

FIGHT NOW UPDATE

Eat & Live Proactively Against Breast Cancer

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**FIGHT NOW BEFORE BREAST CANCER STRIKES.
PREVENTION IS THE BEST CURE.**

Stress Increases Breast Cancer Metastasis

Previous research has shown us that chronic stress can increase breast cancer risk, while reducing chronic stress can improve survival after breast cancer recurrence. However, the impact of chronic stress on breast cancer metastasis and the mechanisms involved remain unclear.

A new breast cancer research study in a mouse model of breast cancer metastasis recently explored these relationships with profound results. For this new breast cancer research study, investigators took breast cancer cells and injected them with the firefly luciferase gene so that they would glow and be easily tracked. These breast cancer cells were then injected into two groups of mice. One group of mice was placed in an over-crowded environment that prevented them from moving freely for 2 hours per day for 20 days in order to induce chronic stress. The second group of mice (control group) remained in their more expansive home conditions without the stress-inducing restraint. The growth and spread of these breast cancer cells was monitored in addition to changes in sympathetic nerve system function and immune function. The breast cancer researchers reported that:

- Chronic stress caused nearly a 40-fold increase in the metastasis of breast cancer cells from the primary tumor. The stressful conditions resulted in a 37-fold increase in metastasis to the lungs and a 67% increase in the spread of breast cancer cells to lymph nodes.
- Chronic stress induced an infiltration of macrophages, a specific immune system cell type, into the primary breast cancer tumors by 53% on average.
- Chronic stress enhanced the expression of pro-inflammatory genes, genes involved in the promotion of breast cancer metastasis, and some growth factor genes involved in breast cancer progression. Additionally, genes with a protective function were reduced by chronic stress.
- Treatment with the beta-blocker drug propranolol blocked stress-induced breast cancer metastasis in stressed mice, but had no effect in non-stressed, control mice.

- Furthermore, treatment with propranolol suppressed the invasion of primary breast cancer tumors by immune system macrophages.
- Treatment of mice with a drug designed to directly inhibit macrophage function successfully reduced breast cancer metastasis.

These are important and exciting breast cancer research results that show us two important things. First, this new breast cancer research shows us that chronic stress increases breast cancer metastasis and does so by altering the sympathetic nervous system, enhancing the recruitment of immune cells to the breast cancer tumor, and increasing the production of growth and inflammatory factors that promote breast cancer metastasis. Secondly, this new breast cancer research shows that drugs that block the stress-induced effects on the sympathetic nervous system and drugs that directly block macrophage function can successfully suppress breast cancer metastasis. These results might open new avenues in breast cancer treatment that can proactively target and suppress breast cancer metastasis.

Natural ways to reduce chronic stress can also be an important aspect to breast cancer treatment plans. Regular exercise has many benefits and has been reported to help reduce stress. Additionally, practices like breathing exercises and meditation have been reported to reduce chronic stress. Reducing chronic stress naturally or blocking physiological pathways involved in stress with new breast cancer treatments might help reduce breast cancer progression and metastasis.

Fighting Breast Cancer-Related Fatigue

Cancer patients, including breast cancer patients, have to deal with a wide variety of side effects related to their breast cancer treatments. While many of us might first think about side effects like impaired memory, osteoporosis development, infertility, and more, the most common side effect associated with cancer treatment is cancer-related fatigue. According to some reports, 60-93% of cancer patients undergoing radiotherapy and 80-96% of cancer patients undergoing chemotherapy experience cancer-related fatigue. It has been reported that as many as 99% of breast cancer patients experience cancer-related fatigue. Unlike fatigue experienced by healthy individuals, breast cancer-related fatigue is more severe, more distressing, and is not well relieved by simply resting.

Despite the high rate of cancer-related fatigue experienced by breast cancer patients, it remains somewhat unclear what factors are associated with the severity of cancer-related fatigue and what can be done by breast cancer patients to alleviate cancer-related fatigue. A new breast cancer study explored factors possibly linked to cancer-related fatigue in 315 Chinese breast cancer patients. The breast cancer patients in this study had either completed endocrine therapy (17%) or were undergoing endocrine therapy (83%) and were asked to complete 3 questionnaires on cancer-related fatigue, physical activity levels, and dietary habits. Analysis of the relationships between these questionnaires as well as some clinical and treatment characteristics revealed that:

- Among the 315 breast cancer patients, 60% (189 patients) experienced cancer-related fatigue as mild (44.8%), moderate (9.8%) or severe (5.4%). Of these 189 patients, nearly 92% experienced a decrease in cancer-related fatigue over time.
- Factors linked to cancer related-fatigue included: greater body mass index, being premenopausal, more advanced stage of breast cancer, longer duration of endocrine therapy, physical activity, and diet. Age, type of endocrine therapy drug, alcohol intake, and smoking were not linked to breast cancer-related fatigue.
- The level of physical activity was linked to the relief of cancer-related fatigue - the majority of breast cancer patients who exercised between 10 and 20 metabolic hours per week had only mild cancer-related fatigue. In contrast, breast cancer patients who exercised less than 3.3 metabolic hours per week experienced the most severe cancer-related fatigue.
- Breast cancer patients who most closely met the Dietary Guidelines for Chinese Residents were more likely to experience only mild or moderate cancer-related fatigue, while breast cancer patients with poor dietary habits were more likely to experience more severe cancer-related fatigue.

Cancer-related fatigue can have a major impact on the quality of life of breast cancer patients, such that it interferes with a breast cancer patient's normal daily activities and even to the point of being debilitating. While some of the factors shown in this study to be linked to more severe cancer-related fatigue are beyond an person's control (menopausal status and stage of cancer development), several of the other factors are of the type individuals can actively control. According to this breast cancer study, developing healthy eating habits, getting adequate amounts of exercise and maintaining a healthy body weight were all linked to milder forms of cancer-related fatigue. So while breast cancer patients might not be able to fully reduce the cancer-related fatigue that they are experiencing, there are some changes they can make in their lifestyle that can fight back against breast cancer-related fatigue.

Breast Cancer Benefits of Eating Watercress

Isothiocyanates are plant compounds that are produced from other plant chemicals known as glucosinolates. These isothiocyanates have been well studied in relation to cancer protection, including breast cancer protection. The results of numerous research studies have reported that plant isothiocyanates can reduce cancer cell growth, induce cancer cell death, and modulate enzymes involved in cancer development. The presence of isothiocyanates in cruciferous vegetables, like broccoli, cabbage, Brussels sprouts, and kale, are what make these vegetables such important cancer-fighting foods. Another source of isothiocyanates is the vegetable watercress; however, not as much is known about the breast cancer protective benefits of watercress.

Watercress is a rich source of phenethyl isothiocyanate, which has been reported to possibly reduce cancer risk. Phenethyl isothiocyanate has been shown to decrease the activity of a protein (4E-BP1) involved in the activation of hypoxia-inducible factor (HIF), which is an important stimulator of blood vessel growth. Blood vessel growth is a vital

component of breast cancer tumor formation and growth, so the ability to reduce the activity of HIF suggests that watercress might have the potential to reduce breast cancer risk.

In a new breast cancer research study, investigators explored the breast cancer protective effects of watercress and phenethyl isothiocyanate in cell cultures and human study volunteers. For the pilot clinical study, breast cancer survivors consumed 80 grams of watercress and had blood samples collected to measure changes in phenethyl isothiocyanate and 4E-BP1 levels. The breast cancer researchers reported that in their cell culture studies, a crude extract of watercress inhibited breast cancer cell growth and reduced the activity of hypoxia-inducible factor. Analysis of blood samples from breast cancer survivors showed that eating watercress resulted in a substantial increase in blood levels of phenethyl isothiocyanate and a significant decrease in 4E-BP1, the protein important in the activation of HIF, within 6 hours of watercress consumption.

The pathway whereby 4E-BP1 activates HIF, which in turn stimulates blood vessel growth in cancer tumors, including breast cancer tumors, is a potentially important pathway for breast cancer development and growth. Breast cancer therapies or dietary interventions that can block this pathway might have an important role in breast cancer protection. This new breast cancer research study suggests that dietary consumption of watercress, a cruciferous vegetable rich in phenethyl isothiocyanate, might fight breast cancer by inhibiting this breast cancer pathway. While the results of this study were positive, this was a small pilot study of 9 breast cancer survivors. Future, larger, studies will be needed to confirm the potential benefits of consuming watercress for breast cancer protection. However, as a member of the cruciferous vegetable family, it is quite possible that watercress will have similar cancer-fighting benefits.

Obesity Increases Risk of Advanced Breast Cancer

As I have mentioned in several other newsletters and blog posts, being overweight or obese is a major risk factor for developing breast cancer. For example, research studies have reported that being overweight can increase breast cancer risk by about 50% and gaining more than 10 lbs as an adult can increase breast cancer risk by about 60%. This relationship between being overweight or obese and increased breast cancer risk appears to be due to the dramatically higher levels of growth and inflammation factors in obese patients.

New breast cancer research has explored the possible relationship between obesity and the risk for advanced stages of breast cancer. In this new breast cancer study, investigators examined pathological, clinical, and demographic information from 831 women diagnosed with their first primary invasive breast cancer. Relationships between body mass index and breast cancer stage and grade were analyzed. The breast cancer researchers reported that compared to normal weight women, obese women had an 80% greater risk of developing advanced stages (Stage III and IV) of breast cancer. Additionally, obese women had an 80% greater risk of having a poorly differentiated grade of breast cancer.

The results of this new breast cancer research provide us with important information regarding the relationship between obesity and breast cancer severity. Based on this study, being obese puts a person at greater risk for more severe stages of breast cancer. Additionally, being obese puts a person at increased risk for a higher grade of breast cancer tumors. Poorly differentiated breast cancers are generally considered to be more aggressive and breast cancer patients with poorly differentiated breast cancers typically have a worse prognosis. Overall, these study results continue to confirm the link between obesity and breast cancer risk and emphasize the importance of maintaining a healthy body weight throughout life.

Vitamin D Metabolism Is Deregulated During Breast Cancer Development

As I have mentioned previously, getting enough vitamin D appears to be important for reducing breast cancer risk. The benefit of vitamin D in the fight against breast cancer has been reported to be due to the ability of vitamin D to modulate cell growth, cell death, and invasion. However, the regulation of vitamin D metabolism in breast tissues, particularly during breast cancer development are less clear.

Vitamin D metabolism and action is generally regulated through the vitamin D receptor and two enzymes, CYP27B1 and CYP24A1. The first of these enzymes, CYP27B1, is responsible for the synthesis of active vitamin D, while the second of these enzymes, CYP24A1, is involved in the breakdown of vitamin D. Therefore, the level and activity of these two enzymes help determine the amount of vitamin D available to bind to vitamin D receptors. A new breast cancer research study has explored the relationship between these factors in normal, benign, and malignant breast tissue samples. For this breast cancer research study, investigators analyzed the presence of the vitamin D receptor and the two vitamin D metabolic enzymes in 29 normal breast tissues samples, 379 samples from benign breast lesions, 189 samples from in situ breast cancers, and 350 samples from invasive breast cancers. The breast cancer researchers reported:

- The vitamin D receptor was present at high levels in normal breast tissue samples (100%) and in benign lesions (~94%); however, vitamin D receptor levels were reduced in tissues from in situ breast cancer (47%) and invasive breast cancer (56%) samples.
- The enzyme responsible for the production of active vitamin D, CYP27B1, was present in generally stable levels (64% of normal breast tissue samples, 56% of benign lesion samples, and 66% of in situ breast cancer samples); however, expression of this enzyme was reduced to 45% of invasive breast cancer samples.
- CYP24A1, the enzyme responsible for the breakdown of vitamin D, is present in a greater percent of breast cancer samples. The expression levels of this enzyme were low in normal (30%) and benign (19%) breast tissue samples, but increased in invasive and in situ breast cancers (54-56%).

This is an important breast cancer research study showing us how vitamin D metabolism is altered during breast cancer development. According to the results of this study, normal breast tissues and benign lesions have high levels of vitamin D receptors, relatively high levels of the enzyme responsible for the synthesis of active vitamin D, and low levels of the enzyme responsible for vitamin D breakdown. This translates to a higher level of vitamin D available to bind to a high level of receptors and exert possible protective effects. In contrast, breast cancer tissues show lower levels of the vitamin D receptor, lower levels of the vitamin D synthesis enzyme, and higher levels of the vitamin D breakdown enzyme. This profile in breast cancer tissues translates to a lower level of vitamin D and a reduced ability to exert protective effects. This deregulation of vitamin D metabolism towards lower vitamin D availability and action appears to favor breast cancer development. Finding ways to re-balance vitamin D metabolism or prevent the deregulation of vitamin D metabolism during the early stages of breast cancer might become an important part of future breast cancer therapy.

Alcohol Consumption Increases Risk of Breast Cancer Subtypes

Previous research has clearly shown us that alcohol consumption increases breast cancer risk. This is true for even small amounts of alcohol consumption, which in contrast has been reported to have heart health benefits. However, it is less clear whether alcohol consumption affects the risk for different forms of breast cancer differently.

A new breast cancer research study examined the impact of alcohol consumption on overall invasive breast cancer risk as well as the risk for invasive lobular carcinoma and invasive ductal carcinoma. For this study, breast cancer researchers collected information gathered from over 87,000 postmenopausal women who took part in the Women's Health Initiative Observational Study and assessed the relationship between alcohol consumption and breast cancer incidence (nearly 3,000 breast cancer patients were diagnosed during follow up). The study investigators reported:

- Alcohol consumption was positively linked to overall breast cancer risk, risk for invasive lobular carcinoma, and hormone receptor-positive breast cancer risk.
- Consuming alcohol was more strongly linked to hormone receptor-positive breast cancers than hormone receptor-negative breast cancers.
- Postmenopausal women who drank 7 or more alcoholic drinks per week were nearly twice as likely to develop hormone receptor-positive lobular carcinoma compared to postmenopausal women who did not consume any alcohol.
- Consuming at least one alcoholic beverage per day was also associated with a smaller (about 14%) increase in hormone receptor-positive invasive ductal carcinoma compared to not consuming alcohol.

Overall, this study continues to confirm that even consumption of small to moderate amounts of alcohol increases overall breast cancer risk. However, this new breast cancer study suggests that alcohol consumption is linked more strongly to hormone receptor-positive breast cancers and invasive lobular breast cancers. Alcohol consumption is one of several lifestyle factors that increase breast cancer risk. Avoiding or minimizing alcohol consumption is clearly one way to effectively reduce breast cancer risk.

Citrus Fruits Might Lower Cancer Risk

If you have been reading my newsletter, you are well aware that many studies have suggested that fruits might help reduce cancer, including breast cancer, risk. As I have discussed earlier, fruits like peaches, plums, mangos, and more have been shown to reduce breast cancer cell growth or to kill breast cancer cells in culture systems. These beneficial effects of fruits appear to be due to their various antioxidant phytochemicals.

Researchers in Japan recently published the results of their investigation into possible associations between citrus fruit consumption and cancer incidence. For this study, citrus consumption and cancer incidence was assessed in over 42,000 Japanese adults between 40-79 years of age. Between 1995 and 2003, 3,398 cancer cases were identified. Relative risks of cancer incidence were calculated for different levels of citrus fruit consumption: 'never', 'occasionally', '1-2 times/week', '3-4 times/week', and daily. The cancer investigators reported that:

- When all volunteers were assessed, daily citrus fruit consumption was associated with an 11% reduction in all-cancer incidence.
- Daily citrus fruit consumption was linked to a 14% reduction in all-cancer risk in men and a 7% reduction in all-cancer risk in women.
- Drinking 1 or more cups of green tea per day in addition to eating citrus fruit daily reduced all-cancer risk even more: 17% for all volunteers combined, 17% risk reduction in men, 18% reduction in risk for women.

This new cancer study continues to support the cancer fighting benefits of fruit consumption in general and citrus fruit consumption specifically. Furthermore, including both green tea and citrus fruit as part of one's healthy eating pattern had enhanced cancer fighting benefits. While this study was not specific to breast cancer and breast cancer incidence was not discussed in the study summary, previous studies have shown that many fruits and green tea have breast cancer fighting benefits. Phytochemicals with antioxidant and anti-inflammatory properties found in these fruits are likely to be at least partly responsible for the cancer fighting properties of citrus fruits.

High-Fat Diet During Puberty Might Increase Breast Cancer Risk

Puberty is a critical developmental stage of life during which many changes take place, including changes in breast tissue. Breast tissue changes include the development and growth of ducts and glandular tissue, structures that can be sensitive to many environmental and dietary factors.

New breast cancer research from Michigan State University's Breast Cancer and the Environment Research Center examined the impact of high-fat diets during puberty in mice on breast development. For this study, two strains of mice were fed either a high-fat diet or a control diet during weeks 3-7 or weeks 10-14 of age. Changes in body weight, body fat, and breast tissue development were measured. In one strain of mice, a high-fat diet during puberty resulted in an increase in body weight and body fat, a reduction in breast duct development, and a reduction in breast cell growth. In the second strain of mice, feeding a high-fat diet during puberty had no effect on body weight or body fat, but stimulated an increase in breast cell growth. Additionally, a recent press release from these breast cancer researchers reports that feeding a high-fat diet to mice during puberty increases the production of inflammatory products in the breast tissue of adult mice, which might make them more susceptible to breast cancer.

These are very interesting results indicating that dietary choices during puberty might have a life-long impact on breast cancer risk. In this particular case, it appears that consuming a high-fat diet during puberty causes changes that might increase breast cancer risk. This is particularly important to keep in mind when we consider that a recent study reported that 70% of children eating school lunches consume more saturated fat than recommended by the Institute of Medicine. Additional research will be needed to more clearly define the potential relationship between high-fat diets during puberty and breast cancer risk. Initial plans from MSU indicate that these breast cancer researchers will examine the impact of a high-fat diet during puberty in mouse models of breast cancer, which will be a good first step.

Coffee Suppresses Oxidative DNA Damage

Numerous studies have suggested that drinking coffee might have a variety of health benefits, including a reduction in the risk of some cancers. This potential reduction in cancer risk has been thought to be due to the polyphenolic antioxidants present in coffee. Because of the level of coffee consumption by the population, coffee appears to be one of the richest sources of antioxidants, particularly the antioxidant caffeic acid, in our diet. While the potential health benefits of coffee are thought to be due to its antioxidants, the full mechanism remains uncertain.

A new cancer research study tested the idea that coffee's potential health benefits might be due at least in part to protection of cellular DNA from oxidative damage. To test their theory, the study investigators assigned 38 volunteers to either drink 800 ml (nearly 3.5 cups) of coffee per day or 3.5 cups of water per day over a 5-day period. To assess the antioxidant and DNA effects of coffee consumption, the study investigators measured DNA damage in circulating white blood cells and measured blood levels of several markers of

antioxidant status. The researchers reported that even though coffee consumption did not change any of the antioxidant markers in the blood, DNA damage was reduced by about 12%.

Since DNA damage and the inability to repair it can lead to DNA mutation and the development of cancer, factors that can protect DNA from oxidative damage have the potential to reduce cancer risk. This new cancer research study suggests that daily consumption of coffee and its antioxidant polyphenols might protect DNA from oxidative damage. This DNA-protective effect of coffee is likely to be one of the reasons for the possible health benefits of moderate coffee consumption.

Prophylactic Surgery Lowers Breast Cancer Risk in BRCA Mutation Carriers

Breast cancer development is a complex process that involves many factors. One such factor involves mutations to the BRCA1 and BRCA2 genes. Women who carry either the BRCA1 or BRCA2 gene mutations are at about a 60-80% increased risk for breast cancer. Women with BRCA gene mutations are often faced with the tremendously difficult decision of whether to undergo a mastectomy in order to reduce their risk for developing breast cancer. Previous research has reported that prophylactic mastectomy reduces breast cancer risk in women with BRCA gene mutations; however, it has been unclear whether such breast cancer prevention surgery affects BRCA1 and BRCA2 gene mutations carriers differently and the impact of such surgery on survival benefits.

A new cancer study published in the *Journal of the American Medical Association* explored these questions and more. Investigators studied nearly 2,500 women who carried the BRCA1 or BRCA2 mutations to determine the risk-reducing benefits of breast removal and ovary removal. The women in the study were followed for about 4 years. A number of important findings were reported; some of them are outlined below:

- No breast cancers were detected in the group of women who elected to undergo prophylactic mastectomy, while 7% (98 women) of the women in the group that did not have a prophylactic mastectomy developed breast cancer.
- Among women who chose to have their ovaries removed, risk for a first diagnosis of breast cancer was reduced by 37% in BRCA1 gene mutation carriers and by 64% in BRCA2 gene mutation carriers. This benefit appeared to only be among women who had elected to have their ovaries removed before 50 years of age.
- In women carrying the BRCA gene mutations who had a previous breast cancer, having their ovaries removed did not reduce their risk of developing a second primary breast cancer.
- Women with BRCA gene mutations who elected to have their ovaries removed to reduce their cancer risk also were had a 60% lower risk for all-cause mortality, 56% lower risk of death due to breast cancer and about an 80% lower risk of death due to ovarian cancer.

This study confirms previous smaller studies by showing that breast cancer prevention mastectomy substantially reduced breast cancer risk. While this might seem like an obvious statement, prophylactic mastectomy does not remove all breast cancer risk because some tumor cells can be left behind; however, knowing that breast cancer risk can be reduced for women carrying the BRCA gene mutations by this surgery is important. In addition, to the breast cancer risk reduction benefits observed, this study appears to be one of the first to show that the risk of dying from breast or ovarian cancer can be dramatically reduced in women with the BRCA gene mutations by having their ovaries removed. Overall this is important information for women carrying either of the BRCA gene mutations and enhances our breast cancer awareness. Knowing both the risks and benefits associated with this approach to reducing breast cancer risk is vital to women faced with making these kinds of decisions.



ABOUT DR. TABOR

Dr. Aaron Tabor, MD is the author of *FIGHT NOW*.

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After graduating from The Johns Hopkins School of Medicine, Dr. Tabor devoted his career to helping people live a life they love through medical research. Over 1 million women have already trusted Dr. Tabor for better nutrition and health education. His *prevention through nutrition* research projects with leading hospitals include cancer, weight loss, younger-looking skin, hair, and nails, glycemic-index, cholesterol, pain, and hormonal health. Dr. Tabor educates other doctors about diet and lifestyle research as the Diet & Alternative Medicine Section Editor for *The Journal of Medicine*. He has authored numerous books, papers, and patents in the fields of medicine and nutrition. His recent co-edited book *Nutritional Cosmetics: Beauty from Within* (Elsevier) is the first medical textbook on “inside-out makeover” science—foods and supplements to make you look younger from the inside out. L’Oréal, Nestlé, and others contributed to this cutting-edge work. Dr. Tabor is Founder of Gene Facelift, a Johns Hopkins’ biotech spin-off developing anti-aging and anti-wrinkle gene therapy drugs. Gene Facelift’s drug technology is designed to replace damaged skin DNA in order to heal wrinkles and reverse the aging process.

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