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SHORT COMMUNICATION

Breast cancer and factors affecting survival rate. Narrative review article

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ABSTRACT

Breast cancer is the most common malignancy in women and it was estimated as the fifth cause of death from malignancy in the world. The objective of this review is to illustrate the incidence of cancer breast and demonstrate different factors affecting survival rate.

***Keywords*:** Breast cancer, Estrogen receptor ER, Progesterone receptor (PR)

1. INTRODUCTION

Breast cancer is the most common malignancy in women accounting for about 24.2% of all cancers worldwide; overall, 8.600.000 new breast cancers were diagnosed in 2018. Breast cancer was estimated as the fifth cause of death from malignancy in the world leading to

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4.200.000 deaths. Superior lung cancer, it represented the most frequent cause of death due to malignancy about 15.0% of all cancer deaths in females **(1)**.

A predictive marker can be defined as a factor that shows sensitivity or resistance to a specific treatment. Predictive markers are important in oncology as different cancers differ widely in their response to therapies. Predictive markers are occasionally confused with prognostic markers. Both types of markers are used to provide information on the probable future behavior of a tumor, but whereas predictive factors are used to prospectively select responsiveness or resistance to a specific treatment, prognostic factors give information on outcome independent of systemic adjuvant therapy **(2)**.

Some markers can have both prognostic and predictive utility. For example, the estrogen receptor (ER) in breast cancer not only expects response to endocrine therapy but also correlates with good prognosis, at least in the short term **(3).**

The aim of this review is therefore to provide an overview on the current status of predictive markers in breast cancer survival analysis. Because most work on predictive markers has been carried out on breast cancer, the main, but not exclusive, focus will be on this malignancy. The most widely studied predictive markers in oncology are now reviewed.

2. HORMONE RECEPTORS

The two most widely used predictive factors in cancer are the estrogen receptor ER and the progesterone receptor (PR). Both the ER and PR are ligand-activated transcription factors belonging to the family of nuclear hormone receptors. Nuclear hormone receptors have several common structural features. These include a central DNA-binding domain responsible for targeting the receptors to specific DNA sequences within regulatory regions of their target genes and a ligand-binding domain, detected in the carboxyl-terminal half of the receptor, that distinguishes specific hormone and non hormone ligands **(4)**.

Overall, more than 75% of breast carcinomas express the hormone receptors ER and/or PR. The percentage of cancer cells stained for those biomarkers has valuable prognostic and predictive information **(5).**

ER is an intracellular protein mostly expressed in breast, endometrium, ovarian stroma and hypothalamus. PR is also an intracellular protein and its gene is transcriptionally activated by ER by binding to ER binding sites, so-called ERE, present upstream to PR gene **(6)**. The expression of PR, thus, correlates to that of ER, and, for this reason, the existence of ER-negative/PR-positive breast cancers is highly controversial. ER and PR are currently measured by immunohistochemistry (IHC), which replaced the ligand-binding assay in the US in the early to mid-90s. IHC, which uses a monoclonal antibody-based biochemical method to identify specific sequences on the receptor gene, faces limitations mainly related to inter-laboratory as well as inter-observer discrepancies **(7)**.

The predictive role of ER has been described in a metanalysis of over 20.000 patients from 20 trials of adjuvant tamoxifen vs. no tamoxifen. In ER-positive tumors, tamoxifen was associated to 39% and 30% decrease in the risk of recurrence and death at 15 years, respectively. The results were independent of PR, age, nodal status and use of chemotherapy. By contrast, tamoxifen did not alter survival in patients with ER-negative disease. PR-positive tumors have a better prognosis when treated with tamoxifen.

However, the expression of PR is dependent on ER and the predictive role of PR is therefore unclear, especially when ER status is known **(8).**

Based upon this evidence, trends in mortality variations by screening and early disease systemic treatment have been reinterpreted in a molecular context indicating greater absolute death rate declines in ER-positive (median 17 per 100.000 women, range = 13-21) than ER-negative cancers (median 5 per 100.000 women, range = 3-6) in the years 1975 through 2000, largely owing to the use of tamoxifen. In contrast, similar decrease in death rates was detected for ER-positive and ER-negative cases (median 16.7% vs. 14.0%, respectively), where no adjuvant treatment was assumed. Interestingly, amongst only screening-detected invasive tumors (thus excluding over-diagnoses) the overall 5-year survival probability was higher in ER-negative tumors (35.6% vs. 30.7%), mainly as an effect of the absolute higher survival gain obtained by diagnosis at an earlier stage in this tumor subgroup (25.6% vs. 20.2%) **(9)**. These data provide further support to the molecular and clinical heterogeneity of breast cancer **(10).**

The prognostic relevance of ER and PR has been a matter of debate for many years. Recently, an analysis on 4000 patients enrolled in four clinical trials with a follow-up of 24 years described that ER-positive tumors have a lower annual hazard of recurrence compared to ER-negative tumors during the first 5 years (9.9% vs. 11.5, p 0.01). Beyond 5 years, hazards in ER-positive cancers are higher and remain stable after 10 years from primary diagnosis, nevertheless lymph node statu**s.** PR is a well-known prognostic factor of time to recurrence and overall survival **(11).**

Studies showed that over expression of ER and PR showed a decreased hazard of death **(12)**. Mortality diminished with increasing category of ER protein staining (p = .001 for trend), In Cox proportional hazards models, ER percent positive was no longer related to breast cancer death after adjustment for only age, tumor size, number of positive nodes, and tumor grade, thus adjustment for ER intensity or for PR was not responsible for the loss of significance **(13).**

3. HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR 2 (HER-2)

HER-2 protein, which is also known as c-erbB-2 or *neu*, is a member of subclass 1 of the superfamily of receptor tyrosine kinases. Other members of this family include epidermal growth factor receptor (HER-1), HER-3, and HER-4. All of these proteins have an extracellular ligand-binding domain, a membrane-spanning region, and a cytoplasmic domain with tyrosine kinase activity **(14)**.

Although these receptors share a common structure, naturally occurring ligands have been noticed only for HER-1, HER-3, and HER-4. HER-2 thus appears to be an orphan receptor because no directly binding ligand has yet been identified for it. HER-2, however, can signal as a result of heterodimerization with other HER family members and seems to be the preferred heterodimerization partner. After heterodimerization, HER-2 complexes begin intracellular signaling via the mitogen-activated protein kinase, phosphatidylinositol 3-kinase, and phospholipase C pathways **(14).**

The clinical significance of HER2 in breast cancer has progressed from a marker of poor prognosis to a marker of response to treatment with therapies affecting the receptor **(15)**.

HER2, which normally regulates cell growth, differentiation and survival, The clinical significance of HER2 in breast cancer has evolved from a marker of poor prognosis to a marker of response to treatment with therapies targeting the receptor, which normally regulates cell

growth, differentiation and survival, is overexpressed in 15-20% of invasive breast cancers and correlates with more aggressive cancer features **(16)**. HER2 is a predictive factor of response to HER2-targeted therapies and the advantage from trastuzumab in HER2-positive tumors has been well described both in the early **(17)**, and in the advanced setting **(18).**

Overexpression/amplification of HER2 was found to correlate with a superior survival in a variety of studies, including those in patients with de novo metastatic breast cancer **(19)**.

Correlation of HER-2/neu over-expression and tumor grade was also studied by **(20)** with a sample size of 1,210 cases. According to their study also, HER-2/neu over-expression was associated with a higher tumor grade, as observed in 3.9%, 20.4%, and 38.9% grade 1, 2, and 3 tumors respectively, whereas in our study positivity was shown in 0%, 22.89%, and 31.58%. Similarly, a study conducted in Italy **(21)** showed overexpression of HER-2/neu in 29.7% of breast cancers, significantly correlating with larger tumor size and a decreasing level of ER. Another study by **(22)** in Antalya-Turkey provided comparable results.

HER2 in the absence of systemic therapy, HER2 overexpression is associated with poorer prognosis regardless of the axillary lymph node involvement. HER2 retains a negative prognostic effect even in tumors ≤1 cm with negative lymph nodes **(23).**

4. HORMONE RECEPTOR AND HER2-STATUS

Hormone receptor positive primary breast cancers have a longer survival in the advanced set. Tumors overexpressing both ER and PR have a better prognosis than those expressing either ER or PR **(24)**. When clinically feasible, reassessment of hormone receptor status and HER2 should be performed at least once in metastatic setting **(25)**,change in ER status from positive to negative in primary tumor tissue and metastasis has been related to higher risk of death related with stable ER status. The discordance in HER2 status was also related to shorter post–relapse survival **(26)**.

Overall, 14-32% and 10% discordance rate in hormone receptors and HER2, respectively, between primary tumor and corresponding metastasis has been assessed. Beyond a demonstrated prognostic role, the new expression pattern of ER, PR and HER2 may be of predictive value and according to adept opinions treatment should be guided by the phenotype of the metastasis rather than that of the primary tumor **(27).**

5. CONCLUSIONS

Cancer breast is very important disease and common in female and all female in our family must be aware of it, Improvement of the diagnosis and treatment of patients with breast cancer lead to increased incidence rate of PMPS. Treatment approaches include both pharmacological interventions and non-pharmacological strategies. However, current treatments of the PMPS are near-optimal and prevention much better than treatment. Further investigations are required to achieve the appropriate developments in diagnosis and screening of breast cancer, and evaluation and treatment of PMPS that will provide less side effects, adequate analgesia, and finally, improved quality of life, and patient satisfaction in the future. Frequency of PMPS due to advances in diagnosis and treatment of breast cancer is on the rise. Using proper treatments can improve the patients' quality of life.

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