Triple Negative Breast Cancer: What Surgeons Should Know

Omeed Moaven and Kirby I. Bland*

Department of Surgery, University of Alabama at Birmingham, USA

Abstract

Breast cancer has been classified into different subgroups with discrete tumor behavior, prognosis and therapeutic approaches. Triple negative breast cancer (TNBC) is characterized by lack of expression of estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 (HER-2). TNBC represents a heterogeneous group of tumors with more aggressive biologic behavior and poorer prognosis. Lack of receptor expression, which excludes hormonal therapy and trastuzumab as treatment options, is a therapeutic challenge. In this manuscript, we have reviewed our current knowledge about the epidemiology and contributing risk factors of TNBC, heterogeneity in the molecular landscape, clinical course of TNBC, and current evidence on available therapeutic options and developing novel modalities such as targeted therapy. Molecular heterogeneity is an important contributing factor that could explain the discrepancies in the literature, in terms of various clinical aspects of TNBC. Genetic features should be considered and studied alongside in the prospective trials, to better understand and clinically address the heterogeneous nature of this disease.

Keywords: Breast cancer; Triple negative breast cancer; BRCA

Introduction

Breast cancer is a heterogeneous disease at molecular level with diverse clinical manifestations. Malignant behavior of the tumors and therapeutic strategies are different based on tumors' hormonal activity, determined by expression of estrogen receptor (ER) and progesterone receptor (PR), as well as expression of Human Epidermal Growth Receptor 2 (HER2). Microarray analysis of breast cancers has classified them in 5 different subgroups with different therapeutic options and prognosis, based on their gene expression profiling [1-3]. These transcriptional subtypes include: 1) luminal A (ER and/or PR +, HER2 -); 2) Luminal B (ER and/or PR +, HER2 +); 3) HER2 over expression (ER and PR -, HER +), 4) Basal like [ER and PR -, HER2 +/-, cytokeratin and/or epidermal growth factor receptor (EGFR) +] and finally, 5) normal breast-like (tumors that do not fit into any of the other categories). Two different cell types of mammary glands, luminal and basal (myoepithelioid), represent the cellular basis of this molecular classification.

Triple negative breast cancer (TNBC), which is defined by lack of expression of ER, PR and HER2, represents the most aggressive subtype with higher rate of local recurrence and poorer clinical outcome [4,5]. There is a significant overlap between TNBC and the basal like transcriptional subtype but the 2 entities are not exactly identical. While about 73% of TNBCs are basal like tumors, the rest lack the basal like specific markers [6]. Furthermore, a small proportion of non-TNBCs produce basal like markers [7]. Lack of therapeutic target for hormonal therapy and trastuzumab is the clinical a challenge in TNBC, which limits the available effective medical therapy. In this review, we discuss the epidemiology of TNBC, molecular heterogeneity and their clinical implications, diagnosis, clinical course and available therapeutic modalities.

Epidemiology, Trends and Risk Factors

TNBC comprises 10-20% of all diagnosed breast cancers. There is a consensus, in various widely cited epidemiologic studies, that TBNCs are more frequently seen in younger females below 40 years, nonhispanic patients with African ethnic background and those with low socioeconomic status. However, the data regarding the risk factors of reproductive and menstrual history is more consistent in hormone receptor positive breast cancers and more controversial in TNBC.

Results from Carey et al. [8], confirm that prevalence of basal-like breast cancer was significantly higher in premenopausal African-American (AA) females compared to postmenopausal AA females, and non-AA and the survival was poorer regardless of their age [8]. Bauer et al. in another

population-based study published from the the California Cancer Registry, reported that patients with TNBC more likely tended to be nonhispanic AA and below the age of 40. Survival was lower in patients with TNBC regardless of tumor stage [9]. The larger retrospective populations-based study in 2010, from the California Cancer Registry by Amirikia and Associates [10] included 375,761 invasive breast cancers, supported the previous findings that nonhispanic AA are at higher risk to develop TNBC. Higher incidence of TNBC was observed in younger patients particularly below age 50. Several smaller population-based studies have shown similar results, providing strong evidence for racial disparities in developing TNBC with a trend towards younger patients [11-13].

A multitude of population-based studies have tried to identify the etiology of TNBC. While many of these studies have revealed that the risk factors of developing TNBC are different from other types of breast cancer, further studies are required to better understand the underlying factors responsible for TNBC development. The current data regarding the role of menstrual and reproductive history, breast-feeding and oral contraception, is controversial. Despite the clear inverse relationship between parity and hormonally active breast cancers, most of the studies have failed to confirm any correlation between parity and TNBC. However, Phipps et al. [14] in a large population based study including 155,723 females showed that nulliparity decreases the risk of TNBC and increased parity is associated with increased risk of TNBC. Similar findings were reported in 2 smaller case-controlled studies [15,16].

Older age at first pregnancy has been shown to be associated with increased risk of breast cancers with expression of hormonal receptors while the majority of the studies on TNBC, except two of them, [17,18] did not identify any association between age at first pregnancy and risk of TNBC. Lactation has been shown to have a protective effect against TNBC in multiple studies [14,16,17,19] and lack of breast-feeding is associated with an increased risk of TNBC [20]. Millekan et al. [16] noted a combination of increased parity and lack of lactation was also associated with further increase in risk of TNBC. There is no strong evidence supporting the role of menstrual history in development of TNBC. Multiple studies have demonstrated that age of menopause is not associated with TNBC [14,21,22]. While few studies have reported an association between TNBC and younger age of menarch, [16,21,23] the rest of the studies have not supported this finding.

The data regarding TNBC and oral contraceptive (OCP) or hormonal therapy is also controversial. Ma et al. [24] demonstrated that women who started using OCP before the age of 18 had a 2.9-fold increase in TNBC and Dolle et al. [14] showed OCP consumption more than one year was associated with 2.5-fold increase in TNBC risk. Other studies, however, did not find any association between OCP and TNBC. Current hormonal therapy and not past use, is also reported to be associated with TNBC [19].

Yang et al. [21] pooled the data of 35,568 patients with breast cancer (1997 TNBC) from 34 studies participating in the Breast Cancer Association Consortium and studied various risk factors in different breast cancer subtypes. They noted that lower age at the first full-term birth, and BMI among younger women < 50 years (not older) were only associated with ER or PR positive tumors and not TNBC. age of menarch did not significantly increase the risk of TNBC. They demonstrated that nulliparity had the lowest prevalence in TNBC among different subtypes. Only increase parity was associated with

slight increase in TNBC risk [25]. These findings were consistent with a meta-analysis published earlier and failed to show any association between the above risk factors and TNBC [26].

Overall, there is significant heterogeneity in TNBC and its associated risk factors and our knowledge about epidemiology and etiology of TNBC is limited. Further large prospective population-based studies with adequate diversity are required to provide a better insight regarding the underlying factors that can increase the risk for developing the most aggressive basaloid breast cancer subtype. These data are crucial to design effective prevention strategies with meaningful clinical outcomes.

Cellular and Molecular Biology: Heterogeneity at all Levels

Immunohistochemical classification

By definition, TNBC is diagnosed by lack of expression of ER, PR and HER2. It is critical to accurately classify TNBC, since therapeutic options are different for this group of breast cancers. Immunohistochemistry (IHC) is the standard method for assessment of receptor expression and where the results for IHC are equivocal (for HER2) fluorescent in situ hybridization (FISH) assay will be utilized. There is a wide diversity in preanalytical preparation, assay methods and interpretations of IHC. Guidelines from American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) recommends considering IHC for ER and PR to be interpreted as negative if positive staining for tumor cell is observed in less than 1% of the sample [27]. There is more variability in assessment of HER2 expression. In 2013, ASCO/CAP released new guidelines to unify the detection methods and increase the chances of detecting HER2 amplification [28]. HER2 positive in IHC is defined by 3+ staining i.e. >10% tumor cells. IHC staining of 0 or 1 is considered as negative and 2 + is categorized as equivocal. If IHC is equivocal, further assessment with FISH (single probe or dual probe) should be considered. If FISH results are still equivocal, the HER2 status will not be interpreted as negative and patient will be considered eligible for trastuzumab. In addition to lack of ER, PR and HER2, TNBC tumors are usually positive for EGFR and myoepithelial (basal-cell) cytokeratin 5, 6 and 17 in IHC staining.

Histologic subtypes

TNBCs usually represent as high-grade invasive tumors with high mitotic count and a central necrosis pattern [29]. Various histological subtypes including ductal, metaplastic, medullary and adenoid cystic have been reported for TNBC [30]. Majority of these tumors, categorized as ductal, generally lack distinctive, uniform histological features. The rest of TNBCs are rare entities. Metaplastic tumors represent a heterogeneous subtype with epithelial and mesenchymal components [31]. Medullary phenotype is distinguished by high lymphocytic infiltration and has better outcomes, despite its high-grade histology [32,33]. Adenoid cystic carcinoma represents another rare histologic subtype with an observed indolent course and good clinical outcomes [34].

Molecular heterogeneity

Medical therapy is limited in TNBC given lack of HER2 and hormonal receptor expressions. Thus, it is critical to unravel the molecular landscape of TNBC and identify deranged druggable molecular targets and signaling pathways. Gene expression profiling (GEP) of TNBCs has revealed heterogeneity in mutational phenotype and aberrancy in signaling pathways. In a meta-analysis of various

GEP studies, Lehmann et al. [35] have analyzed 21 breast cancer data sets and classified TNBC into 6 molecular subtypes: basal-like (BL1 and BL2), immunomodulatory (IM), mesenchymal (M), mesenchymal stem-like (MSL) and luminal androgen receptor(LAR). BL1 is characterized by over expression of cell cycle pathways, loss of cell-cycle checkpoints and elevated DNA damage response genes. These features make them susceptible to antimitotic agents (taxanes) and DNA-damaging agents (Cisplatin) and they have shown the highest pathologic complete response (52%) [36]. The hallmark of BL2 subtype is aberrant expression of growth factor signaling pathways and growth factor receptors, with features of myoepithelial origin. In contrast to BL1, this subtype rarely achieves pathologic complete response. Unique characteristic of IM is central role for immune cell signaling at different levels including cell surface antigen and antigen presentation, cytokines and complement cascade. There is a significant overlap between medullary breast cancer and IM subtype. M and MSL subtypes share similar over expression patterns in cell motility and cell differentiation pathways, various growth factor signaling pathways and epithelial-mesenchymal transition markers. What distinguishes MSL, as a separate entity, is amplification of genes associated with angiogenesis and differential expression of some specific growth factor pathways, but lower levels of cell proliferation. Expression profile of M and MSL subtypes are similar to the metaplastic breast cancer. LAR subtype displays enrichment of hormone-regulating pathways such as androgen receptor signaling and steroid synthesis. This subtype is less chemosensitive with only 10% pathologic complete response [36].

BRCA and TNBC

BRCA1 and BRCA2 genes are tumor suppressors that are essential for DNA repair, apoptosis and maintaining genome stability. BRCA protein contributes to DNA double-strand breaks by homologous recombination [37]. Individuals who carry germline mutation in BRCA1 or BRCA2 have a 60-70% lifetime risk for developing breast cancer [38]. TNBC has been shown to have higher frequency of BRCA1 mutation. Among the breast cancer patients who have BRCA1 mutation, 60-80% are TNBC [39,40]. On the other hand, about 10% of TNBC patients have mutation in BRCA, predominantly BRCA1 and to a lesser extent BRCA2 [41-43]. BRCA mutation in TNBC is affected by age, and ethnic background. TNBC patients with BRCA mutations are younger compared to those without BRCA mutation [43]. It is also shown to be more frequent in Caucasian females compared to African Americans [44]. TNBC patients with BRCA1 mutation have significantly higher rates of family history of breast cancer and those with BRCA2 mutations are associated with family history of ovarian cancer, while TNBC patients without BRCA mutations were not associated with a higher familial history of either cancer [43]. National Comprehensive Cancer Network (NCCN) guidelines recommend genetic risk assessment for TNBC patients with BRCA mutation who are not older than 60 years.

Clinical Features

Diagnostic imaging

Efficacy of mammography as a diagnostic tool is lower for TNBC compared to other subtypes of cancer and is considered suboptimal [45]. Breast density is higher in younger patients who have higher likelihood of developing TNBC. Moreover, typical features such as calcification are less frequently seen in mammography of TNBC patients. Ultrasound (US) is a more sensitive diagnostic tool for TNBC, although benign radiologic features of TNBC in 20-40% can interfere with appropriate diagnosis. Magnetic resonance Imaging (MRI) has been shown to be superior to US and mammography in detection of TNBC [46]. [(18)F]2-fluoro-2-deoxy-D-glucose positron emission tomography ((18)F-FDG-PET) has demonstrated to be a non-sensitive tool for the routine initial diagnosis, but it is more sensitive in detection nodal and distant metastasis in TNBC compared to ER positive tumors [47].

Clinical course

TNBC is frequently diagnosed as an interval cancer i.e. between two routine mammograms, which indicates the rapid growth of tumor in this subtype. These tumors have more aggressive biologic behavior with larger tumor size, higher pathologic grade and more locally advanced, although they have lower rate of lymph node involvement. In contrast to other breast tumor types, tumor size and nodal metastasis are not strongly correlated in TNBC [5]. Metastatic pattern in TNBC is distinct with higher rate of lung and brain involvement while metastasis to bone and liver is not as frequent [48]. TNBC patients with distant metastasis experience a rapid progression to death. There is no obvious association between local and distant metastasis, and despite other tumors, local metastasis cannot predict distant metastasis.

Recurrence trends are also unique in TNBC. In general, recurrence occurs faster and after five years the risk declines. While recurrence in more than half of the ER + cancers happen between 5 to 10 years after diagnosis, the majority of TNBC recurrence is observed in the first 1-4 years and rapidly declines thereafter. In a similar fashion, the majority of tumor related deaths are observed in the first five years and mortality declines afterward [5].

Therapeutic Modalities

Surgery

Surgical options including total mastectomy and breast-conserving therapy (BCT), i.e. partial mastectomy followed by radiotherapy, are essentially similar in TNBC compared to other subtypes. Receptor status has not been widely assessed in the major prospective randomized trials that have studied surgical outcomes. Our knowledge about surgical intervention and its outcomes is confined to the data from retrospective or nonrandomized prospective studies, with considerable conflicting findings.

Several groups have studied the need for re-excision after lumpectomy in different subtypes of breast cancer. While Garvey et al. [49] (N=2520) showed no difference in presence of residual disease with re-excision between various breast subtypes, Sioshansi et al. [50] in a smaller study (N=369 with 12.5%TNBC) showed a 20% higher chance of residual tumor in re-excision, in TNBC. Multivariate analysis demonstrated an increased risk of residual invasive cancer in TNBC. Pilewskie et al. [51] have studied the effect of margin width after BCT on local recurrence in TNBC patients and showed that negative margin >2 mm was not associated with lower local recurrence.

A multitude of studies have evaluated treatment outcomes in various breast cancer subtypes. Ten studies have compared locoregional recurrence after BCT in TNBC vs. other subtypes. In a randomized trial (N=498 with 68 TNBC), Millar et al. [52] showed that TNBC could be predictive of local recurrence. Four other retrospective studies demonstrated increased local recurrence in TNBC [53-56]. While the remainder, failed to show any significant difference [57-61]. In a meta-analysis of the five cohorts among these

studies, Pan et al. [62] demonstrated that local control after BCT is similar in TNBC vs. non-TNBC. Other studies have compared the locoregional recurrence of both surgical options (BCT and total mastectomies) between TNBC and receptor positive tumors and while some reports demonstrated increased local recurrence in TNBC, [63-65] others did not show any significant difference [65-67]. Lowery et al. [68] have reported a meta-analysis of 15 studies including both BCT (n=7,174) and mastectomy (n=5,418) and their analysis revealed that local recurrence is increased in TNBC after both surgical interventions. In contrast, a retrospective study including 768 TNBC patients showed that mastectomy without radiation therapy in patients with no node metastasis had a higher rate of local recurrence compared to patients who underwent BCT [69]. Overall, despite the fact that metastasis and survival is poorer in TNBC, the data regarding local control and recurrence after surgery is controversial. Although the trend is toward increased local recurrence in TNBC, it is not well established if the type of surgical intervention has any impact on local recurrence and if the tumor subtype should impact the decision for the type of surgery offered to the patient. The answer, based on the current literature is no, but future prospective randomized trials should address this important issue.

Radiation therapy

The paucity of large randomized prospective trials focusing on impact of radiation therapy in TNBC has been the reason for lack of consensus guidelines specific to TNBC. Radiation therapy can be delivered in two different approaches: as part of BCT or post mastectomy radiation therapy (PMRT). Despite some conflicting findings, studies have generally indicated advantages of radiation therapy in management of TNBC. As showed above, radiation as part of BCT is demonstrated to decrease the locoregional recurrence in TNBC when compared to mastectomy without radiation [69]. A meta-analysis of 22 randomized trials on all types of breast has shown PMRT reduces both local and distant recurrence in patients with 1-3 positive axillary nodes. In line with these findings, a report from Danish Breast Cancer Cooperative Group Trial showed an increased risk of distant metastasis in patients who did not receive PMRT [70]. In contrast, other reports showed the increase in distant recurrence is not significant without PMRT [71]. In a meta-analysis of 12 studies in patients with TNBC including 2 randomized clinical trials, O'Rorke et al. [72] demonstrated that adjuvant radiation therapy, regardless of the surgical approach (both BCT and PMRT), significantly decreases the risk for locoregional recurrence. While they failed to show any overall survival benefits, subgroup analysis revealed improved survival in younger patients with more advanced TNBC (younger than 40 yrs, T3-4, N2-3). These findings should be cautiously interpreted, as this study was underpowered in these specific subgroups. There is a clear necessity for future randomized trials to accurately identify which TNBC patients would benefit from radiation therapy [72].

Chemotherapy

Lack of drug-specific targets with absence of hormonal and HER2 receptor, to this date, is the major obstacle in medical management of TNBC. Nonetheless, TNBC has a better response to chemotherapy when compared to other subtypes, despite its aggressiveness and higher likelihood of recurrence, which is referred to as "triple negative paradox" [73]. There is no single preferred chemotherapy agent for TNBC but it has been demonstrated that dose intensification has higher therapeutic efficacy [74,75]. Neoadjuvant chemotherapy is administered with two different strategies: down staging an inoperable breast cancer to an operable tumor, and also down staging

to make the tumor amenable to BCT. Anthracyclines and Taxanes are the preferred agents shown to be effective neoadjuvant regimens in TNBC [76]. Complete pathologic response has been reported in about 30% of TNBCs and is associated with excellent prognosis [77]. In contrast, tumors that are less sensitive to chemotherapy have worse clinical outcome [73]. In a prospective randomized trial, Golshan et al. [78] demonstrated that neoadjuvant chemotherapy, converted 42% of BCT-ineligible tumors, amenable to BCT, which was a 14% absolute increases in the eligibility for BCT. NCCN guidelines recommend adjuvant therapy for TNBCs with node involvement or tumors larger than 1 cm. It is also recommended that adjuvant chemotherapy be considered for tumors with 0.6-1 cm, although data is limited for patients older than 70 years. The preferred regimen is dose-dense doxorubicin/ cyclophosphamide followed by paclitaxel.

Defective DNA repair is a feature in a subgroup of TNBC, namely BRCA1 positive tumors. This characteristic has put platinum-based agents forward as attractive chemotherapy agents for neoadjuvant and adjuvant therapy in TNBC. In cells with DNA repair defect, platinum based agents can cause apoptosis by breaking DNA crosslink strands. Although preclinical data and subsequently a small prospective data supported this concept, [79] RCTs have shown controversial results. While CALGB 40603 trial has shown a significantly improved pathologic complete response with addition of carboplatin to the above regimen [78], a meta-analysis failed to prove any meaningful impact, of adding platinum based agents to the chemoregimen, on patients' survival [80]. Thus, current data does not strongly support a generalized application of platinum based agents in TNBC.

Targeted therapy

Molecular heterogeneity of TNBC and lack of specific medical therapy, such as hormonal therapy, as well as resistance to conventional regimens make targeted therapy and personalized medicine an area of interest in TNBC translational and clinical research. Only about 30% of the patients have pathologic complete response to the conventional chemotherapy. Non-responders, who are the majority comprising about 70% of the patients, are the ones who would benefit from novel therapies and are patients in whom targeted therapy has better outcomes. Various molecular pathways have been studied to identify targetable aberrations that can be potentially translated to an effective therapeutic tool. Poly (ADP-ribose) polymerase (PARP) inhibitors in patients with BRCA mutation with subsequent homologous recombination can cause double-strand break in replicating cells; with defective DNA repair, this will lead to selective tumor cell cytotoxicity. Several ongoing trials are currently studying various PARP inhibitors, yet no conclusive clinical benefit has reported to introduce them as part of practice guidelines.

Anti androgen therapy has been studied in LAR subtype and potential efficacy in patients positive for androgen hormones have been reported [81]. The PI3K/AKT/mTOR pathway controls various cellular functions including metabolism, proliferation and motility. Aberrant activation of this pathway has been shown in about 60% of TNBCs [82]. PI3K inhibitors are being tested in clinical trials and a phase I trial has reported improved progression free survival in metastatic TNBC with addition of PI3K/AKT/mTOR inhibitors to conventional chemotherapy [83]. Overall, more than 100 clinical trials are actively studying various targeted therapies including the abovementioned targets in addition to a multitude of other targets. Some of the widely studied targets include but not limited to receptor tyrosine kinase (RTK) such as EGFR and vascular

endothelial growth factor receptor (VEGFR), mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK), Heat shock proteins (HSP), antiangiogenics and also Immune-checkpoint inhibitors including anti-programmed cell death 1 (PD-1), anti-programmed cell death 1 ligand 1 (PD-L1) and anti-cytotoxic T-lymphocyte protein 4 (CTLA-4) monoclonal antibodies.

Conclusions and Future Directions

TNBC represents a heterogeneous subgroup of breast cancer with aggressive tumor behavior and poor clinical outcomes. Molecular profiling has helped to better classify the heterogeneity of these tumors, but our knowledge is yet limited about clinicopathological features of these tumors. Large prospective studies with special focus on environmental-biological-molecular interactions are required to better delineate underlying causes of triple negative breast tumors. These data are crucial to accurately define at-risk population and design preventive strategies. We know younger females and those with African ethnic background are at higher risk of developing TNBC but other risk factors, which contribute to tumorigenesis in hormone receptor and/or HER2 positive tumors, such as reproductive, menstrual and OCP consumption history, are not considered to be as significant contributing factors, homogenously across all the TNBCs.

This might imply the heterogenic molecular nature of this disease with a variety of risk factors differentially contributing to various subclasses, an area which still would warrant extensive epidemiological studies.

Despite the unique and heterogeneous nature of this subgroup, we still do not have a specific and targeted therapeutic plan confined to the features of TNBC. Currently, we are applying similar rules for our therapeutic approach to TNBC, as other subgroups. Future studies are required to define when and which surgical approach would have better outcomes, and whether, molecular profiles could serve as markers that can direct our therapeutic decision-making. Lack of hormonal/HER2 receptors excludes conventional targets for directed therapy in TNBC and although these tumors are more sensitive to achieve pathologic complete response with conventional chemoregimens, the majority of these tumors is not good responders and eventually would have worse outcomes. It is unclear why a subgroup of patients has excellent medical response while the rest have poor clinical outcomes; expanding our knowledge of non-responder will help to better define the nature of therapeutic obstacles in curing TNBC. Finding druggable targets and testing these targeted therapies, either alone or in conjunction with conventional therapies is subject of a broad spectrum of translational research and clinical trials. Despite all the advancements in the area of breast cancer, our knowledge in regards to TNBC is still limited. Designing therapeutic plans specific to TNBC is the focus of a substantial number of current studies with the goal to improve the outcomes of this aggressive breast neoplasm.

References

1. Sorlie T, Perou CM, Tibshirani R, Aas T, Geisler S, Johnsen H, et al. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proc Natl Acad Sci. 2001; 98: 10869-10874.

2. van't Veer LJ, Dai H, van de Vijver MJ, He YD, Hart AA, Mao M, et al. Gene expression profiling predicts clinical outcome of breast cancer. Nature. 2002; 415: 530-536.

3. Sorlie T, Tibshirani R, Parker J. Repeated observation of breast tumor subtypes in independent gene expression data sets. Proc Natl Acad Sci. 2003; 100: 8418-8423.

4. Perou CM, Sorlie T, Eisen MB. Molecular portraits of human breast tumours. Nature. 2000; 406: 747-752.

5. Dent R, Trudeau M, Pritchard KI. Triple-negative breast cancer: clinical features and patterns of recurrence. Clin Cancer Res. 2007; 13: 4429-4434.

6. Rody A, Karn T, Liedtke C. A clinically relevant gene signature in triple negative and basal-like breast cancer. Breast Cancer Res. 2011; 13: 97.

7. Tan DS, Marchio C, Jones RL. Triple negative breast cancer: molecular profiling and prognostic impact in adjuvant anthracycline-treated patients. Breast Cancer Res Treat. 2008; 111: 27-44.

8. Carey LA, Perou CM, Livasy CA. Race, breast cancer subtypes, and survival in the Carolina Breast Cancer Study. JAMA. 2006; 295: 2492-2502.

9. Brown M, Cress RD, Parise CA, Caggiano V. Descriptive analysis of estrogen receptor (ER)-negative, progesterone receptor (PR)-negative, and HER2-negative invasive breast cancer, the so-called triple-negative phenotype: a population-based study from the California cancer Registry. Cancer. 2007; 109: 1721-1728.

10. 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. 2011; 117: 2747-2753.

11. Morris GJ, Naidu S, Topham AK. Differences in breast carcinoma characteristics in newly diagnosed African-American and Caucasian patients: a single-institution compilation compared with the National Cancer Institute's Surveillance, Epidemiology, and End Results database. Cancer. 2007; 110: 876-884.

12. Lund MJ, Trivers KF, Porter PL. Race and triple negative threats to breast cancer survival: a population-based study in Atlanta, GA. Breast Cancer Res Treat. 2009; 113: 357-370.

13. Moran MS, Yang Q, Harris LN, Jones B, Tuck DP, Haffty BG. Long-term outcomes and clinicopathologic differences of African-American versus white patients treated with breast conservation therapy for early-stage breast cancer. Cancer. 2008; 113: 2565-2574.

14. Phipps AI, Malone KE, Porter PL, Daling JR, Li CI. Reproductive and hormonal risk factors for postmenopausal luminal, HER-2-overexpressing, and triple-negative breast cancer. Cancer. 2008; 113: 1521-1526.

15. Xing P, Li J, Jin F. A case-control study of reproductive factors associated with subtypes of breast cancer in Northeast China. Med Oncol. 2010; 27: 926-931.

16. Millikan RC, Newman B, Tse CK. Epidemiology of basal-like breast cancer. Breast Cancer Res Treat. 2008; 109: 123-139.

17. Li CI, Beaber EF, Tang MT, Porter PL, Daling JR, Malone KE. Reproductive factors and risk of estrogen receptor positive, triple-negative, and HER2-neu over expressing breast cancer among women 20-44 years of age. Breast Cancer Res Treat. 2013; 137: 579-587.

18. Martinez ME, Wertheim BC, Natarajan L. Reproductive factors, heterogeneity, and breast tumor subtypes in women of mexican descent. Cancer Epidemiol Biomarkers Prev. 2013; 22: 1853-1861.

19. Tamimi RM, Colditz GA, Hazra A. Traditional breast cancer risk factors in relation to molecular subtypes of breast cancer. Breast Cancer Res Treat. 2012; 131: 159-167.

20. Gaudet MM, Press MF, Haile RW. Risk factors by molecular subtypes of breast cancer across a population-based study of women 56 years or younger. Breast Cancer Res Treat. 2011; 130: 587-597.

21. Yang XR, Sherman ME, Rimm DL. Differences in risk factors for breast cancer molecular subtypes in a population-based study. Cancer Epidemiol Biomarkers Prev. 2007; 16: 439-443.

22. Islam T, Matsuo K, Ito H. Reproductive and hormonal risk factors for luminal, HER2-overexpressing, and triple-negative breast cancer in Japanese women. Ann Oncol. 2012; 23: 2435-2441.

23. Trivers KF, Lund MJ, Porter PL. The epidemiology of triple-negative breast cancer, including race. Cancer Causes Control. 2009; 20: 1071-1082.

24. Ma H, Wang Y, Sullivan-Halley J. Use of four biomarkers to evaluate the risk of breast cancer subtypes in the women's contraceptive and reproductive experiences study. Cancer Res. 2010; 70: 575-587.

25. Yang XR, Chang-Claude J, Goode EL. Associations of breast cancer risk factors with tumor subtypes: a pooled analysis from the Breast Cancer Association Consortium studies. J Natl Cancer Inst. 2011; 103: 250-263.

26. Ma H, Bernstein L, Pike MC, Ursin G. Reproductive factors and breast cancer risk according to joint estrogen and progesterone receptor status: a meta-analysis of epidemiological studies. Breast Cancer Res. 2006; 8: 43.

27. Hammond ME, Hayes DF, Dowsett M. American Society of Clinical Oncology/College Of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. J Clin Oncol. 2010; 28: 2784-2795.

28. Wolff AC, Hammond ME, Hicks DG. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. J Clin Oncol. 2013; 31: 3997-4013.

29. Criscitiello C, Azim HA, Schouten PC, Linn SC, Sotiriou C. Understanding the biology of triple-negative breast cancer. Ann Oncol. 2012; 6: 13-8.

30. Livasy CA, Karaca G, Nanda R. Phenotypic evaluation of the basal-like subtype of invasive breast carcinoma. Mod Pathol. 2006; 19: 264-271.

31. Weigelt B, Kreike B, Reis-Filho JS. Metaplastic breast carcinomas are basal-like breast cancers: a genomic profiling analysis. Breast Cancer Res Treat. 2009; 117: 273-280.

32. Huober J, Gelber S, Goldhirsch A. Prognosis of medullary breast cancer: analysis of 13 International Breast Cancer Study Group (IBCSG) trials. Ann Oncol. 2012; 23: 2843-2851.

33. Bertucci F, Finetti P, Cervera N. Gene expression profiling shows medullary breast cancer is a subgroup of basal breast cancers. Cancer Res. 2006; 66: 4636-4644.

34. Fusco N, Geyer FC, De Filippo MR. Genetic events in the progression of adenoid cystic carcinoma of the breast to high-grade triple-negative breast cancer. Mod Pathol. 2016.

35. Lehmann BD, Bauer JA, Chen X. Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies. J Clin Invest. 2011; 121: 2750-2767.

36. Masuda H, Baggerly KA, Wang Y. Differential response to neoadjuvant chemotherapy among 7 triple-negative breast cancer molecular subtypes. Clin Cancer Res. 2013; 19: 5533-5540.

37. Yun MH, Hiom K. CtIP-BRCA1 modulates the choice of DNA double-strand-break repair pathway throughout the cell cycle. Nature. 2009; 459: 460-463.

38. Antoniou A, Pharoah PD, Narod S. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case Series unselected for family history: a combined analysis of 22 studies. Am J Hum Genet. 2003; 72: 1117-1130.

39. Lakhani SR, Van De Vijver MJ, Jacquemier J. The pathology of familial breast cancer: predictive value of immunohistochemical markers estrogen receptor, progesterone receptor, HER-2, and p53 in patients with mutations in BRCA1 and BRCA2. J Clin Oncol. 2002; 20: 2310-2318.

40. Atchley DP, Albarracin CT, Lopez A. Clinical and pathologic characteristics of patients with BRCA-positive and BRCA-negative breast cancer. J Clin Oncol. 2008; 26: 4282-4288.

41. Cancer Genome Atlas N. Comprehensive molecular portraits of human breast tumours. 2012; 490: 61-70.

42. Foulkes WD, Stefansson IM, Chappuis PO. Germline BRCA1 mutations

43. Couch FJ, Hart SN, Sharma P. Inherited mutations in 17 breast cancer susceptibility genes among a large triple-negative breast cancer cohort unselected for family history of breast cancer. J Clin Oncol. 2015; 33: 304-311.

44. Greenup R, Buchanan A, Lorizio W. Prevalence of BRCA mutations among women with triple-negative breast cancer (TNBC) in a genetic counseling cohort. Ann Surg Oncol. 2013; 20: 3254-3258.

45. Dogan BE, Turnbull LW. Imaging of triple-negative breast cancer. Ann Oncol. 2012; 23: 23-29.

46. Dogan BE, Gonzalez-Angulo AM, Gilcrease M, Dryden MJ, Yang WT. Multimodality imaging of triple receptor-negative tumors with mammography, ultrasound, and MRI. AJR Am J Roentgenol. 2010; 194: 1160-1166.

47. Straver ME, Aukema TS, Olmos RA. Feasibility of FDG PET/CT to monitor the response of axillary lymph node metastases to neoadjuvant chemotherapy in breast cancer patients. Eur J Nucl Med Mol Imaging. 2010; 37: 1069-1076.

48. Kennecke H, Yerushalmi R, Woods R. Metastatic behavior of breast cancer subtypes. J Clin Oncol. 2010; 28: 3271-3277.

49. Garvey EM, Senior DA, Pockaj BA. Rates of residual disease with close but negative margins in breast cancer surgery. Breast. 2015; 24: 413-417.

50. Sioshansi S, Ehdaivand S, Cramer C, Lomme MM, Price LL, Wazer DE. Triple negative breast cancer is associated with an increased risk of residual invasive carcinoma after lumpectomy. Cancer. 2012; 118: 3893-3898.

51. Pilewskie M, Ho A, Orell E. Effect of margin width on local recurrence in triple-negative breast cancer patients treated with breast-conserving therapy. Ann Surg Oncol. 2014; 21: 1209-1214.

52. Millar EK, Graham PH, O'Toole SA. Prediction of local recurrence, distant metastases, and death after breast-conserving therapy in early-stage invasive breast cancer using a five-biomarker panel. J Clin Oncol. 2009; 27: 4701-4708.

53. Arvold ND, Taghian AG, Niemierko A. Age, breast cancer subtype approximation, and local recurrence after breast-conserving therapy. J Clin Oncol. 2011; 29: 3885-3891.

54. Solin LJ, Hwang WT, Vapiwala N. Outcome after breast conservation treatment with radiation for women with triple-negative early-stage invasive breast carcinoma. Clin Breast Cancer. 2009; 9: 96-100.

55. Nguyen PL, Taghian AG, Katz MS. Breast cancer subtype approximated by estrogen receptor, progesterone receptor, and HER-2 is associated with local and distant recurrence after breast-conserving therapy. J Clin Oncol. 2008; 26: 2373-2378.

56. Zaky SS, Lund M, May KA. The negative effect of triple-negative breast cancer on outcome after breast-conserving therapy. Ann Surg Oncol. 2011; 18: 2858-2865.

57. Gangi A, Chung A, Mirocha J, Liou DZ, Leong T, Giuliano AE. Breast-conserving therapy for triple-negative breast cancer. JAMA Surg. 2014; 149: 252-258.

58. Siponen ET, Vaalavirta L, Joensuu H, Vironen J, Heikkila P, Leidenius MH. Ipsilateral breast recurrence after breast conserving surgery in patients with small (</= 2 cm) breast cancer treated with modern adjuvant therapies. Eur J Surg Oncol. 2011; 37: 25-31.

59. Haffty BG, Yang Q, Reiss M. Locoregional relapse and distant metastasis in conservatively managed triple negative early-stage breast cancer. J Clin Oncol. 2006; 24: 5652-5657.

60. Freedman GM, Anderson PR, Li T, Nicolaou N. Locoregional recurrence of triple-negative breast cancer after breast-conserving surgery and radiation. Cancer. 2009; 115: 946-951.

and a basal epithelial phenotype in breast cancer. J Natl Cancer Inst. 2003; 95: 1482-1485.

61. Barbieri V, Sanpaolo P, Genovesi D. Prognostic impact of triple negative phenotype in conservatively treated breast cancer. Breast J. 2011; 17: 377-382.

62. Pan XB, Qu S, Jiang YM, Zhu XD. Triple Negative Breast Cancer versus Non-Triple Negative Breast Cancer Treated with Breast Conservation Surgery Followed by Radiotherapy: A Systematic Review and Meta-Analysis. Breast Care (Basel). 2015; 10: 413-416.

63. Billar JA, Dueck AC, Stucky CC. Triple-negative breast cancers: unique clinical presentations and outcomes. Ann Surg Oncol. 2010; 3: 384-390.

64. Gabos Z, Thoms J, Ghosh S. The association between biological subtype and locoregional recurrence in newly diagnosed breast cancer. Breast Cancer Res Treat. 2010; 124: 187-194.

65. Voduc KD, Cheang MC, Tyldesley S, Gelmon K, Nielsen TO, Kennecke H. Breast cancer subtypes and the risk of local and regional relapse. J Clin Oncol. 2010; 28: 1684-1691.

66. Mersin H, Yildirim E, Berberoglu U, Gulben K. The prognostic importance of triple negative breast carcinoma. Breast. 2008; 17: 341-346.

67. Ihemelandu CU, Naab TJ, Mezghebe HM. Treatment and survival outcome for molecular breast cancer subtypes in black women. Ann Surg. 2008; 247: 463-469.

68. Lowery AJ, Kell MR, Glynn RW, Kerin MJ, Sweeney KJ. Locoregional recurrence after breast cancer surgery: a systematic review by receptor phenotype. Breast Cancer Res Treat. 2012; 133: 831-841.

69. Abdulkarim BS, Cuartero J, Hanson J, Deschenes J, Lesniak D, Sabri S. Increased risk of locoregional recurrence for women with T1-2N0 triple-negative breast cancer treated with modified radical mastectomy without adjuvant radiation therapy compared with breast-conserving therapy. J Clin Oncol. 2011; 29: 2852-2858.

70. Kyndi M, Sorensen FB, Knudsen H. Estrogen receptor, progesterone receptor, HER-2, and response to postmastectomy radiotherapy in high-risk breast cancer: the Danish Breast Cancer Cooperative Group. J Clin Oncol. 2008; 26: 1419-1426.

71. Dragun AE, Pan J, Rai SN, Kruse B, Jain D. Locoregional recurrence in patients with triple-negative breast cancer: preliminary results of a single institution study. Am J Clin Oncol. 2011; 34: 231-237.

72. O'Rorke MA, Murray LJ, Brand JS, Bhoo-Pathy N. The value of adjuvant radiotherapy on survival and recurrence in triple-negative breast cancer: A systematic review and meta-analysis of 5507 patients. Cancer Treat Rev. 2016; 47: 12-21.

73. Carey LA, Dees EC, Sawyer L. The triple negative paradox: primary tumor chemosensitivity of breast cancer subtypes. Clin Cancer Res. 2007; 13: 2329-2334.

74. Gluz O, Nitz UA, Harbeck N. Triple-negative high-risk breast cancer derives particular benefit from dose intensification of adjuvant chemotherapy: results of WSG AM-01 trial. Ann Oncol. 2008; 19: 861-870.

75. Citron ML, Berry DA, Cirrincione C. Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: first report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741. J Clin Oncol. 2003; 21: 1431-1439.

76. Bianchini G, Balko JM, Mayer IA, Sanders ME, Gianni L. Triple-negative breast cancer: challenges and opportunities of a heterogeneous disease. Nat Rev Clin Oncol. 2016; 13: 674-690.

77. von Minckwitz G, Untch M, Blohmer JU. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. J Clin Oncol. 2012; 30: 1796-804.

78. Golshan M, Cirrincione CT, Sikov WM. Impact of neoadjuvant chemotherapy in stage II-III triple negative breast cancer on eligibility for breast-conserving surgery and breast conservation rates: surgical results from CALGB 40603 (Alliance). Ann Surg. 2015; 262: 434-439.

79. Byrski T, Gronwald J, Huzarski T. Pathologic complete response rates in young women with BRCA1-positive breast cancers after neoadjuvant chemotherapy. J Clin Oncol. 2010; 28: 375-379.

80. Cortazar P, Zhang L, Untch M. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet. 2014; 384: 164-172.

81. Gucalp A, Tolaney S, Isakoff SJ. Phase II trial of bicalutamide in patients with androgen receptor-positive, estrogen receptor-negative metastatic Breast Cancer. Clin Cancer Res. 2013; 19: 5505-5512.

82. Kalimutho M, Parsons K, Mittal D, Lopez JA, Srihari S, Khanna KK. Targeted Therapies for Triple-Negative Breast Cancer: Combating a Stubborn Disease. Trends Pharmacol Sci. 2015; 36: 822-846.

83. Ganesan P, Moulder S, Lee JJ. Triple-negative breast cancer patients treated at MD Anderson Cancer Center in phase I trials: improved outcomes with combination chemotherapy and targeted agents. Mol Cancer Ther. 2014; 13: 3175-3184.