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Basal-like and Triple Negative Breast Cancers: Searching For Positives Among Many Negatives

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Keywords

triple negative breast cancer; breast cancer subtypes; basal breast cancer

Introduction

Triple negative breast cancers (TNBC) are a heterogeneous group of tumors defined by negative immunohistochemical staining for estrogen receptor (ER) and progesterone receptor (PR) and lack of human epidermal growth factor receptor 2 (Her2/*neu*) overexpression¹. TNBC is often used as a surrogate for identifying the aggressive basal breast cancer subtype, and while the two patterns share many similarities they are not biologically-synonymous. The basal subtype, is defined by a distinct gene expression signature characterized by strong expression of basal markers such as cytokeratins 5,6 and 17 and also encompasses a diverse group of tumors². Both basal-like and triple negative breast cancers are associated with poor clinical outcomes and show disproportionately higher prevalence in women of African descent³. Intense investigations are currently underway to study the underlying molecular pathways that drive the growth and dissemination of these tumors and to develop effective targeted therapies against them.

In one of the earliest illustrations of the utility of gene expression analyses in unmasking the heterogeneity of a disease process, Sorlie et. al. employed cDNA microarrays to classify breast carcinomas into five subtypes that correlated highly significantly with clinical outcomes, including overall survival (OS) and recurrence free survival (RFS)⁴. These subtypes, in addition to a normal breast-like group, included luminal A and luminal B tumors that encompassed the estrogen receptor positive cancers, ERBB2 + subtype characterized by high expression of ERBB2 and a basal-like subtype which show high expression of basal markers. Luminal A tumors are the most commonly diagnosed subtype among all breast cancers (40%) and, fortunately, also carry the best prognosis. Luminal B tumors are less common (20%) and differ from the luminal A subtype in having relatively lower expression of ER (while still being ER+) and higher expression of proliferation-related genes. The ERBB2+ subtype comprises of approximately 15% of breast cancers and show high expression of ERBB2 cluster and proliferation-related genes. Finally, the basal

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sub-type constitute 15-20% of breast cancers and are characterized by expression of basal epithelial markers such as keratin 5 and 17, laminin and fatty acid binding protein 7 and low expression of luminal genes.

Since performing gene expression analysis on clinical samples is resource and time intensive, simpler immunohistochemical methods were developed to determine the ER, PR and ERBB2 expression status to categorize tumors into various subtypes that guide treatment decisions. Such sub-typing not only provides prognostic information but also allows tailoring the therapy to target the specific oncogenic drivers such as estrogen signaling and ERBB2 pathways that drive the growth and dissemination of the tumors. It is this immunohistochemical classification based on ER, PR and ERBB2 expression status that led to the introduction of the term “triple negative” to refer to cancers that are negative for all the three markers¹. The term also underscores the lack of effective targeted therapies for triple negative disease that have otherwise revolutionized the treatment of breast cancer.

Clinical and histopathologic features

Although the terms triple negative and basal-like breast cancers are used interchangeably, it is important to note that they are not synonymous. A variety of prognostically-diverse histopathologic patterns are more likely to be triple negative, further underscoring the heterogeneity of this breast cancer subset. For example, the prognostically favorable medullary and secretory tumors as well as the biologically-aggressive metaplastic breast cancers are all associated with increased frequency of triple negativity.

In a study aimed at determining the concordance rate between TNBC and the basal breast cancer subtype, Bertucci and co-workers reported that 71% of TNBC were found to be basal-like while 77% of basal-like cancers were triple negative in nature⁵. Furthermore, since TNBC is a diagnosis of exclusion defined by the lack of expression of certain markers rather than by the presence of any unifying features, it remains a heterogeneous disease entity that presents a formidable challenge to developing effective treatments³. Similarly, the basal-type has been reported to encompass a diverse array of tumors.

Both basal-like and triple negative breast cancers are associated with aggressive pathologic features and poor clinical outcomes. In a study of 1601 women diagnosed with breast cancer between January 1987 and December 1997 at Women’s College Hospital in Toronto, Dent et. al. noted that patients diagnosed with triple negative disease had younger mean age at diagnosis (53.0 versus 57.7 years) and more likely to have grade III (66% versus 28%) and larger size tumors (mean tumor size of 3.0 versus 2.1 cm) when compared to patients diagnosed with non-triple negative breast cancers⁶. Furthermore, unlike other breast cancers, TNBCs did not show a clear association between tumor size and positive lymph node status. For instance, the risk of lymph node positivity was 19.3%, 39.3% and 59.5% for tumors > 1cm, 1-2cm and 2-5 cm, respectively, for non-triple negative breast cancers. Lymph node positivity for similar size triple negative tumors was 55.6%, 55.6% and 48.9%, respectively⁶. On the other hand, data also support the prognostic advantage of screening and early detection of TNBC. A study from Memorial Sloan Kettering Cancer Center reported on nearly 200 cases of node-negative, subcentimeter TNBC. More than two-thirds

were screen-detected, and five-year overall survival rates were excellent (greater than 90%) regardless of whether or not adjuvant chemotherapy was delivered⁷.

Compared with other breast cancer patterns, triple negative breast cancers are more likely to be occult on mammography and ultrasound imaging (36% versus 36%). In a study of 95 interval cancers (i.e. breast cancers that develop between screening intervals) diagnosed between 1996 and 2001 as part of a population-based Norwegian Breast Cancer Screening Program, Collett et. al. noted that patients with interval cancers were more likely to be younger, have estrogen receptor negative tumors, basal epithelial phenotype and dense breasts than patients with size-matched, screen-detected tumors⁸.

Dent et. al. also noted that patients with triple negative breast cancer had a shorter median time to death (4.2 versus 6 years), higher propensity for distant recurrence (33.9% versus 20.4%) and shorter mean time to local (2.8 versus 4.2 years) and distant recurrences (2.6 versus 5.0 years) compared to those with other breast cancers⁶. Intriguingly, all deaths in the triple negative group occurred within 10 years of diagnosis whereas deaths due to other breast cancers continued to accrue up to 18 years after diagnosis. Furthermore, patients with triple negative breast cancer had higher rates of recurrence in the first 4 years after diagnosis but this risk declined rapidly after 5 years and no distant recurrences occurred after 8 years of follow up. These differences in the patterns of recurrence suggest that the biology of triple negative breast cancer is likely distinct from other breast cancers. This is further corroborated by the observation that the distant sites in TNBC with propensity for recurrence were different from other breast cancers³. While bone (40%) and liver (30%) were the most common sites of first distant recurrence in non-triple negative breast cancers, recurrence at these sites is less common in triple negative disease (10 and 20%, respectively). Instead, distant recurrence in lung (40%) and brain (30%) is more common in triple negative breast cancers.

Epidemiology and Risk Factors

Interestingly, more than 75% of BRCA1 mutation-carrying breast cancer patients were found to have triple negative and/or basal-like phenotype⁹. On the other hand, in patients with a TNBC phenotype, the prevalence of BRCA1 mutations has been found to range from 6.5 to 34.4%¹⁰. The close correlation between TNBC and BRCA1 mutation carrier status has led to revised, updated recommendations for genetic counseling and testing among TNBC patients. Patients younger than 50 years of age diagnosed with TNBC are now routinely recommended to undergo genetic counseling and BRCA mutation testing regardless of whether they have a family history of breast/ovarian cancer, and some centers refer TNBC patients for genetic counseling at any age.¹¹⁻¹³

Other risk factors for triple negative and/or basal-like breast cancers include higher body mass index and waist-to-hip circumference ratio, higher parity and lower duration of breast-feeding^{14,15}. It has become clear that reproductive risk factors that historically have been associated with increasing breast cancer risk (nulliparity; late age first childbirth) are primarily responsible for higher population-level burden of estrogen receptor-positive breast

cancer. In contrast, multiparity appears to increase the risk of triple negative breast cancer^{14,16}.

The epidemiology of triple negative breast cancer has attracted significant attention following the observation that racial background may be an independent risk factor for this disease. Initial evidence for such a relationship came from population-based case control studies such as the Carolina Breast Cancer Study, which showed that basal-like breast cancers were more prevalent among premenopausal African American women¹⁷. In a subsequent study, Kurian et. al. determined the lifetime risk of triple negative breast cancer across various racial/ethnic groups based on data from breast cancers diagnosed in California from 2006 to 2007 and noted that it was highest among African American women (1.98%) and lowest among Asian women (0.77%)¹⁸. Hispanic women (1.04%) and White women (1.25%) had intermediate risk in this study.

In a recent study, we carried out a large population-based study on the incidence rates of breast cancer among White, Hispanic and African American women by analyzing the California Cancer Registry data from 1988 to 2006¹⁹. The analysis encompassed a total of 375,761 cases of invasive breast cancer and demonstrated that while White Americans had the highest lifetime incidence of breast cancer among the three study groups, African American women had the highest incidence of triple negative disease across all age categories. Incidence rates of stage III and stage IV disease were highest for African American women. For women aged less than 44 years, population-based breast cancer incidence rates were also highest for African American women. Since the risk of TNBC is particularly prominent for African American women aged less than 50 years, the study argues that mammographic screening to aid early detection of this biologically aggressive disease is particularly relevant among younger African women. This concept therefore argues against widespread adoption of the 2009 United States Preventive Services Task Force (USPSTF) recommendation to delay initiation of screening mammography until the age of 50 years²⁰.

The strikingly higher prevalence of triple negative disease among African American women along with a disproportionately high mortality rate prompted speculation that African ancestry may be an independent risk factor for TNBC. For instance, African Americans account for 8% of all estimated new cases of breast cancer in the United States but account for 13% of all estimated breast-cancer related deaths. While some of this is likely related to socio-economic factors and reduced access to care, we hypothesized that African ancestry may contribute to certain unique risk factors that impact breast cancer-specific mortality. In our initial work, we reviewed the English-language literature on breast cancer published between 1988 and 2004 in the gold coast region of Africa (where most of the colonial slave trade occurred)²¹. We found that women from sub-Saharan Africa had a lower incidence of breast cancer but the average age at diagnosis was around 10 years lower when compared with breast cancer patients from western nations. The African patients also had more advanced disease and a higher mortality rate.

In a subsequent study, we examined the prevalence of triple negative breast disease among White American (n=1008) and African American women (n=581) diagnosed with invasive

breast cancer between January 1, 2001 and December 31, 2007 at the Henry Ford Health System in Detroit, MI and compared it to prevalence in a study population comprised of African women (n=75) with invasive breast cancer diagnosed/or treated at the Komfo Anokye Teaching Hospital, Ghana between January 1, 2007 and December, 31 2008²². We observed a dramatically higher proportion of triple negative disease among the African cohort (82%) compared to African American (26%) or White American (16%) women. The mean age at the time of diagnosis was 48.0 years for Ghanaian women, 60.7 years for African American women and 62.4 years for White American women. Mean primary breast tumor size was 3.2 cm, 2.3 cm and 1.95 cm for Ghanaian, African American and White American women, respectively. While the study cohort from Ghana was from a single institution with a relatively small sample size and, thus, subject to selection bias, such high proportion of triple negative disease was nevertheless quite striking. Currently larger multi-institutional studies are underway in Ghana to validate these findings.

Nevertheless, other studies have reported high proportion of receptor negative and triple negative disease among African women. For instance, Huo et. al. looked at the distribution of various molecular sub-types of breast cancer among 507 patients diagnosed with breast cancer in multiple geographic locations in Nigeria and Senegal between 1996 and 2007²³. They noted that hormone-receptor negative cancer was predominant and the proportions of ER-positive, PR-positive and Her-2 positive tumors were 24%, 20% and 17%, respectively. Furthermore, majority of patients presented with large (4.4 cm) and high-grade tumors (83%) and positive lymph nodes (72%). The mean age at presentation was 44.8 years. Burson et. al. reviewed the medical records of all breast cancer patients receiving treatment at Ocean Road Cancer Institute in Tanzania between July 2007 and June 2009 and found that most of the patients had stage III and IV disease and over 49% of patients were ER- and PR-²⁴.

To further investigate the molecular basis for the biological aggressiveness of breast cancer in African women, we evaluated the expression of aldehyde dehydrogenase 1 (ALDH1) in breast tissue obtained from 173 Ghanaian women receiving treatment at Komfo Anokye Teaching Hospital, Ghana between 2006 and 2010. Among the women with invasive breast cancer, 56.3% had triple negative disease and 75.7% had ER-breast cancer²⁵. Interestingly, the triple negative sub-type had statistically significant higher expression of ALDH1 expression compared to non-triple negative subtypes. High ALDH1 expression has previously been associated with aggressive features such as high histologic grade, high mitotic rate and ER/PR negativity²⁶.

The strong association between African ancestry and triple negative breast cancer led investigations to look for inheritable risk factors that account for such high prevalence in this group. In one such study aimed at searching for risk alleles that differed significantly in frequency between African American and European American women and contribute to specific breast cancer phenotypes that do not express ER and PR, Fejerman and coworkers performed whole genome admixture scan and typed at approximately 1500 ancestry-informative markers after pooling six population-based studies of 1484 African American women with invasive breast cancer²⁷. They investigated the association between breast cancer predisposition loci and disease phenotypes and found significant ancestral differences

between ER+ PR+ and ER– PR– negative breast cancers. After controlling for other confounders, patients with ER+ PR+ breast cancers and localized tumors were found to have higher European ancestry. Although no specific loci that contribute to differences in the observed risk were identified, more advanced approaches with better resolution such as whole genome sequencing technologies may shed light on the genetic basis for racial differences in prevalence of triple negative breast cancer. Similarly, Palmer et al²⁸ found genetically-defined African ancestry to be associated with risk of TNBC in a nested case-control breast cancer study from the Black Women's Health Study.

Targeted therapies

The advent of highly effective targeted therapies against ER+ and Her2+ breast cancers has dramatically improved clinical outcomes in breast cancer. However, targeted therapies for TNBC remain elusive and chemotherapy remains the only systemic treatment option at this time. No appreciable improvements in survival have been achieved for this patient population over the last few decades. The following section reviews recent advances towards development of targeted therapies for TNBC.

PARP inhibition

Studies of carriers of germline BRCA1 mutations have shown that these patients predominately have a basal-like and triple negative phenotype⁹. Furthermore, although most basal-like breast cancers do not carry BRCA1 mutations, a high degree of BRCA1 dysfunction with lower levels of BRCA1 mRNA expression was reported in this group compared to matched controls²⁹. The specific susceptibility of BRCA-deficient tumors to poly(ADP-ribose)polymerase (PARP1) inhibitors has generated interest in evaluating the efficacy of PARP inhibitors in basal-like and triple negative breast cancers. The safety and efficacy of PARP inhibition with oral dosing of olaparib as a single agent has previously been demonstrated in a phase 2 multicenter clinical trial in advanced breast cancer patients with BRCA1 or 2 mutations³⁰. The term “synthetic lethality” is often used to describe the specific susceptibility of BRCA deficient tumors to PARP inhibition³¹. PARP is an important mediator of genomic stability and is important for repair of DNA single strand breaks (SSBs) by base excision repair (BER)³². However, normal cells can withstand PARP inhibition by upregulating homologous recombination (HR), which serves as an alternate error-free DNA repair pathway. Thus, unrepaired SSBs as a result of PARP inhibition collapse replication forks into double strand breaks (DSBs), which are repaired by BRCA-mediated HR. However, PARP inhibition in the background of deficient HR results in “synthetic lethality” secondary to accumulation of DNA SSBs and DSBs. Consistent with this hypothesis, in preclinical studies, triple negative breast cancer cells were found to be more sensitive to PARP inhibition both as a single agent as well as in combination with gemcitabine and cisplatin than non-triple negative breast cancer cells³³. This initial promise promoted clinical evaluation of PARP inhibitors in triple negative breast cancers. In an open label phase 2 clinical trial, niraparib, a small molecule PARP inhibitor, was evaluated in combination with gemcitabine and carboplatin in metastatic triple negative breast cancer³⁴. The combination regimen was found to improve the overall response from 32 to 52%, prolonged median progression-free survival from 3.6 to 5.9 months and median overall

survival from 7.7 to 12.3 months. A follow up phase III clinical trial, however, did not demonstrate any improvement in overall survival. Furthermore, there is controversy surrounding the mechanism of action of iniparib and the target of this drug remains to be identified. Currently, there are multiple clinical trials underway evaluating the clinical efficacy of Olaparib in combination with chemotherapy although a phase II study of olaparib as monotherapy in heavily pretreated metastatic triple negative breast cancer did not show any response³⁵.

EGFR inhibition

The epidermal growth factor receptor is a transmembrane receptor tyrosine kinase that has been shown to be highly expressed in basal-like tumors. For instance, Nielsen et. al. employed breast carcinoma tissue microarrays from 930 patients and noted that EGFR expression was observed in 54% of basal-like tumors (versus 11% of non-basal-like tumors) and was a predictor of poor survival independent of nodal status and tumor size³⁶. Similarly, EGFR expression was found to be high in basal-like cell lines but low in luminal cell lines. Furthermore, basal-like breast cancer cell lines were found to be more sensitive to EGFR inhibition compared to luminal cell lines. These findings suggested that EGFR could serve as a targeted therapy for treatment of basal-like breast cancers. In a randomized phase II clinical trial, Carey et. al. evaluated Cetuximab, an anti-EGFR monoclonal antibody, as a single agent as well as in combination with carboplatin in metastatic triple negative breast cancer³⁷. Unfortunately, the response rate in this study was only 6% to cetuximab and 17% for cetuximab and carboplatin combination. The time to progression and overall survival were short at 2.1 months and 10.4 months, respectively. Among sixteen patients who had tumor biopsies before and one week after therapy, activation of the EGFR pathway was noted in thirteen patients. However, therapy-induced inhibition of the EGFR pathway was detected in only five patients. Given the known efficacy of cetuximab on EGFR, it is likely that constitutive/non-ligand dependent pathways of EGFR activation may exist in TNBC. Therefore, downstream mediators of EGFR pathway may be necessary to derive therapeutic benefit. In BALI-1, a randomized phase II clinical trial, Baselga et. al. compared cisplatin versus cisplatin and cetuximab for treatment of metastatic triple negative breast cancer. While the overall response rate was improved with addition of cetuximab (20% vs 10% for cisplatin alone), there was no statistically significant improvement in overall survival³⁸. Currently, several small molecule inhibitors of EGFR are in various stages of pre-clinical and clinical development³⁵.

Angiogenesis inhibitors

TNBCs are highly vascular and studies have shown higher levels of expression of vascular endothelial growth factor (VEGF) in TNBCs compared to non-TNBCs³⁹. This prompted clinical evaluation of VEGF inhibitors in this subgroup of cancers. In a meta-analysis of patients with TNBC from three randomized phase III trials (E2100, AVADO and RIBBON-1) of bevacizumab, a monoclonal VEGF antibody, in combination with standard chemotherapeutic agents versus chemotherapy alone in metastatic breast cancer as first line therapy, O'Shaughnessy et. al. reported that addition of bevacizumab improved objective response rate (42% versus 23%) and median progression-free survival (8.1 months versus 5.4 months) but no statistically significant improvement in overall survival⁴⁰. Brufsky and

coworkers reported subgroup analysis of the TNBC patient subset of the RIBBON-2 trial, which evaluated the efficacy of bevacizumab in combination with chemotherapy versus chemotherapy alone in metastatic breast cancer as second line therapy⁴¹. They report an improvement in PFS with the combination regimen compared to chemotherapy alone (6.0 versus 2.7 months) with a trend towards improvement in OS. However, two large randomized clinical trials evaluating the efficacy of bevacizumab in combination with chemotherapy in the neoadjuvant setting produced contrasting results. A large phase III clinical trial (BEATRICE Study) evaluating bevacizumab in combination with chemotherapy in the adjuvant setting TNBC patients is currently underway. However, the recent withdrawal of approval of bevacizumab for treatment of advanced breast cancer due to concerns of significant toxicity cast a shadow on the safety of this agent in TNBC patients.

In addition to the agents discussed above, a number of novel targeted therapies for triple negative breast cancer are at various stages of development and include inhibitors for various pathways/targets such as PI3K/AKT/mTOR pathway, Hedgehog signaling pathway, Notch signaling pathway, apoptotic pathways, HSP90, JAK2 and androgen receptor^{35,42}.

The failure of various targeted therapies to show significant efficacy in clinical trials in spite of strong preclinical data underscores the challenges that lie ahead for improving clinical outcomes in TNBC. The heterogeneity within the triple negative and basal-like tumors certainly serves as a major impediment for developing therapies with efficacy against the entire group. In a genomic landscape study of 104 cases of primary TNBC, Shah et. al. noted that these cancers exhibited a very broad spectrum of genomic evolution and varied widely in their clonal frequencies⁴³. In a study aimed at further subtyping triple negative breast cancers and identifying “driver” signaling pathways that could be pharmacologically targeted, Lehmann et. al. analyzed gene expression profiles of 587 TNBC cases from 21 breast cancer data sets and employed cluster analysis to identify six unique TNBC subtypes⁴⁴. They include basal-like 1 and 2 (BL1 and BL2), immunomodulatory (IM), mesenchymal (M), mesenchymal stem-like (MSL) and luminal androgen receptor (LAR) subtypes. Each of these TNBC subtypes were then matched up with TNBC cell line models that were representative based on gene expression analysis. The efficacy of various chemotherapeutic agents and selective inhibitors that target the “driver” signaling pathways was then evaluated for each subtype. BL1 and BL2 subtypes were characterized by higher expression of cell cycle and DNA damage response genes and representative cell lines showed preferential response to cisplatin. M and MSL subtype cell models responded to PI3K/mTOR and abl/src inhibitors and showed enrichment for genes involved in epithelial-mesenchymal transition and growth factor pathways. The IM subtype, as the name suggested, showed upregulation of immune signaling pathways. The LAR subtype was characterized by AR signaling and decreased relapse-free survival and representative cell lines were sensitive to AR antagonist bicalutamide.

The general utility of the above approach has been validated in other studies. Speers and co-workers identified distinct kinase expression signatures based on gene expression microarray analysis and subtyped ER-breast cancers into four clusters: cell cycle regulatory cluster, S6 kinase regulatory cluster, immunomodulatory kinase-expressing cluster and

mitogen-activated protein kinase pathway cluster⁴⁵. In patient survival analyses, these clusters conferred differential survival with the S6 kinase pathway cluster showing the least favorable and the immunomodulatory kinase-expressing cluster showing the most favorable prognosis. The authors went on to identify a panel of breast cancer cell lines with matching kinase expression profile for each of the clusters and performed kinase knock down studies to show that many of the overexpressed kinases were necessary for the growth of ER-breast cancer cell lines but not ER+ cell lines.

In a related but slightly different approach, Kothari et. al. analyzed the transcriptome data from a compendium of 482 cancer and benign samples, including breast cancer, generated by RNA sequencing to identify “individual sample-specific outlier kinases”⁴⁶. They defined outlier as a kinase with the highest level of absolute expression in a sample compared to the rest of kinome and the highest level of differential expression when compared with the median level of expression of that particular kinase across the compendium. This approach ensures that kinases that are highly overexpressed in only a subset of samples are prioritized and not lost in the noise when their expression is averaged across the whole compendium. The authors hypothesized that the extremely high level of expression of the outliers is due to their clonal selection and imparts dependence on the growth of the tumor. Consistent with this hypothesis, the authors identified several sample specific outlier kinases, including in triple negative breast cancer clinical samples and cell lines. Targeting of the outlier kinases with available inhibitors was shown to result in growth inhibition both in cell lines and in xenograft models. Clinical evaluation of such highly personalized treatment approaches for TNBC remains a goal for the future.

Conclusions

In spite of tremendous advances in the targeted therapy of breast cancer that have revolutionized clinical care, effective treatment of triple negative and basal-like breast cancers remains a major challenge. Currently chemotherapy remains the only systemic treatment option for these disease subtypes. Undoubtedly, clinical evaluation of novel targeted therapeutic agents will remain a priority. The failure of some of these agents such as PARP inhibitors and EGFR inhibitors to show efficacy in advanced stages of clinical trials in spite of their early promise in pre-clinical studies casts doubt on whether a magic bullet for triple negative disease will ever be a reality. Nevertheless, development of reliable biomarkers that predict susceptibility to these agents in subsets of patients with triple negative and basal-like breast cancers may allow design of more effective clinical trials in the future. Furthermore, highly personalized treatment approaches such as kinase outlier profile analyses which attempt to identify putative oncogenic targets that are essential for the growth of these tumors at an individual patient level may be necessary to treat this highly aggressive and biologically heterogeneous group of diseases. While clinical effectiveness of these approaches remains to be determined, the success of such approaches could herald a new era in the arena of personalized medicine and precision therapy. Until then, the search for positives among many negatives of triple negative and basal-like breast cancers continues.

References

1. Brenton JD, Carey LA, Ahmed AA, Caldas C. Molecular classification and molecular forecasting of breast cancer: ready for clinical application? *J Clin Oncol.* Oct; 2005 23(29):7350–7360. [PubMed: 16145060]
2. Perou CM, Sorlie T, Eisen MB, et al. Molecular portraits of human breast tumours. *Nature.* Aug 17; 2000 406(6797):747–752. [PubMed: 10963602]
3. Foulkes WD, Smith IE, Reis-Filho JS. Triple-negative breast cancer. *N Engl J Med.* Nov; 2010 363(20):1938–1948. [PubMed: 21067385]
4. Sorlie T, Perou CM, Tibshirani R, et al. Gene expression patterns of breast carcinomas distinguish tumor subclasses with. *Proc Natl Acad Sci U S A.* Sep 11; 2001 98(19):10869–10874. [PubMed: 11553815]
5. Bertucci F, Finetti P, Cervera N, et al. How basal are triple-negative breast cancers? *Int J Cancer.* Jul; 2008 123(1):236–240. [PubMed: 18398844]
6. Dent R, Trudeau M, Pritchard KI, et al. Triple-negative breast cancer: clinical features and patterns of recurrence. *Clin Cancer Res.* Aug; 2007 13(15 Pt 1):4429–4434. [PubMed: 17671126]
7. Ho AY, Gupta G, King TA, et al. Favorable prognosis in patients with T1a/T1bN0 triple-negative breast cancers treated with multimodality therapy. *Cancer.* Oct 15; 2012 118(20):4944–4952. [PubMed: 22392492]
8. Collett K, Stefansson IM, Eide J, et al. A basal epithelial phenotype is more frequent in interval breast cancers compared with screen detected tumors. *Cancer Epidemiol Biomarkers Prev.* May; 2005 14(5):1108–1112. [PubMed: 15894660]
9. Foulkes WD, Stefansson IM, Chappuis PO, et al. Germline BRCA1 mutations and a basal epithelial phenotype in breast cancer. *J Natl Cancer Inst.* Oct; 2003 95(19):1482–1485. [PubMed: 14519755]
10. Hartman AR, Kaldete RR, Sailer LM, et al. Prevalence of BRCA mutations in an unselected population of triple-negative breast cancer. *Cancer.* Jun 1; 2012 118(11):2787–2795. [PubMed: 22614657]
11. Hutchinson L. Screening: BRCA testing in women younger than 50 with triple-negative breast cancer is cost effective. *Nat Rev Clin Oncol.* Nov.2010 7(11):611. [PubMed: 21049572]
12. Andres R, Pajares I, Balmana J, et al. Association of BRCA1 germline mutations in young onset triple-negative breast cancer (TNBC). *Clin Transl Oncol.* Aug 27.2013
13. Rummel S, Varner E, Shriver CD, Ellsworth RE. Evaluation of BRCA1 mutations in an unselected patient population with triple-negative breast cancer. *Breast Cancer Res Treat.* Jan; 2013 137(1): 119–125. [PubMed: 23192404]
14. Millikan RC, Newman B, Tse CK, et al. Epidemiology of basal-like breast cancer. *Breast Cancer Res Treat.* May; 2008 109(1):123–139. [PubMed: 17578664]
15. Yang XR, Sherman ME, Rimm DL, et al. Differences in risk factors for breast cancer molecular subtypes in a population-based study. *Cancer Epidemiol Biomarkers Prev.* Mar; 2007 16(3):439–443. [PubMed: 17372238]
16. Phipps AI, Chlebowski RT, Prentice R, et al. Reproductive history and oral contraceptive use in relation to risk of triple-negative breast cancer. *J Natl Cancer Inst.* Mar 16; 2011 103(6):470–477. [PubMed: 21346227]
17. Carey LA, Perou CM, Livasy CA, et al. Race, breast cancer subtypes, and survival in the Carolina Breast Cancer Study. *Jama.* Jun 7; 2006 295(21):2492–2502. [PubMed: 16757721]
18. Kurian AW, Fish K, Shema SJ, Clarke CA. Lifetime risks of specific breast cancer subtypes among women in four racial/ethnic groups. *Breast Cancer Res.* 2010; 12(6):R99. [PubMed: 21092082]
19. Amirikia KC, Mills P, Bush J, Newman LA. Higher population-based incidence rates of triple-negative breast cancer among young African-American women: Implications for breast cancer screening recommendations. *Cancer.* Jun; 2011 117(12):2747–2753. [PubMed: 21656753]
20. Nelson HD, Tyne K, Naik A, Bougatsos C, Chan BK, Humphrey L. Screening for breast cancer: an update for the U.S. Preventive Services Task Force. *Ann Intern Med.* Nov 17; 2009 151(10):727–737. W237–742. [PubMed: 19920273]

21. Fregene A, Newman LA. Breast cancer in sub-Saharan Africa: how does it relate to breast cancer in. *Cancer*. Apr 15; 2005 103(8):1540–1550. [PubMed: 15768434]
22. Stark A, Kleer CG, Martin I, et al. African ancestry and higher prevalence of triple-negative breast cancer: findings from an international study. *Cancer*. Nov; 2010 116(21):4926–4932. [PubMed: 20629078]
23. Huo D, Ikpat F, Khramtsov A, et al. Population differences in breast cancer: survey in indigenous African women. *J Clin Oncol*. Sep 20; 2009 27(27):4515–4521. [PubMed: 19704069]
24. Burson AM, Soliman AS, Ngoma TA, et al. Clinical and epidemiologic profile of breast cancer in Tanzania. *Breast Dis*. 2010; 31(1):33–41. [PubMed: 21109721]
25. Schwartz T, Stark A, Pang J, et al. Expression of aldehyde dehydrogenase 1 as a marker of mammary stem cells in benign and malignant breast lesions of Ghanaian women. *Cancer*. Feb 1; 2013 119(3):488–494. [PubMed: 22930220]
26. Resetkova E, Reis-Filho JS, Jain RK, et al. Prognostic impact of ALDH1 in breast cancer: a story of stem cells and tumor microenvironment. *Breast Cancer Res Treat*. Aug; 2010 123(1):97–108. [PubMed: 19911270]
27. Fejerman L, Haiman CA, Reich D, et al. An admixture scan in 1,484 African American women with breast cancer. *Cancer Epidemiol Biomarkers Prev*. Nov; 2009 18(11):3110–3117. [PubMed: 19843668]
28. Palmer JR, Ruiz-Narvaez EA, Rotimi CN, et al. Genetic susceptibility loci for subtypes of breast cancer in an African American population. *Cancer Epidemiol Biomarkers Prev*. Jan; 2013 22(1):127–134. [PubMed: 23136140]
29. Turner NC, Reis-Filho JS, Russell AM, et al. BRCA1 dysfunction in sporadic basal-like breast cancer. *Oncogene*. Mar; 2007 26(14):2126–2132. [PubMed: 17016441]
30. Tutt A, Robson M, Garber JE, et al. Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or. *Lancet*. Jul 24; 2010 376(9737):235–244. [PubMed: 20609467]
31. Hiller DJ, Chu QD. Current Status of Poly(ADP-ribose) Polymerase Inhibitors as Novel Therapeutic Agents for Triple-Negative Breast Cancer. *International journal of breast cancer*. 2012; 2012:829315. [PubMed: 22295252]
32. Dantzer F, de La Rubia G, Menissier-De Murcia J, Hostomsky Z, de Murcia G, Schreiber V. Base excision repair is impaired in mammalian cells lacking Poly(ADP-ribose). *Biochemistry*. Jun 27; 2000 39(25):7559–7569. [PubMed: 10858306]
33. Hastak K, Alli E, Ford JM. Synergistic chemosensitivity of triple-negative breast cancer cell lines to poly(ADP-Ribose) polymerase inhibition, gemcitabine, and cisplatin. *Cancer Res*. Oct; 2010 70(20):7970–7980. [PubMed: 20798217]
34. O'Shaughnessy J, Osborne C, Pippen JE, et al. Iniparib plus chemotherapy in metastatic triple-negative breast cancer. *N Engl J Med*. Jan; 2011 364(3):205–214. [PubMed: 21208101]
35. Crown J, O'Shaughnessy J, Gullo G. Emerging targeted therapies in triple-negative breast cancer. *Ann Oncol*. Aug; 2012 23(Suppl 6):vi56–65. [PubMed: 23012305]
36. Nielsen TO, Hsu FD, Jensen K, et al. Immunohistochemical and clinical characterization of the basal-like subtype of. *Clin Cancer Res*. Aug 15; 2004 10(16):5367–5374. [PubMed: 15328174]
37. Carey LA, Rugo HS, Marcom PK, et al. TBCRC 001: randomized phase II study of cetuximab in combination with carboplatin in stage IV triple-negative breast cancer. *J Clin Oncol*. Jul; 2012 30(21):2615–2623. [PubMed: 22665533]
38. Baselga J, Gómez P, Greil R, et al. Randomized phase II study of the anti-epidermal growth factor receptor monoclonal antibody cetuximab with cisplatin versus cisplatin alone in patients with metastatic triple-negative breast cancer. *J Clin Oncol*. Jul; 2013 31(20):2586–2592. [PubMed: 23733761]
39. Linderholm BK, Hellborg H, Johansson U, et al. Significantly higher levels of vascular endothelial growth factor (VEGF) and shorter survival times for patients with primary operable triple-negative breast cancer. *Ann Oncol*. Oct; 2009 20(10):1639–1646. [PubMed: 19549711]
40. O'Shaughnessy J, Romieu G, Diéras V, Byrtek M, Duenne A, Miles D. Meta-Analysis of Patients with Triple-Negative Breast Cancer (TNBC) from Three Randomized Trials of First-Line Bevacizumab (BV) and Chemotherapy Treatment for Metastatic Breast Cancer (MBC). 2010

41. Brufsky A, Valero V, Tiangco B, et al. Second-line bevacizumab-containing therapy in patients with triple-negative breast cancer: subgroup analysis of the RIBBON-2 trial. *Breast Cancer Res Treat.* Jun; 2012 133(3):1067–1075. [PubMed: 22415477]
42. O'Toole SA, Beith JM, Millar EK, et al. Therapeutic targets in triple negative breast cancer. *J Clin Pathol.* Jun; 2013 66(6):530–542. [PubMed: 23436929]
43. Shah SP, Roth A, Goya R, et al. The clonal and mutational evolution spectrum of primary triple-negative breast cancers. *Nature.* Jun; 2012 486(7403):395–399. [PubMed: 22495314]
44. Lehmann BD, Bauer JA, Chen X, et al. Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies. *J Clin Invest.* Jul; 2011 121(7):2750–2767. [PubMed: 21633166]
45. Speers C, Tsimelzon A, Sexton K, et al. Identification of novel kinase targets for the treatment of estrogen. *Clin Cancer Res.* Oct 15; 2009 15(20):6327–6340. [PubMed: 19808870]
46. Kothari V, Wei I, Shankar S, et al. Outlier kinase expression by RNA sequencing as targets for precision therapy. *Cancer Discov.* Mar; 2013 3(3):280–293. [PubMed: 23384775]

Key Points

1. Triple negative breast cancers are defined as invasive breast cancers that fail to express the estrogen receptor, the progesterone receptor, and the HER2/*neu* marker
2. Triple negative breast cancer and the basal breast cancer subtype (defined by genetic profile) share similarities but they are not synonymous.
3. The triple negative breast cancer category includes a spectrum of histopathologically and genetically-diverse range of tumors.
4. Triple negative breast cancers tend to be more challenging to treat because they are more likely to be of a basal subtype and because they cannot be manipulated with either endocrine therapy or targeted anti-HER2/*neu* treatments.

Synopsis

Triple negative breast cancers (TNBC) are defined by their failure to express the estrogen receptor, progesterone receptor, and Her2/*neu* protein markers. This basic feature is clinically relevant because it indicates that these cancers cannot be managed with endocrine or anti-HER2 systemic therapies. Furthermore, the majority of TNBC cases are also characterized as being of the genetically-defined basal subtype, which is an inherently and biologically more aggressive pattern of disease. The two terms however are not synonymous and there are some TNBC cases that are prognostically more favorable. TNBC differs from non-TNBC in risk factor profile, pattern and rate of metastatic spread.