Prognostic and diagnostic markers of carcinoma Breast

Dr.Peela Jagannadha rao,MD,NRCC-CC(USA),FACB.
Assistant professor, Department of Biochemistry,
Faculty of Medicine, Quest International University Perak,
30250 Ipoh, Malaysia.
Ph: +60105010039 e-mail: peela.jagannadha@qiup.edu.my & pjagannadharao@hotmail.com

Abstract: With the high prevalence of breast cancer among females all over the world, early diagnosis and management is important, and necessitates the need for the tumor markers. Since several markers have evolved over time, it becomes important to understand what markers are best in different clinical situations. After a review of the literature, I have summarized the most frequent markers used. Though the search for an ideal tumor marker remains obscure in breast cancer, still seem to be advantageous in terms of prognosis. A tumor marker should have high specificity, sensitivity, a wide diagnostic window allowing prompt, early diagnosis. The available tumor markers are mostly useful for predicting response to treatment, postoperative surveillance and presence of recurrence. CA 15-3 and BR 27.29 are useful for postoperative surveillance and monitoring therapy. Tissue based markers like estrogen receptor, progesterone receptor and HER-2 are better for predicting response to hormone therapy in early and advanced tumors. BRCA 1 and BRCA2 genes are used to identify individuals at high risk of developing breast or ovarian cancer in high risk families. These two genetic markers are in clinical use in specialized centres and there is need for expert opinion before going for these tests.

Key words: Breast, cancer, tumor marker, females, oestrogen and progesterone.

Introduction: Global burden of cancer is 14.1 million new cases and 8.2 million cancer related deaths in 2012. Breast cancer is the most common cancer affecting women worldwide nearly 1.7 million cases diagnosed in 2012 representing 12% of all new cases and 25% of all cancers in women. 6.3 million Patients are living with breast cancer for the past 5 years. In India alone 83000 new cases are diagnosed each year with 19 per 100000 females whereas the number is 210 per 100000 females in USA may be in part due to improved screening and better awareness
about the problem. There are around 270000 patients living with breast cancer in India with a mortality of 10.4 per 100000 females [1]. The mortality incidence ratio of breast cancer is highest in Philippines i.e., 0.58 with rate of 27 deaths per 100000 females, this ratio is lowest in USA i.e., 0.19 and in India it is 0.54. The likelihood of surviving after the diagnosis is better in USA whereas it is low in India though the incidence is low when compared with USA [2].

Tumor markers should be ideally 100% sensitive i.e., its presence or rise if tumor is present and 100% specific i.e., its absence if there is no tumor. An ideal tumor marker is useful to screen, diagnose, to determine prognosis, to monitor response to treatment and to identify recurrence. Measurement of tumor marker must be less invasive, less expensive and easy to detect from urine or serum. Currently ideal tumor marker is non-existent for any of the tumors [3].

**Tumor markers of the breast cancer:**
Early detection of breast cancer is presentation of lump, change in nipple structure with or without discharge and change in skin contour of breast. Regarding screening, currently the most effective method is mammography, hence the role of tumor markers is limited in early diagnosis of breast cancer. The definitive diagnosis requires a biopsy and histopathological examination. Currently available tumor markers of breast cancer are mainly used for prognosis, to monitor treatment response either hormone or chemotherapy and recurrence. Tumor markers of breast cancer are broadly divided in to 3 types. They are 1. Tissue based tumor markers 2. Serum based markers and 3. Tissue cells.

**Tissue based markers**
**Estrogen receptor and progestrogen receptor** evaluation in patients of breast cancer are mostly useful for predicting response to hormone therapy in early and advanced tumors[4][5]. Routine use of these two markers are recommended by American society of clinical oncology (ASCO), European group of tumor markers (EGTM), National academy of clinical Biochemistry (NACB), European society of clinical oncology (ESMO), National comprehensive Consensus network (NCCN) and St Galen conference consensus panel. ER and PR are better markers of prognosis and tumor recurrence [6][7]. Assay of ER and PR can be obtained by methods like Ligand binding assay, ELISA and Immuno histo chemistry (IHC). IHC
is most effective than the other two methods in association with other prognostic factors like tumor grade, stage and involvement of lymph nodes. ER and PR estimation is also useful for determination of short term prognosis in newly diagnosed cases.

**HER-2:** Determination of HER-2 is recommended for all newly diagnosed invasive breast cancers. It is highly recommended for patients undergoing treatment with Trastuzumab in early and advanced breast cancers [8] [9]. It is also useful for determining prognosis and of some value in anthraxcyclin based adjuvant chemotherapy [10] [11]. Assay of HER-2 is mainly done by two methods, one is IHC and another is fluorescent in situ hybridization technique (FISH).

**uPA:** Urokinase plasminogen activator is strong independent risk factor in breast cancer in axillary lymph node negative patients. This tumor marker is mostly validated in some European countries especially in Germany. This is also under evaluation for predicting resistance to hormone therapy in advanced breast cancers and also enhanced response to chemotherapy in early cancers. Measurement of uPA is done by ELISA but tissue must be stored in liquid nitrogen before processing [12] [13].

**PAI-1:** Plasminogen activator inhibitor-1 is assayed along with uPA for determining prognosis in breast cancer sub group with node negative disease. This test is mostly accepted in some European countries mainly Germany. This is also under evaluation for predicting resistance to hormone therapy in advanced tumors. Assay is by ELISA like uPA for determination of PAI-1 also tissue must be stored in liquid nitrogen [13].

**Cathepsin-D:** Cathepsin-D is determined for prognostic use but its results are conflicting. Only useful for node negative tumors. Assayed by a specific ELISA technique [14] [15].

**p53:** p53 protein is evaluated for prognostic purpose. This protein is determined by IHC. Specific mutations of p53 gene correlates with adverse outcome [16]. It is recommended to estimate this protein along with gene mutation [17]. Role of p53 in predicting response to chemotherapy or hormone therapy is still under evaluation since the results are conflicting. Hence it is not been used clinically in any centers [18].
**Oncotype DX™ (a multiplex RT-PCR assay)**

It is mainly useful for predicting recurrence in lymph node negative, ER positive patients receiving adjuvant tamoxifen [19][20]. May also predict usefulness from adjuvant chemotherapy in node negative, ER positive patients [21]. Validated in prospectively designed studies, assay can be carried out on paraffin embedded tissue [22]. This marker is in clinical use validation of chemo predictive utility is under way gene expression and benefit of chemotherapy in node negative, oestrogen positive tumours [23].

**Serum based markers:**

CA 15-3: Carbohydrate antigen 15-3 is one of the most useful marker for the carcinoma breast for postoperative surveillance with evidence of no disease [24] [25] [26]. This test is widely in use but not validated with high evidence. It is also useful tool for monitoring therapy and assessment of prognosis [27]. High preoperative levels may lead to adverse outcomes [28].

BR 27.29: This is another marker that provides similar information as CA 15-3 but not widely used as former. This also may be useful for postoperative surveillance and monitoring therapy [29] [30].

As per the NACB panel recommendation, the routine use of CA 15-3 and BR 27.29 should not be done for early detection of recurrence and metastasis in asymptomatic patients with diagnosis of breast cancer. These markers may be used in combination with radiology and clinical examination to monitor therapy and sustained rise of concentration suggests progressive disease.

**CEA:** Carcino embryonic antigen is useful for postoperative surveillance in patients with evidence of no disease [31]. This is not as sensitive as CA 15-3 and BR 27.29. High preoperative levels predict adverse outcome. This is more useful in monitoring therapy when there is no rise of CA 15-3 and BR 7.29[32] [33]. Routine use of CEA measurement is not advised in diagnosed breast cancer as per NACB guidelines. CEA is assayed by many commercially available kits.
**TPA and TPS:** Tissue polypeptide antigen and Tissue polypeptide specific antigen is used for postoperative surveillance with no evidence of disease. It is more useful in monitoring therapy in advanced disease if there is no rise of CA 15-3, BR 27.29 and CEA. These two markers are of clinical use in certain countries mostly for postoperative surveillance and monitoring therapy [34].

**Serum HER-2 (Shed form):** HER-2 in serum may be of value in monitoring Trastuzumab therapy with advanced breast cancer. This marker in serum not yet established for clinical use is under evaluation. Predicting response to hormone therapy, chemotherapy and postoperative surveillance when there is no rise of CA 15-3, BR 27.29 and CEA [35].

**Detection of tumor cells in various tissues:**
Tumor cells in bone marrow, axillary lymph nodes, sentinel lymph nodes and in circulation: Tumor cells can be detected other than hematoxylin and eosin staining. Tumor cells in bone marrow are of prognostic value validated in pooled analysis but not in clinical use [36][37]. Detection of tumor cells in axillary lymph nodes predicts bad prognosis [38]. Tumor cells in sentinel node [39][40] and circulation are still under evaluation not in clinical use[40][41].

**BRCA1 and BRCA2**

**BRCA 1 and BRCA2** genes are used to identify individuals at high risk of developing breast or ovarian cancer in high risk families. These two genetic markers are in clinical use in specialized centres and there is need for expert opinion before going for these tests [43][44].

Early breast and ovarian cancer screening are recommended for individuals with BRCA1 mutations and early breast cancer screening for those with BRCA2 mutations. [45]. Recommendation was not made for or against prophylactic surgery.

Surgical prophylaxis is only optional for people who are carrying mutated genes but there are reports of recurrence of cancer following prophylaxis. It is recommended that individuals considering genetic testing should be counselled regarding the efficacy of measures to reduce risk and care for individuals with cancer-predisposing mutations [45].

According to the 2005 consensus panel of the 8th St Gallen Conference, treatment decisions for women with mutations in BRCA1 or BRCA2 genes need to include consideration of bilateral mastectomy with plastic surgical reconstruction, prophylactic oophorectomy, chemoprevention
and intensified surveillance. The NACB panel supports the statements published by CGSC, ASCO, US Preventive Services Task Force, and the St Gallen Consensus Panel [43-45]

References:

2. Taiwan cancer registry annual report 2005 (Taiwan); GLOBOCAN 2002, IARC (all countries).


