Content available at: https://www.ipinnovative.com/open-access-journals

IP Journal of Diagnostic Pathology and Oncology

Journal homepage: https://www.jdpo.org/

Original Research Article

Survivin and p53 expression in benign and malignant lesions of breast

Swati Raj[1,*], Shristi Soni[2], Durre Aden[3], Alka Yadav[4], Sameeksha Raj[5]

[1]*Dept. of Pathology, Government Doon Medical College, Dehradun, Uttarakhand, India*
[2]*Dept. of Pathology, Government Medical College, Orai, Uttar Pradesh, India*
[3]*Dept. of Pathology, Hamdard Institute of Medical Sciences & Research (HIMSR), New Delhi, India*
[4]*Dept of Pathology, ESI Hospital, Faridabad, Haryana, India*
[5]*Salesforce, India*

ARTICLE INFO

Article history:
Received 16-09-2022
Accepted 27-10-2022
Available online 14-01-2023

Keywords:
Immunohistochemistry
Breast Carcinoma
Survivin
p53

ABSTRACT

Background: Breast cancer is the most common malignancy in women, accounting for 14 % of all cancers in India; it accounts for < 1% of all cancer cases in men. Breast cancer is the leading cause of death worldwide. The study aims to assess the expression of p53 and Survivin in Fibroadenoma and Invasive carcinoma of no special type and its prognostic importance.

Material and Methods: A total number of 75 cases are included in the study, out of which 34 are reported by two histopathologists as invasive carcinoma NST (ductal) and 41 reported as Fibroadenoma. All the cases included in the study are females. Immunohistochemistry for p53 and Survivin performed in both the groups with positive and negative controls. Cytoplasmic or nuclear IHC expression for Survivin is considered to be positive. Whereas, nuclear positivity is considered for p53. A semi quantitative scoring system performed consisting of intensity and % of positive cells.

Results: The expression of Survivin and p53 is found to be high in IDC, 79% and 85% respectively. The correlation is found to be significant (p value = 0.002, Spearman Rho correlation). However, the expression of Survivin is seen in one third of all the cases of Fibroadenoma (37.5%) and p53 expression is expectedly low, seen in 12% cases.

Conclusion: Over expression of Survivin in IDC patients compared to benign cases is found to be correlated with p53 expression. Though Survivin is likely to contribute to apoptosis resistance, its expression is found to confer resistance to chemotherapy and radiotherapy in IDC. Henceforth, Survivin over expression along with p53 in invasive breast carcinoma defining overall poor prognosis and low survival rates.

This is an Open Access (OA) journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: reprint@ipinnovative.com

1. Introduction

Carcinoma of breast is most common non- skin malignancy in women. Women who lives upto age 90 has a one in eight chance of developing breast cancer and one in every 10 new cancer diagnosed in Indian women.

Breast cancer is the most common malignancy in women, accounting for 14 % of all cancers in India; it accounts for < 1% of all cancer cases in men. Breast cancer is the leading cause of death worldwide, accounting for 2.26 million cases. Early diagnosis by triple assessment (Clinical details, Mammogram & FNAC). Surgery, medication and radiation can successfully treat the disease. FNA in breast plays a pivotal role in the early management, atypical features particularly Category 3 & 4 according to the IAC Yokohama system for reporting breast Cytopathology.

* *Corresponding author*.
E-mail address: drsraj29@gmail.com (S. Raj).

https://doi.org/10.18231/j.jdpo.2022.054
2581-3714/© 2022 Innovative Publication, All rights reserved.

However, benign lesions of the breast are far more frequent than malignant ones.[1,2] The incidence of benign breast lesions begins to rise during the second decade of life and peaks in the fourth and fifth decades, as opposed to malignant diseases, for which the incidence continues to increase after menopause, although at a less rapid pace.[3,4] Nowadays, seeing the breast cancer burden in younger females in our country, many hospitals and research institutes started "Breast clinic" to encourage early detection and to educate females for self examination.

Invasive carcinoma of no special type(ductal) being the most common type of carcinoma followed by lobular, medullary, mucinous, papillary, tubular and inflammatory carcinoma.[5]

Immunohistochemistry (IHC) has an expanding role in the diagnosis and management of mammary disease. Anti-survivin mAb 8E2 specifically reacted with breast carcinoma cells, with positive staining of the cytoplasm of cancer cells whereas no expression of Survivin was observed in adjacent normal tissues; therefore, Survivin expression in benign cases is likely to be the result of dysplastic transformation of the breast epithelium. As Survivin plays a dual role, as apoptotic inhibitor and as mitotic effector, its positivity is of interest.

p53 is a tumor suppressor gene product identified in a wide variety of tumors. Accumulation of mutant p53 detected by immunohistochemical staining has been reported in breast cancer..Disruption of p53 gene function seems to have a pivotal role in carcinogenesis. It has been demonstrated by Rohan et al, 2006[6] that p53 gene changes occur before the development of breast cancer and therefore influence breast cancer risk. Nearly one third of breast cancers have mutations of the tumor suppressor gene p53, which are associated with high histological grade and clinical aggressiveness**.**

The study aims to assess the expression of p53 and Survivin in Fibroadenoma and Invasive carcinoma of no special type (ductal) breast and its prognostic importance.

2. Materials and Methods

The present study is a cross-sectional study has been conducted in Department of Pathology, MLB Medical College, Jhansi on the tissue material obtained from patients admitted in Department of Surgery being Tru cut biopsy, breast conservation surgery or MRM during the time period of 18 months (October 2018-April 2020). The special care has been taken for immediate tissue fixation in 10% formalin, proper dehydration while processing and to exclude any technical errors while performing IHC.

A total number of 75 cases are included in the study, out of which 34 are reported by two histopathologists as invasive carcinoma NST (ductal) and 41 are reported as Fibroadenoma. All the cases included in the study are females. The complex fibroadenoma/cellular fibroadenoma and with features of atypia are excluded from the study.

2.1. Methodology

Immunohistochemistry for p53 and Survivin performed in both the groups with positive and negative controls. Positive control for Survivin are obtained from TCC bladder and for p53 carcinoma breast, is taken. The interpretation has been done by the same histopathologists. Cytoplasmic or nuclear IHC expression for Survivin is considered to be positive. Whereas, nuclear positivity is considered for p53. A semi quantitative scoring system performed consisting of intensity and % of positive cells.

The level of expression was scored as follows:

0 = negative, less than 5% of cells staining.

1+ = weak staining, between 6% and 25% of cells staining

2+ = moderate staining, between 26% and 50% of cells staining.

3+ = medium strong staining, between 51% and 75% of cells staining.

4+ = strong staining, more than 75% of cells stain.

3. Results

In the present study, total 34 cases of invasive breast carcinoma are from age 21 to 72 yrs. Out of 34 cases, most common age group is 41-50yrs (38%)followed by 31-40yrs (33%).

The age group of all cases of Fibroadenoma varies from 11yrs to 50 yrs. Out of 41 cases, most common age group is 11-22yrs (44%) followed by 21-30yrs (33%) and 41-50yrs (19%).

As most of patients seeking health care in our hospital belonged to rural area. Same was observed in our study i.e. 58 cases (78.00%) belonged to rural area.

Amongst malignant cases, patients most commonly presented with left breast lump (21%) followed by right breast lump. Most common site seen is upper outer quadrant (68%). Only 9% of cases, presented with axillary swelling and pain. One case is associated with bloody nipple discharge, however on cytology it is found to be negative for malignant cells. It is also noted that none of the cases show Paget's disease of nipple and dermal lymphatics involvement.

The most common size of malignant cases is found to 2-5 cm (62%) followed by 5-7 cm (23%) and <2 cm (15%). However, Fibroadenoma show most common size is 2- 5 cm(78%) followed by <2 cm(14%) and >5 cm (08%). It has noted that most common presentation in Fibroadenoma is breast lump(78%) and cyclical pain (58%).

The most common overall grade in IDC found to be grade 1 (27%), and least being grade 3(1%). Approximately half of the IDC cases show moderate nuclear variation-score 2 (47%), followed by mild variation-score 1 (30%).(Table 1)

Table 1: Distribution according to nuclear pleomorphism.

Nuclear pleomorphism	Score	No. of cases (n=34)	%
Small, uniform cells	1	10	30
Moderate variation	2	16	47
Marked variation	3	08	23

Table 2: Survivin and P53 expression in invasive ductal carcinoma and fibroadenoma

	Total cases (n=75)	Survivin Positivity	P 53 Positivity
Invasive breast carcinoma	34	27(79.40%)	29(85.30%)
Fibroadenoma	41	15(37.50%)	5(12.19%)

Table 2 The expression of Survivin and p53 is found to be high in IDC, 79% and 85% respectively. The correlation is found to be significant (p value = 0.002, Spearman Rho correlation). However, the expression of Survivin is seen in one third of all the cases of Fibroadeoma (37.5%)and p53 expression is expectedly low, seen in 12% cases .

4. Discussion

Survivin is a member of the 'inhibitors of apoptosis' gene family that controls mitotic progression and induces tumor cell invasion. Its over expression has been shown to be associated with parameters of poor prognosis in most of the human cancers, including carcinoma of the lung, esophagus, etc

Survivin is over expressed in majority of breast carcinomas.[7] The over expression of survivin is found to be correlated with HER 2 and EGFR expression. Survivin expression has been found to confer resistance to chemotherapy and radiation. Survivin targeting in experimental models improves survival of cancer patients.[8,9]

A systematic review of 12 studies,[10] p53 expression among women diagnosed with benign breast disease. Most of selected studies analyzed p53 expression among breast tissues with non-proliferative lesions. Benign breast disease corresponds to 34.39% of p53 expression. BBD with major breast cancer risk was poorly represented among selected studies. Given the importance of p53 protein in the breast cancer development, studies related to p53 expression among benign breast disease are of out most importance; especially in hyperplasic lesions that show major risk for breast cancer progression.[10]

In the present study, significant difference in the expression of Survivin between benign breast disease (37.5.%) and breast carcinoma (79.40%) was observed. Our result is consistent with the observation of Nassar et al,2008[11] who had reported 81% Survivin positivity in breast cancer cases. whereas according to Zhang et al.2001[12] Survivin was expressed in 42.7% of benign breast tumors and increases with increased histological grades of the disease.

In other study, Ranade KJ et al,[13] showed 53% Fibroadenoma cases expressed Survivin and 13% expressed p53 protein. Statistically significant increase in Survivin and p53 protein expression was observed in carcinoma cases. Our study showed Survivin expression in one third of all the cases of Fibroadeoma (37.5%) and p53 expression in 12% cases. The p53 expression showed almost similar expression in both the studies.

Normally Survivin is undetectable in terminally differentiated adult tissues; therefore, Survivin expression in benign cases is likely to be the result of dysplastic transformation of the breast epithelium. As Survivin plays a dual role, as apoptotic inhibitor and as mitotic effector, its localization was of interest to the scientists.

It has been recently suggested that anti-p53 drugs could reactivate mutant p53 and restore the tumor suppression activity in a preclinical model.[14–16] It is important to select appropriate patients with TP53 mutation to use these drugs and ensure successful results in clinical studies. Accurate detection of TP53 mutation would be a necessary precondition of anti-p53 therapies. Although next generation sequencing (NGS) allows whole genomic evaluation, it is still impractical in most clinical laboratories to use NGS to determine p53 mutational state due to high cost and complex interpretation. By contrast, IHC is still considered a valuable diagnostic tool with easy accessibility and well-established efficacy in investigating target agents and predicting clinical outcome in cancer. It also overcomes discrepancies between mRNA and protein expression by transcriptional and translational regulation.[17,18]

Higher p53 and Survivin immunostaining are correlated significantly with more advanced stages of breast IDC cases. Although there are still unknown mechanisms in tumor progression, we demonstrated that p53 and Survivin were applicable biomarkers to predict clinicopathological parameters. Therefore, the development of pharmacological agents to target the Survivin pathway may prolong survival time and slow tumor progression in patients with breast IDC.

5. Conclusion

Over expression of Survivin in IDC patients compared to benign cases is found to be correlated with p53 expression. Though Survivin is likely to contribute to apoptosis resistance, its expression is found to confer resistance to chemotherapy and radiotherapy in IDC. Henceforth, Survivin over expression along with p53 in invasive breast carcinoma defining overall poor prognosis and low survival rates.

6. Abbreviations

IDC- Invasive Ductal Carcinoma, FNAC- Fine Needle Aspiration Cytology, IHC- Immunohistchemistry, TCC- Transitional Cell Carcinoma, MRM- Modified Radical Mastectomy.

7. Source of Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

8. Conflicts of Interest

None to declare.

References

1. Kelsey JL, Gammon MD. Epidemiology of breast cancer. *Epidemiol Rev*. 1990;12:228–40. doi:10.1093/oxfordjournals.epirev.a036056.
2. Cole P, Elwood JM, Kaplan SD. Incidence rates and risk factors of benign breast neoplasms. *Am J Epidemiol*. 1978;108(2):112–20. doi:10.1093/oxfordjournals.aje.a112594.
3. Donegan WL. Cancer of the breast. In: WL D, JS S, editors. Common benign conditions of the breast . St Louis, MO: Saunders; 2002. p. 67–110.
4. London SJ, Connolly JL, Schnitt SJ, Colditz GA. A prospective study of benign breast disease and the risk of breast cancer. *JAMA*. 1992;267(7):941–4.
5. Berg JW, Hutter RV. Breast cancer. *Cancer*. 1995;75(1):257–69. doi:10.1002/1097-0142(19950101)75:1+<257::aid-cncr2820751311>3.0.co;2-y.
6. Rohan TE, Li SQ, Hartwick R, Kandel RA. p53 Alterations and protein accumulation in benign breast tissue and breast cancer risk: A cohort study. *Cancer Epidemiol Biomarkers Prev*. 2006;15(7):1316–23. doi:10.1158/1055-9965.EPI-06-0195.
7. Kennedy SM, O'Driscoll L, Purcell R, Fitz-Simons N, McDermott EW, Hill AD, et al. Prognostic importance of survivin in breast cancer. *Br J Cancer*. 2003;88(7):1077–83. doi:10.1038/sj.bjc.6600776.
8. KJha, Shukla M, Pandey M. Survivin expression and targeting in breast cancer. *Surg Oncol*. 2012;21(2):125–31. doi:10.1016/j.suronc.2011.01.001.
9. Martínez-Sifuentes MA, Bassol-Mayagoitia S, Nava-Hernández MP, Ruiz-Flores P, Ramos-Treviño J, Cruz JHS, et al. Survivin in Breast Cancer: A Review. *Genet Test Mol Biomarkers*. 2022;26(9):411–21. doi:10.1089/gtmb.2021.0286.
10. da Costa R, da Silva I. P53 Expression in benign Breast Disease Development: A Systematic Review. *Asian Pacific J Cancer Prev*. 2020;21(9):2485–91.
11. Nassar A, Sexton D, Cotsonis G, Cohen C. Survivin expression in breast carcinoma: Correlation with apoptosis and prognosis. *Appl Immunohistochem Mol Morphol*. 2008;16(3):221–6. doi:10.1097/PAI.0b013e3180c317bc.
12. Acs G, Lawton TJ, Rebbeck TR, Livolsi VA, Zhang PJ. Differential expression of E-cadherin in lobular and ductal neoplasms of the breast and its biologic and diagnostic implications. *Am J Clin Pathol*. 2001;115(1):85–98. doi:10.1309/FDHX-L92R-BATQ-2GE0.
13. Ranade KJ, Nerurkar AV, Phulpagar MD, Shirsat NV. Expression of survivin and p53 proteins and their correlation with hormone receptor status in Indian breast cancer patients. *Indian J Med Sci*. 2009;63(11):481–90.
14. Synnott NC, Bauer MR, Madden S, Murray A, Klinger R, O'Donovan N, et al. Mutant p53 as a therapeutic target for the treatment of triple-negative breast cancer: preclinical investigation with the anti-p53 drug. *Cancer Lett*. 2018;414:99–106. doi:10.1016/j.canlet.2017.09.053.
15. Duffy MJ, Synnott NC, Crown J. Mutant p53 in breast cancer: potential as a therapeutic target and biomarker. *Breast Cancer Res Treat*. 2018;170(2):213–9. doi:10.1007/s10549-018-4753-7.
16. Synnott NC, Murray A, Mcgowan PM, Kiely M, Kiely PA, O'Donovan N, et al. Mutant p53: a novel target for the treatment of patients with triple-negative breast cancer? *Int J Cancer*. 2017;140(1):234–46. doi:10.1002/ijc.30425.
17. Jing-Ping L, Xiang-Mei Z, Zhang Z, Zheng LH, Jindal S, Liu YJ, et al. Association of p53 expression with poor prognosis in patients with triple-negative breast invasive ductal carcinoma. *Medicine (Baltimore)*. 2019;98(18):e15449. doi:10.1097/MD.0000000000015449.
18. Khan S, Bennit HF, Turay D, Perez M, Mirshahidi S, Yuan Y. Early diagnostic value of survivin and its alternative splice variants in breast cancer. *BMC Cancer*. 2014;14:176. doi:10.1186/1471-2407-14-176.

Author biography

Swati Raj, Assistant Professor

Shristi Soni, Associate Professor

Durre Aden, Assistant Professor

Alka Yadav, Senior Resident

Sameeksha Raj, Senior Success Engineer

Cite this article: Raj S, Soni S, Aden D, Yadav A, Raj S. Survivin and p53 expression in benign and malignant lesions of breast. *IP J Diagn Pathol Oncol* 2022;7(4):229-232.