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Biomakers of breast cancer: Overview

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Abstract

Breast cancer management depends on biomarkers including estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 (ER/PR/HER2). Though existing scoring systems are widely used and well validated, they can involve costly preparation and variable interpretation. Additionally, discordances between histology and expected biomarker findings can prompt repeat testing to address biological, interpretative, or technical reasons for unexpected results. The levels of these markers can influence how a person with breast cancer is treated in the clinic.

Keywords: breast cancer, cancers, biomarkers of breast cancer, staging of cancer, prognosis of breast cancer

Introduction

Biomarkers currently play an indispensable role in the management of patients with breast cancer, especially in deciding the type of systemic therapy to be administered. In 2005, the European Group on Tumor Markers (EGTM) published guidelines on the use biomarkers in breast cancer (Molina, 2005). However, since then, a number of important new developments have been reported, especially with tissue-based biomarkers. These include the use of multi-parameter signatures for predicting patient outcome and the use of HER2 for the upfront identification of likely response to several different forms of anti-HER2 therapy. In addition, new recommendations have been published for performing a number of breast cancer biomarker assays such as estrogen receptors (ERs), progesterone receptors (PRs) and HER2 (Cardoso, 2017).

Breast cancer is the most common cancer in women(Aizaz *et al.*, 2023; Obeagu *et al.*, 2021; Obeagu and Obeagu, 2023; Obeagu *et al.*, 2021; Ahiara *et al.*, 2022; Obeagu *et al.*, 2022; Obeagu and Babar, 2021) , accounting for about one-third

of cancer cases in women and more than 10% of all cancers worldwide (Bertozzi, 2018), and its incidence experienced an important increase, thanks to the introduction at the beginning of this century of a systematic mammographic screening in the most developed countries, and the subsequent successful detection of an always greater number of early breast cancers (Bleyer, 2012). The incidence of breast cancer is also rapidly rising in developing countries, so that it will become in the next decades a major health burden in both developed and developing countries.

Breast cancer is the second most common malignancy in women. The lifetime risk of developing breast cancer for women in Africa, breast cancer is responsible for 28% of all cancers and 20% all cancer deaths in women. (16% & 11% both sexes) Incidence rates are still generally low in Africa, estimated below 35 per 100,000 women in most countries (compared to over 90–120 per 100,000 in Europe or North America (Kantel hardt, 2015). The most important risk factors are increased estrogen exposure, advanced age, and genetic predisposition(Ofor *et al.*, 2016; Obeagu and Obeagu, 2016; Obeagu *et al.*, 2016; Obeagu, 2018; Obeagu, 2018; Obeagu, 2018). The majority of tumors are adenocarcinomas. The two most common types of breast cancer are invasive ductal carcinoma and the less aggressive invasive lobular carcinoma. In most cases, breast cancer is detected during routine mammography screening, which is recommended in women starting at 50 years of age. Mammographic abnormalities and breast masses require further radiographic evaluation, and, if there are signs of malignancy or the results are inconclusive, biopsy and subsequent histopathologic analysis (Anders, 2022).

History of Breast Cancer

Ancient Egyptians were the first to note the disease more than 3,500 years ago. The condition was described fairly accurately in both Edwin Smith and George Ebers papyri. One of the descriptions refers to bulging tumors of the breast that has no cure. (Mandal, 2019).

Biomarker' is a term that is cropping up more and more frequently. The history of the term dates back to the 1950s, when it was first included in the English language. It began to be widely used during the 1980s. It then took nearly another two decades for The National Institute of Health's Biomarkers Definitions Working Group to officially recognise the term 'biomarker' in 1998. (Mark, 2019).

In 460 B.C., Hippocrates, the father of Western Medicine, described breast cancer as a humoral disease. He postulated that the body consisted of four humors - blood, phlegm, yellow bile, and black bile. He suggested that cancer was caused by the excess of black bile. In appearance of the breast cancer too black, hard tumors are seen that burst forth if left untreated to yield a black fluid. He named the cancer *karkinos*, a Greek word for "crab," because the tumors seemed to have tentacles, like the legs of a crab (Mandal, 2019). Thereafter in A.D. 200, Galen described the cancer as well. He also suggested excessive black bile but, unlike Hippocrates, he postulated that some tumors were more dangerous than others. He suggested medications like opium, castor oil, licorice, sulphur, salves etc. for medicinal therapy of the breast cancers. During this time of history breast cancer was a disease that affected the whole body and thus surgery was not considered (Mandal, 2019).

Kinds of Breast Cancer

The most common kinds of breast cancer are—

- **Invasive ductal carcinoma.** The cancer cells begin in the ducts and then grow outside the ducts into other parts of the breast tissue. Invasive cancer cells can also spread, or metastasize, to other parts of the body.

- **Invasive lobular carcinoma.** Cancer cells begin in the lobules and then spread from the lobules to the breast tissues that are close by. These invasive cancer cells can also spread to other parts of the body (John, 2022)

Testing for breast cancer treatment

Biomarker testing is a way to look for genes, proteins, and other substances that can provide information about cancer. Each person's cancer has a unique pattern of biomarkers. Some biomarkers affect how certain cancer treatments work. Biomarker testing may help you and your doctor choose a cancer treatment for you (Lichtenfeld and Winkler, 2023)

Biomarker testing for cancer treatment may also be called:

- tumor testing
- tumor genetic testing
- genomic testing or genomic profiling
- molecular testing or molecular profiling
- somatic testing
- tumor subtyping

The purpose of genetic testing for breast cancer biomarkers

Gaining information on your breast cancer tumor characteristics at the genetic level may give information that is useful for making treatment decisions; those are sometimes called "biomarkers." Some clinical trials require the presence or absence of a certain biomarker / genetic alteration. Those trials may require this information in advance of application to the trial, while others may ask for a biopsy of your tumor, and perform the testing on site. (Lichtenfeld and Winkler, 2023)

Histological grade of breast cancer

Histological grade is a parameter that has independent prognostic value at all stages of breast cancer that adds to axillary status and tumour size. All invasive breast carcinomas should therefore be graded (Rakha, 2010). The combined histological grade simply and efficiently provides biological information about the tumour, directly related to proliferation (mitosis), abnormal architecture, nuclear shift, and the expression of chromosomal instability (Rakha, 2010). The World Health Organization (WHO) classification and the College of American Pathologists (CAP) guidelines recommend using the Nottingham (Elston–Ellis) modification of the Patey–Scarff and Bloom–Richardson grading system (Lakhani SR, 2012). The inter-observer agreement level is very high when these recommendations are strictly followed. Also, they can be applied to tissue obtained by core-needle biopsy (CNB) (O'Shea, 2011).

Estrogen receptor and progesterone receptor

Expression of estrogen receptor (ER)-alpha is a favourable prognostic factor and strongly predictive of a response to hormone therapy (Manni, 1980). Approximately 30–40% of patients with ER-expressing advanced breast cancer will have an objective response to hormone treatment, and a further 20% of patients will achieve disease stabilisation. Moreover, the hormone therapy response in patients with early ER-expressing breast cancer, in terms of overall and disease-free survival, is well known (Dowset, 2015). Hormone therapy is relatively non-toxic. Its long-lasting clinical activity justifies its use in any patient with an ER-expressing mammary tumour.

The technique used to test for ER can be applied inexpensively to fixed, paraffin-embedded tissue. It is therefore readily available in most Pathology Departments. Examining tissue under the microscope means that positive reactions can be assessed in tumour cells only, avoiding problems with low cell density or normal breast tissue included in the tumour growth. Detailed guidelines addressing methods for the immunohistochemical analysis of ERs and progesterone receptors (PRs) are available (Hammond, 2010).

In general, 70–75% of invasive breast carcinomas express ER-alpha. A positive reaction is seen in the nucleus. Staining intensity and the percentage of positive cells can vary. The morphological context should be taken into account. In apparently negative cases of certain special histological types, such as tubular, mucinous or lobular carcinoma, or in histological grade I, confirmation of the results should be considered.

The cut-off point for defining a positive result is ≥ 1% of nuclei positive, irrespective of staining intensity. The reported results should include the antibody clone used. It is advisable to include the percentage of positive cells. Alternatively, 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)(Prat *et al.*, 2010). It is also useful to test for ER-alpha in ductal carcinoma in situ, because hormone suppression treatment can reduce the recurrence risk by 50% in patients expressing this receptor.

PRs are regulated by ER-alpha, so expression of PRs suggests that the oestrogen/ER-alpha pathway is functional. As with ER-alpha, biochemical methods to test for PR expression were replaced in the 1990s by immunohistochemistry, which is the recommended technique (Hammond, 2010). PRs are expressed in 60–70% of cases of invasive ductal carcinoma of the breast. In general, 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. Fewer than 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. The methodology and quantification used are the same as for ER-alpha, with positive cases usually defined as 1% or more. Some recent studies suggest that low-level PR expression (< 20%) might have negative prognostic implications. Including it as one of the parameters for distinguishing the Luminal subtype has therefore been suggested (Braun, 2013).

Ki-67

Immunohistochemical assessment of Ki-67 is the method most widely used in clinical practice to determine the proliferative activity of breast cancer. Ki-67 is particularly important for distinguishing risk groups in carcinomas positive for ER-alpha and PR. The available guidelines on Ki-67 assessment in breast cancer address methodological issues in the various phases (Dowsett, 2011). Calibrating the method in different laboratories substantially increases the concordance between results (Polley, 2015). There is no absolute agreement regarding cut-off points. It has been recommended that each pathology department should set its most appropriate cut-off points (Dowsett, 2011). Some guidelines 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% (Polley, 2015).

In combination with PR expression levels, the St Gallen consensus established four categories based on Ki-67 levels: < 14, 14–19, 20–25 and > 25%. A 20% cut-off was recommended for distinguishing between Luminal A-like and Luminal B-like tumour types. A recent meta-analysis concluded that a Ki-67 level of over 25% is associated with a worse prognosis (Petrelli, 2015).

Ki-67 quantification appears to have clinical applicability in the choice of adjuvant therapy for ER-expressing tumours. In combination with other clinical factors, its validity is comparable to that of more complex gene expression analyses. However, American Society of Clinical Oncology (ASCO) guidelines on using biomarkers to guide decisions on adjuvant therapy do not recommend its use. More international studies of a collaborative nature are needed, to standardise values of this marker so that it can be clinically validated (Slamon, 1998).

HER2

Along with hormone receptors, HER2 is the most important prognostic and predictive marker in breast cancer. Since the early studies by Slamon in 1987, it has been known that breast cancers that overexpress HER2 represent a highly aggressive biological subtype (Slamon, 1998). However, the 1998 approval of trastuzumab for therapeutic use changed the outcome in these patients, whose clinical course improved very significantly. The

introduction of new targeted anti-HER2 therapies, such as lapatinib, pertuzumab and trastuzumab emtansine (T-DM1), the last one administered with no requirement for simultaneous cytostatics, underlines the importance of identifying patients with HER2-positive breast cancer. Fixation time is much more standardised for CNBs (normally 6–24 h) than for surgical specimens, and concordance between the two tests is very high (98–99%) (Chen, 2012). Using CNB material also means that the information is available for clinicians before making a decision about possible neoadjuvant therapies. This test is performed by immunohistochemistry and/or in situ hybridisation (ISH), fluorescence in situ hybridisation (FISH) or chromogenic in situ hybridisation (CISH or SISH), (Slamon, 1998).

Prognostic genetic platforms: molecular phenotypes and translation

In the last few years, clinical practice in Spain has witnessed the arrival of four genetic platforms for determining the prognosis of patients with ER-positive, HER2-negative tumours of favourable prognosis, without lymph nodes involved. All these platforms are used to evaluate the risk of recurrence. However, they differ substantially in the methodology used to quantify gene expression, the genes tested, the clinical and pathological variables included, risk group stratification, and whether or not testing takes place in centralized laboratories. It should therefore come as no surprise that, although they are all of proven clinical usefulness and analytically validated, results from the various platforms can place the same patient into different risk categories (Yuan, 2014).

MammaPrint

The MammaPrint 70-gene expression platform yields a signature that divides breast carcinomas into two risk categories, i.e. high and low (van de Vijver, 2002). In 2007, the platform was approved by the Food and Drug Administration (FDA) for determining prognosis in patients aged 60 years or under with node-negative, stage I–II tumours measuring ≤ 5 cm. In 2009, it obtained a second approval for patients over 60 years old. More recently, MammaPrint® has been validated for paraffin-embedded material (Sapino, 2014).

Various studies have indicated its prognostic value for determining 10-year distant metastasis-free survival in patients with breast cancer involving 1–3 axillary lymph nodes, in women at low risk, and for HER2-positive tumours. It has also been shown that MammaPrint® is useful for establishing the benefit of administering chemotherapy (Drukker, 2013).

Oncotype Dx

Oncotype DX tests the expression of 21 genes (16 cancer-related genes and 5 reference genes) and calculates a Recurrence Score (RS). Oncotype DX® methodology has been optimized for application to formalin-fixed tissue, and its results have a proven impact on treatment decisions. The RS defines three groups: low RS with a value under 18; intermediate RS from 18 to 30; and high RS with values of 31 or over. Several studies have shown that the 10-year distant recurrence rate is 7% in the low RS group, 14% in the intermediate RS group, and 30% in high RS patients (Habel *et al.*, 2006).

The value of Oncotype DX for predicting the benefit provided by chemotherapy and hormone therapy in these risk groups has been examined in various studies, involving both node-negative and node-positive patients, although the 2016 ASCO Guideline recommends the use of Oncotype to guide decisions about adjuvant chemotherapy only in cases without lymph node involvement (Sparano, 2015). Oncotype DX has been shown to provide information above and beyond the clinical and pathological features in postmenopausal patients with hormone-dependent breast cancer treated with an aromatase inhibitor.
TAILORx (Trial Assigning Individualized Options for Treatment [Rx]) was a prospective trial designed to determine the prognosis of a group of patients who had undergone surgery for ER-positive, HER2-negative, node-negative breast cancer, with an RS of 11–25 (Sparano, 2015). Recently published results from the

RS < 11 group reported a distant recurrence risk of 0.7%, and a 1.3% risk of any other recurrence. These results were confirmed in the Surveillance, Epidemiology and End Results (SEER) database registry (Dinan, 2015).

Conclusion

In order to plan an adequate adjuvant therapy in patients with primary breast cancer, pathology reports must include in all cases the expression and levels of ERalpha, PR, HER2 and Ki-67, in addition to histological grade, to assist prognosis and to establish current therapeutic options available, including hormone therapy, chemotherapy and anti-HER2 therapy. In node-negative ER-positive breast cancer patients, one of several available genetic prognostic platforms may be used in order to establish a prognostic category and to discuss with the patient whether adjuvant treatment may be limited to hormonal therapy. Newer technologies including NGS, liquid biopsy, tumor-infiltrating lymphocytes or PD-1 determination are still experimental at this point.

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