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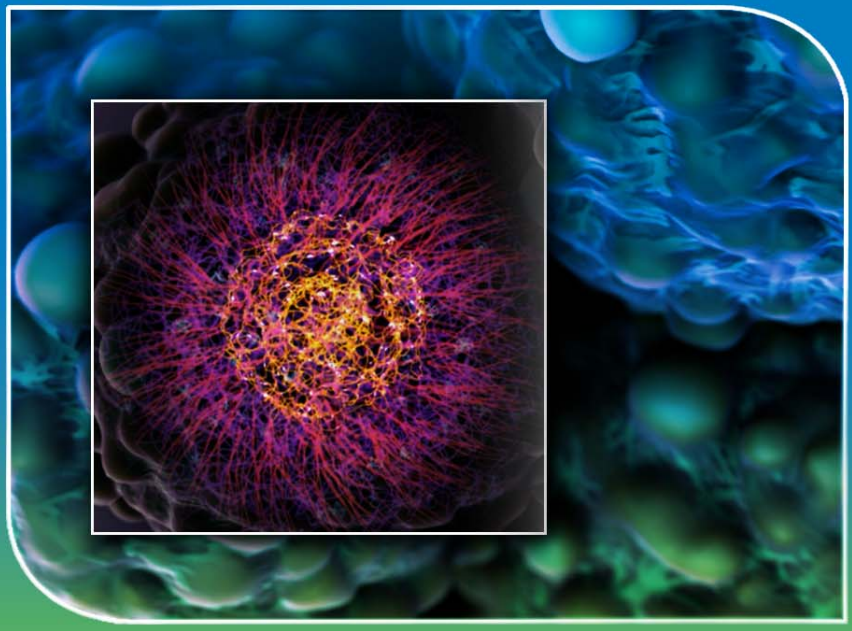
Triple-Negative Breast Cancer:

Understanding the Molecular, Biologic, and Clinical Characteristics



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ONCOLOGY

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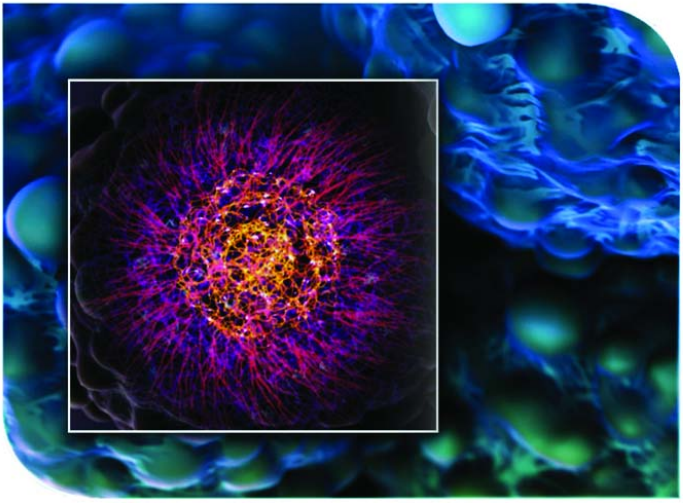


Introduction

In the United States, more than 2.5 million women are living with a history of breast cancer, emphasizing the magnitude of this public health concern.[1] In 2010, an estimated 207,090 women in the United States will be diagnosed with invasive breast cancer, and an estimated 39,840 will die of their disease.[1,2] Although great progress has been made in recent years and the overall 5-year survival of breast cancer is 89%, distinct subtypes within this highly heterogeneous disease exhibit diverse natural histories, responses to therapy, and prognoses.[1,3-5]

Until recently, invasive breast cancer was classified based on histology, grade, and the expression of estrogen receptor (ER) and progesterone receptor (PR) status.[3] More recently, the expression of HER2 (also known as Erb-B2 or ERBB2) has been added to the routine pathological evaluation of breast cancer. In addition to the options of surgery and radiotherapy for appropriate candidates, clinical decisions for patients with breast cancer are now based on 3 broad characteristic subgroups:

- Hormone receptor-positive tumors, for which patients typically receive ER-targeted therapy with or without chemotherapy

- HER2-positive tumors, for which patients are eligible to receive a HER2-targeted therapy
- Both ER- and PR-negative and HER2-negative tumors (known as triple-negative breast cancer) for which the only available systemic treatment is chemotherapy, due to the lack of an established therapeutic target[6,7]

Today, genome-wide microarray analysis allows a further refined classification of breast cancers into 5 main molecular groups (see page 6). Unfortunately, less progress has been made in treating the worst prognosis phenotype, the basal-like breast cancers, which most often have a negative ER, PR, and HER2 status. The clinical need for optimal therapy for patients with triple-negative breast cancer drives a growing investigational interest.[6]

> Between 10% and 15% of breast tumors are characterized as triple-negative (ER-, PR-, HER2-), which translates into almost 30,000 cases annually.

Between 10% and 15% of breast tumors are characterized as triple-negative (ER-, PR-, HER2-), which translates into almost 30,000 cases annually (Figure 1).[8-13] Triple-negative breast cancer is highly aggressive and has a poor prognosis.[14-16] Specifically, triple-negative breast cancer exhibits an earlier pattern of metastases and worse overall and disease-free survival than other breast cancer subtypes.[8,15]

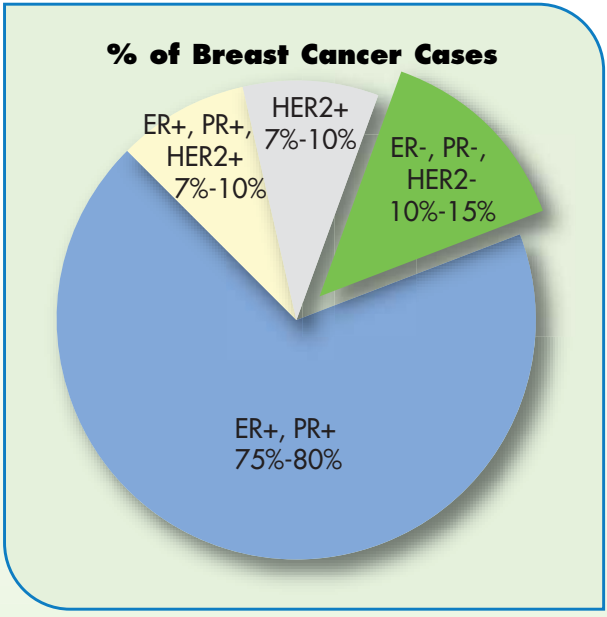
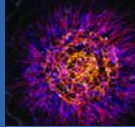


Figure 1. Generalized receptor expression in breast tumors.[4,11-13] Approximately 10% to 15% of all breast cancers are triple-negative for the hormonal and HER2 receptors.[8,9,18]

This monograph will review the current knowledge of the molecular, biologic, and clinical characteristics of triple-negative breast cancer. Research is ongoing in this field, and it is hoped that the expanded understanding of the basic science and clinical characteristics of triple-negative breast cancer will lead to strategies that will improve outcomes for patients.

Epidemiology and Risk Factors

Breast cancer is a highly heterogeneous disease that varies in incidence and mortality across demographic groups. These differences are underscored in women with triple-negative



breast cancer. Common characteristics reported among large cohorts of triple-negative breast cancer patients include younger age and lower socioeconomic status. In addition, triple-negative breast cancer is often diagnosed at a more advanced stage, has poorly differentiated histology, and a high mitotic index.[8,17,18]

Age

Several large analyses have found that triple-negative breast cancer occurs significantly more often in younger women than other types of breast cancer. One large analysis of 92,358 California women diagnosed with breast cancer between 1999 and 2003 found that the median age at diagnosis for those with triple-negative tumors was 54 years of age. Of the women with triple-negative disease, 63% were diagnosed before 60 years of age, which was the median age at diagnosis for those patients with other subtypes of breast cancer.[8] The California Cancer Registry study also found that women younger than 40 years of age were 1.53 times more likely to be diagnosed with triple-negative disease than women between the ages of 60 and 69 years.[8]

Several large analyses have found that triple-negative breast cancer occurs significantly more often in younger women than other types of breast cancer.

Race and Ethnicity

When considering all breast cancer subtypes, breast cancer is more common in white women than other racial and ethnic groups in this country. However, African American and, in some studies, Hispanic women have been found to have a higher incidence of triple-negative breast cancer than white women.[8,10,18,19] Despite the lower incidence of breast cancer in general in African American women, several population-based studies have reported that African American women have a higher mortality, as do Hispanic women.[1] African American women also have a higher mortality from triple-negative breast cancer than others.[8]

Even when potential socio-cultural factors are excluded, African American ethnicity is a significant independent predictor of reduced breast cancer survival, supporting a rationale for genetic or biologic factors impacting this population.[20] Studies have indicated that the highest prevalence of this poor prognosis subgroup is in premenopausal women of African American descent who are 2 to 3 times as likely to have a triple-negative tumor as white women.[8,10,18,19] Despite this important association, triple-negative breast cancer also presents in appreciable numbers of younger white women, as well as older African American women.

Risk Factors

In addition to demographic features, various reproductive and anthropometric characteristics increase the risk of triple-negative breast cancer.[10,21,22] The factors associated with reproduction include: early onset of menarche; young age at first-term pregnancy;

multiple births; lower incidence of breastfeeding; shorter duration of breastfeeding; and greater use of lactation suppressants.[10,21,22] The association between the risk of triple-negative breast cancer and having had several children or giving birth at a young age is in contrast to the greater risk of breast cancer in general in women who never had children or had their first full-term pregnancy at age 30 or older.[23] Several of the reproductive risk factors imply that a DNA damage repair defect may be a fundamental precursor to triple-negative or basal-like breast cancers due to their association with increased proliferation of breast epithelial cells.[24]

> Clinically applied risk assessment models may require modification to identify women at high risk for triple-negative breast cancer.

Premenopausal status is another known risk factor for the development of triple-negative breast cancer. The Carolina Breast Cancer Study (CBCS) found this breast cancer subtype to be more prevalent among premenopausal women in general and premenopausal African American women in particular.[18] Triple-negative breast cancer was found in 24% of premenopausal women compared with 15% of postmenopausal women; 39% of premenopausal African American women compared with 14% of postmenopausal African American women and 16% of non–African American women.

The primary anthropometric risk factor for triple-negative breast cancer is excess body weight. Triple-negative breast cancer occurs more often in overweight women, as defined by a high waist-to-hip ratio or abdominal adiposity.[10,21] The mechanism underlying the impact of obesity on triple-negative breast cancer risk is unclear; it may relate to insulin resistance and increased mitotic activity in breast epithelial tissue.[10]

Heredity

Familial and hereditary associations with triple-negative breast cancer suggest that genetics influence the etiology of these tumors.[22] For example, a higher prevalence of triple-negative breast cancer appears to exist among patients with the BRCA1 mutation, and most BRCA1-related breast cancers show a basal-like phenotype.[25] A recent analysis of the 482 breast cancer patients with marker data available found that among those with the BRCA1 mutation, 80% were identified as having triple-negative breast tumors.[14] In addition, a greater percentage of patients with triple-negative breast cancer had strong family histories of breast cancer and were more likely to be of African American descent than those who had other breast cancer subtypes.[14]

An analysis of data from the North Carolina Central Cancer Registry (NCCCR), which included 1803 breast cancer cases, and 1564 control cases enrolled during the years 1993 through 2001, found that some risk factors for triple-negative breast cancer may be associated with racial background.[10] Differences in risk factors between African American and white women were particularly strong when the women were

subdivided into 2 age groups (Table 1). The CBCS found that triple-negative breast cancer was significantly more common among women of African American descent who had given birth to 3 or more children, had children before age 24, had breastfed fewer children, and had breastfed fewer months overall.[10]

Influencing Risk

Clinically applied risk assessment models may require modification to identify women at high risk for triple-negative breast cancer. Justification also exists for reducing the risks of triple-negative breast cancer. Recent analysis indicates that encouraging those at higher risk to increase breastfeeding, lose weight, and increase physical activity

Table 1.
Distribution of Selected Triple-Negative Breast Cancer Risk Factors by Race and Age[10]

Risk Factor	African American Aged <40 yr	White Aged <40 yr	African American Aged 40-49 yr	White Aged 40-49 yr
Parity ≥3	24%	13%	41%	19%
	P = .45		*P* = .0001	
Never breastfed	82%	61%	75%	61%
	P = .01		*P* = .0003	
Parity ≥3 and never breastfed	18%	5%	30%	7%
	P = .002		*P* <.0001	
Lactation suppressants, ever use	34%	19%	61%	42%
	P = .06		*P* = .0003	
Parous women: age at first-term pregnancy <26 years	78%	59%	86%	61%
	P = .04		*P* <.0001	
Parous women ≥2 children breastfed	9%	37%	14%	27%
	P <.0001		*P* <.0001	
≥4 months breast-feeding per child	9%	39%	10%	26%
	P <.0001		*P* <.0001	
Waist-to-hip ratio ≥.77	61%	46%	80%	55%
	P = .31		*P* <.0001	

may be beneficial.[10] For example, public health interventions targeted towards reducing obesity in high-risk populations may help reduce the risk of triple-negative breast cancer in selected populations. In the NCCCR analysis, if the 2 most easily modified risk factors (breastfeeding and elevated waist-to-hip ratio) were eliminated, approximately 53% of the cancers with this high-risk disease might have been avoided in the overall population.[10] While efforts to influence population behaviors, though difficult to achieve, are certainly worthwhile and are being pursued, an immediate need exists for research targeted at improving survival through a better understanding of the molecular features and basic science of triple-negative breast cancer.

Molecular Features

Defining Triple-Negative Breast Cancer

Triple-negative breast cancer is defined as the absence of ER, PR, or HER2 receptors. The tumor is said to be ER-, PR-, and HER2-negative based on easily available immune assays, or immunohistochemistry (IHC).[24] Although often used interchangeably with the term "basal-like breast cancer," triple-negative breast cancer and basal-like breast cancer refer to 2 different entities. These groups overlap significantly and share important similarities; however, the terms are not necessarily interchangeable.[26,27] The term "basal-like breast cancer" describes a rigorously defined subtype with specific gene expression.[26] In practice, triple-negative breast cancer is determined using clinical assays for ER, PR, and HER2, while basal-like breast cancer describes a phenotype determined using genetic characterization or more comprehensive profiling.[24]

> Although often used interchangeably with the term "basal-like breast cancer," triple-negative breast cancer and basal-like breast cancer actually refer to 2 different entities.

Breast Cancer Phenotypes

Recently, breast cancers have been robustly categorized and divided into distinct subtypes based on gene expression, or molecular phenotypes, achieved using DNA microarray analysis.[4,5,7] Based on gene expression patterns, breast cancers have been divided into 5 distinct groups:

- Luminal A
- Luminal B
- HER2+/ER-
- Basal-like
- Normal breast-like (Figure 2)[5]

A sixth subtype, luminal C, is sometimes distinguished from luminal A and luminal B tumors by an elevated expression of a unique set of genes of unknown function, a characteristic making these tumors more similar to the basal-like and ERBB2+ subtypes and slightly less similar to the luminal A and luminal B subtypes.[5]

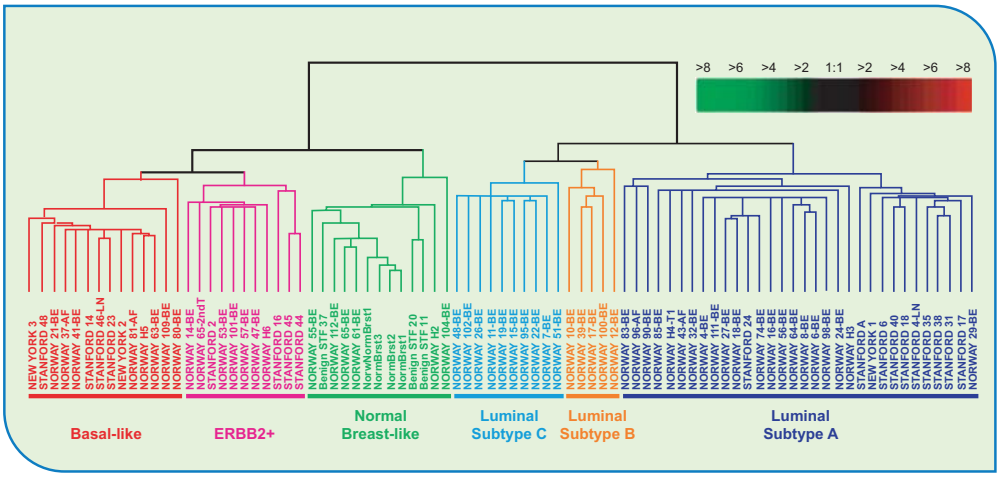


Figure 2. Gene expression patterns depicting the phenotypic breast cancer subtypes.[5] DNA microarray analysis allows separation of breast cancers into 5 or 6 distinct subtypes based on gene expression. Sorlie T, Perou CM, Tibshirani R, et al. *Proc Natl Acad Sci U S A.* 2001;98:10869-10874, Copyright 2001 National Academy of Sciences, U.S.A.

Clinically, these different subtypes vary significantly in terms of prognosis, outcomes, and the therapeutic targets they express.[5,28] Of particular relevance to therapeutic decisions, the basal-like phenotype stands out as the genetic profile with the shortest survival times and worst prognosis.[5]

Basal-like Breast Cancer

The poor prognosis basal-like phenotype accounts for approximately 15% of breast cancers; these tumors typically have low expression of ER and HER2, and most are classified as triple-negative breast cancers.[5] An analysis of 88 evaluable triple-negative tumors revealed that 91% also were classified as basal-like tumors using microarray analysis.[29] Although this indicates that most triple-negative tumors are basal-like, and conversely most basal-like tumors have been found to exhibit triple-negative profiles, there is a 10% to 30% inconsistency between the groups.[13,28,29]

Other aspects of the basal-like breast cancer phenotype are noteworthy and the observed genetic characteristics of basal-like tumors may hold biologic implications. Logically, impacts on growth rate, activity along a specific signaling pathway, and cellular composition are aligned with expression of specific gene subsets.[4] For example, a large distinct set of genes, known as the "proliferation cluster," is a group of genes that correlates with cellular proliferation rates. Expression levels of these genes further correlate with the mitotic index observed in a tumor. Basal-like breast tumors specifically

exhibit a high expression of genes characteristic of the basal epithelial cell layer, including cytokeratins 5,6, and 17, as well as epidermal growth factor receptor (EGFR), and c-KIT.[4] Basal-like cancers express HER1/EGFR more often than other subtypes, with this marker present in as many as 60% of basal-like breast cancers.[28,30] HER1 is relevant not only as a potential molecular target, but is also applicable in identifying basal-like breast cancers. The relationship between c-KIT and basal-like breast cancer is also notable, and the majority of c-KIT-positive breast tumors belong to the basal-like subtype.[28] In an analysis comparing basal-like tumors to other breast cancer subtypes, 31% of basal-like tumors stained positive for c-KIT, while this marker was present in only 11% of tumors with other phenotypes ($P < .001$).[28]

In addition to HER1/EGFR and c-KIT, basal-like breast cancer is associated with several other indicators of more aggressive tumor behavior such as the presence of TP53 (p53) mutations, and this phenotype has been linked to the BRCA1 pathway.[5,25,28,30,31] One study found that 82% of basal-like tumors expressed a p53 mutation compared with only 13% in tumors of the luminal A phenotype.[5] In addition to p53 mutations, the BRCA1 gene, another molecule involved in DNA repair, is associated with basal-like breast cancers.

Although the full biology of triple-negative breast cancer remains to be defined, several molecular characteristics of these tumors are potentially targetable.

Not only is BRCA1 mutation one of the most important forms of hereditary breast cancer, tumors in most BRCA1 mutation carriers are classified as a basal-like subtype.[25,31,32] In an analysis of 17 specimens from women with BRCA1 mutations, 88% were identified as basal-like breast cancers (OR = 9.9; 95% confidence interval [CI], 1.9-43; $P = .002$).[25] Another evaluation of tumors in 18 BRCA1 mutation carriers revealed that 100% of these were basal-like breast cancers.[31] This association implies that breast cancers arising in women carrying the BRCA1 mutation may have a similar etiology to basal-like breast cancer.[32]

BRCA1 is involved in a number of cellular processes, one of which is as part of the DNA damage response.[33] Cells that lack BRCA1 or have dysfunctions in this gene are unable to repair DNA double-strand breaks by the normal mechanism of homologous recombination. Repair of these lesions must take place using other potentially mutagenic mechanisms that lead to genetic instability. It has been hypothesized that this instability contributes to the predisposition for malignancy in patients with mutations that remove BRCA1 function.[32,33] A potential therapeutic opportunity may exist for such tumors, as cells with an already impaired DNA repair function may have an innate sensitivity to certain systemic agents.[13,34]

Potential Molecular Targets

Although the full biology of triple-negative breast cancer remains to be defined, several molecular characteristics of these tumors are potentially targetable. Potential therapeutic targets for this disease include EGFR or c-KIT, protein kinase components of the mitogen

activated protein (MAP)-kinase pathway, protein kinase components of the protein kinase B (Akt) pathway, and proteins involved in DNA repair such as poly (ADP-ribose) polymerase-1(PARP-1) (Figure 3).[13]

Identifying Patients

Although gene expression profiling using DNA microarrays is the most reproducible method of identifying the prognostic breast cancer genetic subtypes, this technology is not widely available to most clinicians. In the absence of full genetic profiling, a basal-like breast cancer profile can be suggested using other methods for clinical practice. Because it is easily accessible to clinicians, "triple-negative" is sometimes used as a proxy for "basal-like" breast cancer in patient care decisions. In the absence of DNA microassay or additional basal markers, clinicians can gain an indication of the likely tumor subtype based on the ER, PR, and HER2 status (Table 2).

However, identifying basal-like breast cancer based on the absence of ER, PR, and HER2 staining alone may not identify all basal-like breast cancers due to technical failures during the immunohistochemistry process or because of biologic heterogeneity.[28] Therefore, investigators have sought a widely accessible and clinically applicable assay predictive of poor outcome

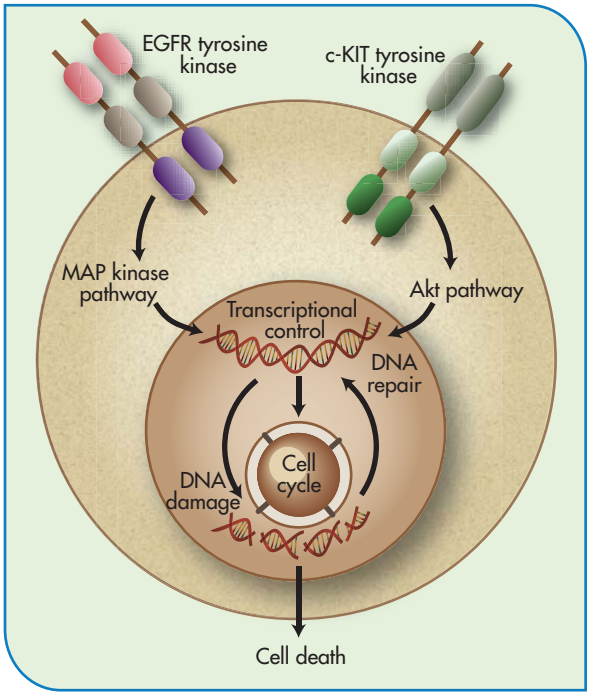


Figure 3. Triple-negative breast cancer: potential therapeutic targets.[13] Molecular features of triple-negative breast cancer pose potential therapeutic targets for new therapies. Adapted from Cleator S, Heller W. *Lancet Oncol.* 2007;8:235-244.

Table 2.
Simplified Receptor Characteristics of Breast Cancer Genetic Subtypes[5,6,18]

Genetic Subtype	ER	PR	HER2
Luminal A	ER and/or PR positive		Negative
Luminal B	ER and/or PR positive		Positive
HER2+/ER-	Negative	Negative	Positive
Basal-like	Negative	Negative	Negative

ER = estrogen receptor; PR = progesterone receptor; HER2 = human epidermal growth factor receptor 2.

basal-like breast cancers.[28] These efforts focused on validating that basal-like breast cancer can be identified by a more robust immunohistochemical profile that includes not only ER, PR, and HER2 but also assesses for additional basal markers such as CK5/6, CK14, CK17, or EGFR.[24] Expression of selected immunohistochemical markers can be combined

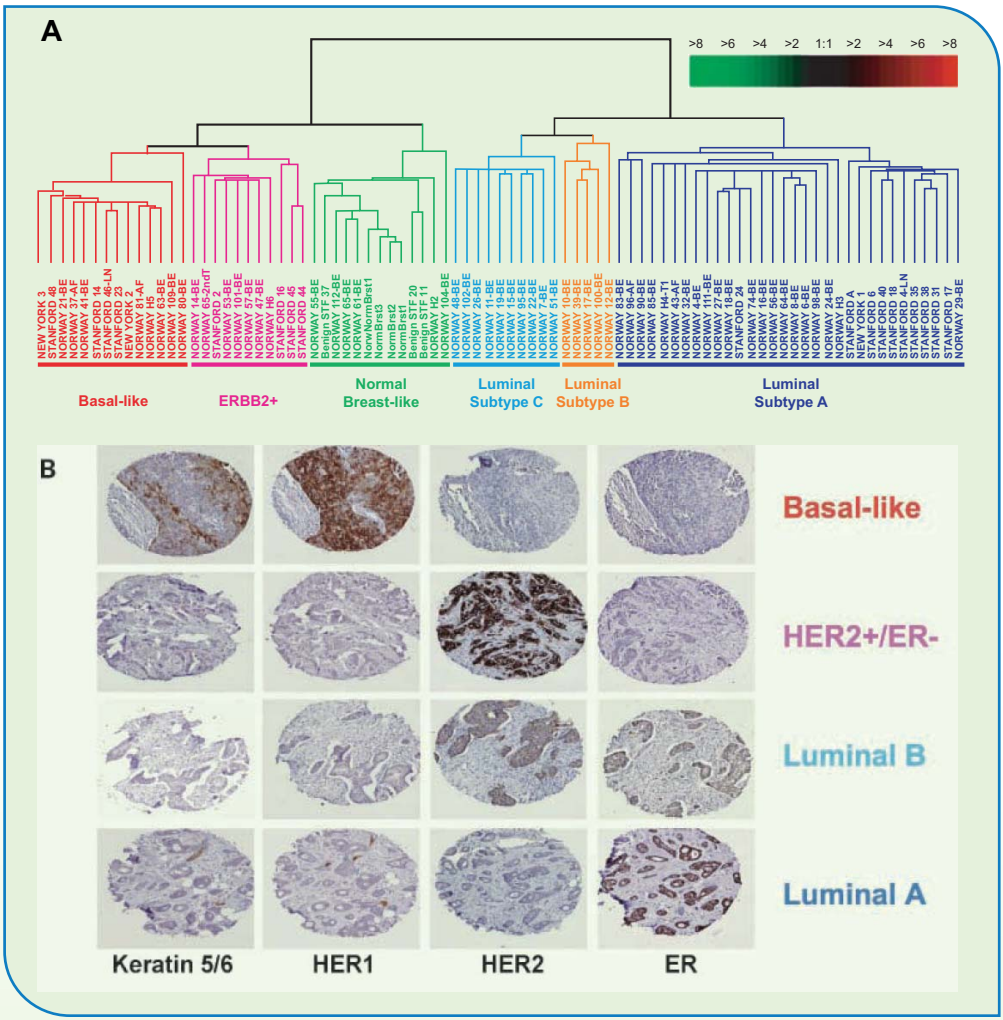


Figure 4. Breast cancer subtypes defined by genetic expression and immunohistochemistry. (A) Subtypes based on gene expression.[5] Sorlie T, Perou CM, Tibshirani R, et al. *Proc Natl Acad Sci U S A.* 2001;98:10869-10874, Copyright 2001 National Academy of Sciences, U.S.A. (B) Microarray results for tissue samples from specimens with selected immunohistochemical profiles.[7,28] Adapted and reprinted by permission from the American Association for Cancer Research: Schneider BR, Winer EP, Foulkes WD, et al. *Clin Cancer Res.* 2008;14:8010-8018.

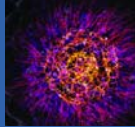


Table 3.
Validated Refined IHC Profile for Breast Cancer Subtypes[18]

Genetic Subtype	ER	PR	HER2	Cytokeratin 5/6	HER1
Luminal A	ER and/or PR positive		Negative		
Luminal B[a]	ER and/or PR positive		Positive		
HER2+/ER-	Negative	Negative	Positive		
Basal-like	Negative	Negative	Negative	Positive for either or both	

ER = estrogen receptor; PR = progesterone receptor; HER2 = human epidermal growth factor receptor 2; HER1 = human epidermal growth factor receptor 1.
[a]This definition of luminal B does not identify all luminal B tumors, as only 30% to 50% are HER2+; in this system, those would be classified as luminal A.

to estimate the different breast cancer phenotypes (Figure 4). Specifically, this system combines ER, PR, and HER2 status with the additional basal markers CK5/6 and/or HER1 added to the profile to predict the presence of the basal-like breast cancer phenotype.[18,28] A pivotal validation of this profiling method evaluated a panel of 21 genetically confirmed basal-like tumors. The investigators found that not only did the profile defined by ER-, HER2-, cytokeratin 5/6+, and/or HER1+ consistently correlate with basal-like breast cancer, the survival outcomes of patients with this immunohistochemical profile also correlated with the poorer survival outcomes seen with the basal-like breast cancer phenotype.[28] Table 3 summarizes the refined immunohistochemical profiling system that predicts the luminal A, luminal B, HER2+/ER-, and basal-like breast cancer phenotypes.

Clinical and Biologic Characteristics

Triple-negative breast cancers have been characterized by several aggressive clinicopathologic features, including later stage at diagnosis, higher average tumor size, higher-grade tumors, high mitotic index, and a high prevalence of tumors with unfavorable histology (Table 4).[9,17,18] In addition to

Table 4.
Clinicopathologic Features of Triple-Negative Breast Cancer

- More likely to be found by breast self-examination or clinical examination
  - More likely to be diagnosed as interval cancer
- More likely to be found at a later stage of disease
- Weak association between tumor size and axillary lymph node involvement
- Rapid recurrence following diagnosis
  - Peak recurrence 1 to 3 years after diagnosis
- Local recurrence rarely precedes distant recurrence
- Majority of deaths occur within 5 years of diagnosis

more aggressive features, triple-negative breast cancer is more likely to be detected through clinical examination or patient self-detection than imaging, possibly due to more rapid growth or differences in the ability to detect these tumors.[17,35] In a cohort of 1601 patients diagnosed between 1987 and 1997, 19.6% of triple-negative tumors were detected by mammography or ultrasound versus 36.0% of patients with other breast cancer subtypes ($P = .0008$).[17] Similar findings were reported in a population-based study.[35] These so-called "interval" tumors present a challenge to early detection and treatment.

In one large analysis of data from 92,358 California women diagnosed with breast cancer between 1999 and 2003, women with triple-negative disease presented with a more advanced stage of disease; and the median tumor size in this group was significantly larger than in other patients. Further, 76% of the triple-negative breast cancers in this series were classified as poorly differentiated, while only 26% of other tumor subtypes were classified as poorly differentiated.[8]

Women with triple-negative breast cancer have a more aggressive clinical course and inferior outcomes compared with women with other breast cancer subtypes.

The association between more aggressive features and the triple-negative subtype was also observed in a subset analysis of data on 1350 patients in the Breast Cancer International Research Group (BCIRG) 001 trial, conducted to compare chemotherapy regimens in patients with node-positive breast cancer. In this study, patients with triple-negative breast cancer, as well as those with HER2-positive tumors, had a significantly shorter 3-year disease-free and overall survival. The study found that triple-negative tumors were more likely to exhibit p53 positivity (OR = 4.19; 95% CI, 3.01-5.85; $P < .0001$) compared to luminal A tumors (Table 5).[9]

Table 5.
Odds Ratio for Tumor Characteristics by Biologic Subtype[9]

Characteristic	Triple-negative/ Basal-like	HER2	Luminal B (Referent)	Luminal A
Type, ductal vs lobular[a]	9.17 ($P < .0001$)	10.61 ($P < .0001$)	1.0	0.38 ($P < .0001$)
Size, >2 vs ≤2 cm	1.40 ($P = .0450$)	1.13 ($P = .5436$)	1.0	0.73 ($P = .0408$)
Grade, 3 vs 1+2	14.50 ($P < .0001$)	4.74 ($P < .0001$)	1.0	0.05 ($P < .0001$)
Vascular invasion, positive vs negative	1.11 ($P = .5612$)	1.22 ($P = .3871$)	1.0	0.46 ($P = .0004$)
P53, positive vs negative	4.19 ($P < .0001$)	4.19 ($P < .0001$)	1.0	0.23 ($P < .0001$)

[a]Includes lobular mixed and pure lobular carcinomas.

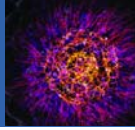


Table 6.
5-Year Breast Cancer–Related Outcomes in a Series of 482 Women With Triple-Negative Disease[14]

Outcome	Triple-negative (N = 117)	Other Subtypes (N = 365)	*P* Value
Breast relapse-free rate	83%	83%	NS
Nodal relapse-free rate	94%	99%	.05
Distant metastasis-free rate	68%	83%	.002
Cause-specific survival rate	72%	85%	.047

NS = not significant.

Recurrence

Women with triple-negative breast cancer have a more aggressive clinical course and inferior outcomes compared with women with other breast cancer subtypes.[14-16] Survival outcomes reported in triple-negative breast cancer are substantially worse compared with other breast cancer subtypes, even when adjusted for stage and race.[8,15] In general, patients with triple-negative breast cancer tend to relapse more rapidly, with a higher percentage of distant metastases and worse disease-free survival than patients with other breast cancer subtypes.[14,16,17] This difference in breast cancer–related outcomes was demonstrated in a series of 482 women with breast cancer, 117 of whom had triple-negative disease (Table 6). This study confirmed significant differences in nodal relapse, distant metastasis, and disease-free survival between those with triple-negative disease and other subtypes.[14] Local recurrences were not significantly different between the 2 groups.

A hallmark of the aggressiveness of triple-negative breast cancers is that these tumors most often recur early, usually between the first and third year after diagnosis.

Recurrence Patterns

A hallmark of the aggressiveness of triple-negative breast cancers is that these tumors most often recur early, usually between the first and third year after diagnosis, while the risk of recurrence for other breast cancers generally is constant over time. Clinical studies report consistently shorter disease-free intervals following therapy for women with triple-negative disease than for those with other breast cancer subtypes.[17,36] A recent study compared outcomes among 1601 patients with breast cancer, 180 of whom had triple-negative disease.[17] In this series, the risk of triple-negative breast cancer recurrence rose sharply following diagnosis, peaking at approximately 3 years, and declining

thereafter.[17] By 10 years of follow up, the differences in recurrence between triple-negative breast cancer and other subtypes are reduced.

Women with triple-negative breast cancer also have a higher risk of death earlier after diagnosis than women with other subtypes. Both 3- and 5-year survival has been reported to be shorter for women with triple-negative breast cancer. One series observed that all triple-negative breast cancer–related deaths occurred within the first 10 years, while other subtypes continued to accrue deaths up to 18 years after diagnosis.[17,36] Once a recurrence occurs, women with triple-negative breast cancers have a shorter median survival time. One series documented only 9 months postrecurrence survival for women with triple-negative breast cancer compared to 20 months for those with other subtypes of breast cancer.[17] This decreased survival following recurrence is observed regardless of the site of the recurrence.[36]

Women with triple-negative breast cancer also have a higher risk of death earlier after their diagnosis than women with other subtypes.

The location of recurrence also is markedly different between triple-negative breast cancers and other phenotypes. Patients with this aggressive subtype are more likely to recur with distant metastases, including lung, visceral, and central nervous system metastases, although these patients are less likely to relapse with bone metastases.[36-39] In one study, the triple-negative subset had a significantly increased likelihood of distant recurrence (hazard ratio [HR], 2.6; 95% CI, 2.0-3.5; $P < .0001$), with 33.9% of patients with triple-negative breast cancers experiencing distant recurrence compared to 20.4% in women with other breast cancers. Consistent with the overall higher risk of recurrence in the first years after therapy, the mean time to these distant metastases was 2.6 years for those with triple-negative breast cancer, while other subtypes experienced distant recurrences at a mean of 5 years ($P < .0001$).[17]

The likely location of triple-negative breast cancer metastasis has been linked to biologic features and pathways specific to the basal-like subtype.[37,40] In-depth analysis has revealed that gene expression patterns for a particular breast cancer subtype, such as the basal-like group, share biology with the preferred metastatic site for that subtype.[37] Specific signaling pathways and chemokines contribute to homing, survival, and proliferation of tumor cells in their new site, facilitating metastasis to specific areas. For example, although bone and lung are common sites of breast cancer metastasis, these areas exert different requirements for circulating cancer cells to establish metastases, and a set of genes has been identified that provides metastatic cells with advantages in the lung microenvironment.[40] Genetic assessment of an intrinsic gene list in 344 patients classified with the different breast cancer subtypes revealed site-specific recurrence patterns.[37] Bone relapse occurred most often in the luminal A subtype, but occurred less than expected in the basal-like phenotype ($P = .0001$). Conversely, lung metastasis occurred more frequently in the basal-like subtype ($P = .01$) than in other subtypes, and there was also a strong predilection for brain metastasis in the patients

with triple-negative breast cancer ($P = .0035$). A retrospective analysis of data from 3193 breast cancer patients found that women with triple-negative breast cancers had the highest risk of developing cerebral metastasis among all subtypes, suggesting that this adds a generally even poorer prognosis for these patients, and extended diagnostics for these distant recurrences might be warranted.[38]

At present, chemotherapy is the only systemic therapy option for these patients, both in the adjuvant and metastatic settings.

Prognostic Factors

Triple-negative breast cancer is potentially associated with several markers of more aggressive tumors including HER1 (EGFR), c-KIT, and p53.[28,30] When a set of classic negative prognostic factors (70-gene profile, recurrence score, activated wound response signature) were applied to a series of genetically determined basal-like breast cancers, the negative prognostic profile correlated to the aggressive disease definition of basal-like breast cancer.[41] The authors concluded that these classic prognostic parameters likely identified a set of biologic properties common in basal-like breast cancer as well.[41]

Clinical Management

Current Clinical Practices

Based on the absence of hormonal receptors and the HER2 receptor, triple-negative breast cancer is by definition minimally responsive to treatments targeting these receptors.[13] Thus, chemotherapy remains the only systemic therapy option for these patients in the adjuvant and metastatic settings (Figure 5).[42] However, the optimal

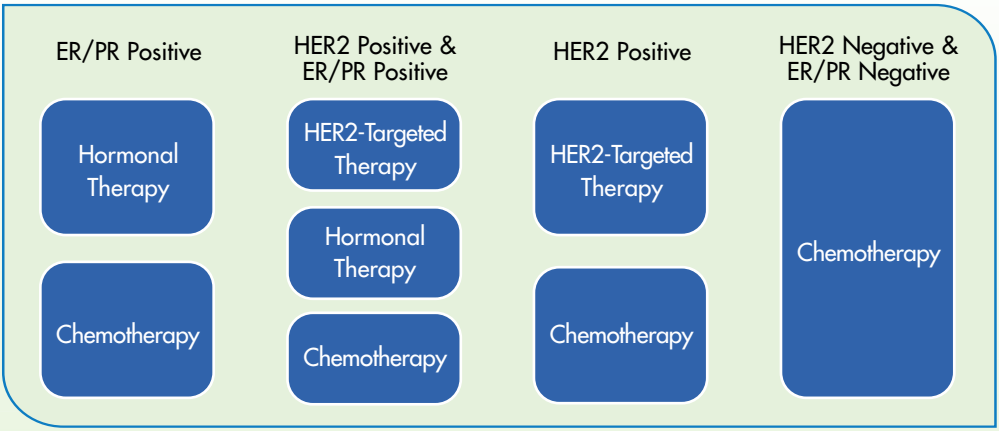


Figure 5. Current therapeutic options based on receptor status.[42] Triple-negative breast cancers do not express hormone or HER2 receptors, rendering current hormonal and HER2-targeted therapies ineffective. Thus, chemotherapy is the only systemic treatment option available for these women.

regimen for these women is not known and no established guidelines for the selection of specific agents are available.[13,42,43] Treatment decisions for women with triple-negative breast cancer rely on a clinical judgment and individual patient considerations.

In clinical practice, despite a lack of definitive evidence, combination and sequential chemotherapeutic regimens are hypothesized to be logical strategies for triple-negative breast cancer.[13] Despite this, women with triple-negative breast cancer generally experience systemic recurrences earlier and have poorer survival than women in other breast cancer subgroups.[14-17]

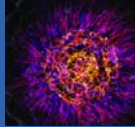
In the adjuvant setting, patients with triple-negative disease tend to be treated more aggressively than patients with other breast cancer subtypes.[44] One registry study indicated than even in breast cancer patients with small tumors (>0.5 cm to ≤1 cm), those with triple-negative disease were more likely to receive aggressive adjuvant chemotherapy.[44] Despite this more aggressive treatment, triple-negative patients have a significantly greater risk of recurrence (HR, 6.57; 95% CI = 2.34).[44]

Overall, the established poor outcomes in women with triple-negative breast cancer emphasize the necessity for new treatment modalities targeting the specific biology of this phenotype. Although the full pathways driving proliferation of triple-negative breast cancers remain to be identified, several potential therapeutic targets, including PARP-1 are being investigated for this disease.

The established poor outcomes in women with triple-negative breast cancer treated with today's conventional chemotherapies emphasize the necessity for new treatment modalities targeting the specific biology of this phenotype.

Conclusion

Triple-negative breast cancer is clinically relevant as a discrete breast cancer subtype based on its unique profile in terms of poor prognosis and aggressive metastatic behavior, as well as its unique molecular and genetic features. Although representing only 10% to 15% of all breast cancers, patients with triple-negative breast cancer pose significant clinical management challenges, as no targeted therapy for them is available. Currently, clinicians must remain vigilant for this aggressive breast cancer subtype with its potential for earlier recurrence patterns and propensity for distant metastasis to the brain, lung, and other visceral sites. Ongoing progress in understanding the molecular science behind triple-negative breast cancer is potentially a route to optimizing outcomes for women with this breast cancer subtype.



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US.ONP.10.08.005

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