# Recent perspectives of breast cancer prognosis and predictive factors (Review)

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**Abstract.** Breast cancer is the most common type of cancer affecting women worldwide. Although there have been great improvements in treating the disease and at present between 80 and 90% of the women survive ≥5-years after their primary diagnosis. However, due to the high incidence of the disease >450,000 women succumb to breast cancer annually worldwide. The majority of improvements in breast cancer survival may be explained through better knowledge of the development and progression of the disease. Consequently, the treatments employed have become more effective. Furthermore, continuous efforts are being made for the identification of novel and efficient biomarkers for the timely prognosis of breast cancer. The present review aims to examine recent perspectives of breast cancer prognosis and the predictive factors involved.

**Contents**



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## 1. Introduction

Breast cancer is responsible for the highest mortality in women worldwide (1). Breast cancer affects women in both developed and developing countries. The incidence of the disease is higher in developed countries, while the risk of succumbing to the disease is higher in developing countries (2). The difference in incidence between countries is partially explained by variations in the use of hormone replacement therapy and reproductive patterns, such as age at first child, number of children, age at menarche, and nutritional factors (3). Furthermore, the variation in the detection rate due to availability of mammography screening and medical care also explain some of the differences (4). Other factors such as high alcohol intake, obesity and inactivity have also been linked to risk of developing breast cancer.

## 2. Lymph node metastasis in breast cancer

The strongest prognostic factor in breast cancer is lymph node metastasis (5). The disseminated cancer cells from the tumor are most often transported by the lymphatic system. These cells can then settle into the local or axillary lymph nodes, and form a lymph node metastasis. The lymph nodes have been suggested to function as filters where the cancer cells can be eliminated by the immune system, thus preventing spread to systemic circulation and distant metastasis (6). Metastasis to the lymph nodes merits further surgical removal of all axillary lymph nodes. It often means that ≤20-30 lymph nodes may be removed. This procedure has shown to decrease the risk of local recurrence; however, whether it protects against systemic metastasis remains to be elucidated (7). Since lymph node metastasis is coupled to worse prognosis, these patients often require systemic chemotherapy and more extensive radiotherapy. Removal of the axillary lymph nodes occasionally leads to lymphedema of the arm, which is associated with reduced quality of life. Other side effects include neurological pain and limited shoulder and arm movement (8). To decrease the number of non-necessary axillary dissections, the sentinel lymph node (SLN) biopsy surgical technique was developed (9). In clinically lymph node-negative women, a blue dye and radioactive labeled fluid are injected in the breast prior to surgery. This allows the surgeon to locate the first lymph node responsible for draining lymphatic fluid from the tumor,

Table I. Different tumor characteristics for estrogen receptor (ER), progesterone receptor (PR), HER2 and proliferation marker Ki67 within the established intrinsic subtypes.

| Luminal A | Luminal B | HER2 | Basal |
|---|---|---|---|
| ERα+ and/or PR+ | ERα+ and/or PR+ | ERα- | ERα- and PR- |
| HER2- | HER2+/- | HER2+ | HER2- |
| Low Ki67 | High Ki67 | Usually high Ki67 | Usually high Ki67 |

the so-called SLN. It has been shown that if the SLN is free from metastasis, this is associated with a low risk of spread to other lymph nodes, which in some studies was <10% (10). Therefore, the benefit of removing all axillary lymph nodes in SLN-negative patients does not outweigh the risk of developing adverse effects from the surgery. Furthermore, previous studies have been unable to demonstrate increased survival in node-negative patients with extended axillary dissection (11).

### 3. Estrogen receptor α

Estrogen receptor α (ERα) is an important biomarker, with approximately 70% of all primary breast cancers being ERα-positive. ERα is considered a good prognostic and predictive marker for endocrine treatment (12). In a study where patients did not undergo chemotherapy, the 5-year survival was 92% in ERα-positive tumors compared to 82% in ERα-negative tumors (13). However, evidence also suggested that ERα loses its prognostic potential with longer follow-up, and after 5 years this difference is insignificant (14). Thus, it has been suggested that ERα expression denotes slower but similar potential of distant metastasis and death (5). The importance of ERα to predicted response to anti-estrogen treatment is used clinically on a daily basis. There are three different classes of anti-estrogen treatments available with different modes of action: selective ER modulators e.g., tamoxifen; aromatase inhibitors; and the estrogen antagonist fulvestrant (14). Traditionally, a cut-off value of 10% of positive cells has been used to separate positive from negative tumors. However, in 2010, the American Society of Clinical Oncology (ASCO) and College of American Pathologists changed their recommendations and a new cut-off value of 1% was implemented (15). The Swedish cut-off guideline remains at 10% positive cells. It has been shown that even patients with only little expression of ERα seem to benefit from endocrine treatment (16). In women with ERα-positive tumors, targeting ERα is effective, reducing the risk of recurrence by 50% for the first 5-years and by a third the following 5-years when tamoxifen is administered (17). Additionally, ERα-negative tumors do not benefit from treatment with tamoxifen at all (17).

### 4. Progesterone receptor

Progesterone receptor (PR) is strongly associated with ERα expression and is measured as a marker of intact ERα signaling. It is therefore believed that PR expression provides improved prediction with regard to which patient is likely to respond to endocrine treatment (15). PR is a target gene of ERα activation. Treatment with estrogen leads to increased PR levels in breast cancer cell lines (18). Several ER-binding sites, so-called ER elements, upstream of the PR gene, are believed to mediate the activation (19). The prognostic value of PR has been shown in several studies, even independent from ERα and other prognostic markers (20). To the best of our knowledge, at present, no cancer treatment module specifically targets PR.

### 5. Proliferation rate

The proliferation rate of breast cancer cells is routinely measured by immunohistochemical staining of the Ki67 protein. Although its function is unknown, Ki67 is expressed in proliferating cells throughout the cell cycle (21). The Ki67 index is particularly important in clinical decision making when determining between administering chemotherapy or not in ERα-positive tumors. Thus, the Ki67 index may be used to discriminate between tumors with high or low risk of recurrence. However, it can also be used as a proxy to discriminate between different intrinsic subtypes, such as tumors from the low proliferating Luminal A subtype with good prognosis, against Luminal B tumors with high proliferation and poor survival (22). However, there have been reports of variability in the reporting of Ki67 between and within laboratories (22). Consequently, no general cut-off value has been established to distinguish between tumors of high and low proliferation (23). There have also been discussions on how to analyze Ki67 most reliably to predict the benefit of chemotherapy. At present the majority of researchers, consider counting the percentage of Ki67-expressing cells within the areas of highest proliferation, the so-called hot spots, to be accurate (24).

### 6. HER2 and breast cancer

HER2 is a biomarker that has evolved from a marker of poor prognosis into a predictive marker of treatment response (25). HER2 is a transmembrane receptor that functions as a tyrosine kinase, although the endogenous ligand has not been identified (26). The overexpression of HER2 was considered to be associated with a high relapse rate. Without targeted treatment, patients have an increased mortality and a relapse rate (27). This is especially evident in node-negative patients (28). Use of treatments targeting the HER2 receptor has led to significant improvement in patient survival (29). Early data described HER2 to be overexpressed in as high as 30% of tumors (30). However, due to improved testing, the percentage of reported

positive tumors has decreased to 15-20%. Thus, fewer false-positive tumors are reported (31). To benefit from the anti-HER2 treatment the receptor needs to be overexpressed and the gene needs to be amplified.

## 7. Staging and prognosis

Staging of breast cancer patients reveals a great deal of information on the prognosis for the individual patient. In breast cancer, staging is performed according to the TNM classification system (32). This system is used in many types of cancer and divides the tumors into stage 0-4 depending on tumor progression. The factors taken into consideration are the size of the primary tumor (T), spread to loco-regional lymph nodes (N), and distant metastasis (M). Stage 0 is non-invasive cancer, such as ductal carcinoma *in situ* and lobular carcinoma *in situ*. Stage 1-3 breast cancer (without distant metastasis) is considered curable, while stage 4 breast cancer (with distant metastasis), is considered incurable. This fact is indicated by a meta-analysis on the prognosis from 36 clinical trials with metastatic disease showing a mean median overall survival of 21.7 months (33).

In women with tumors <1 cm, the 5-year survival has been reported to be as high as 99%. However, patients with 3-5 cm tumors had a survival of 86% (34). Furthermore, the mean time to distant metastasis was shorter for larger tumors compared to smaller tumors (35). The introduction of the mammography screening program increased the number of early-detected tumors. Thus, the average tumor size is currently <2 cm (36).

## 8. Histological grade

The differentiation grade of the tumor is used as a prognostic factor. There are several methods to evaluate tumor differentiation . One of the most used and well-validated methods is the Nottingham histological grading system (also known as Elston-Ellis) (37). This grading system was developed from the Bloom-Richardson system by introducing numerical cut-offs for two of the three criteria (38). The criteria examined in the Nottingham grading system are tubular formation, nuclear pleomorphism, and mitotic count. Each is given a score of 1-3, which is then combined into a total score (39). The tumors are then divided into three separate grades: grade 1, 2 and 3 depending on the scores.

## 9. Intrinsic subtypes

The development of gene expression DNA microarrays lead to a novel way of classifying breast cancer (40). By measuring the gene expression level of several thousands of genes in breast cancer tumors, a set of genes was identified that were differentially expressed between tumors. Using this gene set, the tumors were divided into distinct groups with similar gene expression patterns (41). The classification was termed the intrinsic subtypes (molecular subtypes) and four principal subtypes were identified (Table I). The main dividing factors in the clustering of the tumors were positive ERα expression status. The protein expression of keratin 8/18 was also common in this group. Since genes associated with the luminal cell type were overexpressed, the group was termed, the Luminal subtype. Luminal tumors were later divided into the Luminal A and Luminal B groups. The Luminal A subtype showed a higher ERα expression and a decreased proliferation rate compared to Luminal B tumors (42).

## 10. ERβ in breast cancer

Since the identification of ERβ, its role in breast cancer has been under scrutiny and many studies have examined ERβ1, *in vitro* and *in vivo* (43). For a long period of time, the endogenous expression of ERβ1 was not believed to exist in breast cancer cell lines. However, recent studies have indicated the opposite, although generally the expression is low (44). Using overexpression in cell lines, ERβ1 has been shown to be anti-proliferative and function as a dominant negative regulator of ERα function (45). ERβ1 has also been suggested to have an anti-angiogenic role by decreasing the levels of PDGFβ (46).

Much of the *in vitro* data suggested ERβ1 having a protective role against breast cancer development, with data from prognostic studies on patients showing inconsistent results (43). Several studies have suggested an association of ERβ1 with favorable prognostic variables, such as smaller tumor size, less lymph node metastasis, lower grade, and improved tamoxifen response (47,48). Other studies have failed to show such a correlation (49). In addition, use of tissue microarrays in some studies may lead to loss of prognostic power, primarily due to only a small area of the tumor being analyzed and therefore heterogeneous expression patterns potentially being overlooked. ERβ1 expression has been described in the nucleus and cytoplasm of breast cancer cells, and subcellular localization has been taken into consideration by some, but not all, of the studies (50). The splice variant ERβcx is also commonly expressed in breast cancer tumors. However, it has been less well studied and its role is even less clearly understood than ERβ1.

## 11. Conclusions

The present review shows that new endeavors are being undertaken in the area of breast cancer prognosis and detection. However, clinical confirmatory studies in the form of clinical trials are required to make these new methods gold standard avenues.

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