Molecular Classification of Breast Cancer

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KEYWORDS

• Breast cancer • Molecular classification • Genes • Mutations • Copy number alterations

KEY POINTS

- Breast cancer is a heterogeneous disease.
- It can be classified based on its molecular profiles.
- These molecular subtypes have different prognostic indices and may require different clinical management.

INTRODUCTION

Breast cancer is not a single entity but a heterogeneous group of diseases with highly variable clinical behavior[1]. Pathologists have long recognized this diversity at the morphologic level, and it is reflected in the various special histologic types of breast cancer with their distinct microscopic appearances and associated clinical outcomes. However, 70% to 80% of breast cancers fall into the ductal/no-special-type category (invasive ductal carcinoma [IDC]), which, rather than representing a unique entity, show marked heterogeneity with respect to tumor morphology, underlying molecular biology, and prognosis.[2]

Cancer is driven by DNA alterations, including chromosomal rearrangements, mutations, and epigenetic changes, such as promoter hypermethylation resulting in activation of growth-promoting genes (oncogenes) or suppression of growth-inhibiting genes (tumor suppressor genes). The advent of array-based technologies enabled quantification of DNA copy number changes and global expression profiling of tens of thousands of genes in a single experiment. Recent advances, for example, next-generation sequencing allowed detection of mutations, chromosomal rearrangements, and copy number alterations across the entire genome, including those only present within minor subclones of tumor cells.[3,4] These high-throughput (HT) technologies have changed how we conceptualize and classify breast cancer as well as provide a new level of insight into the complexity of genetic changes and the existence of intratumoural heterogeneity.[5–7]

Historically, patient management decisions have been based on traditional histologic features, including tumor size, histologic grade, lymph node status, and hormone and human epidermal growth factor receptor 2 (HER2) receptor status in conjunction with patient characteristics, such as age.[8,9] These variables show a strong association with survival outcomes but, even when combined in algorithms, such as Nottingham Prognostic Index, Predict, or Adjuvant! Online, are a crude measure of risk in individual patients.[10–15] Accurate prediction of tumor behavior is key to oncological decision-making, avoiding overtreatment with

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harmful drugs in patients with a good prognosis, and more aggressive intervention with first-line chemotherapy in patients with a poor prognosis.[16–18] However, use of algorithms based on these histologic variables result in a significant number of patients being overtreated, with as many as 85% of patients deriving no benefit from chemotherapy. At the other extreme, 20% of patients still die despite receiving maximum therapy.[19]

The ultimate goal of modern oncological management is personalized medicine, with a more precise determination of patient prognosis based on tumor biology and the opportunity for targeted treatment directed at the underlying molecular aberrations driving individual tumor growth. HT molecular techniques offer the potential to revolutionize patient management in this way. But these techniques are currently expensive compared with standard methods, such as immunohistochemistry (IHC); the vast amounts of data generated require complex bioinformatic analyses limiting their clinical use currently.[20]

Intrinsic Subtypes

The mainstays of breast cancer characterization are still histologic subtype, tumor grade, and stage, which provide a basic reflection of the degree of tumor differentiation (tubule formation) and growth rate (size and mitotic count). The seminal article that led to the identification of 5 intrinsic subtypes was published by Perou and colleagues[5] in 2000. The investigators took a series of 38 invasive breast cancers (36 ductal and 2 lobular), 1 case of ductal carcinoma in situ (DCIS), and 4 benign samples and undertook complementary DNA microarray gene expression analysis followed by hierarchical clustering of differentially expressed genes and identified 5 subtypes primarily separated by estrogen receptor (ER) expression; 2 ER-positive luminal subtypes, and 3 ER-negative subtypes (HER2 enriched, basal and normal-like). A follow-up study showed that these subtypes were associated with differences in survival.[21]

These 5 intrinsic subtypes have been validated in other series and have changed how we think about the taxonomy of breast cancer.[22,23] The separation into good and poor prognosis ER-positive, HER2-positive, and triple-negative (ER, progesterone receptor [PR], and HER2 negative: triple-negative breast cancer [TNBC]) groups is highly clinically relevant, given that current therapeutic regimens are centered on antiestrogen therapy, chemotherapy, and HER2-targeted agents. The normal-like subtype has subsequently been dropped, as it is thought to represent contamination by normal glands. Classification of cohorts of breast cancers into the intrinsic subtypes seems robust across studies; however, assignment of individual tumors to a subgroup shows only moderate reproducibility depending on the array platform used, composition of the entire tumor population, and setting of gene expression thresholds.[24–26] Identification of the basal-like group is most reproducible, with the luminal B and HER2 groups the most poorly reproducible.[26,27] The commercially available Prediction Analysis of Microarray 50(PAM50) classifier (Prosigna),[28,29] based on expression of 50 genes that can separate tumors into the intrinsic subtypes, has been shown to be an independent marker of prognosis.[30–33] Attempts to replicate these groups using IHC-based panels, including ER, PR, HER2, Ki67, and basal cytokeratins, have produced modest concordance between gene expression and IHC-defined intrinsic subtypes at best.[22,34]

Luminal Breast Cancer

Luminal breast cancers are enriched for ER-positive tumors and include special type cancers, such as tubular, cribriform, lobular, and mucinous carcinomas. Luminal cancers form a continuous spectrum that can be arbitrarily divided into 2 subgroups based on the expression of proliferation-related genes. Luminal A tumors are typically low grade with an excellent prognosis, ER/PR positive and HER2 negative, with high expression of ER-related genes and low expression of proliferation-related genes.[23,35] In contrast, luminal B tumors are higher grade with worse prognosis and may be PR negative and/or HER2 positive with high expression of proliferation-related genes.[36,37] Clinically, the luminal A group is likely to benefit from hormonal therapy alone, whereas luminal B tumors with their increased proliferation may be candidates for chemotherapy.

Molecular signatures that separate ER-positive tumors into good and poor prognosis subgroups form the basis for many of the multi-gene assays that are currently available for clinical use, such as Oncotype Dx, Mammaprint, and EndoPredict.[38–40] Although there is little overlap in the specific genes that make up these signatures, they all include genes involved in proliferation and ER signaling.[27,41] In studies whereby multiple signatures are applied to the same patient cohort, they all identify low- and high-risk groups with a significantly different prognosis; however, there is disagreement at the individual patient level in many cases.[42–46]