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Subtypes of Breast Cancer

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Abstract: Breast cancer is a genetically and clinically heterogeneous disease with multiple subtypes. The classification of these subtypes has evolved over the years. The most common and widely accepted classification of breast cancer is from an immunohistochemical perspective, based on the expression of the following hormone receptors: estrogen (ER), progesterone (PR) and human epidermal growth factor (HER2). Accordingly, the following four subtypes of breast cancer are widely recognized: luminal A, luminal B, HER2-positive, and triple-negative. With the recent advances in cancer research, and an increased molecular understanding of breast cancer, the current clinical model for classification of breast cancer may be benefit from the addition of several molecular markers such as miRNAs (let-7, miR-155, miR-150, miR-153) and mutations (p53, BRCA 1 and 2 genes). This chapter provides an overview of the characteristics of these four subtypes of breast cancer.

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INTRODUCTION

Breast cancer is the most common cancer in women worldwide. It is a highly heterogeneous neoplasm with distinct subtypes. These subtypes are commonly grouped into four categories based on the immunohistochemical expression of hormone receptors: estrogen receptor positive (ER+), progesterone receptor positive (PR+), human epidermal growth factor receptor positive (HER2+), and triple-negative (TNBC), which is characterized by the lack of expression of any of the above receptors (1). Estrogen receptor (ER) is an important diagnostic determinant, as approximately 70–75% of invasive breast carcinomas are characterized by significantly high ER expression (2, 3). The progesterone receptor (PR) is expressed in more than 50% of ER-positive patients, and very rarely in those with ER-negative breast cancer. PR expression is regulated by ER (4); therefore, physiological PR values inform about the functional ER pathway. However, both ER and PR are abundantly expressed in breast cancer cells, and both are considered diagnostic and prognostic biomarkers of breast cancer (5). Higher expression of PR is positively associated with overall survival, time to recurrence, and time to treatment failure or progression, while lower levels are generally associated with a more aggressive course of disease, as well as poorer recurrence and prognosis (6).

Human epidermal growth factor receptor 2 (HER2) expression accounts for approximately 15–25% of breast cancers and its status is mainly relevant in the choice of appropriate treatment (7, 8). HER2 overexpression is one of the earliest events during breast carcinogenesis (8). HER2 increases the detection rate of metastatic or recurrent breast cancers by 50% and even 80%. Serum HER2 levels are considered a promising real-time marker for the presence or recurrence of tumors. HER2 amplification leads to increased overactivation of proto-oncogenic signaling pathways leading to uncontrolled cancer cell growth, which corresponds with worse clinical outcomes of HER2+ cases. HER2 overexpression also correlates with a significantly shorter disease-free period (9). The Ki67 antigen is a cellular marker of proliferation and is an excellent marker for providing information on cell proliferation. The proliferative activities determined by Ki67 reflect the aggressiveness of the cancer along with response to treatment and time to recurrence (10). Therefore, Ki-67 is crucial in terms of choosing the appropriate treatment therapy, and possible follow-ups for recurrence. It could also be considered as a possible prognostic factor. High expression of Ki67 also reflects lower survival rates (11, 12).

The need for molecular classification is to categorize patients who may benefit from targeted therapy, such as hormone therapy and anti HER2 therapy (13). Recently, the identification of differentially expressed genes, long non-coding RNAs, and RNA binding proteins for each breast cancer subtype were reported: RASDF7 for luminal A, DCTPP1 for luminal B, DHRS11, KLC3, NAG3 and TMEM98 for HER2, and ABDHD14A and ADSSL1 for TNBC, providing preliminary evidence to identify new prognostic biomarkers and therapeutic targets for individual breast cancer subtypes (14). This chapter focuses on the four major subtypes of breast cancer: luminal A,

TABLE 1 Characteristics of subtypes of breast cancer

	Luminal A	Luminal B	HER2	TNBC	Reference
Frequency (%)	50	15	20	15	16, 17
ER	Yes	Yes	Some cases	No	15
PR	Yes	Some cases	Some cases	No	17
HER	No	No	Yes	No	18
miRNAs	*Let*-7f, *Let*-7c, *miR-10*, *miR-29a*, *miR-181a*, *miR-223* and *miR-652*	*miR*155, *miR*-93, *miR*-18a, *miR*-135b, *miR*-718, *miR*-4516, *miR*-210, and *miR*-125b-5p	*miR*-150 and *miR*-142–3p	*miR*-153, *miR*-10b, *miR*-26a, and *miR*146a	19–22
Ki67	Some cases	Some cases	High	High	23
Mutations	No	BRCA2	p53	p53 and BRCA1	24, 25
Prognosis	Good	Middle	Middle/Bad	Bad	26
Therapy	Hormonal	Hormonal/ Chemo	Hormonal/Chemo/ Herceptin	Chemo/ Experimental	27, 28

ER, estrogen receptor; HER, human epidermal receptor; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor; TNBC, triple-negative breast cancer

luminal B, HER2-positive, and TNBC subtypes. The characteristics of these four subtypes are presented in Table 1 (15–28). Luminal cancers mainly express low molecular weight cytokeratins (CK7, CK8, CK18, among others), and three groups are distinguished from the IHC point of view: luminal A, luminal B and HER2 (15).

LUMINAL A SUBTYPE

Luminal A tumors are characterized by the presence of ER and/or PR and the absence of HER2, and have a low expression of cell proliferation marker Ki-67 (less than 20%) (Figure 1). Clinically they are low grade, slow growing, and have the best prognosis with less incidence of relapse and higher survival rate. These carcinomas present a high response rate to hormone therapy (tamoxifen or aromarase inhibitors), and a more limited benefit to chemotherapy (27). For this reason, according to the European Society for Medical Oncology (ESMO) and National Comprehensive Cancer Network from USA (NCCN) Guidelines, the use of genetic platforms is recommended in this group to establish which patients would benefit from adjuvant chemotherapy treatment based on the risk of relapse

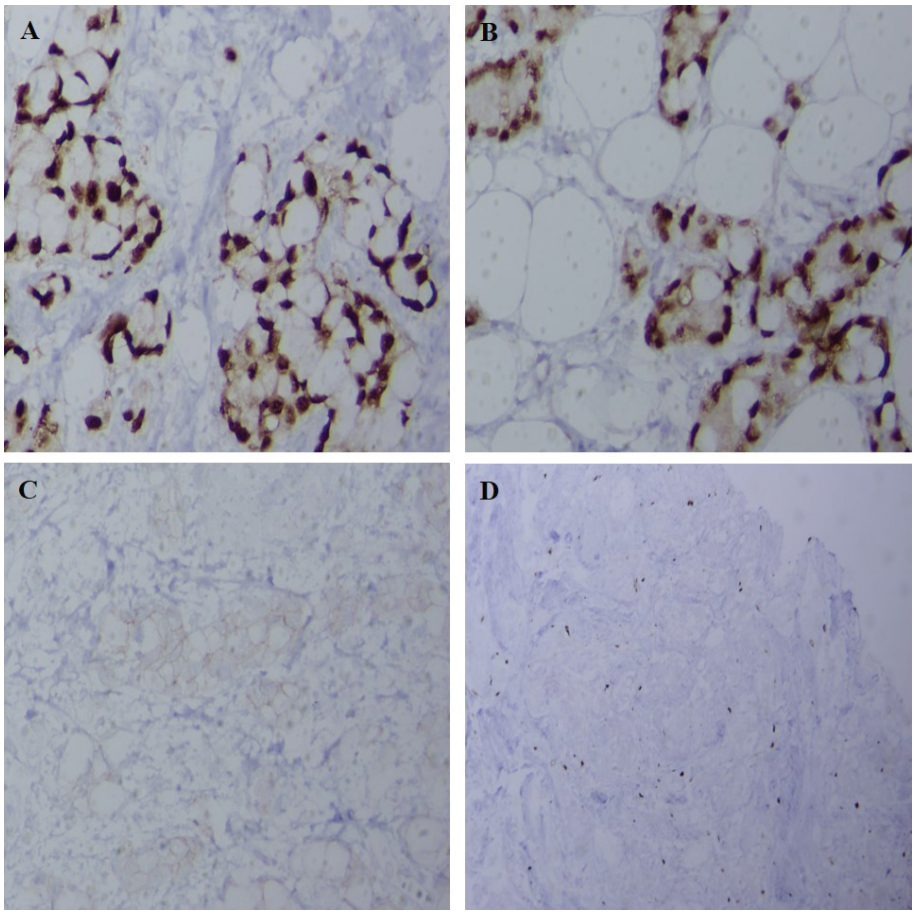

Figure 1. Immunohistochemistry of luminal A invasive breast carcinoma. A, estrogen receptor positive, nuclear staining. **B,** progesterone receptor positive, nuclear staining. **C,** HER-2 1+ negative, membrane staining. **D,** Ki-67 positive 3%, nuclear staining. Images obtained from Dr. Anchondo-Núñez's personal collection.

and survival rate (29, 30). Relapse is more frequent at the bone level, with a lower rate of visceral and central nervous system (CNS) relapses. Likewise, they have a longer survival in case of relapse (31).

LUMINAL B SUBTYPE

Luminal B tumors are of higher grade and worse prognosis compared to Luminal A. They are ER positive and can be PR negative and have a high expression of Ki67 (greater than 20%) (Figure 2). They are generally of intermediate/high histologic grade. These tumors may benefit from hormonal therapy along with chemotherapy. The elevated Ki67 makes them grow faster than luminal A and worse prognosis (32). It constitutes 10–20% of luminal tumors. It has a

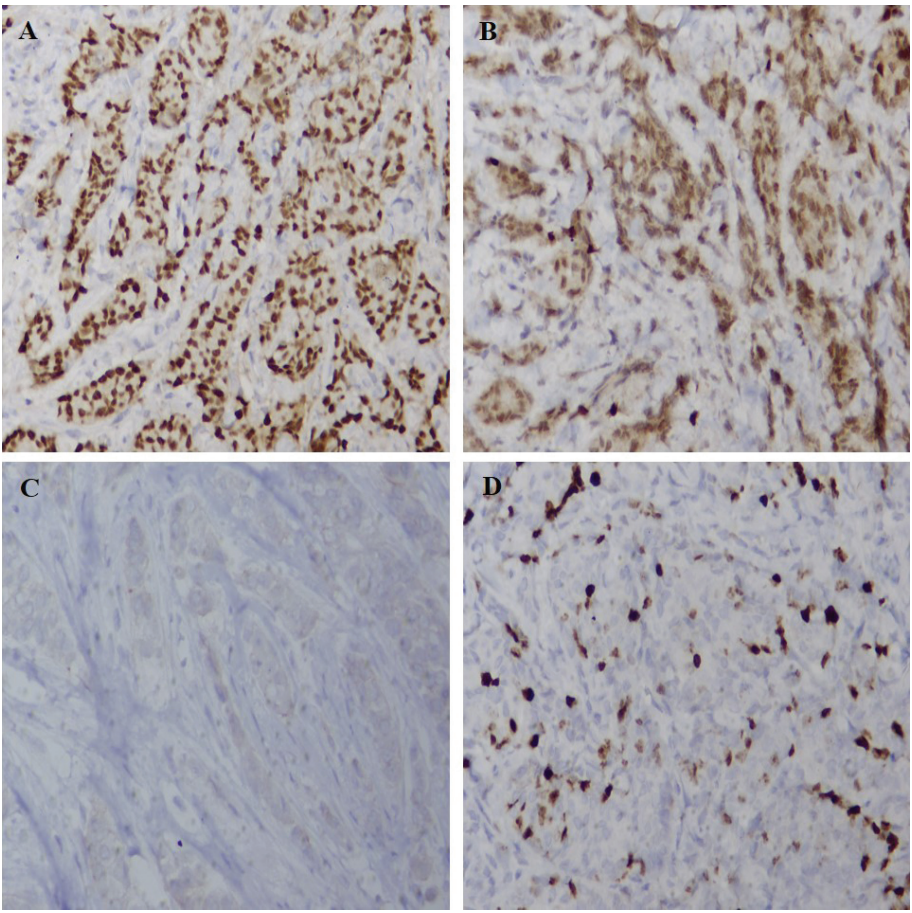

Figure 2. Immunohistochemistry of luminal B invasive breast carcinoma. A, estrogen receptor positive, nuclear staining. **B,** progesterone receptor positive, nuclear staining. **C,** HER2 1+ negative, membrane staining. **D,** Ki-67 positive 30%, nuclear staining. Images obtained from Dr. Anchondo-Núñez's personal collection.

moderately low expression of estrogen receptors, and increased expression of proliferation and cell cycle genes. It represents the group of luminal tumors with the worst prognosis. They benefit from hormone therapy and in a higher percentage from chemotherapy compared to the previous group (33). Although bone recurrence is frequent, they have a higher rate of visceral recurrence, and survival from diagnosis to relapse is lower (34, 35).

HER2 SUBTYPE

The HER2-positive group constitutes 10–15% of breast cancers and is characterized by high HER2 expression with absence of ER and PR (Figure 3). They grow faster than the luminal ones and the prognosis has improved after the

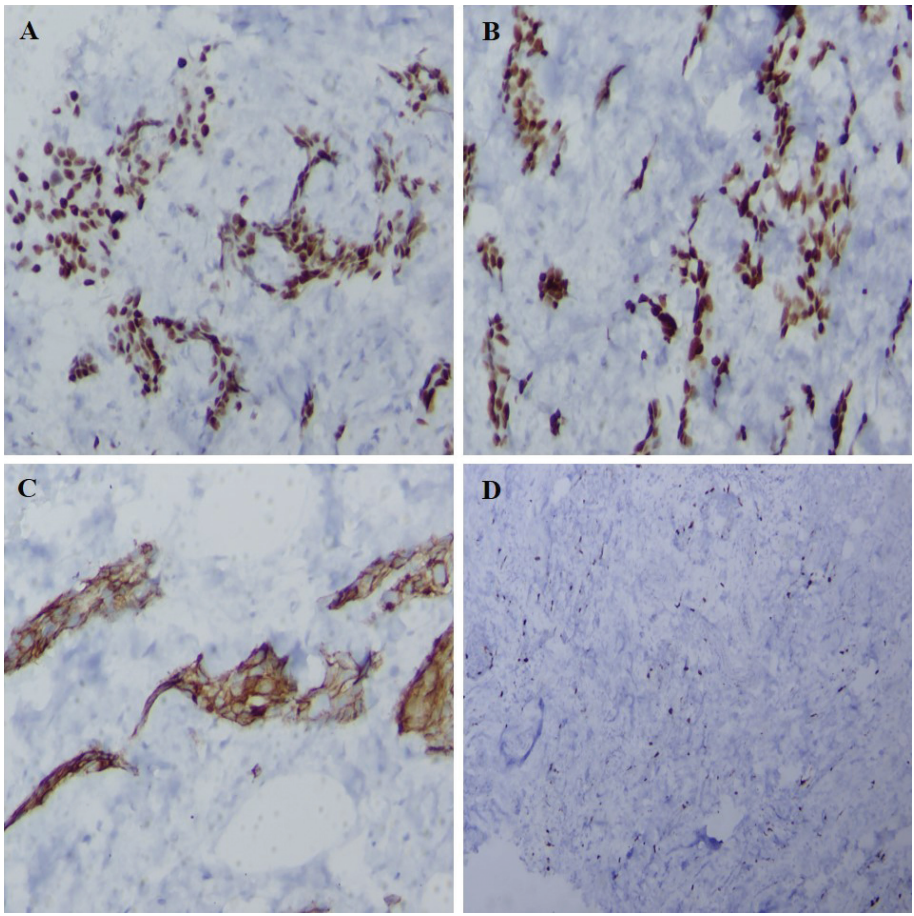

Figure 3. Immunohistochemistry of HER2 invasive breast carcinoma. A, estrogen receptor positive, nuclear staining. **B,** progesterone receptor positive, nuclear staining. **C,** HER2 3+ positive, membrane staining. **D,** Ki-67 positive 5%, nuclear staining. Images obtained from Dr. Anchondo-Núñez's personal collection.

introduction of HER2-targeted therapies. The HER2-positive subtype is more aggressive and fast-growing. Within this, two subgroups can be distinguished: luminal HER2 (E+, PR+, HER2+ and Ki-67:15–30%) and HER2-enriched (HER2+, E-, PR-, Ki-67>30%) (36). They have a worse prognosis compared to luminal tumors, and require specific drugs directed against the HER2/neu protein, including trastuzumab, trastuzumab combined with emtasin (T-DM1), pertuzumab, and tyrosine kinase inhibitors such as lapatinib and neratinib, among others, in addition to surgery and treatment with precise chemotherapy (37). They have a high response rate to chemotherapy schemes (38). Bone localization is the most common site for disseminated disease, and visceral relapses are also more frequent in this subgroup compared to the previous group (39, 40).

TNBC SUBTYPE

Triple-negative breast cancer is ER-negative, PR-negative, and HER2-negative (Figure 4). They constitute about 20% of all breast cancers. It is most common among women under 40 years of age, and in African-American women. The TNBC subtype is further classified into several additional subgroups including basal-like (BL1 and BL2), claudin-low, mesenchymal (MES), luminal androgen receptor (LAR), and immunomodulatory (IM), the first two being the most frequent with 50–70% and 20–30% of cases (41). Moreover, each of these has unique clinical outcomes, phenotypes, and pharmacological sensitivities. TNBC presents an aggressive behavior and 80% of breast cancer

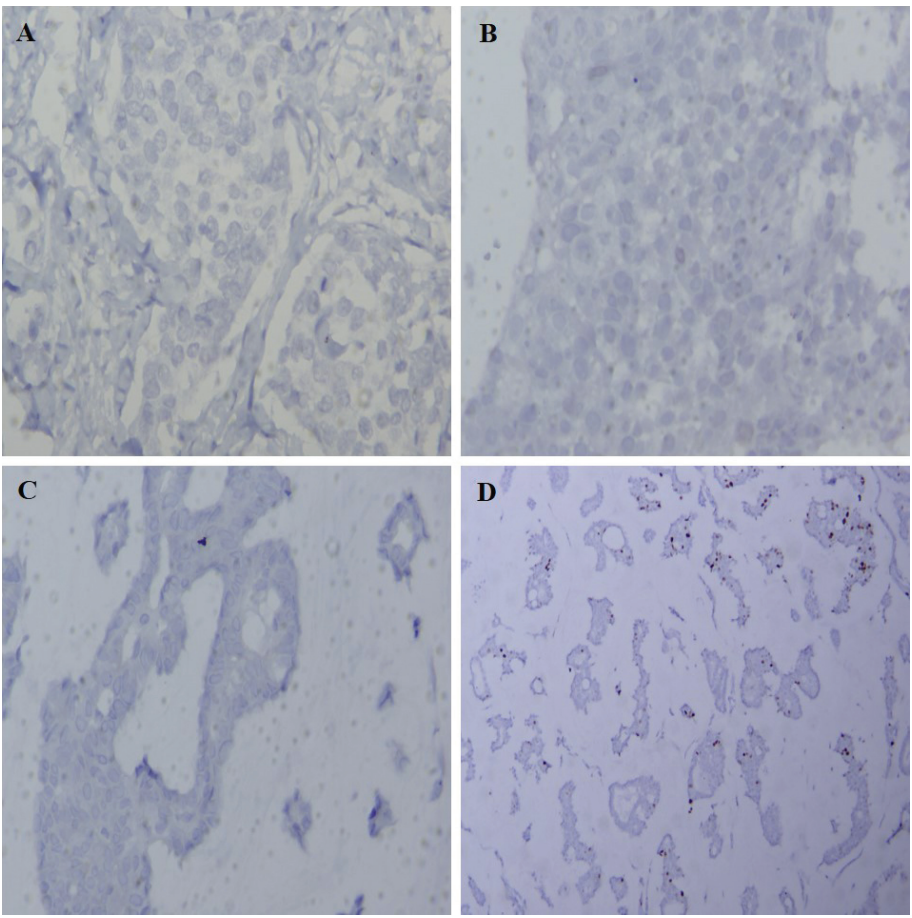

Figure 4. Immunohistochemistry of triple-negative invasive breast carcinoma. A, estrogen receptor negative. **B,** progesterone receptor negative. **C,** HER2 0+ negative, membrane staining. **D,** Ki67 positive 10%, nuclear staining. Images obtained from Dr. Anchondo-Núñez's personal collection.

tumors (tumor suppressor gene BRCA1 and BRCA2) belong to this group (28). The risk of developing TNBC varies with genetics, race, age, overweight and obesity, breastfeeding patterns, and parity (41, 42). TNBC is characterized by its aggressiveness, early relapse, and a greater tendency to present in advanced stages. It presents a high proliferation rate, alteration in DNA repair genes and increased genomic instability. Histologically, it is a poorly differentiated, highly proliferative, heterogeneous neoplasm, including subsets of variable prognosis. Immunohistochemically, they are subdivided into basal and non-basal TNBC; the former characterized by expression of cytokeratins (CK)5/6 and human epidermal growth factor receptor type 1 (EGFR1), while the non-basal do not express CK5/6 cytokeratins.

METASTASIS, OVERALL SURVIVAL, AND RELAPSE

Given the early detection and multiple treatments available against breast cancer, the mortality rate has decreased. However, distant metastases are not uncommon, and for women with advanced breast cancer, the median survival time is 2–3 years (43, 44). In most cases, metastatic breast cancer is uncommon at initial presentation, occurring in about 6–7% of newly diagnosed cases; however, approximately 30% of patients initially diagnosed with earlier stages of breast cancer eventually develop recurrent or metastatic disease (45–47).

In 2018, Xiao et al. (48) performed a detailed analysis of the association between breast cancer subtypes and the risk of developing distant metastasis. They found that newly diagnosed breast cancers presented with bone (3.28%), lung (1.52%), liver (1.2%), and brain (0.35%) metastasis at diagnosis. They also reported that, metastatic sites and subtypes significantly affected the overall survival after metastasis. Moreover, they found that luminal B subtype significantly correlated with elevated bone metastasis risk, whereas luminal A did not. Both luminal subtypes were significantly associated with higher rates of liver, brain, and lung metastasis, while the highest odds ratio was observed in liver metastasis. TNBC had a higher rate of brain, liver, and lung metastases, but a significantly lower rate of bone metastases than luminal A subtype.

Regarding survival rate, the National Cancer Institute (49) reports the '5-year relative survival percentage', showing that the best survival pattern was for women with luminal A subtype with 94.4% survival rate, followed by the luminal B subtype with 90.7%, HER2 subtype with 84.8%, and the TNBC subtype had the worst survival, with 77.1%. It is important to mention that, although the breast cancer subtype affects survival, stage at diagnosis may be the most powerful factor in determining survival outcome.

Finally, relapse of breast cancer may differ depending on the subtype (50). Ignatov et al. (51) investigated relapse in breast cancer patients. They found that HER2 and TNBC had the highest rate of local and regional recurrence, 7.5 and 3.4% for HER2 and 7.6 and 3.3% for TNBC, respectively. Luminal A subtype were recurrent in 1.5 and 0.7% local and regional, respectively, and luminal B subtype was associated in 2.9 and 1.5% of the cases with local and regional relapse. Moreover, the authors found that, even though the rate of

recurrence for luminal and luminal B subtypes was initially low, recurrence can occur even after 10 years. These data suggest that breast cancer subtypes are associated with different pattern and time of recurrence and these factors should be considered during treatment decision.

CONCLUSION

Knowing the subtype of breast cancer can help clinical practice to establish the best treatment. Gene expression studies have shown heterogeneity of breast — cancer, and this heterogeneity has a molecular basis; however, to date, it has not been determined whether these molecular characteristics would influence unequivocally the clinical management of breast cancer (52). The identification of miRNAs and specific genes associated with breast cancer may reveal additional heterogeneity among breast cancer subtypes and may become relevant in the development of more specific drugs for each subtype, generating therapies that give a longer life expectancy. Probably these studies will also help to detect cancer in early stages, increasing the possibility of survival of patients. Molecular classification is useful not only in prognosis, but also for targeted therapy. Therefore, it should be adopted as part of the routine histopathologic report.

Conflict of Interest: The authors declare no potential conflicts of interest with respect to research, authorship and/or publication of this manuscript.

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