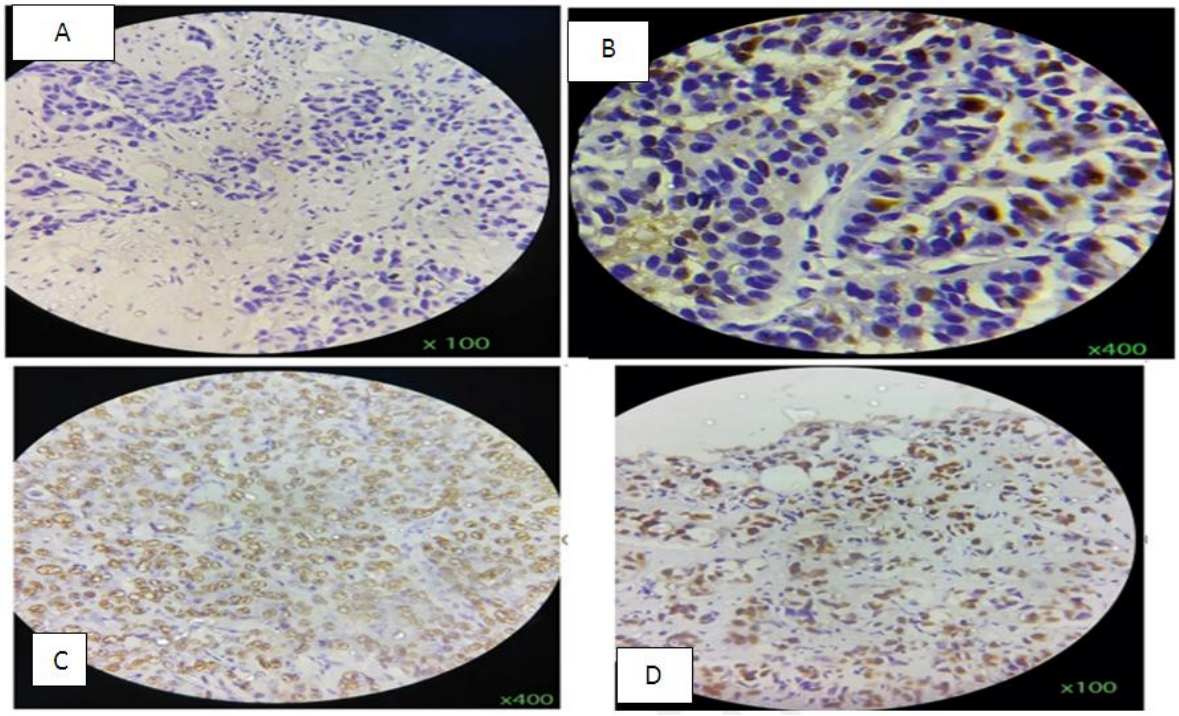

Fig. 2. p53 score (A: p53 negative, B, C and D show p53 positive staining)

Table 4. Expression of p53 in different histological types and grades of Breast Carcinoma

Histological Type/Grade of breast Carcinoma	p53 expression		Total frequency
	Negative (%)	Positive(%)	
Invasive Ductal Carcinoma	39(97.5)	40(88.9)	79
Lobular Carcinoma	0(0)	1(2.2)	1
Metaplastic Carcinoma	1(2.5)	4(8.9)	5
Total	40 (100%)	45 (100%)	
Histological grade			
1	0(0)	3(6.7)	3
2	22(55)	19(42.1)	41
3	18(45)	23(51.1)	41
Total	40(100)	45(100)	

Histological Grade 3 tumours account for the highest number of positive p53 cases 23 (51.1%). Whereas grade 2 and grade 1 tumours were positive for p53 in 19 (42.1%) and 3 (6.7%) cases respectively**.** There was, however, no statistically significant difference in the p53 staining pattern in these histological types and grades (p=0.283) (Table 4).

4. DISCUSSION

4.1 Demography of Patients with Breast Carcinoma

The mean age of breast carcinoma diagnosis observed in this study is similar to that reported by other studies conducted in Nigeria [12], Malaysia, and Iran [13,14]. This also correlates with findings by Ohene-Yeboah et al [15] in Ghana and Kallel et al in Tunisia who reported a mean age of 49.19 and 50 years respectively [16]. The percentage of the study population reported is similar to Adelusola's study and other previous studies from this Institution. In most studies in Africa, the highest peak age of breast cancer is seen in the 5th decade, unlike in this study where we observed a peak in the 5th and 6th decades [17]. Some other studies also showed a similar peak age group [1,18,19]. Adelusola et al20 in Ile-Ife observed peak age groups of 40-49 and 60-69 years. Literature has also supported that, in Africa, breast carcinoma occurs more in the premenopausal period unlike in Europe and America [21].

4.2 Histological Types and Grades of Breast Carcinoma

Invasive Ductal Carcinoma (Not Otherwise Specified) of the breast was the commonest histological type. This is not different from the observation by other authors [9,22]. This is similar to Rambau and colleagues [23] in a Tanzanian retrospective study that used a larger sample size (328), with a frequency of 91.5%. Other studies in South West Nigeria by Daramola et al, [24] in Lagos and Titiloye et al [9] in Ile-Ife have also reported Invasive Ductal Carcinoma (Not Otherwise Specified) as the commonest histological type, even though lower frequencies of 63.5% and 87.3% were reported respectively in their series.

Metaplastic carcinoma was the second most common type of breast carcinoma case in this series (5/85 (6%). This is similar to Daramola et al, [24] in Lagos who also had metaplastic carcinoma as the second most commonest in their series, but with a much higher frequency of 14.8%. This difference may be due to a representative piece of the biopsy cases used in this study as metaplastic carcinomas have classical pathologic features, where their ductal component may be partially or totally replaced by non-ductal (non-glandular) components [25] and this can be affected by sampling errors. It may also be due to the possibility of special types of invasive ductal carcinomas being under-diagnosed in the cases reviewed.

The number of cases graded 2 and 3 in this study cohort outweighs the low-grade tumours. The high histological grade is commonly seen in blacks [26,9,13]. A similar finding has been observed in a previous study in Ile-Ife by Titiloye et al and in Ghana by Ohene Yeboah et al. Some of the reasons are said to be related to genetic factors and late presentation [21,23]. In particular, BRCA1/2 gene mutations which are associated with breast cancer are described in black populations [27,28,29]. However, other mutated genes associated with breast cancer have also been identified in white populations such as HER2, APOBEC3B, RAD50 and SMAD4 genes [30]. Late presentation may de-

differentiate the tumours into higher grades over time. Our observation agrees with others that higher grades are seen more in African Blacks than their European counterpart [9,21,31].

4.3 p53 Expression in Breast Carcinomas

This study is unique being the first study in our centre to determine the p53 expression of breast carcinoma and relate it to other known prognostic indices. Many researchers have supported the finding that p53 expression in breast cancer usually signifies a more aggressive behaviour [32-33], thus we may conclude that there is an intrinsically more aggressive tendency of tumours in our local environment as evidenced by the higher p53 expression. A lower percentage (29.6%) was reported in Malaysia, although, the sample size of the Malaysian study was higher at three hundred and eighty-two [13].

4.4 Age-related Expression of p53 in Breast Carcinomas

We also observed that the younger age groups had higher expression of positive p53 expression. This may be difficult to explain from this study, although many studies have observed that p53 protein expression and Tp53 gene mutation are associated with poor prognosis [32,34]. Few reports have mentioned the relationship of p53 with early onset of breast cancer in ages younger than forty years, except in Li-Fraumeni syndrome in which in addition to early onset of breast cancers, patients also present with other childhood tumours [4,35,36].

4.5 Relationship of p53 Expression, Histological Types and Histological Grades

The histological type of breast carcinoma is a known prognostic factor that is related to tumour biology. This study showed a greater percentage of Invasive Ductal Carcinoma (NOS), however, metaplastic and lobular carcinoma of special types showed a high expression of p53 immunostaining. Observations from other studies have shown that some special histological types (Metaplastic, micropapillary subtypes) are associated with bad prognosis [4,34].

Furthermore, high histological grades and p53 mutation in invasive carcinoma is an indicators of a bad prognosis [32-33]. Different observations are documented on p53 expression in association with grade and other traditional prognostic factors in breast carcinoma. In this cohort, our findings were in agreement with what is in the literature, that higher-grade tumours generally tend to have high p53 expression [37,13]. More so, most cases that expressed the p53 protein were grade 3 (high grade) tumours and all the low grade expressed p53. This is in contrast to what might be expected of these low-grade tumours and that p53 expression alone cannot be used as a sole factor in prognosticating breast carcinomas.

Olufemi and colleagues in Lagos noticed a similar trend in which 89.6% of breast carcinomas positive for p53 were seen in high-grade tumours [26]. The high grade in their series corresponds to grades 2 and 3 in this study. The smaller sample size used in this study may explain the higher percentage observed in our study. The high level of p53 expression in this study may explain the aggressive nature of breast cancers, in addition to late presentation, poor access to quality health delivery system and financial constraints experienced in our country.

The histological grade is one of the factors considered to indicate the clinical course of breast carcinoma. In our study, there was no association between p53 expression and histological grade of breast carcinomas. Similar to us, Olufemi et al, [26] from Lagos and Robab et al [38] from Iran reported that there was no statistically significant association between p53 expression and the histological grades. Joudi et al [13] noticed a statistically significant association between p53 expression and histological grade. The reason for this conflicting finding may be attributed to inter-observer variability associated with grading especially the intermediate grade 2. It may also be that many other factors including other genetic mutations determine the grades of breast cancer asides from Tp53 gene mutation in this study.

5. CONCLUSION

In conclusion, a key finding of this research was that the majority of our study population were in their 5^{th} and 6^{th} decade. This same age group was found to have the highest percentage of p53 expression. Most of the cases that showed immunoreactivity to p53 had a high histologic grade. We did not find any statistically significant association between the histological types and the different histological grades with their expression of p53.

6. LIMITATIONS

The cohort of cases we studied was obtained from a tertiary hospital that accepts patients from far and wide, therefore the conclusions derivable from it may not accurately be referred to a general population.

The sample size would have been larger except that some of the cases had to be excluded from the study for various reasons such as minimal residual tissue, highly fragmented tissue, and inadequate tissue blocks. These are the drawbacks of using archival tissue blocks.

Immunohistochemistry detection of nuclear p53 staining indicate p53 mutation but may not be able to determine the full spectrum that is the different types, location, and the number of p53 mutations and molecular sequencing need to be examined in the near future.

There is no conflict of interest to be declared by all the authors. We did not obtain any financial assistance from any Organisation or company for this study.

CONSENT

It is not applicable.

ETHICAL APPROVAL

Ethical approval was obtained from the Ethics and Research Committee of the Obafemi Awolowo University Teaching Hospitals Complex with assigned number-ERC/2019/08/06.

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