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# Correlation Between Histological Grade and Hormone Receptor Status in Breast Carcinoma

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## Abstract

**Background:** Breast carcinoma is the most prevalent malignancy among women globally and a leading cause of cancer-related mortality. The assessment of histological grade and hormone receptor status, including estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2/neu), plays a pivotal role in determining prognosis and guiding individualized treatment strategies. Histological grade reflects the aggressiveness of the tumor, while hormone receptor status helps tailor targeted therapies. Studying the correlation between these parameters. It is crucial to optimize patient care.

**Aim and Objectives:** The aim of the study was to evaluate the correlation between histological grade and hormone receptor status in invasive breast carcinoma. The objectives included grading tumors using the Nottingham modification of the Bloom-Richardson system and assessing ER, PR, and HER2/neu expression by immunohistochemistry.

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**Methodology:** This was a cross-sectional observational study conducted over a period of 18 months in the Department of Pathology at a tertiary care hospital. A total of 120 histopathologically confirmed cases of invasive breast carcinoma were included. Tumor grading was done using the Nottingham grading system based on tubule formation, nuclear pleomorphism, and mitotic count. Immunohistochemical staining was performed for ER, PR, and HER2/neu, and the results were interpreted according to ASCO/CAP guidelines. Statistical analysis was conducted using the Chi-square test to evaluate the correlation between histological grade and receptor status.

**Results:** Out of 120 cases, Grade II tumors were most common (48.3%), followed by Grade III (32.5%) and Grade I (19.2%). ER and PR positivity were significantly higher in Grade I and II tumors, while HER2/neu positivity and triple-negative profile were more frequently associated with Grade III tumors. An inverse correlation was observed between histological grade and hormone receptor expression, which was statistically significant ($p < 0.05$).

**Conclusion:** The study demonstrated a significant inverse relationship between histological grade and hormone receptor positivity. Lower-grade tumors exhibited higher ER and PR expression, indicating better prognosis and responsiveness to hormonal therapy. In contrast, higher-grade tumors were more frequently HER2-positive or triple-negative, which are associated with aggressive clinical behavior and limited treatment options. These findings emphasize the importance of combined histological and immunohistochemical evaluation in the management of breast carcinoma.

**Keywords:** Breast carcinoma, histological grade, estrogen receptor, progesterone receptor, HER2/neu, immunohistochemistry, hormone receptor status.

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## INTRODUCTION

Breast cancer remains the most commonly diagnosed malignancy among women worldwide, accounting for a significant proportion of cancer-related morbidity and mortality [1]. In India, the rising incidence of breast carcinoma, especially

among premenopausal women, has highlighted the urgent need for early diagnosis, accurate grading, and personalized treatment approaches [2]. The histological grade of a tumor, assessed using the Nottingham modification of the Bloom-Richardson system, serves as an important prognostic indicator by reflecting the degree of tumor differentiation [3].

Alongside histological grading, hormone receptor status—primarily the expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2/neu)—is vital for guiding treatment decisions. Hormone receptor-positive tumors generally respond well to endocrine therapy and are associated with favorable outcomes, whereas HER2-positive and triple-negative tumors often require more aggressive treatment and are linked to poorer prognosis [4,5].

Several studies have explored the relationship between histological grade and hormone receptor status, with findings suggesting that lower-grade tumors tend to be hormone receptor-positive, while higher-grade tumors are often HER2-positive or triple-negative [6,7]. Understanding this correlation is essential in the context of precision oncology, as it can help predict tumor behavior, therapeutic response, and long-term prognosis.
This study aims to assess the correlation between histological grade and hormone receptor status in patients with invasive breast carcinoma in a tertiary care setting.

## Methodology

This hospital-based cross-sectional observational study was conducted in the Department of Pathology at a tertiary care hospital over a period of 18 months. A total of 120 histopathologically confirmed cases of invasive breast carcinoma were included. The sample size was calculated using the formula:

$$n = Z^2 \times p \times (1 - p) / d^2$$

With a prevalence of 76.8% for ER positivity based on the study by Ravikumar et al., [8], a 95% confidence level (Z = 1.96), and 8% absolute precision, the required sample size was approximately 107. Considering exclusions and dropouts, it was rounded to a final sample of **120 cases**.

### ❖ Inclusion Criteria

- Histopathologically confirmed cases of invasive breast carcinoma (lumpectomy or mastectomy specimens)
- Adequate tumor tissue available for grading and immunohistochemistry (IHC)

### ❖ Exclusion Criteria

- Patients who received neoadjuvant chemotherapy or radiotherapy
- Poorly fixed or necrotic tissue samples not suitable for IHC
- Cases with equivocal HER2/neu (2+) without confirmatory FISH testing

### ❖ Histopathological Evaluation and Grading Procedure

- **Grossing:** All specimens were received in 10% neutral buffered formalin and fixed for 24–48 hours. Gross examination included tumor size, location, distance from resection margins, and lymph node status.
- **Tissue processing:** Representative sections of tumor were processed using a standard automated tissue processor. Blocks were embedded in paraffin.
- **Sectioning and staining:** 4–5 µm sections were cut and stained with Hematoxylin and Eosin (H&E).
- **Tumor grading:** Histological grade was determined using the Nottingham modification of the Bloom-Richardson grading system [3], which assesses:
    - **Tubule formation**

- **Nuclear pleomorphism**
- **Mitotic count**

Each feature was scored from 1 to 3. The sum of the three scores classified tumors as:

- Grade I (Well differentiated): Score 3–5
- Grade II (Moderately differentiated): Score 6–7
- Grade III (Poorly differentiated): Score 8–9

❖ **Immunohistochemistry (IHC) Procedure**

- IHC was performed on 4–5 µm formalin-fixed, paraffin-embedded (FFPE) sections mounted on poly-L-lysine coated slides.
- Slides were deparaffinized in xylene and rehydrated through graded alcohols.
- **Antigen retrieval** was performed using a pressure cooker in citrate buffer (pH 6.0) for 20 minutes.
- Endogenous peroxidase activity was blocked using hydrogen peroxide (3%) for 10 minutes.
- Sections were incubated with **primary monoclonal antibodies** against:
  - **ER (clone SP1)**
  - **PR (clone PgR 636)**
  - **HER2/neu (clone CB11)**
- Secondary detection was carried out using a polymer-based detection system (HRP-conjugated) and visualized using **DAB (diaminobenzidine)** chromogen.
- Slides were counterstained with hematoxylin, dehydrated, and mounted.

❖ **Interpretation of IHC (as per ASCO/CAP 2020 Guidelines) [9]**

- **ER and PR positivity**: Defined as ≥1% nuclear staining in tumor cells.
- **HER2/neu**:
  - **Score 0 or 1+**: Negative
  - **Score 2+**: Equivocal (FISH recommended)
  - **Score 3+**: Positive (uniform intense membrane staining in >10% of tumor cells)

Only HER2 0, 1+, and 3+ cases were included for correlation; equivocal cases were excluded if FISH was not performed.

### ❖ Data Compilation and Statistical Analysis

All data including histological grade, estrogen receptor (ER), progesterone receptor (PR), and HER2/neu expression status were compiled and organized using **Microsoft Excel**. Statistical analysis was performed using **IBM SPSS Statistics version 26.0**. Descriptive statistics were calculated and presented as **frequencies and percentages** to summarize categorical variables. To evaluate the association between histological grade and hormone receptor status (ER, PR, and HER2/neu), the **Chi-square test** was applied. A **p-value less than 0.05** was considered **statistically significant**, indicating a meaningful correlation between the studied variables.

## Results

A total of 120 histologically confirmed cases of invasive breast carcinoma were analyzed in the present study. The age of patients ranged from 28 to 78 years, with a **mean age of 52.4 ± 10.2 years**, indicating that the disease predominantly affects middle-aged to elderly women. The majority of tumors belonged to the **invasive ductal carcinoma – not otherwise specified (NOS)** subtype (95%).

### ❖ Histological Grade Distribution

The tumors were graded using the Nottingham modification of the Bloom-Richardson system. Grade II (moderately differentiated) tumors were most frequent, accounting for 48.3% of cases. This was followed by Grade III (poorly differentiated) tumors in 32.5% of cases and Grade I (well differentiated) in only 19.2% of cases. This pattern suggests that moderately to poorly differentiated tumors were more commonly encountered in this patient group, reflecting an overall intermediate to aggressive tumor biology.

**Table 1: Distribution of Cases According to Histological Grade (n = 120)**

| Histological Grade | Frequency (n) | Percentage (%) |
|---|---|---|
| Grade I | 23 | 19.2% |
| Grade II | 58 | 48.3% |
| Grade III | 39 | 32.5% |
| Total | 120 | 100% |

### ❖ Correlation of Estrogen Receptor (ER) Expression with Histological Grade

Among the 120 cases, ER positivity was observed in 72 cases (60%). When stratified by grade, Grade I tumors showed the highest ER expression (86.9%), followed by Grade II (62.1%), while Grade III tumors had the lowest ER positivity (35.9%). This shows a statistically significant inverse relationship between tumor grade and ER expression ($p = 0.002$), indicating that well-differentiated tumors are more likely to be hormone receptor-positive and may benefit from hormonal therapy.

### Table 2: Correlation of ER Status with Histological Grade

| Histological Grade | ER Positive (n) | ER Negative (n) | Total | p-value |
|---|---|---|---|---|
| Grade I | 20 (86.9%) | 3 (13.1%) | 23 | **0.002** |
| Grade II | 36 (62.1%) | 22 (37.9%) | 58 | |
| Grade III | 14 (35.9%) | 25 (64.1%) | 39 | |
| **Total** | **72** | **48** | 120 | |

### ❖ Correlation of Progesterone Receptor (PR) Expression with Histological Grade

Out of 120 cases, PR positivity was detected in 66 cases (55%). Similar to ER, PR expression was highest in Grade I tumors (82.6%), moderate in Grade II (58.6%), and lowest in Grade III (28.2%). The difference was found to be highly statistically significant ($p < 0.001$). These findings support the concept that poorly differentiated tumors lose hormonal receptor expression, thus impacting prognosis and treatment planning.

**Table 3: Correlation of PR Status with Histological Grade**

| Histological Grade | PR Positive (n) | PR Negative (n) | Total | p-value |
|---|---|---|---|---|
| **Grade I** | **19 (82.6%)** | **4 (17.4%)** | **23** | **<0.001** |
| **Grade II** | **34 (58.6%)** | **24 (41.4%)** | **58** | |
| **Grade III** | **11 (28.2%)** | **28 (71.8%)** | **39** | |
| **Total** | **64** | **56** | **120** | |

### ❖ Correlation of HER2/neu Expression with Histological Grade

HER2/neu overexpression (3+ score) was observed in 28 cases (23.3%). When analyzed by tumor grade, Grade III tumors showed the highest HER2/neu positivity (41.0%), followed by Grade II (15.5%) and Grade I (4.3%). The increasing trend of HER2 overexpression with higher tumor grade was statistically significant ($p = 0.001$), which reflects the known aggressive nature and poor prognostic implications of HER2-positive tumors.

**Table 4: Correlation of HER2/neu Status with Histological Grade**

| Histological Grade | HER2 Positive (n) | HER2 Negative (n) | Total | p-value |
|---|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| Grade I | 1 (4.3%) | 22 (95.7%) | 23 | **0.001** |
| Grade II | 9 (15.5%) | 49 (84.5%) | 58 | |
| Grade III | 16 (41.0%) | 23 (59.0%) | 39 | |
| **Total** | **26** | **94** | 120 | |

❖ **Correlation of Triple-Negative Breast Cancer (TNBC) Phenotype with Histological Grade**

A total of 20 cases (16.7%) were classified as triple-negative breast cancer (ER-, PR-, HER2-). Among these, the majority were Grade III tumors (33.3%), compared to 10.3% in Grade II and only 4.3% in Grade I. The statistically significant p-value (0.003) indicates that TNBCs are more likely to be high-grade tumors, reinforcing their aggressive clinical behavior and limited therapeutic options.

**Table 5: Distribution of Triple-Negative Phenotype by Histological Grade**

| **Histological Grade** | **TNBC (n)** | **Non-TNBC (n)** | **Total** | **p-value** |
|---|---|---|---|---|
| Grade I | 1 (4.3%) | 22 (95.7%) | 23 | **0.003** |
| Grade II | 6 (10.3%) | 52 (89.7%) | 58 | |
| Grade III | 13 (33.3%) | 26 (66.7%) | 39 | |
| **Total** | **20** | **100** | 120 | |

## Discussion

Breast carcinoma is a biologically heterogeneous disease, and its prognosis and therapeutic response depend significantly on histological grade and molecular receptor status. In the present study, we evaluated 120 cases of invasive breast carcinoma to assess the correlation between tumor grade and expression of hormone receptors (ER, PR) and HER2/neu.

In our study, Grade II tumors (moderately differentiated) were the most prevalent (48.3%), followed by Grade III (32.5%) and Grade I (19.2%). This grading pattern aligns with previous studies conducted in Indian populations. For instance, Ghosh et al. also reported Grade II as the most common histological grade in their cohort of 150 cases [4].

With regard to estrogen receptor (ER) expression, we observed an overall positivity of 60%, which showed a significant inverse correlation with tumor grade ($p = 0.002$). ER positivity was highest in Grade I tumors (86.9%) and lowest in Grade III tumors (35.9%). This finding is consistent with the study by Bhagat et al., who reported ER positivity in 68.3% of breast carcinomas, predominantly in low-grade tumors [5]. Similarly, Choudhury et al. observed that ER expression was significantly reduced in higher-grade tumors, suggesting increasing tumor aggressiveness with loss of hormone receptor expression [6].

Progesterone receptor (PR) expression in our study followed a similar pattern, with overall positivity of 55%, showing a statistically significant decline with increasing histological grade ($p < 0.001$). Grade I tumors showed 82.6% PR positivity compared to only 28.2% in Grade III tumors. This is in agreement with a study by Bhatt et al., who also found a strong association between lower histological grades and higher PR positivity [7]. This reinforces the prognostic implication that well-differentiated tumors are more likely to respond to hormone therapy.

In contrast, HER2/neu overexpression was most frequent in Grade III tumors (41%), with much lower rates in Grade II (15.5%) and Grade I (4.3%). The difference was statistically significant ($p = 0.001$), indicating that HER2-positive tumors are typically of higher grade and biologically more aggressive. These findings are supported by Rakha et al., who concluded that HER2 positivity is associated with higher histological grade, increased proliferation index, and poor outcome [10].

Additionally, our study found that triple-negative breast cancers (TNBC) constituted 16.7% of total cases and were significantly associated with Grade III tumors (33.3%) ($p = 0.003$). TNBCs are known to lack hormone receptors and HER2 amplification, limiting treatment options and often resulting in a more aggressive clinical course. Our findings are corroborated by the study of Kumar et al., who reported 18% TNBC prevalence, predominantly in poorly differentiated tumors [11].

Overall, the present study demonstrates a clear and statistically significant inverse relationship between histological grade and hormone receptor (ER/PR) expression, and a positive association between higher grade and HER2/neu or TNBC status. This emphasizes the prognostic relevance of combining histological grading with immunohistochemical profiling in breast cancer. Patients with low-grade, ER/PR-positive tumors may benefit from hormonal therapy and have better outcomes, whereas those with high-grade HER2-positive or TNBCs may require aggressive multimodal treatment and closer surveillance.

## Conclusion

The current study concludes that histological grade strongly correlates with hormone receptor status in invasive breast carcinoma. Lower-grade tumors were significantly associated with higher ER and PR expression, suggesting a more favorable biological behavior and responsiveness to endocrine therapy. In contrast, higher-grade tumors showed increased HER2/neu expression and TNBC phenotype, both of which are markers of aggressive disease requiring intensive therapeutic approaches. These findings support the routine evaluation of both histological grade and hormone receptor profile in all cases of breast cancer to guide personalized treatment and prognostication.

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