HSR (LONDON),
HOUGHTON STREET REVIEW JOURNAL
ISSN: 2058-5519|Impact factor-15.9
http://houghtonstreetreview.com/index.php/hsr

# CLINICAL, MORPHOLOGICAL, AND IMMUNOHISTOCHEMICAL PREDICTORS OF BREAST CANCER PROGNOSIS: A REVIEW OF CURRENT EVIDENCE

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Doi: https://doi.org/10.5281/zenodo.22481105

**Annotation:** Breast cancer remains one of the most common malignant neoplasms among women and is characterized by significant biological and clinical heterogeneity. Accurate assessment of prognostic factors is essential for predicting disease progression and selecting individualized treatment strategies. This review summarizes current evidence on the prognostic significance of clinical, morphological, and immunohistochemical characteristics of breast cancer. Particular attention is given to tumor size, lymph node involvement, histological grade, estrogen and progesterone receptors (ER and PR), HER2 status, and the Ki-67 proliferation index. The available evidence indicates that the combined assessment of these parameters provides a more comprehensive evaluation of tumor biology and individual risk of recurrence and metastasis. An integrated prognostic approach may improve risk stratification and support personalized treatment and follow-up of patients with breast cancer.

**Keywords:** breast cancer, prognosis, ER, PR, HER2, Ki-67, tumor proliferation, recurrence, metastasis, personalized medicine.

According to published studies, the prevalence of HER2-positive breast cancer varies depending on the population studied, the diagnostic criteria applied, and the molecular and clinical characteristics of the tumor. HER2 overexpression or amplification may occur in both hormone receptor-positive and hormone receptor-negative tumors, highlighting the biological heterogeneity of breast cancer and the importance of comprehensive assessment of estrogen receptor (ER), progesterone receptor (PR), and HER2 status.Breast cancer is the most frequently diagnosed malignant neoplasm among women worldwide and remains a major cause of cancer-related mortality. Although the majority of breast lesions can be adequately classified using routine hematoxylin and eosin staining, immunohistochemistry (IHC) is essential in specific diagnostic and prognostic situations. IHC contributes to the differential diagnosis of ductal and lobular carcinomas, the distinction between in situ and invasive lesions, the evaluation of atypical ductal hyperplasia and ductal carcinoma in situ, the characterization of papillary and spindle-cell lesions, and the identification of metastatic breast carcinoma. In addition, IHC plays a central role in determining prognostic and predictive biomarkers [1].Among the most clinically relevant immunohistochemical markers are ER, PR, HER2, and Ki-67. These biomarkers provide important information regarding the biological characteristics of the tumor, potential response to systemic treatment, and individual prognosis. HER2 is particularly important because its assessment has both prognostic and predictive implications and directly influences the selection of HER2-targeted therapy.The Ki-67 proliferation index is widely used to estimate the proliferative activity of breast cancer cells. Higher Ki-67 expression is generally associated with more aggressive tumor characteristics and may provide additional prognostic information. Other biomarkers,

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including p53 and additional molecular markers, have also been investigated as potential prognostic or predictive factors. However, their routine clinical application remains more controversial because of differences in analytical methodology and insufficient standardization. Although most breast pathology is diagnosed using sections stained with haematoxylin and eosin, in some cases immunohistochemistry is required for proper evaluation. We have investigated such cases, including the distinction between ductal and lobular carcinoma, carcinoma in situ and invasive carcinoma, typical ductal hyperplasia and atypical ductal hyperplasia/ductal carcinoma in situ, assessment of papillary and spindle cell lesions, assessment of metastases, and evaluation of prognostic and therapeutic markers[1]. Many laboratories also evaluate other factors for clinical use using immunohistochemical methods, including, among others, the c-erbB-2, p53, and Ki-67 proliferation indices. While the available research suggests that these factors may indeed be useful in making treatment decisions, their clinical utility is still controversial and, as with hormone receptor evaluation, there are important unresolved technical issues such as tissue preparation, reagents used, and, most importantly, interpretation of the results. Several laboratories have made significant efforts to develop reproducible methods for assessing these factors and have conducted comprehensive studies demonstrating the predictive and predictive value of their results. However, most of the labs offering these tests have not properly validated them and may not even be aware of the issues that need attention. If laboratories do not validate their tests or follow the procedures of others who have done so, they risk reporting meaningless and potentially harmful results. In the future, these and other factors will be included in a prognostic index that will better reflect the biodiversity of breast cancer and that will more accurately predict clinical outcome[2].

The HER-2/neu oncogene is a member of the erbB-like family of oncogenes and is related to, but distinct from, the epidermal growth factor receptor. This gene has been shown to be amplified in human breast cancer cell lines. This study examined changes in this gene in 189 primary human breast tumors. HER-2/neu amplification has been found to increase 2–20-fold in 30% of tumors. The correlation of gene amplification with several parameters of the disease was evaluated. Amplification of the HER-2/neu gene was a significant predictor of both overall survival and time to recurrence in patients with breast cancer. It retained its significance even after adjusting for other known prognostic factors. Moreover, HER-2/neu amplification had a greater prognostic value than most currently used prognostic factors, including hormone receptor status, in metastatic lymph node lesions. These findings indicate that this gene may play a role in the biological behavior and/or pathogenesis of breast cancer in humans. [3]The clinical usefulness of immunohistochemical biomarkers depends not only on the biological relevance of the marker but also on the quality and reproducibility of the testing process. Important methodological variables include tissue fixation and processing, antibody selection, staining protocols, internal and external quality control, and, particularly, interpretation and scoring of the results. Consequently, standardized and validated IHC procedures are essential for obtaining clinically reliable information[4].Thus, current evidence supports the use of ER, PR, HER2, and Ki-67 as an integrated immunohistochemical panel rather than interpreting individual markers in isolation. Combining these biomarkers with tumor size, lymph-node status, histological grade, and clinical stage may provide a more comprehensive assessment of tumor biology and improve individual risk stratification and treatment planning in patients with breast cancer.

According to published studies, the prevalence of HER2-positive breast cancer varies across populations and depends on the criteria used for HER2 assessment, as well as on the molecular and clinical characteristics of the tumor. HER2-positive tumors may occur in both hormone receptor-positive and hormone receptor-negative breast cancers, reflecting the considerable biological heterogeneity of the disease. Therefore, comprehensive assessment of estrogen receptor (ER),

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progesterone receptor (PR), and HER2 status is essential for accurate tumor characterization and treatment planning.[5]

Routine histopathological examination using hematoxylin and eosin staining remains the principal method for morphological assessment of breast lesions. However, immunohistochemistry (IHC) is indispensable in a number of diagnostic and prognostic situations, including differentiation between ductal and lobular carcinoma, distinction between in situ and invasive carcinoma, assessment of atypical ductal hyperplasia and ductal carcinoma in situ, characterization of papillary and spindle-cell lesions, and identification of metastatic breast carcinoma. In addition, IHC provides essential information regarding prognostic and predictive biomarkers [6].

Among the most clinically important biomarkers, ER, PR, HER2, and Ki-67 have particular significance. ER and PR reflect the hormonal responsiveness of the tumor and are essential for determining the potential benefit of endocrine therapy. HER2 has both prognostic and predictive significance and is a key determinant of eligibility for HER2-targeted treatment[7]. Ki-67 reflects tumor-cell proliferative activity and may provide additional information regarding tumor aggressiveness and the risk of disease recurrence[8,12].

Other immunohistochemical markers, including p53 and additional proliferation-associated biomarkers, have also been investigated as potential prognostic and predictive factors. However, their routine clinical application remains controversial because of insufficient standardization and variability in analytical and interpretative approaches[9,10].

The reliability of immunohistochemical assessment depends on several technical factors, including tissue fixation and processing, antibody selection, staining procedures, quality control, and interpretation of staining intensity and percentage of positive tumor cells. These methodological differences may contribute to interlaboratory variability and limit the comparability of results between studies[11].

Consequently, current evidence supports an integrated approach to immunohistochemical assessment, in which ER, PR, HER2, and Ki-67 are interpreted together with clinical stage, tumor size, histological grade, lymph-node status, and other relevant morphological characteristics. Such a comprehensive approach provides a more accurate characterization of tumor biology, improves prognostic stratification, and facilitates individualized treatment planning for patients with breast cancer.

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ISSN: 2058-5519|Impact factor-15.9
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