

What is Triple-Negative Breast Cancer?

by Barbara MacDonald, ND, LAc

Two out of three breast cancers are ERPR-positive, meaning they have receptor sites that are sensitive to estrogen and progesterone.¹ Around twenty percent of breast cancers are stimulated by a protein called human epidermal growth factor. These are called HER2-positive. There is a less common type of breast cancer that is not sensitive to, or stimulated by, estrogen, progesterone or HER2. These are called “triple-negative breast cancer” (TNBC) and they make up approximately fifteen percent of all invasive breast cancers diagnosed in the United States.²

While there are an increasing number of studies being done on TNBC, there are still, many unanswered questions. A few years ago, I began seeing more and more women with TNBC in my practice. However, rates of TNBC actually went down from 2006-2010.³ This article explains what is known about TNBC, who tends to get it, its risk factors, prognosis, conventional treatments and the little data that is known about natural medicines that have been studied to confront it. It is my hope that more studies will illuminate the nature of this less common and more aggressive form of breast cancer.

The pathology of triple-negative breast cancers

TNBC is considered to be a more aggressive type of breast cancer. It is typically characterized by a ductal histology, high grade, high proliferation and mitotic rates. It is associated with poorer disease-free survival rates regardless of stage at diagnosis.⁴ TNBC has a higher likelihood of local recurrence, especially when multiple nodes are positive. The risk of recurrence in patients with TNBC is higher in the first three years compared to those with the

hormone-positive/HER2-negative type.⁵ There are higher rates of distant metastasis to the lung, liver and brain than non-TNBC and lower rates of metastasis to the bones.⁶ Rates of BRCA gene mutations tend to be high among women with TNBC, particularly when diagnosed at a young age.⁷

It is only in the last few years that pathologists began characterizing breast cancers by their molecular subtypes. In order to delineate each subtype through gene-expression profiling, a new classification system was created. The most common type of breast cancer is called 'luminal A' which is ER-positive and/or progesterone-positive, HER2-negative. 'Basal-like' breast cancers are ER-negative, PR-negative and HER2-negative, cytokeratin 5/6-positive and/or epidermal growth factor receptor-positive.⁸ This is helpful for research studies, however, it leaves room for confusion when discussing TNBC. Approximately 75% of TNBCs express basal markers.⁹ Basal-like breast cancers are triple-negative but not all TNBCs are basal-like.

Epidemiology of triple-negative breast cancer

Black women of diverse backgrounds are three times more likely than non-black women to have TNBC, regardless of age or weight. In the United States, TNBC makes up 15-20% of the total invasive breast cancers. The prevalence of TNBC among white Americans is 10% and among African-Americans is 33%. The total number of cases of TNBC globally is approximately 170,000.¹⁰ The prevalence of TNBC in Ghana, however is 82% - the highest percentage of breast cancers of this subtype globally.¹¹ The incidence of TNBC, as a particularly aggressive type of breast cancer, may contribute to the lower survival rates among women of color.

Younger age, premenopausal status, increased parity, high histological grade and advanced disease have been associated independently with TNBC.¹²

Genome studies identified 25 known breast cancer susceptibility loci as risk factors for TNBC.¹³ Among them, there is an association between CYP2C19 deletion; a single nucleotide polymorphism related to estrogen catabolism.¹⁴ Immune signatures vary among those with TNBC as well. A cytokine known as IL-5, which plays a role in certain allergic and inflammatory conditions, is particularly high among premenopausal women with TNBC.¹⁵

We have also learned from studies of Chinese women, with early stage primary TNBC, that having type 2 diabetes (T2DM) increases ones chances of local recurrence and metastasis (from 4.6% in the non-T2DM group to 23% in the diabetic group). The two year survival rates among TNBC patients without diabetes was 97% compared to 78% in the diabetic group.¹⁶

Etiology of TNBC

The risk factors that contribute to triple-negative breast cancer are varied and not yet fully understood. Associations between TNBC and weight, menopausal status, parity, breastfeeding, cigarette smoking and alcohol have all been studied – most with conflicting results.

Weight

Being overweight or obese increases the risk of breast cancer in general. However, among studies of triple-negative breast cancer the studies are contradictory. TNBC incidence was studied within one white, socioeconomically deprived, population in West Virginia. TNBC occurred more frequently among younger women, with later stage at diagnosis, and was associated with obesity.¹⁷ Another study found weight to be a factor in the development of TNBC among premenopausal women.¹⁸ While these and other studies did find this association between menopausal status, weight and TNBC, another found the opposite among African-Americans. Stead, et al reported that TNBC was equally common in black women diagnosed

before and after age 50, and who were obese and non-obese. Considering all patients in the study, as body mass index increased, the proportion of TNBC decreased.¹⁹

Parity and Breastfeeding

Parity and nursing seems to affect one's risk of TNBC. One study author determined that TNBC cases tended to be younger at diagnosis and African-American and were more likely to have not breastfed if they three or more children.²⁰ In another study, compared to non-TNBC cases, women with TNBC had a shorter duration of nursing each child and a higher parity.²¹ Among participants in the Women's Health Initiative, never having children was associated with decreased risk of TNBC but increased risk of ER-positive breast cancer. Among those who had children, the more births, the higher the risk of TNBC.²²

Oral Contraceptive Use

Studies reporting an association between TNBC and use of oral contraceptives are varied as well. The author of one such study found that using birth control pills for more than one year was associated with a 2.5-fold increased risk of TNBC and no increased risk among non-TNBCs.²³ Another study found no such risk association.²⁴

Cigarette smoking and alcohol consumption

According to a study published using the Women's Health Initiative, cigarette smoking is not associated with risk of TNBC. Alcohol use was found to reduce the risk compared to those who have never drank alcohol among postmenopausal breast cancer patients. However both exposures increased the risk of ER-positive breast cancer.²⁵

BRCA Gene Mutations

Seventy-five to eighty percent of BRCA1-associated breast cancers are basal-like TNBCs. One study of 469 women with TNBC found that 31% had a BRCA mutation; 106 with BRCA1 and 32 with BRCA2 mutations. The rates of TNBC among those with BRCA mutations decreased with age - from 44% among those diagnosed before age 40 compared to only 13% of those in their 60's who were BRCA-positive with TNBC.²⁶

Conventional Treatments of TNBC

Conventional treatment of hormone sensitive (luminal A), breast cancer is well established and has specific guidelines based on a well-established criteria. This is not yet the case for triple-negative breast cancer. Due to a lack of research on this type of cancer, there are no established guidelines for the treatment of TNBC.

Surgical recommendations currently follow the same guidelines as non-TNBC unless the patient also has a BRCA gene mutation. It is recommended that patients remember, however that there is a higher likelihood of local recurrence in the first three years than in those with non-TNBC.

To date, there are no FDA-approved single target therapies for TNBC. In general, oncologists recommend chemotherapy even if the tumor is small and node negative. This is due, in part, because of the higher risk of spread to internal organs and partly because TNBC responds very well to chemotherapy. The studies on which chemotherapy agent(s) work best, however are limited.

Future studies appear to be targeting the five subtypes of TNBC based on the signaling pathways unique to each. Some authors recommend molecular testing prior to choosing chemotherapy.²⁷ TNBC responds better to chemotherapy administered prior to surgery

(neoadjuvant) than other breast cancer subtypes. Having neoadjuvant chemotherapy has been found to induce a pathological complete response in about 30%, which means that the chemotherapy resolved any evidence of the cancer by the time of surgery.²⁸ Those who reached pathological complete response correlated with better prognosis in all the neoadjuvant trials.²⁹ It was also found that among premenopausal women with TNBC, those who were 35 years or younger more often achieved a pathological complete response to neoadjuvant chemotherapy.³⁰

TNBC, like luminal A breast cancer, has been identified as sensitive to taxanes and anthracycline chemotherapeutic drugs. Standard Adriamycin, Cytosin followed by Taxol (AC/T) is often prescribed. More recently, it has been observed that Cytosin and Taxotere are being combined. Platinum agents are effective in TNBC patients with BRCA1-gene mutation, either alone or in combination with poly-adenosine-diphosphate polymerase-1 inhibitors. Combinations of ixabepilone and capecitabine have added to progression-free survival (PFS) without survival benefit in metastatic TNBC.³¹ The 2013 San Antonio Breast Cancer Symposium reported an improved outcome when veliparib and carboplatin were added to standard AC/T chemotherapeutic regimen.³² Lastly, it was found that those who began chemotherapy within 30 days after surgery, had better overall survival than those who waited longer to start chemotherapy.³³

There are no established guidelines for the prescription of radiotherapy among those with TNBC. Standard indications for radiation therapy apply. Unlike those with estrogen receptor-positive breast cancer, who are offered oral medications (to block hormones) after chemotherapy and surgery, there are no post-chemo oral drug therapies recommended for those with TNBC.

Three conventional medications that are used for other diseases have been studied in-vitro with TNBC however. Metformin, an anti-diabetic drug, has been found to selectively kill

TNBC cell lines.³⁴ In addition, a proton pump inhibitor used for gastroesophageal reflux, esomeprazole, suppresses growth of TNBC cells independently while sensitizing cells to doxorubicin (Adriamycin).³⁵ Finally, early in-vitro and animal studies found that aspirin may play a role in the fight against TNBC³⁶ as it slows the growth of TNBC cell lines and reduces tumor growth in mice.³⁷ However, in a retrospective look at breast cancer patients it was found that regular aspirin use was not associated with any protection from developing TNBC.

Finally, twelve percent of women with metastatic estrogen/progesterone receptor-negative breast cancer tested positive for androgen receptors in one study. Twenty-one percent remained stable for at least 6 months in response to treatment with an anti-androgen drug, called bicalutamide, commonly used for prostate cancer. All but one of these were Her2-negative.³⁸

Natural Therapies for TNBC

There are several natural therapeutic agents showing promise when studied to retard the growth of TNBC cell lines in-vitro and in animals. The following natural therapies provide us with tools to consider in prevention of recurrence strategies:

- Those with the triple-negative breast cancer phenotype have the lowest average **vitamin D** levels and the highest percentage of patients that are vitamin D deficient.³⁹ Vitamin D given to a mouse model suppressed multiple proteins that are required for survival of triple-negative/basal-like breast cancer cells.⁴⁰
- A product called **BreastDefend™** that contains medicinal mushrooms (Coriolus versicolor, Ganoderma lucidum, Phellinus linteus), medicinal herbs (Scutellaria barbata, Astragalus membranaceus, Curcuma longa), and purified biologically active nutritional compounds (diindolylmethane and quercetin), was found to

prevent breast-to-lung cancer metastases in an orthotopic animal model of triple-negative human breast cancer.⁴¹

- **Melatonin** showed effectiveness in reducing tumor growth and cell proliferation, as well as in the inhibition of angiogenesis in TNBC-induced mouse model.⁴²
- **Silibinin**, given orally from the milk thistle plant, significantly suppressed tumor volume in a TNBC mice model.⁴³
- **Epigallocatechin-3-Gallate (EGCG)**, from green tea, induces apoptosis, inhibits cell proliferation and migratory behavior of TNBC cells.⁴⁴
- **Curcumin** induces apoptosis and inhibits the proliferation of TNBC cells.⁴⁵
- **Ginseng** sapogenins are potent inhibitors of MDA-MB-231 human TNBC cell lines.⁴⁶
- **Piperine**, an alkaloid from black pepper, inhibits the growth and motility of TNBC and enhances radiotherapy in vitro.⁴⁷
- **Omega three polyunsaturated fatty acids** have a pronounced inhibitory effect against triple-negative basal breast cancer cell lines in-vitro.⁴⁸

In conclusion

Information about triple-negative breast cancer is lacking in general. It is reassuring, however that the interest in studying TNBC appears to be high. The most interesting research, to me, is among those studying individualization of treatment based on gene-expression profiling. Until more information is available, I recommend that those with TNBC get an opinion from an oncology facility in a major metropolitan area. I encourage patients to request genetic testing from their oncologist and be open to neoadjuvant chemotherapy and mastectomy if recommended.

Look for an experienced, licensed, naturopathic physician in your area to help during treatment to reduce side effects and negative interactions between drugs and natural therapeutics. Complementary care providers can also offer prevention of recurrence strategies. These range from specific dietary and fitness recommendations to individualized treatment plans including vitamins, minerals and botanical medicines found to reduce the risk of recurrence of breast cancer.

To find experts in your area, go to the American Association of Naturopathic Physicians (naturopathic.org) or the Oncology Association of Naturopathic Physicians (oncnp.org). For more information on Triple Negative Breast Cancer in general, go to tnbcfoundation.org.

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