

# The latest progress in research on triple negative breast cancer (TNBC): risk factors, possible therapeutic targets and prognostic markers

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**Abstract:** Triple negative breast cancer (TNBC) is one type of breast cancer (BC), which is defined as negative for estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor-2 (Her2). Its origins and development seem to be elusive. And for now, drugs like tamoxifen or trastuzumab which specifically apply to ER, PR or Her2 positive BC seem unforeseeable in TNBC clinical treatment. Due to its extreme malignancy, high recurrence rate and poor prognosis, a lot of work on the research of TNBC is needed. This review aims to summarize the latest findings in TNBC in risk factors, possible therapeutic targets and possible prognostic makers.

**Keywords:** Triple negative breast cancer (TNBC); risk factor; therapeutic target; prognostic marker

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## Introduction (What is TNBC?)

Triple negative breast cancer (TNBC) is characterized by the absence of estrogen receptor (ER) and progesterone receptor (PR), as well as human epidermal growth factor receptor-2 (Her2) (1). Recently when referring to TNBC, the terms basal-like breast cancer (BC) and claudin-low BC should be mentioned. Gene expression profiling and molecular pathology have revealed that BC naturally divides into luminal A and B, HER2-enriched, basal-like and claudin-low subtypes (2). The basal-like BC is tumor that possesses characteristics of breast basal epithelial cells at the gene level (3). The claudin-low BC is characterized by loss of tight junction markers (notably claudins) and high expression of markers of epithelial-to-mesenchymal transition (EMT), in addition to being enriched for markers of mammary stem cells (4). And they are also associated with low expression of hormone receptor (HR) and HER-2, a trait shared by TNBC. However, since micro-array

gene expression assays are only used in the research, it's not practical for clinicians to make such pathologic diagnosis. What's more, Falck, *et al.* advice against using the markers to define the basal-like and claudin-low subtypes, considering them insufficiently reproducible (5). For these reasons, BC in the clinical setting is more typically categorized by routine immunohistochemistry as TNBC as a proxy for the basal-like and claudin-low subtypes.

TNBC is characterized by a typically ductal histology, high grade, and high proliferation and mitotic rates. It is associated with poor prognosis, a high risk of the local recurrence rate (LRR), and poor disease-free survival (DFS) and cancer-specific survival (CSS) (6). A study of 906 women with early-stage invasive BC demonstrated that, instead of margin status, TNBC subtype and increasing number of positive lymph nodes were associated with local recurrence (7). And the risk of recurrence in patients with TNBC is higher in the first 3 to 5 years after diagnosis than

those with ER positive BC (8-10).

For the time being, there are only few therapeutic options, and the conventional chemotherapy is probably the only treatment which may be effective for patients after surgery (11). And several studies showed that TNBC was more sensitive to adjuvant or neoadjuvant chemotherapy than other subtypes of BC (1,12). It had been shown that pathologic complete response (pCR) correlated with better prognosis in all the neoadjuvant trials. Within the TNBC group, those who reached pCR had an overall survival similar to that of the non-TNBC group who also reached pCR. In one of these studies (12), the authors analyzed a total of 1,118 patients who had undergone neoadjuvant chemotherapy (mainly anthracyclines alone or in combination with taxanes). Of these, 255 patients (23%) had TNBC. This particular subgroup of BC correlated with significantly higher pCR rates when compared to non-TNBC patients (22% *vs.* 11%, respectively) (1). However, when comparing the patients that did not reach pCR in both groups, those with TNBC had a worse outcome (13,14). The risk of recurrence was higher for the TNBC group only in the first three years but not thereafter (15-17); and the median survival time from recurrence to death was significantly shorter in the TNBC subtype when compared with the non-TNBC group (12). It is a pity that only a minority of TNBC patients is extremely sensitive to chemotherapy and may have an excellent outcome. And who are sensitive to it remains unknown. So there are two assumptions: TNBC is chemo-sensitive, more than those types with positive ER and/or PR; but when, by yet unknown mechanisms, it escapes control by conventional treatment, the relapse is more aggressive and confers worse overall survival (1).

### Risk factors

Although the specific pathogenesis of TNBC has not been found, studies suggest that there are many risk factors may lead to its occurrence.

Research indicated that BC subtypes were related with race and age. Premenopausal women and African American women were far more likely to develop basal-like BC and far less likely to develop luminal A BC than their postmenopausal and white counterparts (8,18-22). TNBC prevalence in the study population was higher than that reported in white patients with BC (6). The prevalence is 10-13% in white patients (6), 23-30% in African-American patients (23), 82% in Ghana (24), 39% in Saudi Arabia (25),

19.3% in Chinese Mainland (26), and 15.9% in Taiwan (10,27), 10-19.2% in Hispanic (6,10) which much similar to the Japanese series (8-14%) (26,28).

Lara-Medina, *et al.* suggested that younger age, premenopausal status, increased parity, hormonal contraceptive use, high histological grade, and advanced disease were associated independently with TNBC (6). They did not observe a correlation between over-weight or obesity and a diagnosis of TNBC when all patients considered. In premenopausal women, body mass index (BMI) was associated inversely with HR expression. However, in postmenopausal women, BMI had a positive association with HR and HER2 levels (6). In contradistinction to luminal BC, higher parity and young age at first birth may be risk factors for basal-like BC, whereas lack of breast feeding and early age of menarche may be stronger risk factors for luminal BC (8,21,29,30).

Genome-wide association study identified 25 known BC susceptibility loci (LGR6, MDM4, CASP8, 2q35, 2p24.1, TERT-rs10069690, ESR1, TOX3, 19p13.1, RALY, PEX14, 2q24.1, 2q31.1, ADAM29, EBF1, TCF7L2, 11q13.1, 11q24.3, 12p13.1, PTHLH, NTN4, 12q24, BRCA2, RAD51L1-rs2588809, MKL1) as risk factors for TNBC. And two SNPs independent of previously reported signals in ESR1 and 19p13.1 were associated with TNBC. A polygenic risk score (PRS) for TNBC based on known BC risk variants showed a 4-fold difference in risk between the highest and lowest PRS quintiles. It suggested that genetic variation may be used for TNBC risk prediction (31).

In addition, several studies had investigated the associations between height, weight, BMI (32-34), PA (35), cigarette smoking (36) and BC risk. However, only a few or even no patients in those studies were TNBC patients. Future research needs to be focused on TNBC patients.

### Possible therapeutic targets

Targeted therapies for TNBC patients remain under study. Many researchers have been studying on this thorny problem from different focus as BRCA1, endothelial growth factor receptor (EGFR), Notch receptors, etc. There are lots of new researches from different aspects as follows.

#### Gene level

MicroRNAs (miRNAs or miRs) are a family of small (19 to 25 nucleotides in length) non-coding RNAs that regulate gene expression by the sequence-selective targeting of

mRNAs (37). Radojicic, *et al.* used RT-PCR to study the 49 primary TNBC cases and found that among the investigated 9 miRNAs, miR-21, miR-210 and miR-221 were significantly overexpressed, whereas miR-10b, miR-145, miR-205 and miR-122a were significantly under-expressed in the TNBC. The molecular data supported the hypothesis that miR-221/222 contribute to the aggressive clinical behavior of basal-like BC (38). Furthermore, Zhao, *et al.* demonstrated that plasma miR-221 can be considered as a predictive biomarker for chemo-resistance in BC patients who have previously received neoadjuvant chemotherapy. The expression level of miR-221 was significantly associated with the HR status. Patients with higher plasma miR-221 levels tended to be HR-negative (39). So, in miRNA therapeutics, miRNA silencing therapies may be a valuable approach in conjunction with anticancer drugs and chemotherapy treatments. Peptide nucleic acid (PNA) is a DNA analogue in which the sugar-phosphate backbone is replaced by N-(2-aminoethyl) glycine units (37). Although this is a hypothesis that miRNA-targeted molecules based on PNA can be successfully applied to treat human diseases, it is still to be hoped that this can be applied to relevant patients based on the data of clinical trial.

Maire, *et al.* showed that TTK/hMPS1 was an attractive therapeutic target for TNBC (40). High levels of TTK mRNA had been found in BC, particularly in TNBC where it has been shown to protect cancer cells from aneuploidy (41). With immunohistochemistry and reverse phase protein array, Maire, *et al.* confirmed that TNBC expressed higher levels of TTK protein compared to the other BC subgroups. They determined the biological effects of TTK depletion by RNA interference, through analyses of tumorigenic capacity and cell viability in different human TNBC cell lines. TTK siRNA-treated TNBC cells exhibited a remarkable decrease in their ability to form colonies in semi-solid medium. The depletion of TTK in TNBC cells leads to a strong reduction in cell viability as a result of an induction of apoptosis. These results indicated TTK as a protein kinase over-expressed in TNBC, which may represent an attractive therapeutic target specifically for this poor prognosis associated subgroup of BC (40).

Recently, it is founded that RB1 expression is lost in ~20% of TNBC, which is identified by recent genomic sequencing, transcriptome analysis, epigenetic and proteomic analysis (42). Robinson, *et al.* demonstrated that RB-negative TNBC cell lines were highly sensitive to gamma-irradiation and moderately more sensitive to doxorubicin and methotrexate compared to RB-positive

TNBC cell lines. In contrast, RB1 status did not affect sensitivity of TNBC cells to multiple other drugs including cisplatin (CDDP), 5-fluorouracil, idarubicin, epirubicin, PRIMA-1 met, fludarabine and PD-0332991, some of which are used to treat TNBC patients. The results suggested that patients carrying RB-deficient TNBC would benefit from gamma-irradiation as well as doxorubicin and methotrexate therapy, but not necessarily from many other anti-neoplastic drugs (43).

What's more, studies had shown aldehyde dehydrogenase 1 (ALDH1) and cyclooxygenase 2 (Cox-2) gene products were involved in a variety of tumor processes including tumor cell proliferation, tumor invasion, and metastasis of TNBC. Therefore, ALDH1 and Cox-2 may be ideal targets for developing agents for TNBC treatment (15).

### Receptors

MUC1 is a binding partner for EGFR, and more specifically, MUC1 and EGFR interact in the nucleus of BC cells to facilitate the association of EGFR with transcriptionally active promoter regions (44). In addition, MUC1 inhibited the degradation of ligand-activated EGFR, and this association might promote cell transformation through the inhibition of EGFR degradation (45). This finding suggested that most TNBC expressed MUC1 to a degree that might render these tumors sensitive to MUC1-based peptide vaccines. One study of MUC1 vaccination had demonstrated the activation of cellular immunity in patients with advanced cancers (46). Siroy, *et al.* demonstrated that MUC1 was expressed in 94% of early-stage high-grade TNBC according to 52 cases patients and the expression of MUC1 in most TNBC provided a rationale to treat patients who had completed standard therapy for early-stage TNBC with a vaccine that generates immunity against MUC1 (47).

Exploratory biomarker assessment suggested that patients with high pretreatment plasma VEGFR-2 might benefit from the addition of bevacizumab (48). A neoadjuvant trial showed a weaker bevacizumab effect in TNBC than in HR-positive disease (49). A multinational open-label randomized phase 3 trial showed that the addition of bevacizumab to chemotherapy during adjuvant therapy did not improve invasive disease-free survival (IDFS) in patients with TNBC. Bevacizumab cannot be recommended as adjuvant treatment in unselected patients with TNBC. HR-negative tumours were associated with high concentrations of VEGF (50). Plasma VEGFR-2 concentrations showed no prognostic value but potential

predictive value for bevacizumab efficacy (48).

Androgen receptor (AR) expression had been observed in about 50% of patients with TNBC (51). Clinical studies had shown that the response of BC to high-dose Medroxyprogesterone-Acetate (MPA) therapy was dependent on the expression of AR, but not ER or PR (52). And the data from Xiangying, *et al.* provided clinical evidence that MPA/megestrol acetate (MA) therapy might be an alternative treatment for patients with recurrent TNBC, especially for multi-treated patients with poor physical conditions (53). However, the study was observational and the sample (51 patients) was small. Further studies with larger datasets and prospective research are needed to provide confirmatory evidence for or against the feasibility of MPA/MA treatment for recurrent TNBC.

### Immunomodulatory

Engel, *et al.* showed that NK-cell induced lysis was significantly increased in four TNBC cell lines [MDA-MB231, MDA-MB468, HCC-1937 (BRCA 1 mutated) and HCC-1806 TNBC cells] compared to ER + MCF 7 cells (54). The largest study to investigate tumor samples of more than 1,400 patients and found that Treg infiltration was associated with TNBC (55). TNBC cells provided more significant stimulation to the NK-cell immune response than ER positive BC cells which could explain why infiltration with immunosuppressive Tregs is increased in human specimens of TNBC with and without mutated BRCA 1 (54). Accordingly, immunomodulatory treatment strategies should be further explored in TNBC.

### Signaling pathway

Serin/threonin kinase AKT is emerging as a key target in oncology. Except for its immunosuppressive properties, the signaling pathway is involved in resistance to apoptosis and chemotherapy, as well as in cell proliferation and metabolism (56). López-Knowles, *et al.* found alterations of the AKT pathway in basal-like BC significantly increased, accounting for more than 70 % of the TNBC population (57). However, Engel, *et al.* only found increased expression of AKT in TNBC with BRCA 1 mutation, while this might be due to the small sample size, which became the major limitation of the study (54).

The extracellularly regulated kinase/mitogen activated protein kinase (ERK/MAPK) signaling pathway is a critical regulator of cellular processes in adult and developing

tissues. Depending on the cellular context, MAPK cascade can act as a rheostat, a switch, or an oscillator (58). We know that EGFR is expressed in 13% to 70% of TNBC (1,47). And it is a member of the HER family. Ono, M. and M. Kuwano demonstrated that the ligand binding to HER family leads to activation of various signal cascades including MAPK (59). What's more, Park, *et al.* found that the activation of ERK/MAPK pathway is required for TGF- $\alpha$  and EGF-induced upregulation of Matrix metalloproteinase 1 (60).

### Others

Recently, a Phase 2 trial of everolimus and carboplatin combination in patients with triple negative metastatic BC had a conclusion that Everolimus-carboplatin was efficacious in metastatic TNBC. Dose limiting hematological toxicity was observed when AUC5/6 of carboplatin was combined with everolimus. However, carboplatin AUC 4 was well tolerated in combination with everolimus with continuing responses (61).

### Possible prognostic markers

In addition to the known ones, such as, EGFR and ALDH1, there are new possible prognostic makers for TNBC including Lysyl Oxidase-Like 2 protein (LOXL2), Synuclein gamma (SNCG), LDHB (Lactate Dehydrogenase B).

Ahn, *et al.* demonstrated that LOXL2 was an independent prognostic factor in BC patients (62). In univariate analysis for OS, higher expression of LOXL2 was associated with poor outcome after a median follow-up time of 9.3 years. The clinical and preclinical data confirmed that the rate of positive LOXL2 was higher in TNBC than non-TNBC tumors. LOXL2 expression promoted epithelial-mesenchymal transition (EMT) and invasiveness of basal-like BC cell lines, a finding that was compatible with previous *in vitro* study results (63). Silencing of LOXL2 resulted in a marked decrease in migratory ability and invasion capacity. It potentially suggested that the interruption of the LOXL2-dependent activity contributing to metastasis could bring survival benefit to BC patients, as well as in a preclinical condition.

SNCG, identified as BC-specific gene 1, was an independent predictive marker for recurrence and metastasis in BC. 34.3% TNBC showed moderate to strong positive SNCG expression. Wu, *et al.* found that tumor size was significantly associated with SNCG expression. Patients



whose tumors expressed SNCG had significantly shorter DFS and a higher probability of death when compared with those whose tumors did not express SNCG (64).

McClelland, *et al.* identified that LDHB was an essential gene for triple-negative BC by an integrated genomic screen (65). And Dennison, *et al.* suggested that LDHB was able to predict the prognosis of the basal-like subtype within the HR-positive/HER2-negative and TNBC groups with a high degree of power (66). BC with high LDHB was most responsive to neoadjuvant chemotherapy independently of established prognostic factors (grade, tumor size) and molecular markers (HR status and PAM50 subtyping) (66).

### Conclusions

As one special type of BC, the pathogenesis of TNBC is at present yet to know. Clinical data demonstrated that risk factors like race, age, premenopausal status, increased parity, hormonal contraceptive use, high histologic grade, and advanced disease were independently associated with TNBC. As there are no first-line therapies specific for these patients at the moment, lots of researchers are working on this from different aspects, such as Gene level, Receptors, Immunomodulatory, Signaling pathway and others. Researchers also found some possible prognostic markers like EGFR, ALDH1 LOXL2, SNCG and LDHB. However, most of these studies on TNBC were at the cellular level and subject to its limitation. Due to the low incidence of the disease, there are only a few clinical trials for TNBC patients so far. Therefore, we are expecting more large scale clinical trials to be conducted in the future.

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