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REVIEW ARTICLE – BREAST ONCOLOGY

# The 2014 Society of Surgical Oncology Susan G. Komen for the Cure Symposium: Triple-Negative Breast Cancer

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**ABSTRACT** Triple-negative breast cancer (TNBC) is an operational term that refers to a heterogeneous collection of breast cancers lacking expression of estrogen receptor (ER), progesterone receptor, and HER2. These tumors account for 12–17 % of all breast cancers, preferentially affect young women, are more frequent in women of African and Hispanic descent, and are enriched in the population of patients diagnosed with "interval cancers." TNBCs account for the majority of breast cancers arising in *BRCA1* germline mutation carriers (approximately 80 %), and approximately 11–16 % of all TNBCs harbor *BRCA1* or *BRCA2* germline mutations. Well-known risk factors for ER-positive cancers, such as reproductive history and hormonal factors, do not appear to have the same correlations for TNBC, and histologic risk factors for TNBC have not been identified. Patients with TNBC have a higher risk of both local and distant recurrence, but this is not mitigated by bigger surgery, and standard criteria should be used to select the approach to local therapy in these patients. Although platinum drugs have shown promise in the treatment of TNBC, standard chemotherapy remains the standard of care outside of a clinical trial.

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Triple-negative breast cancers (TNBCs) represent a distinct clinical and molecular subtype of breast cancer defined by the lack of estrogen receptor (ER), progesterone receptor (PR), and HER2 expression. Negativity for these three molecular markers represents the unifying feature for this phenotype, but substantial heterogeneity exists within the TNBC subset. Nonetheless, several epidemiologic and clinical patterns have been identified that distinguish the majority of TNBC from non-TNBC tumors. The current state of the literature on the epidemiology and molecular pathology of TNBC, as well as local and systemic therapy considerations, were the focus of the 2014 Society of Surgical Oncology Susan G. Komen for the Cure Symposium, March 2014.

## EPIDEMIOLOGY OF TNBC

*Lisa A. Newman, MD, MPH*

*Incidence and Outcome* TNBC accounts for an estimated 15 % of breast cancers in women in the United States. The frequency and population-based incidence rates of these tumors are approximately twofold higher for African-American women compared to white/Caucasian-American women.[1–4]

Patterns of metastatic relapse also differ for TNBC and non-TNBC.[1,5,6] TNBC is more likely to metastasize to the brain and lungs compared with non-TNBC, which preferentially metastasizes to bone. The overwhelming majority of metastases from TNBC occur within the first 5 years of diagnosis, and patients who have not recurred in this timeframe are largely considered to be "cured." In contrast, whereas a prolonged disease-free interval has prognostic value with ER-positive breast cancer, distant

organ metastatic disease is well-documented to occur even decades after initial treatment.

*Clinical Features* The average age of diagnosis for TNBC tends to be 5–10 years younger than for non-TNBC patients, and this is partially explained by the association between TNBC and BRCA mutation status, as discussed below. TNBC tumors tend to be larger than non-TNBC; they are more likely to present as mammographically occult, yet palpable, breast cancers, and they are more likely to develop as "interval" breast cancers—dominant invasive tumors that become clinically evident between regularly scheduled annual screening mammograms.[7–10] Several studies have demonstrated that TNBCs are less likely to be associated with mammographically evident microcalcifications. Magnetic resonance imaging (MRI) features that have been associated with TNBC include rounded or oval borders with surrounding edema and rim enhancement.[11] Similarly, ultrasound imaging of these lesions features prominent posterior shadowing.[12]

While the inherent aggressiveness of many TNBC tumors represents a legitimate concern, it is nonetheless important to emphasize the importance of screening and the prognostic value of early detection with these breast malignancies. In a Memorial Sloan Kettering Cancer Center study of nearly 200 TNBC tumors no larger than 1 cm, more than two-thirds were detected by screening, and 5-year disease-free survival rates were approximately 95 %, regardless of whether adjuvant chemotherapy was delivered.[13]

## *Risk Factors*

*Hereditary Susceptibility* Strong associations have been observed between TNBC and BRCA mutation status, with the association being strongest for BRCA1 mutations. Approximately 70–90 % of BRCA1 mutation-associated breast cancers are triple-negative and 16–23 % of BRCA2 mutation-associated cancers are triple-negative; conversely, 8–30 % of TNBC tumors are found to occur in BRCA1 mutation carriers.[1,5,6,14] Kwon et al.[15] demonstrated that BRCA testing is cost-efficient for any TNBC diagnosed younger than age 50 years, regardless of family history. As shown by Greenup et al.[16] the yield from BRCA mutation testing in TNBC patients varies by age as well as by racial/ethnic identity. Among 469 TNBC patients undergoing genetic testing, this group found an overall BRCA1 mutation positivity rate of 31 %. For patients younger than age 40 years, the frequency of BRCA1 mutation was 44 % compared with patients age 60–69 years, where the frequency was 13 %. Twenty percent of the African-American TNBC cases tested positive for a BRCA1 mutation compared with 33 % of the white/Caucasian TNBC cases. The 2013 National Comprehensive Cancer Network guidelines recommend genetic counseling referral for any TNBC patient diagnosed at age 60 years or younger.

*Reproductive History and Hormonal Factors* Menstrual history and childbearing patterns are well-established factors that impact the population-based breast cancer burden, and they also are included in individualized breast cancer risk assessment tools, such as the Gail Model. The predominant observation has been that patterns associated with exposure of mammary tissue to an increased volume of estrogen cycles over the lifetime (e.g., early menarche, late menopause, nulliparity, late age at first childbirth) result in a higher risk of breast cancer. However, recent epidemiologic studies of these reproductive factors stratified by breast cancer subtype have demonstrated that these correlations are mainly predictive for risk of hormone receptor-positive breast cancer.[17–20] A 2014 meta-analysis by Anderson et al.[21] reviewed 34 studies of reproductive history and risk of TNBC versus non-TNBC. The most consistent data reveal that while multiparity protects against hormone receptor-positive breast cancer, it increases the risk of TNBC, whereas lactation/breast feeding reduces the risk of both TNBC and non-TNBC.[19,21,22] Hormone replacement therapy (HRT) in postmenopausal women can increase risk of any breast cancer subtype, but the association appears to be strongest for risk of hormone receptor-positive disease, and at least two studies demonstrated a trend for reduced risk of TNBC among women with a history of HRT use.[20,23–27]

*Racial/Ethnic Identity and Nationality* TNBC is more common among women with African ancestry (African-American and sub-Saharan African women). This correlation was first reported by Carey et al., based on data from the Carolina Breast Cancer Study, where frequency of TNBC tumors associated with other basal subtype features (such as positivity for selected basal cytokeratins by immunohistochemistry) was approximately twofold higher for premenopausal African-American breast cancer patients compared with white/Caucasian-American patients.[3] This race/ethnicity-associated predisposition for TNBC has been confirmed by multiple single-institution studies as well as population-based studies in the United States, and it is seen within all deciles of age.[2] Among male breast cancer patients as well, TNBC is more common in African-Americans compared with white Americans.[28] Studies of breast cancer patients in Africa also reveal an increased frequency of TNBC compared with comparable data for white/Caucasian-American and European women. Reported frequencies of TNBC among breast cancers diagnosed in Ghana, Uganda, Nigeria, and Kenya range from 20 % to as high as 80 %; most studies demonstrated

that more than one-third of breast cancers in sub-Saharan Africa are TNBC.[29–32] In contrast, data from Canada, England, Italy, France, Turkey, Greece, and China demonstrate that TNBC accounts for 8–22 % of all breast cancer cases.[27,33–38]

*Other Breast Cancer Risk Factors* While a variety of lifestyle and mammary tissue characteristics have been well studied in the context of overall breast cancer risk, data are sparse regarding their association with TNBC susceptibility. Of the commonly cited body habitus and lifestyle risk factors, obesity and breast density have been the most convincingly associated with increased likelihood of developing TNBC. A meta-analysis of 11 studies by Pierobon and Frankelfeld demonstrated that obesity increased risk of TNBC by 20–24 %, with the strongest association among premenopausal women.[39] Obesity and a sedentary lifestyle also were shown to increase risk of postmenopausal TNBC based on data from the Women's Health Initiative.[40] Mammographic analyses from the Breast Cancer Surveillance Consortium demonstrated that increased breast density is a risk factor for both TNBC and non-TNBC.[41] Interestingly, data from the Women's Health Initiative have demonstrated that while alcohol intake was associated with increased risk for ER-positive breast cancer, it appeared to reduce the risk of TNBC.[42]

Atypical hyperplasia and lobular carcinoma in situ, often detected as incidental findings in otherwise benign breast biopsy specimens, are well-established risk factors for breast cancer. Existing data reveal that the majority of these lesions are ER positive and that chemoprevention with selective ER modulators (which only prevent ER-positive tumors) is effective in mitigating the risk associated with these lesions.[43–46] Inferentially, it therefore appears unlikely that these proliferative breast patterns would be associated with risk for TNBC.

Therapeutic chest wall irradiation during adolescence and early adult life increases risk for subsequent primary breast cancers, and data from the Carolina Breast Cancer Study demonstrated a trend for this exposure increasing the risk of premenopausal ER-negative disease.[47] Conversely, a small prospective study of MR surveillance in patients who received radiation for Hodgkin's disease demonstrated ER positivity in 88 % of the screen-detected breast cancer cases.[48]

In summary, TNBCs are more common among African-American women, and there is a strong association between TNBC and BRCA1 mutation status. Well-known risk factors for ER-positive cancers, such as reproductive history and hormonal factors, do not appear to have the same correlations for TNBC. Histologic risk factors for TNBC have not been identified (Table 1).

**TABLE 1** Risk factors associated with TNBC versus non-TNBC

| Risk factor | TNBC | Non-TNBC |
|---|---|---|
| Parity | Multiparity increases risk[19,21,22] | Multiparity decreases risk[17,19,21] |
| Lactation | Prolonged lactation decreases risk[19,21] | Prolonged lactation decreases risk[19,21] |
| Benign proliferative changes | Inadequate data | Atypia, lobular neoplasia increase risk[43–45a] |
| Hereditary susceptibility | Most strongly associated with BRCA1 mutation[89] | Most strongly associated with BRCA2 mutation[89] |
| Ancestry/ nationality | African-American and African identity/ ancestry associated with increased frequency[1–4, 30,31] | White/Caucasian-American and European identity/ ancestry associated with increased frequency (compared to women with African ancestry)[1–4, 33–35] |
| Postmenopausal hormone replacement therapy | Sparse data, but may increase risk[b20,23–25, 90] | Increases risk[20,23–90] |
| Obesity | Increases risk[39,40] | Increases risk[39,40] |
| Breast density | Increases risk[41] | Increases risk[41] |
| Alcohol intake | Sparse data, but may decrease risk[42,90] | Increases risk[42,90] |

*TNBC* triple-negative breast cancer, *HRT* hormone replacement therapy

[a] Inferential association, based on estrogen receptor positivity observed in majority of atypia and lobular neoplasia lesions

[b] Inconsistent data on association; at least two studies demonstrate reduced risk of TNBC associated with HRT history[26,27]

## MOLECULAR PATHOLOGY OF TNBC

*Jorge S. Reis-Filho, MD, PhD*

From a histopathologic standpoint, TNBCs show a remarkable diversity of histologic patterns and subtypes. Although the majority of these cancers are high-grade invasive ductal carcinomas of no special type, often with central necrosis or fibrosis and not uncommonly displaying a brisk lymphocytic infiltrate, some special histological types of breast cancers almost invariably display a triple-negative phenotype (e.g., carcinomas with medullary features and metaplastic breast cancers).[49–53] In addition, there is a subset of TNBCs that displays a rather indolent clinical behavior, namely adenoid cystic carcinomas and secretory carcinomas.[52,54] These rare types of indolent TNBCs also have in common the characteristic of harboring recurrent chromosomal translocations that result in the formation of oncogenic

chimeric fusion genes (i.e., *MYB-NFIB* and *ETV6-NTRK3* in adenoid cystic carcinomas and secretory carcinomas, respectively), and unlike the common types of TNBCs, they not only have a less-aggressive clinical behavior, but also patients with these cancers seem not to benefit from the mainstay of chemotherapeutic regimens offered to patients with triple-negative disease.[37,49,52,54,55]

Given the histopathologic diversity of TNBCs, their heterogeneity at the molecular level should not come as a surprise. Albeit initially perceived as a synonym for basal-like breast cancers, TNBCs have now been shown to be remarkably heterogeneous at the transcriptomic level.[37,50] Several subtypes of triple-negative disease have been identified over the years. Unsupervised analyses of breast cancers in general have revealed at least three distinct subtypes of tumors preferentially of triple-negative phenotype: basal-like, claudin-low, and molecular apocrine.[56–58] Basal-like breast cancers are tumors preferentially of high histological grade and have transcriptomic profiles characterized by the expression of genes usually found in basal/myoepithelial cells of the normal breast. Although initially thought to originate from basal cells of the mammary gland, there are multiple lines of evidence that basal-like breast cancers likely originate from ER-negative luminal progenitor cells of the breast. As a group, basal-like breast cancers have an aggressive clinical behavior; however, up to 40 % of these cancers seem to respond to current chemotherapy regimens.[49,50,56] It is unclear whether identifying the subset of TNBCs with a basal-like phenotype has clinical significance.[49,50] Claudin-low tumors were originally perceived as a subset of TNBCs enriched for the so-called cancer initiating cells; however, this notion has been called into question, because 33 % of claudin-low tumors express ER, 22 % express HER2, and, contrary to the majority of TNBCs, up to 62 % of claudin-low cancers are of histologic grades 1 or 2.[57,59] Molecular apocrine cancers are an aggressive subtype of breast cancers characterized by lack of ER and expression of androgen receptor, androgen receptor-related genes, and genes associated with apocrine differentiation.[58]

From a subtyping perspective, a microarray-based gene expression profiling study focusing only on TNBCs revealed the existence of at least six stable subtypes of this disease: basal-like 1, basal-like 2, mesenchymal-like, mesenchymal stem-like, immunomodulatory, luminal androgen receptor, and a subset of TNBCs that could not be stably classified.[60,61] These subtypes were subsequently validated in an independent dataset of TNBCs, and a molecular classifier was employed to identify breast cancer cell lines that would recapitulate the different subtypes of triple-negative disease.[60,61] Preclinical studies using these models have demonstrated that there is an interaction between these subtypes and response to specific therapeutic agents (e.g., luminal androgen receptor subtype and sensitivity to bicalutamide, and mesenchymal-like subtype and sensitivity to dual PIK3CA and mTOR inhibition), and initial clinical studies have suggested that subtyping of TNBCs may help to predict response to neoadjuvant chemotherapy.[60–62] Interestingly, these molecular subtypes may be underpinned by distinct patterns of somatic genetic alterations. For instance, luminal androgen receptor subtype has been shown to harbor recurrent *PIK3CA* hotspot mutations in up to 40 % of cases, whereas androgen receptor-negative TNBCs display these mutations in approximately 4 % of cases.[63]

From a therapeutic standpoint, despite the rather aggressive clinical behavior of TNBC, approximately 40 % of patients with TNBC benefit from chemotherapy.[49,50] Interestingly, independent retrospective analyses of samples from prospective clinical trials have demonstrated that quantifying the lymphocytic infiltrate in TNBCs provides strong prognostic information for patients with triple-negative disease treated with current chemotherapy regimens, which is now supported by level I evidence.[64,65] Hence, standardized histologic approaches to quantify the amount of lymphocytic infiltrate will have to be implemented in the pathology work-up for patients with TNBCs.[66]

## LOCAL THERAPY OF TNBC

*Monica Morrow, MD*

The increased mortality rate seen with TNBC has raised questions as to whether this subtype also is associated with an increased risk of locoregional recurrence and thus might influence the selection of breast-conservation therapy (BCT) versus mastectomy, or the use of sentinel node biopsy alone in patients with involvement of one or two sentinel nodes being treated with BCT.

The presenting features of breast cancer relevant to surgical decision making differ based on ER, PR, and HER2 status. Wiechmann et al., in a retrospective review of 6,072 patients, demonstrated that patients with TNBC were less likely to have multifocal or multicentric cancer than their counterparts with other subtypes, and a follow-up study of 11,000 cases also found a lower incidence of lymphovascular invasion in TNBC.[67,68] Despite this, multiple studies have shown an increased rate of local recurrence (LR) after BCT for the triple-negative subtype, even for tumors 1 cm or less in size.[69] In a meta-analysis of 7,174 cases, the relative risk of LR after BCT for non-TNBC was 0.49 [95 % confidence interval (CI) 0.33–0.73] compared with TNBC.[70] When HER2 overexpressing cancers not treated with trastuzumab were removed from analysis, the relative risk decreased to 0.33 (95 % CI 0.1–0.61) for non-TNBC. Just as the majority

of distant metastases occur within 5 years of diagnosis of TNBC, so do the majority of LRs.[71] Gangi et al. found that TNBCs were more likely to occur in younger patients, be larger, and be of higher grade and higher stage than other subtypes, and that after adjustment for these features, the 5-year rate of LR did not vary by subtype.[72] A meta-analysis of LR after mastectomy ($n = 5{,}418$) also demonstrated an increased rate of LR for TNBC with a relative risk of 0.66 (95 % CI 0.53–0.83) for non-TNBC when all subtypes were considered, which decreased to 0.51 (95 % CI 0.36–0.73) when HER2 overexpressing cases were removed.[70] In aggregate, these studies suggest that the behavior of TNBC is not influenced by the choice of BCT versus mastectomy, a finding confirmed in three retrospective studies that have directly compared the outcome of mastectomy and BCT in TNBC and found no difference in rates of LR or survival between procedures.[73–75] It is noteworthy that although rates of LR are increased in TNBC, the 5-year cumulative rate of locoregional recurrence was only 4.2 and 5.4 %, respectively, for patients having BCT and mastectomy in the most recent of these studies.[75] Pilewskie et al. examined the impact of margin width on LR after BCT in TNBC and found no significant difference based on margins $\leq$2 mm and $>$2 mm (5-year LR, 4.7 % vs. 3.7 %; $p = 0.11$) in a series of 535 consecutive patients, further supporting the concept that excellent local outcomes can be achieved in TNBC.[76]

The impact of TNBC on axillary management has been more controversial. The American College of Surgeons Oncology Group (ACOSOG) Z0011 trial established the safety of sentinel node biopsy alone for patients with metastases in one or two sentinel nodes undergoing BCT with whole breast irradiation, but 83 % of the patients in this study had ER- or PR-positive cancers.[77] There is no a priori reason to believe that TNBC is more likely to metastasize to axillary nodes, and several studies have shown nodal metastases to be significantly less frequent in this subtype.[67,78] Ugras et al. found that after adjustment for other features, patients with TNBC were significantly less likely to have metastases to four or more nodes compared with those with other subtypes ($p < 0.0001$).[68] Additionally, large studies examining factors associated with nodal recurrence after axillary dissection have not identified ER status as significant predictor.[79,80] These findings are supported by a prospective study from Memorial Sloan Kettering Cancer Center, which examined the applicability of the ACOSOG Z0011 findings to a consecutive series of 287 patients meeting ACOSOG Z0011 eligibility criteria.[81] Only 16 % of clinically node-negative patients in this study required axillary lymph node dissection (ALND), and ER status was not a predictor of the need for ALND.

In summary, available literature indicates that while patients with TNBC have a higher risk of both local and distant recurrence than other subtypes, this is not mitigated by bigger surgery. A diagnosis of TNBC is not an indication for mastectomy or ALND; standard criteria should be used to select the approach to local therapy in these patients.

## TNBC SYSTEMIC THERAPY: IS IT DIFFERENT?

*Lisa A. Carey, MD*

There are a few things we know about systemic therapy for TNBC. The first is that prognosis in this subtype, as with all other subtypes, is driven not only by biology, but also by clinical variables. There is no subtype in which a stage I cancer is high risk. That said, some stage I TNBCs do relapse. Despite great enthusiasm for genomic prognostic assays to determine need for adjuvant chemotherapy in this subtype, none of the existing assays are effective. Finally, although recent studies suggest both heterogeneity and potential targetability within TNBC, at this time chemotherapy is the only treatment option for either early or advanced disease.

TNBC has been defined by various cutpoints; however, it is increasingly clear that the most rigorous definition using American Society of Clinical Oncology/College of American Pathologists guidelines of $<$1 % ER, $<$1 % PR staining by immunostains (IHC), and HER2 negative by IHC or FISH, is appropriate. However, TNBC is itself heterogeneous and includes a large number of molecular entities. All the molecular intrinsic subtypes can be found in TNBC, including the basal-like (at least 50 %), and claudin-low (up to 30 %) subtypes that have low expression of both hormone receptor-related and HER2-related genes; the remainder is made up of HER2 enriched or luminal subtypes.[82] The therapeutic implications of this molecular heterogeneity are as yet uncertain.

In the early TNBC setting, there are two main debates. The first surrounds when to recommend adjuvant chemotherapy. Recent studies suggest that small (T1ab) node-negative breast cancers do well. Even in those with triple-negative phenotype, 5-year distant disease-free and overall survival exceed 90 % without therapy, and an impact of adjuvant chemotherapy is uncertain.[83,84] Online prognostic tools overestimate risk in these very small node-negative tumors. For example, in AdjuvantOnLine, relapse risk in T1abN0 is estimated at close to 20 %; however, much of this risk represents LR or second primary; the 10-year risk of death is less than 10 %. For this reason, with very small tumors, it may be best to use mortality estimates when estimating baseline risk of recurrence. The second issue is the nature of the chemotherapy itself and whether chemotherapy choices should be different in triple-negative

disease. Multiple neoadjuvant chemotherapy studies in unselected breast cancer have found high pathologic complete response rates (pCR) in TNBC with conventional anthracycline- or anthracycline/taxane-based regimens. Preclinical data suggest that some TNBCs, particularly those with a germline deleterious mutation in BRCA1, may be particularly sensitive to the effects of direct DNA-damaging agents, such as platinums or ionizing radiation; clinical support for this hypothesis came from a small study of cisplatin alone in 13 known BRCA1-associated breast cancers, in whom 83 % had pCR.[85] While randomized trials in unselected TNBC have had more mixed results, the largest, CALGB 40603, found a significant increase in pCR from 46 to 60 % with the addition of carboplatin to paclitaxel followed by AC.[86] What remains unclear is whether this advance will translate into clinically meaningful endpoints; a recent meta-analysis of the relationship of pCR to disease-free and overall survival failed to demonstrate an impact of modest (<3-fold) changes in pCR on outcome.[87]

In the recurrent setting, the CALOR trial has informed clinical practice in TNBC. In that study, patients with isolated operable LR were randomized to receive "read-juvant" chemotherapy or not. Despite considerable methodological and statistical obstacles, this trial demonstrated a strong advantage to those patients who received chemotherapy, particularly those with hormone receptor-negative tumors, in whom 5-year disease-free survival improved to 67 % from 35 %.[88] This management strategy differs from that recommended for distant recurrence, which is considered incurable and is managed with palliative chemotherapy, typically using sequential single agents.

In summary, TNBC is made up of a variety of biologic subtypes; however, this knowledge has not yet translated into therapy changes. Prognosis is driven in part by the biology of triple-negative disease but also is driven by clinical variables such as tumor size and nodal involvement. Standard chemotherapy should be used as (neo)adjuvant therapy. Alternatives, such as platinum drugs, show promise but have not demonstrated an outcome advantage. Unlike distant disease, which can be managed with palliative intent, isolated LR should be managed with multimodality therapy, including systemic polychemotherapy.

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