Original Research Article

Role of p53 as a prognostic marker in breast carcinoma and its correlation with tumor size, tumor grade and lymph node metastasis

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A R T I C L E   I N F O

A B S T R A C T

Introduction: Breast cancer is the most frequently diagnosed cancer among females worldwide. p53 tumor suppressor gene regulates the cell cycle and DNA repair and its over-expression in breast cancer is associated with a worse prognosis.

Objective: This study was done to correlate p53 over-expression with histopathological parameters such as tumor size, tumor grade and lymph node metastasis in breast carcinoma.

Materials and Methods: This retroprospective study was conducted in a tertiary care centre, western U.P. retroprospectively from July 2014 to June 2019. Immuno-histochemical evaluation of 50 histologically confirmed cases of breast carcinoma was done.

Results: A total of 50 patients of breast carcinoma were analysed. Most common was Invasive carcinoma of no special type (NST). Most common age group involved was 40-49 years and majority were of age more than 45 years of age. Majority of breast carcinoma cases were of left breast and involving upper outer quadrant. In majority of cases, the tumor size was of more than 2 to 5cms. Majority of cases of breast carcinoma were of grade II according to Nottingham Modified Bloom Richardson System. More than half of patients with lymph nodes showed metastatic deposits. Majority of cases were in moderate prognostic index group. Out of 50 cases, 24(48%) cases showed p53 expression (≥5%). High p53 expression (>50%) was seen in 8(16%) cases of breast carcinoma.

Conclusion: A statistically significant association was found between p53 expression, tumor size and lymph node metastasis. No statistically significant association was found between p53 overexpression and tumor grade. Overall, p53 overexpression was found to be poor prognostic factor and its detection may help in risk catergorization and designing future target therapies.

1. Introduction

Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer death among females worldwide, with an estimated 2.08 million cases and 626679 deaths in 2018.[1] Cases are generally high in American and European countries while low in most of Africa and Asia.[2] The international variation in incidence rates is mainly due to reproductive and hormonal factors and early detection.[3] Breast cancer projection for India during time periods 2020 suggests the number to go as high as 1797900.[4]

Early diagnosis and appropriate treatment can prolong the survival of patient diagnosed with breast cancer.[5] The number of cancer-related parameters available to predict the prognosis in breast cancer patients has grown considerably in recent years. Prognostic factors of breast cancer include histological features (histological type, histological grade, lymphovascular invasion), tumor size, lymph node status, steroid hormone receptors status and age.[6–8] Prognostic and predictive biomarkers including p53 was also identified in breast cancer.

p53 tumor suppressor gene is the most frequently mutated tumor suppressor gene in human malignancy and

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30% breast cancers have p53mutation.[9] p53(also known as TP53) is located on chromosome 17p13 and encodes p53 transcription factor. p53 plays a vital role in determining cell fate exposed to DNA damage stimuli.[10]In response to DNA damage, p53 activates p21 and arrests the cells in G_1 phase—this constitutes the major G_1/S checkpoint. Induction of p53 can also lead to apoptosis by activating pro-apoptotic proteins such as BAX, PUMA, and NOXA.[11]

Unlike normal p53, nonfunctional mutated p53 accumulates in the nucleus of tumor cells, and therefore, it can be detected by immunohistochemical analysis. Multiple studies have shown that p53 over expression in breast cancer is associated with a worse prognosis.[12]

So, aim of this study is to find out role of p53 over-expression in breast carcinoma and its correlation various histological parameters such histological type, tumor grade and lymph node metastasis.

2. Materials and Methods

The present study was conducted in a tertiary care centre, western U.P. retroprospectively from July 2014 to June 2019. Immuno-histochemical evaluation of a total 50 cases was conducted who were confirmed to have breast carcinoma histologically. The haematoxylin & eosin (H&E) stained slides of the cases were retrieved & screened for confirmation of diagnosis followed by selection of the appropriate paraffin blocks. The representative neoplastic tissue blocks (paraffin embedded) were cut at 3.0μ on poly-L-Lysine coated slides. One of the sections was routinely stained with H&E. The histological grading of the tumor was done on H&E stained sections according to Modified Bloom & Richardson Grading.

Out of 50 patients, 36 patients were of modified radical mastectomy and 14 patients were of lumpectomy. Patient without consent for IHC, inadequate tissue samples, improperly preserved tissues were excluded. Breast carcinoma was used as a positive control. Tumor cells with nuclear staining were accepted as positive. p53 overexpression were taken as Negative, Low, Moderate, High when less than 5%, 5%- 19%, 20% - 50%, >50% of cells were positive for p53. Tumor size was divided into three groups < 20mm, 20 mm– 50mm, >50mm on gross examination.

Descriptive statistical analysis has been carried out in the present study. Chi square test was applied using SPSS version 2.0, p value <0.05 was considered as the minimum level of significance.

3. Results

In present study, age range of these patients were from 20 to 90 years with mean age 49.5 years. Majority of patients (16/50,32%) were in the age group of 40-49 years. Women of age more than 45 years of age

were 32/50(64%). Out of 50 cases, 28(56%) were on the left side and 24(44%) on the right side and no case was found involving both breast. Majority of cases were in upper outer quadrant (24/50,48%) followed by central quadrant (14/50,28%), lower outer(7/50,14%), upper inner(3/50,6%) and lower inner(2/50,4%). Tumor size ranges from 1.5 cm to 15 cm and majority of breast tumors (29/50,58%) were of size >2 cm to 5 cm followed by (15/50,30%) tumors with size >5 cms and least (6/50,12%) were tumor of size $\leq$ 2.0 cm. In the present study, invasive (infiltrating) carcinoma of no special type was the commonest histological type (41/50,82%) followed by invasive lobular carcinoma (4/50,8%), invasive carcinoma with neuroendocrine differentiation (2/50,4%), metaplastic carcinoma (2/50,4%) and mucinous carcinoma (1/50,2%). All the cases were graded according to Nottingham modification of Bloom Richardson method and majority of the cases were in grade II (21/50,42%) followed by grade I (16/50,32%) and grade III (13/50,26%). According to Nottingham prognostic index, majority of patients were in moderate prognostic group (17/36,47.2%) followed by poor prognostic (12/36,33.3%) and good prognostic group (7/36,19.5%). Out of 36 cases with lymph nodes, 20 cases were positive for metastatic deposits (20/36, 55.55%).

In present study, p53 expression (positive, $\geq$5%) was seen in (24/50, 48%) cases and rest were negative for p53 expression (Table 1). Maximum p53 positivity ($\geq$5%) was seen in invasive breast carcinoma of special type (22/41,53.7%) followed by invasive carcinoma with neuroendocrine differentiation (1/2,50%) and metaplastic carcinoma (1/2,50%). No p53 positivity (<5%) was seen in infiltrating lobular carcinoma and mucinous carcinoma of breast. In cases with tumor size $\leq$2cm, p53 expression (>5%) was seen in (3/6,50%) cases. In cases of tumor size of >2-5cm, p53 expression ($\geq$5%) was seen in (12/29,41.%) and in tumor size >5 cm, p53 expression(>5%) was seen in (9/15,60%) cases (Table 2). Above results was found to be statistically significant (p=0.008917).

9/13(69.2%) of grade III breast tumors were positive for p53 expression ($\geq$5%) followed by grade II breast tumors (10/21,47.6%) and grade I tumors (5/16,31.3%)(Table 3). Above results were found to be statistically insignificant (p value=0125724). p53 expression was seen maximum in cases with lymph node metastatic deposits (13/20,65%) as compared to lymph node with no metastatic deposits (5/16,31.2%)(Table 4). Above results was found to be statistically significant (p=0.044171).

4. Discussion

Breast cancer, one of the most common malignancy in women and alone accounts for 25% of all cancer cases and 15% of all cancer deaths among females. In India, breast cancer develops almost a decade earlier than their Western counterparts.[13]Breast cancer is highly

Table 1: p53 expression in cases of breast carcinoma.

p53 expression	Number of cases (n)	Percentage (%)
Negative	26	52
Low positive (5-19%)	02	04
Moderate positive (20-50%)	14	28
High positive (>50%)	08	16
	50	100

Table 2: p53 expression according to tumor size.

Tumor size	Number of patients	P53 expression			
		<5%	5-19%	20-50%	>50%
≤2cm	06	3	0	3	0
2-5cm	29	17	2	5	5
>5cm	15	6	0	6	3
Total	50	26	2	14	8

Value= 0 008917, Statistical significant

Table 3: p53 expression in breast carcinoma according to grade of tumor.

Tumor grade	Number of patients	p53 expression			
		<5%	5-19%	20-50%	>50%
Grade I	16	11	1	3	1
Grade II	21	11	1	5	4
Grade III	13	4	0	6	3
Total	50	26	2	14	8

Value= 0 125724, not significant

Table 4: p53 status in breast carcinoma according to lymph node metastasis

Lymph node metastasis	Number of patients	p53 expression			
		<5%	5-19%	20-50%	>50%
Positive	20	7	1	5	7
Negative	16	11	0	5	0
Total	36	18	1	10	7

Value= 0 044171, Statistical significant

heterogeneous disease with a wide range of biological, pathological & clinical characteristics. Role of hormone receptors such as ER/PR & HER-2/neu is well known in treatment of breast cancer whereas new studies has shown the role of p53 in prognosis and overall survival of patients of breast cancer.

In present study, out of total 50 cases, 36(72%) cases were of modified radical mastectomy with lymph nodes and 14 (28%) cases were of lumpectomy.

In present study, majority of cases (16/50, 32%) were in the age group of 40-49 years. The age range of patients ranged from 20 to 90 years with mean age of 49.5 years which is similar to studies done by Nikhra P et al. (2014)[14] and Yadav R et al. (2016).[15] Women of age less than or equal to 45 years were 18/50(36%) and more than 45 years were 32/50(64%) in present study which is similar to study done by Lodha R et al., 2011.[16] Kakarala et al., 2010[17] in their study found that in Indian population, 16.2% were pre-menopausal, 29.9% were peri-menopausal and 53.9% were post menopausal.

Majority of tumors were on left side 28/50(56%) in comparison to right side 22/50(44%). It has been observed in the past also that breast carcinomas are more common in the left breast than the right. The possible explanations are that the left breast being more bulky and having a larger volume of breast tissue comparatively.[18,19] Sandhu et al.(2010)[20] and Geethamala et al. (2015)[21] observed the similar findings. The upper outer quadrant, which is the most common site for carcinoma breast according to Sainsbury RC (2004)[22] was the most common site for the tumor with 53.03% of the tumors situated in this location and in the present study also, 24/50(48%) cases were found in upper outer quadrant.

In the present study, tumor size ranges from 1.5 cm to 15 cm and majority of breast tumors (29/50,58%) were of size >2 cm to 5 cm followed by 15/50(28%) tumors with size >5 cms and least (6/50, 12%) were tumor of size ≤ 2.0 cm. Almost similar observations have been reported in other studies such as Sharma M et al (2016),[23] Gupta K et al (2016)[12] and Pan Y et al (2017).[9] In India owing to the
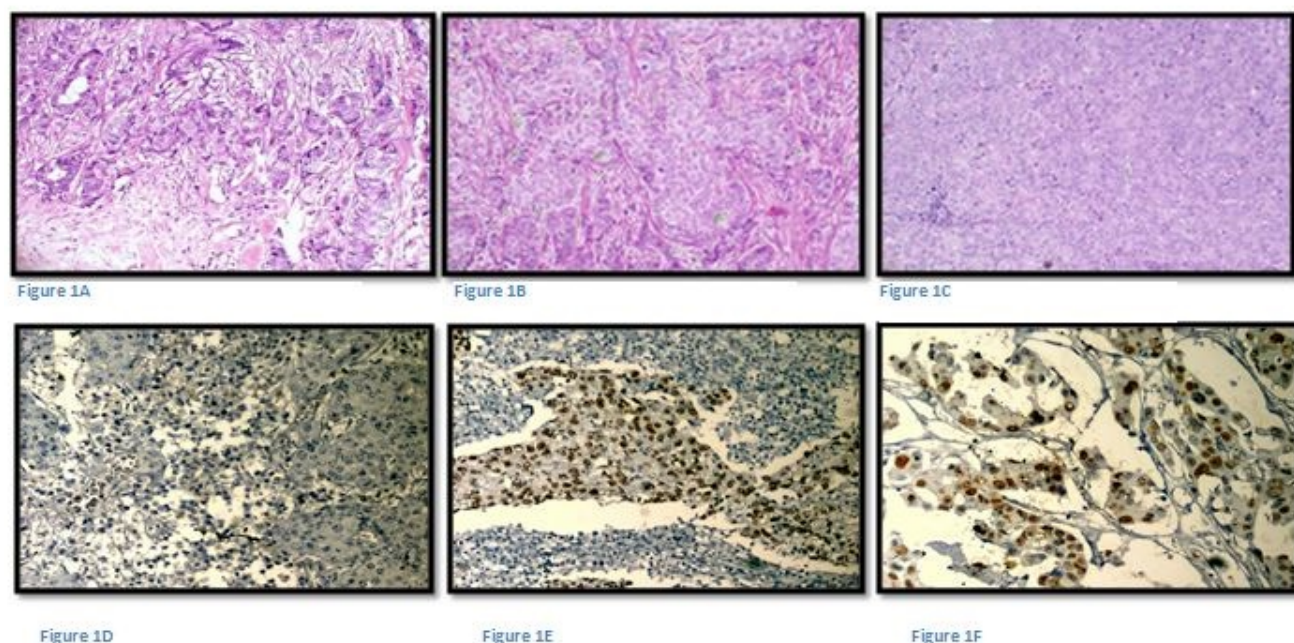
Fig. 1: A: Invasive carcinoma of no special type (NST) showing tubule formation, Grade I (H & E, 200X); **B:** Invasive carcinoma of NST showing moderate differentiation, Grade II(H&E,200X); **C:** Invasive carcinoma of NST poorly differentiated, Grade III (H & E, 200X); **D:** Expression of p53: photomicrograph showing nuclear staining in 5-19% of invasive tumor cells. (IHC, 200X); **E:** Expression of p53: photcaricrograph showing nuclear stainingin20-50% of invasive tumor cells. (IHC, 200X); **F:** Expression of p53: photomicrograph showing nuclear staining in >50% of invasive tumor cells. (IHC,200X).

lack of awareness of this disease and in absence of a breast cancer screening program, the majority of breast cancers are diagnosed at a relatively advanced stage. [16]

The terminology for the most common histological type of breast carcinoma has changed from invasive ductal carcinoma, not otherwise specified (NOS) 2003 to invasive (infiltrating) carcinoma of no special type (NST) 2012. [24] In the present study, invasive carcinoma of no special type was the commonest histological type (41/50, 82%) followed by invasive lobular carcinoma (4/50,8%), invasive carcinoma with neuroendocrine differentiation (2/50,4%), metaplastic carcinoma (2/50,4%) and mucinous carcinoma (1/50,2%). Almost similar results have been reported in the past by various workers Ayadi L et al. (2008), [25] Nikhra et al. (2014), [14] Yadav R et al. (2016), [15] Puvitha RD et al. (2016) [26] and Hashmi AA et al. (2018). [27] Results of the present study were in close proximity to study done by Ayadi L et al. (2008), [25] except for inflammatory carcinoma of breast which is more common in Tunisia and the region of North Africa. On the contrary Nikhra et al. (2014) [14] recorded a higher incidence, 95.34% for infiltrating ductal carcinoma.

All the cases were graded according to Nottingham modification of Bloom Richardson method. In present study, majority of the cases were in grade II (21/50,42%) followed by grade I (16/50,32%) and grade III (13/50,26%). A large number of studies have reported the similar findings such

as Ambroise et al., 2011, [19] Puvitha RD et al., 2016 [26] and Pan Y et al., 2017. [9] However, Geethamala K et al. (2015) [21] found grade I (54%) to be more common than other grades in their study.

In the present study, most of breast carcinoma cases were positive for lymph node metastasis (20/36, 55.55%) which is similar to studies done by Azizun-Nisa A et al. (2008), [28] Sharma M et al. (2016) [23] and opposite to study done by Payandeh M et al. (2015). [29]

The NPI is the most widely accepted prognostic index [30,31] and developed through multivariate analysis. In clinical practice, three prognostic groups are identified, a good prognostic group with scores less than 3.4, a moderate prognostic group with scores of 3.4-5.4 and a poor prognostic group with score of over 5.4. The respective 15 years survival rates are good, moderate, poor in 80%, 42% and 15% respectively.

In present study, majority of patients were in moderate prognostic group (17/36,47.2%) followed by poor prognostic (12/36,33.3%) and good prognostic group (7/36,19.5%) similar to findings reported by Haybittle JL et al. (1982), [30] Todd JH et al. (1987) [31] and Rolland P et al. (2006). [32]

The p53 gene appears to play a prime role in controlling cell proliferation and apoptosis, and in DNA repair. The genetic changes most commonly found in breast cancer are alterations in the p53 tumor-suppressor gene, withan

Table 5:

p53 expression	Payendah M et al, 2015[29] (%)	Gupta K et al, 2016[12] (%)	Pan Y et al, 2017[9] (%)	Present study (%)
Positive	34	88.9	73.1	48
Negative	66	11.1	26.9	52

incidence ranging from 15 to 50% in different series. In present study, p53 over-expression (positive, $\geq$5%) was seen in (24/50, 48%) cases and rest were negative for p53 expression. Out of overall p53 positive cases, majority of cases show moderate over-expression (14/24, 58.33%) for p53 followed by high over-expression (8/24, 33.34%). Various studies done by Payendah M et al. (2015)[29], Gupta K et al. (2016),[12] Pan Y et al. (2017)[9] also reported p53 over-expression in 34%, 88.9% and 73.1% cases respectively.

In the present study, invasive carcinoma of no special type was the commonest histomorphological type. Maximum p53 over-expression ($\geq$5%) was seen in invasive carcinoma of no special type (22/41,53.7%) followed by invasive carcinoma with neuroendocrine differentiation (1/2,50%) and metaplastic carcinoma (1/2,50%). Infiltrating lobular carcinoma and mucinous carcinoma of breast were negative for p53 expression. The results were found to be statistically insignificant and correlated with other studies done by Golmohammadi R et al, 2012[33] and Kim T et al, 2015.[34] In this study, maximum p53 expression (>5%) was seen in tumor size of more than 5cm (9/15,60%) followed by tumor size $\leq$2cm (3/6,50%) and >2-5cm (12/29,41%). The results were found to be statistically significant and correlated with other studies done by Rolland P et al., 2007[32] and Hashmi AA et al, 2017.[27] However no statistical correlation was reported by Gupta KK et al., 2016[12] and Pan Y et al., 2017[9].

In the present study, maximum p53 expression ($\geq$5%) was associated with grade III breast tumors (9/13,69.2%) followed by grade II breast tumors (10/21,47.6%) and grade I tumors (5/16,31.3%). The results were found to be statistically insignificant. These findings correlate with studies done by Pan Y et al (2017)[9] and Hashmi et al (2018).[27] However grade association with p53 was found to be significant in studies done by Yamamoto et al, 2014[33] and Gupta K et al, 2016.[12]

p53 expression ($\geq$5%) was seen maximum in cases with lymph node metastasis (13/20,65%) as compared to lymph node with no metastasis (5/16,31.2%) in present study and above result was found to be statistically significant (p=0.044171). These findings correlate with studies done by Kikuchi S et al., 2013[34] (45%) and Gupta K et al., 2016[12] (98.2%). But according to studies done by Han JS et al. (2011)[35] and Yang P et al. (2013),[36] no significant correlation was found.

5. Conclusion

In conclusion, we found a statistical significant correlation of p53 expression with tumor size and lymph node metastasis, but no correlation with histological type and tumor grade. However, p53 expression seems to be higher in patients with higher tumor grade. So, breast cancer aggressiveness appears to be directly related to the percentage of p53 positive cancer cells and its over-expression is directly related to histological grade and cell-proliferation fraction. Cases positive for p53 could be interpreted as those which have lost a mechanism for controlling the inhibition of cell proliferation and have gained an activator for malignancy potential. Above findings and correlation with various studies proved that p53 is an independent and poor prognostic factor and can be a potential target for future treatment in breast carcinoma. However, studies need to be carried out on larger scale.

6. Source of Funding

None.

7. Conflict of Interest

None.

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