RESEARCH PAPER

IMMUNOHISTOCHEMICAL EVALUATION OF RETINOBLASTOMA GENE STATUS IN INVASIVE BREAST CARCINOMA AND ITS CORRELATION WITH CLINICOPATHOLOGICAL VARIABLES

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ABSTRACT

Background: Breast carcinoma is a heterogeneous malignancy characterized by diverse molecular alterations that influence tumour behaviour and clinical outcome. The retinoblastoma gene (RB1) encodes the retinoblastoma protein (pRb), a key regulator of cell-cycle progression. Loss of pRb expression has been implicated in breast cancer development and progression; however, its association with clinicopathological variables remains incompletely understood.

Aim: To evaluate the immunohistochemical expression of retinoblastoma protein (pRb) in invasive breast carcinoma and determine its association with clinicopathological variables.

Materials and Methods: This cross-sectional study with retrospective and prospective components was conducted in the Department of Pathology, Maharishi Markandeshwar Institute of Medical Sciences and Research, Mullana, Haryana, from January 2024 to December 2025. A total of 50 histopathologically confirmed cases of invasive breast carcinoma were included. Immunohistochemical evaluation of pRb expression was performed on formalin-fixed paraffin-embedded tissue sections. pRb expression status was categorized as lost, low, or positive and correlated with age, histological grade, tumour size, lymph node status, hormone receptor status, HER2 status, and molecular subtype. Statistical analysis was performed using appropriate tests, with $p<0.05$ considered statistically significant.

Results: The majority of patients belonged to the 40–49 years age group (30.0%). Invasive carcinoma of no special type constituted 98.0% of cases, and Grade 2 tumours were most common (54.0%). Loss of pRb expression was observed in 64.0% of cases, low expression in 14.0%, and positive expression in 22.0%. No statistically significant association was observed between pRb expression and age ($p=0.476$), histological grade ($p=0.240$), ER status ($p=0.926$), PR status ($p=0.998$), HER2 status ($p=0.764$), tumour size ($p=0.285$), lymph node status ($p=0.193$), or molecular subtype ($p=0.523$).

Conclusion: pRb loss is a frequent finding in invasive breast carcinoma and may play an important role in breast cancer pathogenesis. Although no significant association with clinicopathological variables was identified, the high prevalence of pRb loss highlights its potential prognostic relevance. Further large-scale studies are needed to clarify its clinical significance and therapeutic implications.

Keywords: Invasive breast carcinoma; Retinoblastoma protein; pRb; RB1 gene; Immunohistochemistry; Molecular subtype; Triple-negative breast cancer; Prognostic biomarker.

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INTRODUCTION

Breast carcinoma is the most frequently diagnosed malignancy among women worldwide and remains a leading cause of cancer-related mortality despite significant advances in diagnosis and treatment.[1] The biological behavior of breast cancer is highly heterogeneous, resulting in considerable variations in prognosis, therapeutic response, and survival outcomes. Traditional prognostic parameters such as tumor size, histological grade, lymph node status, and hormone receptor expression continue to play important roles in patient management; however, increasing emphasis is being placed on molecular biomarkers that provide insights into tumor biology and guide personalized therapeutic strategies.[2] Identification of novel prognostic and predictive markers is therefore essential for improving risk stratification and optimizing treatment approaches in invasive breast carcinoma.

The retinoblastoma gene (RB1), located on chromosome 13q14, is one of the most important tumor suppressor genes involved in the regulation of cell cycle progression. RB1 encodes the retinoblastoma protein (pRb), a nuclear phosphoprotein that controls the transition from the G1 to the S phase of the cell cycle through its interaction with E2F transcription factors.[3] Under normal physiological conditions, pRb inhibits cellular proliferation by preventing inappropriate DNA synthesis. Functional inactivation of RB1 leads to uncontrolled cell division, genomic instability, and tumor development.[4] Alterations in the RB pathway have been documented in a variety of human malignancies, including retinoblastoma, osteosarcoma, small-cell lung carcinoma, and breast carcinoma.[5]

Recent molecular studies have highlighted the significant role of RB1 pathway dysregulation in breast cancer pathogenesis. Loss of RB1 function may occur through gene deletion, mutation, promoter methylation, or aberrant phosphorylation of pRb, resulting in reduced or absent protein expression.[6] Several investigations have demonstrated that RB1 alterations are particularly common in aggressive molecular subtypes of breast cancer, including triple-negative and basal-like carcinomas, where they are associated with increased proliferative activity and poor clinical outcomes.[7] Furthermore, RB1 loss has been implicated in resistance to endocrine therapy and CDK4/6 inhibitors, emphasizing its importance as both a prognostic and predictive biomarker.[8]

Immunohistochemistry (IHC) provides a practical and cost-effective method for evaluating pRb expression in routine pathology practice. Assessment of pRb status by IHC allows indirect evaluation of RB1 gene functionality and has emerged as a valuable tool for studying tumorbehavior. Several studies have reported associations between loss of pRb expression and adverse clinicopathological features such as higher histological grade, larger tumor size, lymph node metastasis, elevated Ki-67 index, and hormone receptor negativity.[6–8] However, the reported prevalence of pRb loss and its relationship with clinicopathological variables vary across different populations, necessitating further investigation.

Invasive breast carcinoma constitutes the majority of breast malignancies encountered in clinical practice and exhibits marked biological diversity. Understanding the expression pattern of pRb in these tumors may provide important insights into disease progression and therapeutic responsiveness.[9] Moreover, evaluation of RB1 status may help identify subsets of patients with aggressive disease who could benefit from intensified treatment strategies or targeted therapies aimed at cell-cycle regulatory pathways.[10]

Therefore, the present study aims to evaluate the immunohistochemical expression of retinoblastoma protein in invasive breast carcinoma and to determine its correlation with various clinicopathological parameters. Such an analysis may contribute to a better understanding of the prognostic significance of RB1 alterations and their potential role in personalized breast cancer management.

The present study was undertaken to evaluate the immunohistochemical expression of retinoblastoma protein (pRb) in histopathologically confirmed cases of invasive breast carcinoma and to determine its association with various clinicopathological parameters. The study further aimed to assess the relationship between pRb expression and molecular subtypes of breast cancer, analyse the pattern of pRb loss, and explore its potential prognostic significance in disease progression and outcome.

MATERIALS AND METHODS

Study Design: Cross-sectional observational study with both retrospective and prospective components.

Study Population: Histopathologically diagnosed cases of invasive breast carcinoma received as core needle biopsy, breast conservation surgery (lumpectomy/wide local excision), or mastectomy specimens in the Department of Pathology.

Sample Size:50 cases of invasive breast carcinoma. The sample size was calculated based on an expected prevalence of pRb loss of approximately 30%, with a 95% confidence level and 12% absolute precision.

Study Duration:2 years (January 2024 to December 2025).

Study Place: Department of Pathology, Maharishi Markandeshwar Institute of Medical Sciences and Research (MMIMSR), Mullana, Ambala, Haryana, India.

Inclusion Criteria:

1. Histopathologically confirmed cases of invasive breast carcinoma.
2. Cases received as core needle biopsy (tru-cut biopsy), breast conservation

surgery specimens, or mastectomy specimens.

3. Patients diagnosed during the study period with adequate clinical and pathological data.
4. Cases with sufficient formalin-fixed paraffin-embedded tissue available for immunohistochemical analysis.

Exclusion Criteria:

1. Patients with recurrent breast carcinoma.
2. Patients who had received neoadjuvant chemotherapy and/or radiotherapy before biopsy or surgical excision.
3. Cases of male breast carcinoma.
4. Cases with inadequate tissue for immunohistochemical evaluation.
5. Poorly preserved tissue blocks or slides unsuitable for interpretation.

Ethical Approval: The study was approved by the Institutional Ethics Committee (IEC) of Maharishi Markandeshwar University, Mullana. Written informed consent was obtained for prospective cases, and confidentiality of patient data was maintained throughout the study.

Statistical Analysis: The collected data were entered into Microsoft Excel and analyzed using the Statistical Package for the Social Sciences (SPSS) software version 27.0 (IBM Corp., Armonk, NY, USA). Categorical variables such as age group, histological grade, hormone receptor status, HER2 status, molecular subtype, and pRb expression status were summarized as frequencies and percentages. Continuous variables, where applicable, were expressed as mean ± standard deviation (SD). The association between pRb expression status and clinicopathological variables was assessed using the Chi-square test or Fisher's exact test whenever the expected cell frequency was less than five. A p-value of less than 0.05 was considered statistically significant. The results were presented in the form of tables and charts to facilitate interpretation and comparison of findings.

RESULT

Table 1. Clinicopathological Characteristics of Study Population

Variable	Category	n	%
Age Group (Years)	<40	9	18
	40–49	15	30
	50–59	14	28
	60–69	6	12
	≥70	6	12
Specimen Type	Biopsy	23	46
	Mastectomy	22	44
	BCS/Lumpectomy	5	10
Tumour Laterality	Right	27	54
	Left	23	46
Histological Subtype	Invasive Carcinoma NST	49	98
	Mucinous Carcinoma	1	2
Histological Grade	Grade 1	2	4
	Grade 2	27	54
	Grade 3	21	42

Table 2. Tumour Characteristics and Immunohistochemical Profile

Variable	Category	n	%
ER Status	Positive	24	48
	Negative	26	52
PR Status	Positive	14	28
	Negative	36	72
HER2 Status	Positive (3+)	26	52
	Equivocal (2+)	3	6
	Negative (0/1+)	21	42
Ki-67 Index	<14%	7	14
	14–19%	2	4
	20–29%	4	8
	≥30%	25	50
	Not Done	12	24
Molecular Subtype	Luminal A/B (HER2−)	13	26
	Luminal B (HER2+)	11	22
	HER2-Enriched	15	30
	Triple-Negative	11	22

Table 3. pRb Expression Pattern in Invasive Breast Carcinoma

pRb Expression Status	n	%
Lost (Negative)	32	64
Low Expression	7	14
Positive Expression	11	22
Total	**50**	**100**

Table 4. Association of pRb Expression with Clinicopathological Variables

Variab	Category	Los	Lo	Positi	p-

le		t n (%)	w n (%)	ve n (%)	value
Age Group	<40–≥70 years	32 (64.0)	7 (14.0)	11 (22.0)	0.476
Histological Grade	Grade 1–3	32 (64.0)	7 (14.0)	11 (22.0)	0.24
ER Status	Positive/Negative	32 (64.0)	7 (14.0)	11 (22.0)	0.926
PR Status	Positive/Negative	32 (64.0)	7 (14.0)	11 (22.0)	0.998
HER2 Status	Positive/Equivocal/Negative	32 (64.0)	7 (14.0)	11 (22.0)	0.764
Tumour Laterality	Right/Left	32 (64.0)	7 (14.0)	11 (22.0)	0.09
Specimen Type	Biopsy/Mastectomy/BCS	32 (64.0)	7 (14.0)	11 (22.0)	0.102

Table 5. Association of pRb Expression with Prognostic Variables

Variable	**Category**	**Lost n (%)**	**Low n (%)**	**Positive n (%)**	**p-value**
Tumour Size (n=26)	≤2 cm	3 (75.0)	1 (25.0)	0 (0.0)	**0.285**
	2.1–5 cm	12 (92.3)	1 (7.7)	0 (0.0)	
	>5 cm	6 (66.7)	1 (11.1)	2 (22.2)	
Lymph Node Status (n=24)	Positive	11 (64.7)	4 (23.5)	2 (11.8)	**0.193**
	Negative	7 (100.0)	0 (0.0)	0 (0.0)	
Molecular Subtype	Luminal A/B (HER2–)	8 (61.5)	2 (15.4)	3 (23.1)	**0.523**
	Luminal B (HER2+)	8 (72.7)	1 (9.1)	2 (18.2)	
	HER2-Enriched	7 (46.7)	4 (26.7)	4 (26.7)	
	Triple-Negative	9 (81.8)	0 (0.0)	2 (18.2)	

Figure: 1. Tumour Characteristics and Immunohistochemical Profile

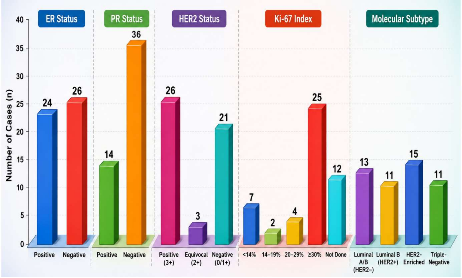

Figure2. Association of pRb Expression with Prognostic Variables

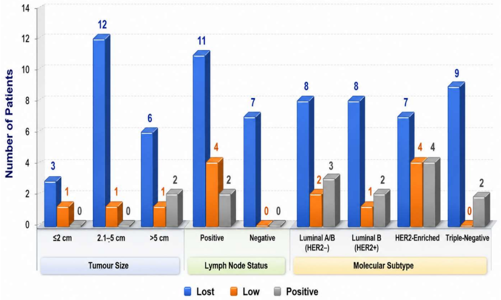

Table 1. A total of 50 histopathologically confirmed cases of invasive breast carcinoma were included in the study. The majority of patients belonged to the age group of 40–49 years (15 cases; 30.0%), followed closely by the 50–59 years age group (14 cases; 28.0%). Patients younger than 40 years constituted 18.0% (n=9) of the study population, while those aged 60–69 years and ≥70 years accounted for 12.0% (n=6) each. Regarding specimen type, core needle biopsy specimens were the most common, comprising 46.0% (n=23) of cases, followed by mastectomy specimens in 44.0% (n=22) and breast conservation surgery (BCS)/lumpectomy specimens in 10.0% (n=5). Tumours were slightly more frequent in the right breast, observed in 54.0% (n=27) of patients, whereas 46.0% (n=23) involved the left breast. Histologically, invasive carcinoma of no special type (NST) was the predominant subtype, accounting for 98.0% (n=49) of cases, while mucinous carcinoma was identified in only one patient (2.0%). Most tumours were of intermediate grade, with Grade 2 carcinoma observed in 54.0% (n=27) of cases, followed by Grade 3 carcinoma in 42.0% (n=21), whereas Grade 1 carcinoma constituted only 4.0% (n=2).

Table 2. Immunohistochemical evaluation revealed estrogen receptor (ER) positivity in 48.0% (n=24) of cases, while 52.0% (n=26) were ER negative. Progesterone receptor (PR) positivity was observed in 28.0% (n=14) of tumours, whereas 72.0% (n=36) were PR negative. HER2 overexpression (3+) was identified in 52.0% (n=26) of cases, while 6.0% (n=3) demonstrated equivocal HER2 expression (2+), and 42.0% (n=21) were HER2 negative. Evaluation of the proliferative index

showed that half of the cases (50.0%; n=25) exhibited a Ki-67 index of ≥30%, indicating high proliferative activity. A Ki-67 index of <14%, 14–19%, and 20–29% was observed in 14.0% (n=7), 4.0% (n=2), and 8.0% (n=4) of cases, respectively, while Ki-67 assessment was unavailable in 24.0% (n=12) of cases. Based on receptor status, HER2 expression, and proliferative activity, the most common molecular subtype was HER2-enriched carcinoma (30.0%; n=15), followed by Luminal A/B (HER2-negative) subtype (26.0%; n=13). Luminal B (HER2-positive) and Triple-Negative Breast Carcinoma (TNBC) each constituted 22.0% of cases (n=11).

Table 3. Assessment of retinoblastoma protein (pRb) expression by immunohistochemistry demonstrated loss of pRb expression in the majority of invasive breast carcinomas. Complete loss of expression was observed in 64.0% (n=32) of cases. Low pRb expression was identified in 14.0% (n=7) of cases, while preserved positive pRb expression was noted in only 22.0% (n=11) of tumours. These findings indicate that alterations in the RB pathway are common in invasive breast carcinoma and suggest a potentially important role of pRb loss in breast cancer pathogenesis and progression.

Table 4. The association between pRb expression status and clinicopathological variables was analysed using appropriate statistical tests. No statistically significant association was observed between pRb expression and patient age group (p=0.476). Similarly, histological grade did not show a significant correlation with pRb expression status (p=0.240). Analysis of hormone receptor status demonstrated no significant association between pRb expression and ER status (p=0.926) or PR status (p=0.998). Likewise, HER2 expression status was not significantly associated with pRb expression patterns (p=0.764). Although loss of pRb expression appeared slightly more frequent among right-sided tumours, tumour laterality did not demonstrate statistical significance (p=0.090). Furthermore, no significant relationship was observed between pRb expression and specimen type, including biopsy, mastectomy, and breast conservation surgery specimens (p=0.102). Overall, pRb loss was observed across all clinicopathological categories without significant variation.

Table 5. The relationship between pRb expression and important prognostic variables was also evaluated. Among cases with available tumour size data (n=26), loss of pRb expression was observed in 75.0% of tumours measuring ≤2 cm, 92.3% of tumours measuring 2.1–5 cm, and 66.7% of tumours larger than 5 cm. However, the association between tumour size and pRbexpression did not reach statistical significance (p=0.285). Analysis of lymph node status among 24 evaluable cases showed pRb loss in 64.7% of node-positive tumours and in all node-negative tumours (100.0%); however, this association was also statistically non-significant (p=0.193).

With respect to molecular subtype, pRb loss was observed in 61.5% of Luminal A/B (HER2-negative) tumours, 72.7% of Luminal B (HER2-positive) tumours, 46.7% of HER2-enriched tumours, and 81.8% of Triple-Negative Breast Carcinomas. Although pRb loss appeared most frequent in the triple-negative subtype and least frequent in HER2-enriched tumours, the differences among molecular subtypes were not statistically significant (p=0.523). Overall, no significant association was identified between pRb expression status and tumour size, lymph node involvement, or molecular subtype in the present study.

DISCUSSION

The present study evaluated the immunohistochemical expression of retinoblastoma protein (pRb) in invasive breast carcinoma and examined its association with various clinicopathological parameters. Loss of pRb expression was observed in 64.0% of cases, indicating that disruption of the RB pathway is a frequent molecular event in breast carcinogenesis. The findings of the current study are broadly consistent with recent literature highlighting the importance of RB1 pathway alterations in breast cancer progression and tumour aggressiveness.

In the present study, the majority of patients belonged to the 40–59 years age group (58.0%). Similar age distributions have been reported by Khokhar et al.[11], who observed that most invasive breast carcinoma patients were diagnosed during the fifth and sixth decades of life. Likewise, Aljamaet al.[12] reported a mean age of presentation between 48 and 55 years in patients undergoing molecular profiling of breast carcinoma. The predominance of middle-aged and older women in the present study reflects the known epidemiological pattern of breast cancer in developing countries.

Regarding histological characteristics, invasive carcinoma of no special type (NST) constituted 98.0% of cases in the present study. Comparable findings were reported by Sethi et al.[13], who observed NST morphology in more than 90% of breast carcinoma cases evaluated for molecular markers. Similarly, Rakha and colleagues[14] noted that invasive carcinoma NST remains the most common histological subtype worldwide and serves as the predominant tumour category in studies assessing cell-cycle regulatory proteins.

Most tumours in the current study were histological Grade 2 (54.0%), followed by Grade 3 (42.0%). These findings are comparable to those reported by Abubakar et al.[15], who found intermediate-grade tumours to be the most prevalent category among invasive breast carcinomas. Grade 2 predominance has also been reported by Choi et al.[16], suggesting that moderately differentiated carcinomas represent the largest subgroup encountered in routine pathological practice.

The immunohistochemical profile of the present study demonstrated ER positivity in 48.0%, PR positivity in 28.0%, and HER2 positivity in 52.0% of cases. Similar receptor distributions have been reported by Yeo et al.[17], who observed ER positivity in approximately half of breast cancer patients and HER2 overexpression in nearly one-third to one-half of cases. Variations across studies may be attributable to differences in patient demographics, tumour biology, and referral patterns. The high proportion of HER2-positive cases observed in the present study may reflect the inclusion of a larger number of biologically aggressive tumours referred to a tertiary care centre.

Analysis of molecular subtypes revealed HER2-enriched carcinoma as the most common subtype (30.0%), followed by Luminal A/B HER2-negative tumours (26.0%). Triple-negative breast carcinoma (TNBC) accounted for 22.0% of cases. In contrast, Kim et al.[18] reported luminal subtypes as the predominant molecular category in their cohort, with HER2-enriched and TNBC subtypes occurring less frequently. Such differences may be explained by geographical and ethnic variations, sample size differences, and institutional referral biases. Nevertheless, the proportion of TNBC observed in the present study remains comparable to that reported in Asian populations.

The most important finding of the present study was the high frequency of pRb loss, observed in 64.0% of invasive breast carcinomas. This prevalence is comparable to that reported by Park et al.[19], who demonstrated RB pathway disruption in approximately 55–65% of high-grade breast carcinomas using immunohistochemical and molecular methods. Similarly, Asghar et al.[20] reported frequent loss of pRb expression, particularly in aggressive molecular subtypes, suggesting that RB pathway inactivation contributes significantly to breast tumour progression. The high prevalence of pRb loss in the present study further supports the role of RB1 dysfunction as an important molecular event in invasive breast carcinoma.

No statistically significant association was identified between pRb expression and patient age (p=0.476). Similar findings were reported by Park et al.[19], who found that RB1 alterations occurred across all age groups without significant age-related variation. These observations suggest that pRb loss is more closely related to intrinsic tumour biology than to patient demographics.

Histological grade also did not show a statistically significant association with pRb expression in the present study (p=0.240). Although several investigators have reported higher rates of pRb loss in poorly differentiated tumours, Asghar et al.[20] observed that the association often becomes non-significant in studies with limited sample sizes. The trend toward greater pRb loss in higher-grade lesions noted in several studies may therefore require larger cohorts for definitive confirmation.

No significant relationship was found between pRb expression and ER status (p=0.926), PR status (p=0.998), or HER2 status (p=0.764). Similar observations were made by Yeo et al.[17], who reported that pRb alterations can occur independently of hormone receptor expression. These findings indicate that RB pathway dysfunction may represent a distinct molecular event that transcends conventional receptor-based classifications.

The present study also demonstrated no statistically significant association between pRb expression and tumour size (p=0.285) or lymph node metastasis (p=0.193). Comparable results were reported by Khokhar et al.[11], who found no consistent relationship between RB1 protein loss and tumour burden parameters. However, some authors have suggested that larger multicentric studies may reveal subtle associations not evident in smaller cohorts.

Although pRb loss was observed most frequently in triple-negative breast carcinoma (81.8%), followed by Luminal B HER2-positive tumours (72.7%), the association with molecular subtype did not reach statistical significance (p=0.523). Similar trends have been reported by Park et al.[19] and Asghar et al.[20], both of whom documented increased frequencies of RB pathway disruption in TNBC. Triple-negative tumours are characterized by genomic instability and aggressive biological behaviour, factors that may explain the higher prevalence of RB1 pathway abnormalities in this subtype.

Overall, the findings of the present study support the growing body of evidence indicating that pRb loss is a common molecular alteration in invasive breast carcinoma. Although statistically significant associations with clinicopathological variables were not demonstrated, the high frequency of pRb loss, particularly among biologically aggressive subtypes, suggests a potential role for pRb as a prognostic biomarker and therapeutic target. Larger multicentric studies incorporating molecular genetic analysis are warranted to further elucidate the clinical significance of RB pathway alterations in breast cancer.

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