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Review Article

Role of immunohistochemical markers in breast carcinoma and other breast pathologies: A review with a note on recent update

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ABSTRACT

Breast cancer is the most common cause of malignancy worldwide in women & second most common cause of death among them.[1] Higher number of cases have been observed from more developed regions than in less developed.[2] In India age adjusted incidence rate of breast cancer is 2.8/100000 than United Kingdom (95/100000).[3]

Breast specimens for histopathological evaluation are one of the most common surgical pathology specimens encountered by a surgical pathologist. In regular breast pathology, immunohistochemistry is a useful tool for both diagnostic and prognostic purposes. Although, most breast lesions may be diagnosed using routine hematoxylin and eosin sections; but, in a few situations, such as morphologically equivocal instances or metastatic cancers of unknown source, immunohistochemistry can help to make a more accurate diagnosis.

This review will focus on diagnostic immunomarkers. However, the main goal of this review is to assess the diagnostic value of the most commonly investigated immunomarkers in the field of breast pathology by a review of the literature utilising the PubMed (US National Library of Medicine, Bethesda, Maryland) database of indexed publications from 1976 to 2022.

1. Introduction

Breast carcinoma is the most prevalent malignant tumour in women and the main cause of cancer-related fatalities, industrialised countries being most commonly affected.[4] Although there are many different forms of breast carcinomas, infiltrating ductal carcinoma is the most prevalent histological type.[5] Where a tumour is localised, surgery is the first line of treatment, followed by chemotherapy (when needed), radiation, and adjuvant hormonal therapy for oestrogen receptor (ER) and progesterone receptor (PR) positive cancers.[6] Breast cancer can be cured if diagnosed early enough. Tumour size, tumour grade, and axillary lymph node metastases are among traditional morphological prognostic markers. Because a considerable majority of patients with early-stage breast cancer have microscopic metastases at the time of diagnosis, biological molecular prognostic markers are now given more weightage.[7] The most important clinical indicators for stratifying breast cancer cases care are hormone receptors (ER and PR) and human epidermal growth factor receptor-2 (HER-2).[8] Understanding hormone receptors and HER-2 expressions is critical for planning and making decisions about breast cancer treatment.[8] In the treatment of breast cancer, prognostic and predictive factors are used. Prognostic factors influence a patient's overall outcome, such as the likelihood of recurrence after treatment. These variables

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aid in the selection of patients for a particular treatment.[9] Predictive factors assess the likelihood of a certain treatment's success. ER, PR, and HER2/neu are prognostic and predictive variables, respectively.[9] By applying a panel of immunomarkers and following a consistent technical and interpretational protocol, immunohistochemistry can be used effectively in the diagnostic and prognostic evaluation of breast cancers.

2. Epidemiology of Breast Cancer

In 2020, 2.3 million women diagnosed with breast cancer and 685 000 deaths occured globally. At the end of 2020, 7.8 million women were diagnosed with breast cancer, making it the world's most prevalent cancer. There was increased lost disability-adjusted life years (DALYs) by women to breast cancer globally than any other type of cancer.[10]

Breast cancer is ranked number one cancer among Indian females with age adjusted rate as high as 25.8 per 100,000 women and mortality 12.7 per 100,000 women. Mortality-to-incidence ratio was found to be high (66 in number) in rural registries and low (8 in number) in urban registries.[11]

The worldwide incidence and mortality are increasing at an alarming rate. In India, it is the commonest cancer in urban females, and the second commonest in females residing in rural areas. Studies suggest that the disease peaks at 40–50 years in Indian women.[12] In India, women present with breast cancer at younger premenopausal age.[13] Early-onset breast cancer tends to be more aggressive than late-onset, with higher stage and grade at presentation with more estrogen receptor-negative or triple-negative subtypes.[14] Risk factors for breast carcinoma include age, ethnicity, family history of breast or ovarian cancer, age of menarche, age at menopause, age of first full term pregnancy.[15] The lifestyle factors such as increase age of marriage, reduced breast feeding, and high calorie diet may be associated with occurrence of breast cancer in younger population in India.[16] Early menarche and late menopause are additional risk factors.[17]

The rate of new cases of female breast cancer was 129.1 per 100,000 women per year. The death rate was 19.9 per 100,000 women per year. These rates are age-adjusted and based on 2014–2018 cases and 2015–2019 deaths. Approximately 12.9 percent of women will be diagnosed with female breast cancer at some point during their lifetime, based on 2016–2018 data.[18] Breast cancer is the most commonly diagnosed cancer and the fifth cause of cancer deaths in the world, with an estimated 2.3 million cases and 685,000 deaths in 2020,[19] and the case load is expected to reach 4.4 million in 2070.[20] The increase in incidence rates are attributed to epidemiological and demographic transitions[21] and the increased use of mammography screening.[22]

3. Classification of Breast Cancers

There have many been classifications put forward at different times based on the morphological patterns of the tumour, however, a definite classification based on molecular nature of the tumour was necessary for appropriate planning of treatment in patients. The Cancer Genome Atlas Network (TCGA) classified breast tumours into 4 subtypes, with distinct genetic and epigenetic aberrations.[23,24]

1. Luminal A or ER positive, PR positive, HER2/neu negative. These tumours have low Ki 67 index. These tumours respond fairly to hormone therapy. They have an overall tumour grade of I or II.
2. Luminal B or triple positive or ER positive, PR positive, HER2/neu positive. They are aggressive and have a bad prognosis.
3. Basal like or triple negative (ER/PR/ HER2/neu negative) breast cancers. They have high recurrence rate.
4. HER2-neu over-expressing.

It has also been found that although most breast lesions have well-defined morphologic criteria for classification; nevertheless, we regularly find instances with ambiguous morphologic features that necessitate additional tests, particularly immunohistochemistry, to provide a correct diagnosis.

4. Application of IHC in Breast Lesions

IHC analysis in breast lesions provides information not only about clinical factors, but also enables patients to have disease targeted treatments.[25] In breast cancer, biomarker analysis has now become a routine practice. It originally began with testing for hormone receptor expression in tamoxifen therapy. Targeted treatments against human epidermal growth factor receptor 2 (HER2) brought a revolution in biomarker field.[26] The most important applications of immunohistochemical markers in breast lesions are:[27]

1. Differentiating between carcinoma in situ and invasive carcinoma
2. Differential diagnosis of lobular versus ductal carcinoma.
3. Differentiating usual type ductal hyperplasia (UDH) versus atypical ductal hyperplasia (ADH) or Ductal carcinoma in situ (DCIS).
4. Confirming the breast as the primary site in metastatic carcinoma from unknown primary (CUP).

The Table 1 below shows the different markers that can be used to solve these problems in cases of breast pathologies.

Table 1: Common scenarios and corresponding immunomarkers

Scenarios	Immunomarkers
DDx of in situ versus invasive	Myoepithelial cell markers (p63, SMMHC, calponin, SMA, maspin, P-cadherin, WT1)
DDx of lobular versus ductal	E-cadherin, p120, catenin, CK903 (clone 34βE12), CK8 (clone CAM 5.2)
DDx of UDH versus ADH or DCIS	HMWCK (CK5/6, CK903), ER, PR
Evaluation of metastatic deposits used to identify breast primary	GATA3, NY-BR-1, ER, MGB, GCDFP-15, TTF1 and TTF3

5. Some Common Markers used Routinely for Breast Carcinoma

1. Estrogen Receptor (ER) and Progesterone Receptor (PR) -70–75% of invasive breast carcinomas express ER-alpha. A positive reaction is seen in the nucleus. The cut-off point for a positive result is ≥ 1% of nuclei positive. The reported results should state the antibody clone used. It is advisable to include the percentage of positive cells. A score can be reported, like the one described by Allred et al., combining the estimated nuclear positivity rate in cancer cells (a score of 0–5, based on the percentage) with staining intensity (intensity 0–3).[28]
   Expression of PRs suggests that the oestrogen/ER-alpha pathway is functional. PRs are expressed in 60–70% of cases of invasive ductal carcinoma of the breast. Correlation between ER-alpha and PR expression is good, although 10% of cases may prove to be ER-alpha-positive and PR-negative. These patients have a higher risk of recurrence than ER-alpha-positive, PR-positive cases. 5% of patients may prove to be PR-positive, ER-alpha-negative. Their prognosis is similar to that of ER-alpha-positive, PR-positive patients. Positive cases usually defined as 1% or more.[28]
2. Her2-neu: It is a member of the four-member family of closely related growth factor receptors, including epidermal growth factor receptor or HER1, HER2, HER3, and HER4. HER2/neu amplification or overexpression is involved in oncogenic transformation and tumorigenesis in breast cancer. Inappropriately increased signalling occurs as a result of receptor overexpression. It may lead to increased and uncontrolled cell proliferation, decreased apoptosis, increased cancer cell motility, and angiogenesis and hence worse prognosis. Neoadjuvant chemotherapy (NAC) is administered to breast cancer patients presenting with advanced disease stages to reduce tumor size prior to surgery, and making inoperable breast conserving surgery a more viable option. Studies have shown that pathological complete response (pCR) after HER2-directed NAC is predictive of recurrence-free survival in HER2+ breast cancers. Although, chances of residual tumor is high. The residual cancer burden (RCB) index was developed by MD Anderson Cancer Center for quantification of pathological review and prediction of survival after NAC for breast cancer. The index includes post-NAC primary tumor dimensions, cellularity of the tumor bed, in situ cancer remaining within the tumor bed, number of involved lymph nodes, and size of largest axillary metastasis.[29]
   At present, determining ER, PR, and HER2/neu receptor status in breast cancer have become a common practice, as there is a survival advantage for patients with hormones receptor positive status by treatment with adjuvant hormonal or chemotherapeutic regimens. It is well-known that strong ER-positive cases benefit from endocrine therapy alone, in contrast to those with low to moderate ER positivity. PR status is independently associated with disease-free and overall survival. Patients with ER, PR-positive tumors have a better prognosis than patients with ER, PR-negative tumors.[30]
3. Ki-67: Ki-67 is a nuclear protein associated with cellular proliferation and was originally identified by Gerdes et al.[31] in the early 1980s, using a mouse monoclonal antibody directed against a nuclear antigen from a Hodgkin's lymphoma-descended cell line. Ki-67 nuclear antigen is expressed in S, G1, G2, and M phases of cell cycle, but not in G0 phase.[31]

Immunohistochemical assessment of Ki-67 is the most widely used method in clinical practice for determining the proliferative activity of breast cancer. Ki-67 is particularly used for classifying risk groups in carcinomas positive for ER-alpha and PR. There is no absolute guidelines regarding the cut-off points. It has been recommended that each pathology department should set its most appropriate cut-off points.[32] Some define "low proliferative activity" as Ki-67 levels below 10%, and "high proliferative activity" as levels above 30%. However, the critical point is usually between 10 and 20%. High levels of Ki-67 are associated with worse prognosis. Ki-67 expression is also used to classify luminal-like breast cancers into luminal A and luminal B.[33]

In 2011, the International Ki-67 in Breast Cancer Working Group (IKWG) was established to review methods of determination of Ki 67 levels in breast cancer.[33,34]

6. IHC Patterns of Various Breast Lesions

1. **Ductal carcinoma in situ (DCIS)** - DCIS lesions are estrogen receptor positive (ER+). DCIS lesions have been characterized through immunohistochemical staining for ER, progesterone receptor, human

epidermal growth factor receptor 2 (HER2), revealing that DCIS lesions can be subdivided into luminal A (ER+/HER2−, 49%), luminal B/HER2− (ER+/Ki-67 high, 9%), luminal B/HER2+ (ER+/HER2+, 17%), HER2 enriched (ER−/HER2+, 16%), and triple negative (ER−/progesterone receptor negative/HER2−, 7%).[35]

2. **Lobular carcinoma in situ (LCIS)-** Classic ILCs typically show a luminal A molecular phenotype with around 90% of cases showing strong oestrogen receptor (ER) positivity along with 60–70% of cases also exhibiting strong progesterone receptor (PR) expression,[36] they are usually negative for human epidermal growth factor receptor 2 (HER2) gene amplification and overexpression.[37] It has long been recognised, that an important subpopulation of cases does not conform to this ER/PR+, HER2− phenotype and is either ER/PR negative, triple negative, or HER2+, with high grade and the pleomorphic ILC (PILC) subtype.[37] Staining for E-cadherin helps in distinguishing lobular carcinoma from invasive ductal carcinoma. Studies have illustrated a link between cadherin (CDH1) gene and invasive lobular breast cancers, with 50% of this subtype of breast cancer containing E-cadherin mutations.[38,39]
3. **Invasive ductal carcinoma**- The absence of myoepithelial cells (MECs),[40] which function as a hybrid of smooth muscle ("myo," with contractile property) and epithelial cells (with cadherin-mediated cell-cell junctions) and immunohistochemically express filamentous smooth muscle actin (SMA), smooth muscle myosin, and intermediate filaments, is a histological hallmark of invasion (the epithelial keratins).[41] On normal hematoxylin-eosin sections, however, the presence or absence of MECs is not always obvious. Several immunomarkers that target different proteins in MECs have been discovered over the years to provide an objective measure of evaluating them when encountering challenging cases, to differentiate carcinoma in situ (CIS) (ductal [DCIS] or lobular [LCIS]) or sclerosing adenosis from invasive breast carcinoma (CA) and benign or atypical papillary lesions from papillary Carcinoma.[42] Myoepithelial cells express basal cell type CKs and specific markers: smooth muscle actin, calponin, S100 and p63, while basal cell types express different cytokeratins (5/6,14,17).[43,44]
4. **Medullary carcinoma**- They are most often negative for estrogen and progesterone receptors and HER2 and express keratins 5/6 and 14, smooth muscle actin, EGFR, P-cadherin, p53, and caveolin-1. They have a high Ki-67 proliferation index. P53 is considered a biological marker for this tumor.[45]
5. **Mucinous carcinoma**- Mucinous (colloid) carcinoma is seen in fewer than 5% of invasive breast cancer cases. Mucin production is the histologic hallmark. Two types; A and B, with AB lesions possessing features of both. Type A mucinous carcinoma represents the classic variety with larger quantities of extracellular mucin. Type B is a variant with endocrine differentiation, with histology showing more granular cytoplasm then type A carcinomas.[46]
6. **Tubular carcinoma**- Tubular carcinoma is nearly always positive for estrogen and progesterone receptors has a low growth fraction and is typically negative for HER2, EGFR, P-cadherin, p53, and high molecular weight keratins.[47]

   Due to its favourable prognosis, the management of tubular carcinoma requires an interprofessional team approach consisting of a surgical oncologist, an oncologist, a pathologist & a radiologist.[48]
7. **Metaplastic breast carcinoma (MpBC)** - MpBC is a triple-negative breast cancer (TNBC), meaning it lacks the expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor 2 receptor (HER2).[49] MpBC carries a worse prognosis in comparison to non-metaplastic TNBC, has high recurrence rate, and has low survival rate.[50] Huvos and colleagues first published the term “metaplastic carcinoma” in 1973.[51] WHO Classification of Breast Tumors classifies MpBC as mixed metaplastic carcinoma, low-grade adenosquamous carcinoma, fibromatosis-like, squamous cell carcinoma, spindle cell carcinoma, and metaplastic carcinoma with mesenchymal differentiation. All these metaplastic variants are aggressive and chemoresistant and have a high tendency to metastasize, except fibromatosis-like carcinoma and low-grade adenosquamous carcinoma.[52]
8. **Phyllodes tumor**- Studies have shown that p53, Ki67, CD117, EGFR, p16, and VEGF (lowest in benign phyllodes tumors and highest in malignant phyllodes tumors) are associated with histologic grades of phyllodes tumors[52] PAX3 and SIX1 expression have recently been identified in borderline and malignant phyllodes tumors and correlate with a poor clinical outcome.[53]
9. **Mammary Paget disease (MPD)** - Immunohistochemical staining is useful to differentiate it from other lesions. The diagnostic panel includes CK7 and CK20, carcinoembryonic antigen (CEA), estrogen receptor (ER), HER2, S-100, and either MART-1 or HMB-45 if melanoma is suspected. It is usually positive for CEA and negative for S-100 protein.[54]

7. Early Detection of Breast Cancer

Screening is a public health intervention intended to improve the health of a precisely defined target population.[55] A woman is considered to have average risk if she doesn't have a personal or strong family history of breast cancer, or a genetic mutation known to increase risk of breast cancer (such as in a BRCA gene) and has not had chest radiation therapy before the age of 30. These women can have mammograms every year. Nowadays, 3D mammograms are also available known as Digital Breast Tomosynthesis for better clarity. For, high risk women (strong family history, known BRCA1/BRCA2 gene mutation etc) should have breast MRI and mammogram every year.[56]

Early breast cancer detection with early treatment could reduce breast cancer death rates significantly. Mammography is the standard breast screening technique, but it is less effective for women under 40 years old and in dense breasts.[57] Contrast-enhanced (CE) digital mammography offers more accuracy diagnosis. Ultrasound and MRI are additional medical imaging tool. Positron emission tomography (PET) is the most accurate method for visualizing the spread of tumors and response to therapy.[58] Breast biopsies are done to distinguish between malignant and benign tissues. Biomarker-based methods such as radioimmunoassay, immunohistochemistry, enzyme-linked immunosorbent assay (ELISA) and fluoroimmunoassay also add to the diagnosis of breast cancer.[59]

8. Recent Advances in Breast Cancer Research

The role of micro-RNAs in the field of oncology has gained significant limelight in recent times. MicroRNAs (miRNAs) are a group of small non-coding RNAs that can interrupt the expression of protein-coding genes by binding to their mRNAs and inhibiting subsequent protein translation.[60] miRNAs can regulate the expression of genes associated with various biological phenomena including homeostasis, development, proliferation, differentiation, and apoptosis. Aberrant expression of miRNAs is important for the initiation and progression of neoplasia as they function as both tumor suppressors and oncogene.[61] The increased expression of some miRNAs, including miRNA-194 and miRNA-425, has been found in breast cancer cells.[62] The commercially available molecular assays (OncotypeDX®, MammaPrint®, Prosigna®, EndoPredict [EPclin], Breast Cancer IndexSM [BCI] and MapQuantDx™ [Genomic Grade Index]), have added prognostic value to immunohistochemistry (IHC). These identify patients in whom the use of chemotherapy can be avoided. Eligibility criteria for these tests include patients who are early stage (I or II), lymph node (LN) negative or have one to three positive LN, hormone receptor (HR) positive and HER2 negative.[63] The MammaPrint 70-gene assay was the first molecular test to have FDA approval. It classifies patients into good and poor prognosis groups based on the probability of metastasis within 5 years.[64] In 2013, FDA approved the Prosigna assay which measures expression of 50 genes, earlier known as PAM50. The test combines a risk of recurrence score (ROR; scale 0–100) with molecular subtype (luminal A, luminal B, HER2-enriched or basal-like), tumour size, LN status and proliferation score, to assign low, intermediate or high 10-year risk of recurrence in postmenopausal HR-positive breast cancer patients.[65]

EndoPredict is an eight-gene signature[66] combined with tumour size and LN status. It predicts distant recurrence in ER-positive disease.[67–69] A modified EndoPredict assay, mEPClin, independently predicts the risk of distant recurrence after neoadjuvant chemotherapy.[66]

9. Conflict of Interest

The authors declare no conflict of interest.

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None.

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