

Triple negative, basal-like and BRCA1-associated breast cancers – what's the difference and should anyone care?

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ABSTRACT

Breast carcinoma is common in women and forms an integral part of the BRCA familial cancer syndromes. As breast cancer is considered a heterogeneous disease, clinicians have traditionally relied on clinical and morphologic findings, as well as hormone receptor/HER-2 status for prognostic and predictive categorisation of tumours. Recently, breast cancer subclassification has been aided by the discovery of various gene expression profiles, compiled after simultaneous examination of multiple tumour biomarker genes. Basal-like breast cancer was delineated using this methodology and demonstrates significant overlap with so-called triple negative and BRCA1-associated breast carcinomas. This article describes the pathology and biology of these three groups of tumours and examines the relationship between them. Therapeutic implications are also briefly discussed.

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Introduction

Breast cancer is the commonest malignancy in women worldwide and an important component of familial cancer syndromes such as BRCA1, which include female genital tract malignancies.¹ It is now well accepted that breast cancer is a heterogeneous disease comprising tumours with differing morphologies, immunohistochemical features and clinical outcomes.²

Categorisation of breast cancer has been undertaken at various levels in order to better appreciate the prognosis and expected response to various therapies of any given tumour. This categorisation has traditionally relied on variables such as axillary lymph node status, tumour size, histologic grade/type, hormone receptor expression and, more recently, HER-2 status.

Hormone receptor and HER-2 status are now routinely determined in the histopathology laboratory. Hormone receptor (particularly oestrogen) protein expression is a weak prognostic factor, but strongly predictive of response to oestrogen blockade.³ HER-2 gene amplification/protein overexpression is associated with a poor prognosis and predicts response to therapy with trastuzumab (Herceptin®), an anti-HER-2 monoclonal antibody.⁴ Although numerous other biomarkers such as p53, cathepsin D, bcl-2 and nm23 have been investigated, none appear to have significant independent prognostic or predictive value if subjected to multivariate analysis.

In the last decade the advent of gene expression profiling has further advanced the categorisation of breast cancer. By evaluating gene expression of multiple biomarkers (including hormone receptors and HER-2) simultaneously, this methodology is able to distinguish between breast cancers with similar tumour characteristics but differing prognosis and response to therapy. In 2001 workers at Stanford university delineated five main groups of breast cancer based on gene profiles, which also reveal some analogy to corresponding normal breast epithelium cell types.⁵ The oestrogen receptor (ER) expressing groups have a better prognosis and comprise a luminal type A and B, whilst the ER negative

tumours include HER-2 positive, normal breast-like and basal-like categories. The latter category appears to have the poorest prognosis. A number of additional prognostic gene expression profiles (or signatures) have subsequently been delineated, including a so-called Wound Healing Signature, OncotypeDX (21 gene profile) and MammaPrint (70 gene profile). The latter two are already available commercially.

Triple negative breast carcinoma (TNBC)

This group of tumours is defined by means of a triple negative phenotype, i.e. negative immunohistochemistry for ER, progesterone receptor (PR) and HER-2 and is therefore easy to identify in a routine histopathology laboratory. The group comprises 10–17% of all breast cancers, the latter figure partly dependent on the receptor scoring scheme/positivity threshold.⁶ Of the two semi-quantitative schemes widely utilised in histopathology, the Allred Quick Score has a lower threshold for positivity than the McCarty H-score.

TNBC is more common in younger (< 50 years old) and African-American patients.⁷ This tumour group typically demonstrates high grade histology (ductal carcinoma grade III according to the modified Nottingham scheme) and sometimes has a metaplastic or medullary morphology. Interestingly, however, approximately 10% have a grade I (well-differentiated) appearance and possibly represent a subgroup of neoplasms with the normal breast-like gene expression profile. TNBC usually has an aggressive biology when compared with non-TNBC.⁸ Studies demonstrate a higher rate of lymph node metastasis at diagnosis, no correlation between tumour size and the presence of lymph node metastasis, and a peak recurrence risk 1–3 years after initial therapy for TNBC. Furthermore, the majority of deaths occur within five years after therapy and there is a significantly shorter survival after the first metastatic event.⁹

Basal-like breast carcinoma (BLBC)

BLBC as delineated by genetic profiling makes up approximately 15% of breast cancers and reveals an expression profile similar to basal/myoepithelial cells in the normal breast. This group can also be identified relatively accurately using immunoperoxidase stains as defined

by Nielsen et al, requiring negative ER and HER-2, as well as positive cytokeratin 5/6 and epidermal growth factor receptor (EGFR) stains (Figure 1).¹⁰ BLBC usually also reveals positivity for other high molecular weight cytokeratins/HMCK (such as CK 14 and 17) and p53 protein. Microscopically BLBC typically has a pushing border, central necrosis/hyalinisation, a prominent lymphocytic infiltrate, and demonstrates a high histological grade as well as high mitotic activity (Figure 2). Over 90% of metaplastic carcinomas and many medullary carcinomas fall into this group. Furthermore, BLBC has an aggressive biology (much like TNBC) and seems to have a characteristic metastatic pattern. When compared to non-BLBC, these tumours more frequently spread via a hematogenous route with a predilection for the brain and lungs, and less frequently involve axillary lymph nodes and bone.¹¹

Figure 1: Composite microphotograph demonstrating ER/PR/HER-2 negative and CK 5/6 positive immunohistochemical profile usually associated with basal-like breast cancer (BLBC)

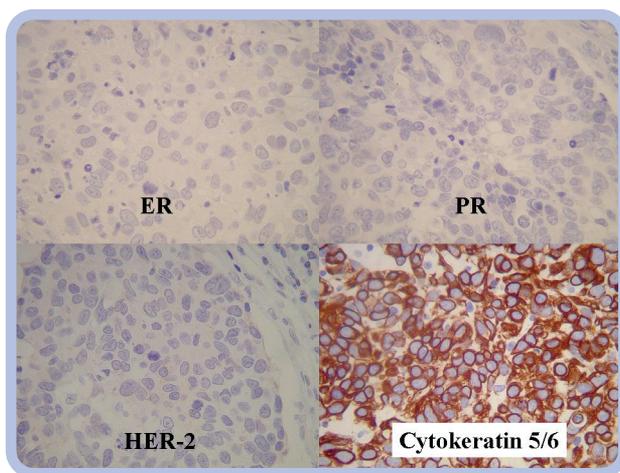
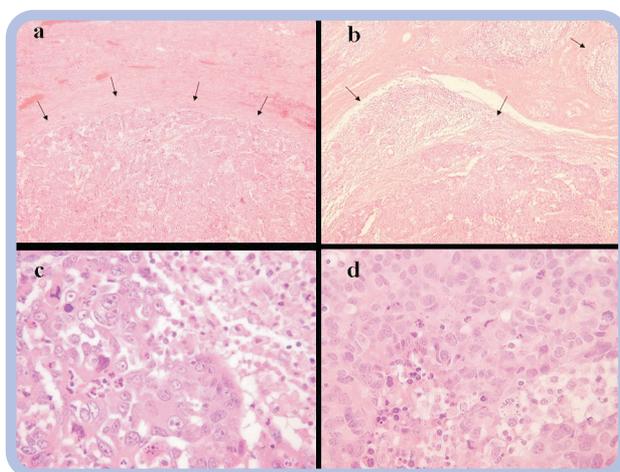


Figure 2: Histological features often seen in basal-like breast cancer: (a) a pushing border (arrows), (b) a prominent lymphocytic infiltrate (arrows), (c) and (d) high histological grade with pleomorphism, solid growth, prominent mitotic activity and areas of necrosis



BRCA1-associated breast carcinoma (BABC)

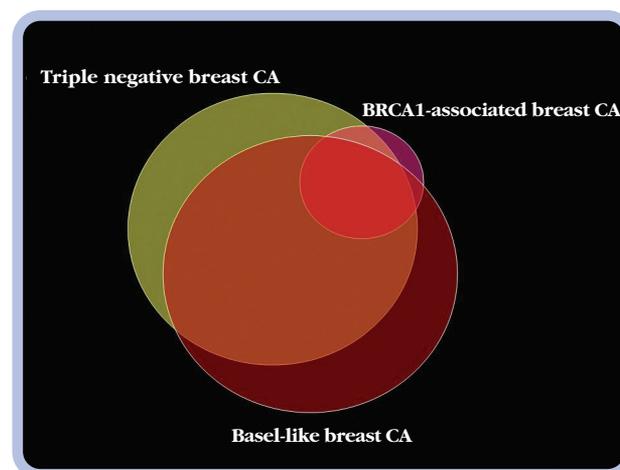
There is mounting scientific evidence linking a subgroup of TNBC and BLBC to the BRCA1 pathway. Sporadic TNBC and BLBC lack BRCA1 somatic mutations but have a dysfunctional BRCA1 pathway with lower

BRCA1 protein expression (possibly mediated by the negative effect of inhibitor of DNA binding 4 / Id4).^{12,13} Thus, the molecular pathway to malignancy in these sporadic tumours demonstrates some similarity to breast cancer in patients with BRCA1 germ line mutations. Accordingly, most breast cancers in BRCA1 germ line mutation carriers have BLBC morphology/phenotype (often medullary-like) and approximately 90% of BABC tumours are triple negative. Interestingly, hereditary BRCA2 and non-BRCA1/2 breast cancers appear to be much more heterogeneous groups without a characteristic morphology or phenotype.

Relationship between TNBC, BLBC and BABC

Whilst it is obvious from the above that a great deal of overlap exists between these three tumour groups, the terms are not synonymous (Figure 3). This is borne out by the fact that only 56–85% of TNBC express HMCK and EGFR (thus have a basal-like phenotype), whilst 15–54% of BLBC do express at least one of ER, PR or HER-2 (thus are not triple-negative).⁶ Furthermore, whilst most (up to 80% of) BRCA1-associated tumours demonstrate a BLBC morphology, not all have this appearance nor are triple negative.

Figure 3: Diagrammatic representation of the relationship between triple negative, basal-like and BRCA1-associated breast carcinoma



Therapeutic implications

From a medical oncology therapeutic perspective, three broad categories of breast cancers exist – those which are hormone receptor positive, those which are HER-2 positive, and those which are negative for ER, PR and HER-2 (thus TNBC). The latter group is particularly problematic as it is not susceptible to hormone receptor antagonists or HER-2 blockade.

Currently the only systemic therapy available for TNBC is chemotherapy. Although this group demonstrates high rates of initial response to neoadjuvant chemotherapy, incomplete pathological response is still associated with a significantly poorer prognosis than non-TNBC.^{14,15} Furthermore, TNBC does not appear to be associated with increased taxane sensitivity despite high proliferation rates and TP53 gene mutations.¹⁶

Nonetheless, promising therapies targeting the unique biology of TNBC are being investigated and include cross linking agents such as platinum salts, anti-EGFR monoclonal antibodies and tyrosine kinase inhibitors (c-kit protein is expressed in many TNBC). Additionally, tumours with a dysfunctional BRCA1 pathway also seem to be extremely sensitive to inhibitors of the poly ADP-ribose polymerase (PARP) enzyme.¹⁷

Table I: Points to remember

- Breast carcinoma, the commonest malignancy in women worldwide, is a heterogeneous disease.
- Prognostic and predictive categorisation of breast cancer has traditionally relied on clinical, pathologic and hormone receptor/HER-2 findings.
- The recent advent of gene expression profiling holds much promise for prognostic and therapeutic categorisation of breast cancer.
- Triple negative breast cancer (TNBC) is defined phenotypically by negative hormone receptors / HER-2 status and usually has an aggressive biology.
- Basal-like breast cancer (BLBC) is defined by gene profiling, but can be diagnosed using a surrogate immunohistochemical panel.
- BLBC has an aggressive biology and usually demonstrates a characteristic morphology as well as metastatic pattern.
- BRCA1-associated breast cancer (BABC) most often has a BLBC morphology and triple-negative phenotype.
- Although much overlap exists between TNBC, BLBC and BABC, the three terms are not synonymous.
- TNBC is problematic from a therapeutic point of view, but numerous promising therapies are being investigated.

Conclusion

The prognostic and predictive categorisation of breast cancer has made some progress with the advent of gene expression profiling. This remains a developing field, however, and clinical trials utilising this methodology are still underway. Whilst tumours with some gene expression profiles can be identified relatively accurately using immunohistochemistry, the use of gene profiles in routine oncology practice at present still remains controversial.

The terms triple negative breast cancer (TNBC), basal-like breast cancer (BLBC) and BRCA1 associated breast cancer (BABC) are sometimes used interchangeably in the literature but are, in fact, not synonymous. The tumour groups do, however, demonstrate a great deal of overlap.

The diagnosis of TNBC is made in the histopathology laboratory utilising routine immunohistochemistry and has definite therapeutic and prognostic implications. It is important to realise, however, that TNBC still comprises a clinico-pathologically heterogeneous group of tumours. Thus, whilst the majority has a biologically aggressive course, there exists a small subgroup of TNBC which appears to have a better outcome.

BLBC is a group of breast tumours delineated by gene expression profiling. It can also be diagnosed relatively reliably using an immunohistochemistry panel and usually has a typical histological/morphologic appearance. At present, the diagnosis of BLBC does not have any additional therapeutic implications provided the tumour is also triple negative. It remains important to recognise this group's typical histological/phenotypic features, however, as such a tumour in a young patient (particularly if a positive family history of breast cancer exists) necessitates active exclusion of hereditary BRCA1-associated breast cancer.

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