Prevention and Treatment of Breast Cancer

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BACKGROUND

Worldwide, more women get breast cancer than any other type of cancer.[1] In the US, breast cancer makes up 30% of all cancers in women.[2] While deaths from breast cancer have decreased, in part due to increased efforts at early detection, we are still in need of more effective treatments with fewer side effects. Most of all, more knowledge is needed to help prevent breast cancer in those of high risk. Fortunately, there are many diet and lifestyle practices that may help to decrease personal risk of breast cancer. While undergoing cancer therapy, it is important to discuss any dietary or lifestyle practices with an oncologist before starting them, in order to avoid potential interactions with conventional treatment.

RISK FACTORS

There are many known risk factors for developing breast cancer, one of which is being born female. Others include current age, as 40.95% of new cases occur in women 40 or older;[3] age of menstruation onset, as younger is a higher risk;[4] age at first giving birth, as older is higher risk;[4] and age of menopause, as older is high risk.[4] Breastfeeding is protective against breast cancer, and for every year of breastfeeding, breast cancer risk decreases by 4.3%.[5] Nulliparity, or never having given birth, increases breast cancer risk.[4]

A personal history of breast cancer on one side increases the risk of developing it on the other side,[6,7] and a family history of breast cancer in a first-degree relative also increases risk.[4] (First degree relatives include parents, offspring, and siblings.) The risk of developing breast cancer is four times higher with one first-degree relative and five times higher with two or more first degree relatives with breast cancer.[4]

Ovarian cancer in a first degree relative also increases the risk of breast cancer, particularly if they are younger than age 50 at the time of diagnosis, as this is often related to BRCA1 and BRCA2 genes. BRCA1 and BRCA2 mutations increase the risk of both breast and ovarian cancers.[4] Variations in other genes such as PTEN, TP53, CHEK2, BRIP1, ATM, RAD51C and PALB2 may also increase breast cancer risk.[8]

Oral contraceptives have been shown to increase the risk of breast and cervical cancers, but decrease the risk of endometrial and ovarian cancers. Those currently using oral contraceptives have a 24% increase in breast cancer risk, which decreases with time. Those who have ever used oral contraceptives have a slight increase in breast cancer risk (7%) which also decreases with time. Ten years after stopping oral contraceptives, the risk is so small that it is no longer measurable.[5,9]

Hormone replacement therapy (HRT) may also increase the risk of breast cancer. The Women's Health Initiative began in 1993 to examine the benefits and risks of HRT. It compared the safety and effectiveness of estrogen plus progesterone to placebo. While it was scheduled to run for 8.5 years, it was stopped after five due to an unacceptable rate of adverse events. Rates of heart attack, stroke, pulmonary embolism (blood clot in lungs), and breast cancer all increased, while rates of hip fractures and colorectal cancers decreased.[10] A meta-analysis ten years later showed a 14% increased risk of breast cancer with HRT, though the studies were observational rather than randomized and controlled.[11] A later randomized controlled trial of post menopausal women with hysterectomy showed that estrogen-only HRT appeared to decrease the risk of breast cancer, though this may not apply to women who still have their uterus.[12]

Xenoestrogen exposure (chemicals similar to estrogen in the environment) may increase the risk of ER+ breast cancer. Examples include certain chemicals such as some pesticides, bisphenol A (BPA), polychlorinated biphenyls (PCBs), and parabens. The most well-known is perhaps BPA, an ingredient in soft plastics and a liner in many canned foods. Data suggest that BPA may not only increase the risk of hormonally-driven cancers such as breast, ovary and prostate cancer, but may also increase the odds of progression and chemotherapy resistance.[13,14] Other studies of BPA's role in breast cancer risk have been less conclusive, and more studies are needed. PCB 138, however, is significantly associated with increased breast cancer risk.[15] Parabens, often found in cosmetics, have been shown to increase breast cancer cell growth in laboratory studies.[16] The Environmental Working Group has a cosmetics database that is a good resource for safer cosmetics that are free of parabens and other problematic ingredients.[17] While some sources have suggested a link between deodorants and/or antiperspirants and breast cancer risk, this remains unconfirmed, though more studies are needed.[18] Regardless, avoiding xenoestrogens such as BPA and parabens is a wise choice for cancer prevention.

Dietary choices may also affect the risk of breast cancer. Higher intake of total meat, red meat, and processed meat are linked with an increased breast cancer risk.[12] High glycemic foods (simple carbs) may also increase breast cancer risk.[12] A higher intake of fruits, vegetables, and complex carbohydrates is protective, and a lower intake of saturated fats and overall calories is also protective.[19] It is recommended to eat a nutritious and balanced diet, limit alcohol, lose weight if needed, and avoid post menopausal weight gain, as obesity also increases risk.[20,21] Lifestyle choices may also increase the risk of breast cancer, including alcohol consumption and smoking.[22,23,24] Exposure to secondhand smoke also increases risk.[25] Other factors that may increase breast cancer risk are working the night shift,[26] exposure to the HPV and EBV viruses,[27,28] and exposure to radiation or environmental pollutants.[29,30,31]

SCREENING

Screening largely consists of regular breast self-exams, clinical breast exams, and mammograms. In the past, self-exams were recommended monthly, though both the American Cancer Society (ACS) and the United States Preventive Services Task Force (USPSTF) no longer recommend them as the practice has not been shown to decrease deaths. It is still a good idea to be familiar with one's body and what is normal to be able to notice when something is different. Similarly, the ACS and USPSTF (whose recommendations determine most insurance coverage) have dropped the official recommendation for yearly clinical breast exams, as it has not been shown to decrease deaths at the population level. The USPSTF recommends biennial (every other year) mammograms for women aged 50-74, but acknowledges that it may make sense for some women to begin screening at age 40.[32]

A mammogram is a low-dose x-ray. The greatest benefit in lives saved through mammograms occurs in ages 60-69, and breast cancer risk is less, though not

absent, outside of this age bracket.[32] Various groups have different screening recommendations, and it should be kept in mind that a mammogram can find a cancerous tumor approximately 2 years before it can be felt as a lump, either by the individual or by their health care professional.[33] Some meta-analyses have estimated the lives saved by mammograms to be as high as 33%,[34] while others estimate the rates of over diagnosis to be as high as 52%.[35] The risks of a false positive and unnecessary procedures need to be balanced with the benefits of early detection.

SIGNS & SYMPTOMS

Aside from a breast lump, common signs and symptoms of breast cancer include a change in breast size or shape, a change in skin over the breast, and recent or new nipple inversion. Nipple discharge (outside of normal lactation) is also of concern, particularly if the discharge contains signs of blood. A new lump in the axilla (armpit) is also a concerning sign, as that is where lymph from the breast drains. Only 5% of cancerous lumps are painful when pressed. While bone pain or difficulty breathing are not symptoms of breast cancer itself, they may be signs of its spread.[36]

DIAGNOSIS

While yearly clinical breast exams are no longer recommended for all women, the clinical breast exam is a vital first step in diagnosis. The health care professional will be looking for any of the visual changes mentioned under "Signs & Symptoms" as well as other characteristics. A hard lump with irregular borders is more likely to be cancerous, as is one that is tightly attached to either skin or muscle.[36]

The next step in diagnosis is a screening mammogram, if one has not already occurred, followed by a diagnostic mammogram. Diagnostic mammograms are more focused on the area of the lump and often contain multiple views. When additional imaging is needed, there are several options.

A breast ultrasound, while unable to detect cancerous calcifications, may be helpful in diagnosing non-cancerous breast lumps such as cysts. It is also helpful in guiding needle biopsies. Breast MRIs are sometimes used to detect breast cancer in women at high risk and in younger women with dense breast tissue. MRIs are used for followup testing in cases where the mammogram was insufficient. It can also be used to monitor the response to chemotherapy.[36]

Nuclear testing such as scintimammography can be used in addition to mammogram when the mammogram is inconclusive. It can be especially useful in women with dense breasts, breast implants, or postoperative scar tissue. PET scans are used to find changes in angiogenesis (new blood vessel formation) that supply tumors. It can also be combined with CT to find signs that the cancer has spread to lymph nodes.[36]

Lastly, there is breast thermography. While it may be useful in some cases, it is not considered effective as either a stand-alone screening tool or as a replacement for mammograms. As a diagnostic test, its sensitivity is quite low (it will only accurately identify 85.7% of breast cancer tumors) and its specificity is even lower (it can only accurately rule out cancer in 78.5% of people who do not have it).[37,38] Baseline images are for needed for comparison, so the test would need to be performed on two separate occasions to give useful information. Many insurances will not cover this, and it can be expensive.

The next diagnostic step after imaging is biopsy. Fine needle biopsies are used to remove fluid samples while core needle biopsies are used to remove tissue samples. Excisional biopsies occur later, with surgical removal of the tumor and lymph node(s).

There are several types of breast cancers and different ways of categorizing them. Breast cancer can be classified by location and/or behavior, such as ductal carcinoma in situ, invasive ductal carcinoma, inflammatory breast cancer, or metastatic breast cancer. Breast cancer can also be categorized by the presence or absence of specific hormone receptors.

Tumor subtypes focus on the presence or absence of estrogen receptors (ER), progesterone receptors (PR) and human epidermal growth factor receptor 2 (HER2). Understanding the differences in hormone receptor positive or negative breast cancer has led to more targeted and effective treatments. The majority of breast cancer tumors are estrogen receptor positive (ER+). New therapies have been developed specific to HER2 positive breast cancer (HER2+). Triple-negative breast cancer lacks all three types of receptors – estrogen , progesterone, and HER2.[39]

While there are different grading systems, they all refer to the visual normality or abnormality of the cancer cells. The more abnormal, the more serious. Grades I-III are used, with grade III the most severe. Staging refers to the amount of spread. Staging uses the Tumor, Node, Metastasis (TNM) system. T refers to tumor size, N to lymph node involvement, and M to metastasis. Zeros are also used, so a tumor with mildly abnormal cells but without lymph node involvement or metastasis would be classified as T1N0M0. Along with grading and staging, receptor status is also designated. ER+ refers to the presence of estrogen receptors within the tumor, PR+ to the presence of progesterone receptors, and HER2+ to the presence of human endothelial growth factor 1 receptors. ER(-), PR(-), and HER2(-) refer to the absence of such receptors, and many cancers have some receptors but not others.[40]

It is worth mentioning a new method of initial diagnosis that is not yet widely available. Dogs have been trained to sniff breath, urine, and serum (blood) for various diseases including breast cancer.[41] The InSitu Foundation trains dogs to detect cancer at the earliest stages when the cancer is "in situ" and has not yet spread. In one double-blinded canine study, the authors used a food reward to train 5 ordinary house dogs to be able to distinguish between breath samples of 31 breast cancer patients, 55 lung cancer patients, and 83 healthy controls. Dogs correctly lay down in front of the cancerous samples and ignored the healthy samples.[42] In another article, two dogs were trained to sniff skin secretions on breast compresses that had been worn overnight. The dogs were able to correctly recognize 90.3% of the breast cancer samples.[43] Some studies show both sensitivity and specificity to be in the range of 95-99%,[42] and a clinical trial titled "Transcutaneous breast cancer diagnosis by canine odorology" is now recruiting.[44]

CONVENTIONAL TREATMENT

There are five main categories of cancer treatment:

surgery, radiation, chemotherapy, biological therapy, and endocrine therapy. Sometimes they are simplified as surgery, radiation, and chemotherapy, though chemotherapy is only one type of medication used in cancer treatment.

Surgery can consist of a lumpectomy or a total mastectomy, depending on the tumor's size, location, and degree of spread. Radiation is often used to eliminate any remaining cancer cells and decrease the risk of recurrence.

Radiation can applied be to the whole breast in the form of external-beam radiotherapy (EBRT) or only part of the breast in partial breast irradiation (PBI). Partial breast irradiation is more targeted.[45]

Chemotherapy can consist of one medication or a combination of medications, most of which interfere with the cell cycle and therefore the cancer's growth and spread. Chemotherapy medications commonly used in breast cancer include docetaxel, doxorubicin, paclitaxel, and capecitabine.[46]

Biological therapies are derived from cells, tissues, or proteins. Targeted antibodies in cancer treatment include trastuzumab, pertuzumab, lapatinib, and neratinib, and have been particularly useful in treating HER2+ tumors.[46]

Endocrine therapy includes several types of medications. Tamoxifen and raloxifene are known as selective estrogen receptor modulators (SERM). They block estrogen receptors, which can be very useful in ER+breast cancer. Medications such as anastrozole and letrozole are known as aromatase inhibitors (AI) and block estrogen production from fat tissue. Luteinizing hormone-releasing hormone agonists (LHRHa) such as goserelin or leuprolide block estrogen production from the ovaries.[46]

DIET

GENERAL RECOMMENDATIONS

A nutritious diet high in fruits and vegetables while low in saturated fat is recommended for breast cancer prevention.

Fats, especially unhealthy fats, increase the risk of breast cancer. A high intake of **saturated fat** increases the risk of breast cancer[47,48] and a high intake of **trans fats** may do the same. Trans fats should be minimized as much as possible for overall health, as their role in cardiovascular disease and diabetes is well known. While one meta-analysis did not show an association between trans fats intake and breast cancer risk,[49] another found that post menopausal women with higher serum (blood) levels of trans fats had a higher risk of breast cancer.[50]

Meat is also an independent risk factor for breast cancer. Most meta-analyses (studies of multiple studies) found an increased risk of breast cancer with a higher intake of red and/or processed meat.[51,52,53] Cooked and especially charred meats are known to increase the risk of colorectal cancer due to the heterocyclic amine (HCA) chemicals produced during the cooking process. While older studies implied a potential association between these chemicals and breast cancer, particularly in post menopausal women and those with certain genetic variants,[54,55] more recent studies have not confirmed this.[56,57,58] Given the robust evidence for the healthfulness of plant-based diets,[59,60] it seems wise to consume meat in moderation and to avoid charred meat. When consumed, organic meats may be of lower risk. One meta-analysis found a healthier fatty acid profile in organic vs. conventionally-raised meat[61] while another found the same in organic milk vs. conventional.[62]

Nitrates and **nitrites** are found in processed meats such as bacon, hot dogs and lunch meats, which are associated with an increased risk of gastrointestinal cancer. While they do not appear to be linked to an increased risk of breast cancer specifically, according to a meta-analysis,[63] it is probably still best to avoid them, given their association with other cancer types.

Alcohol should also be consumed in moderation, if at all. One meta-analysis including 25 cohort studies found that > 20g/day (2 drinks/day) was associated with an increased risk of breast cancer mortality, though not with an increased risk of recurrence.[64] Another meta-analysis found that even very light (≤0.5 drinks/day) and light drinking (≤1 drink/day) mildly increased the risk of breast cancer.[65] In a recent meta-analysis of prior meta-analyses, they found an increased risk of breast cancer even at low levels of alcohol consumption.[66]

Obesity is also a significant cancer risk. A meta-analysis including 82 studies with 213,075 participants found obesity to be strongly associated with increased risk of breast cancer and decreased survival from the same.[67] Randomized controlled trials are needed to determine the potential impact of weight loss and weight maintenance on these risks.

Carbohydrate intake may also impact the risk of breast cancer. In a prospective study of 62,739 French women, while there wasn't an overall increased risk in breast cancer based on carbohydrate consumption alone, there was an increased risk of breast cancer with high carbohydrate intake in overweight women and those with large waist circumference. Increased intake of simple carbohydrates and sugars may also be associated with increased risk of estrogen receptor-negative breast cancer.[68] While a meta-analysis agreed that increased simple carbohydrate intake was linked with post menopausal and hormone receptor negative breast cancer, they did not find a direct correlation with body mass index (BMI).[69]

Organic foods are healthful and may decrease cancer risk. The prevailing scientific view regarding conventional vs. organic agriculture is that "the dose makes the poison." While it is acknowledged that pesticide exposure can harm those responsible for applying it to crops, it is often proposed that residual pesticides on food are minimal and therefore harmless. While there is some evidence that organic food consumption may decrease the risks of conditions as diverse as metabolic syndrome, obesity, and non-Hodgkin lymphoma, study authors point out that people who make healthier food choices tend to have additional health behaviors such as exercise that may play a role.[70,71] The Nutri-Net Santé prospective cohort study with 68,946 participants found that a higher intake of organic food led to a lower risk of cancer, including breast cancer, though more research is needed.[72]

In the meantime, if eating exclusively organic produce doesn't fit within your budget, you might check the Environmental Working Group's current edition of the

"Dirty Dozen/Clean Fifteen" – conventionally-grown produce with the highest and lowest pesticide residues, respectively.[73] Some conventional produce is grown with heavy amounts of pesticides, while others are grown with very few. Having this knowledge will help you to choose which fruits and vegetables are most important to consume organic.

MEDITERRANEAN DIET

The Mediterranean diet consists primarily of fish, vegetables, fruits, nuts, and whole grains.[74] It is also high in mono unsaturated fats (MUFAs) from olive oil.[74] Long known for cardiovascular health, the Mediterranean diet also appears to have benefits in cancer prevention.75,76 In a single-blind, randomized clinical trial studying its impact on breast cancer risk in women with high cardiovascular risk, 4,282 women ages 60-80 were randomly assigned to a Mediterranean diet supplemented with extra virgin olive oil, a Mediterranean diet supplemented with mixed nuts, or a low-fat control diet. After an average followup of 4.8 years, the risk of developing breast cancer was highest in the low-fat control diet and lowest in the Mediterranean diet supplemented with extra-virgin olive oil.[77] A separate meta-analysis found a 6% decrease in breast cancer for those eating a Mediterranean diet.[76]

SHORT-TERM FASTING

Short-term fasting prior to and during chemotherapy may be helpful in HER2(-) breast cancer. One clinical trial was designed from evidence that short-term fasting may help to protect healthy cells against chemotherapy. The women in the study had HER2(-), stage II-III breast cancer. Seven were assigned to the short term fasting arm while the other six were assigned to eat a nutritious diet. The short term fasting group was instructed to fast for 24 hours before and after chemotherapy treatment. Seven days after chemotherapy, both red blood cell counts and platelet counts were significantly higher in the short term fasting group, indicating less toxicity to normal cells. Researchers concluded that short-term fasting during chemotherapy was well-tolerated in study participants and reduced blood measures of toxicity from chemotherapy, specifically TAC chemotherapy (Taxotere/docetaxel, Adriamycin/doxorubicin, and cyclophosphamide).[78]

A second, larger study with 131 patients with HER2(-) stage II/III breast cancer showed similar results. The patients were randomized to either a fasting-mimicking diet or an assigned nutritious diet for 3 days before and during chemotherapy. The fasting mimicking diet consisted of a 4-day plant-based amino acid diet with broths and liquids. The treatment group had less chemotherapy-induced damage in Tlymphocytes, and was much more likely to have their tumors respond to radiotherapy. Fasting has been shown to protect mice with cancer from chemotherapy side effects and this appears to be the case in humans as well. Researchers concluded that it is safe and effective for patients with a normal body weight prior to chemotherapy. Specific chemotherapy varied within the study. The only significant issues with the study were that some in the fasting arm dropped out due to dislike of specific diet components, and some in the non-fasting group decided to fast instead of adhering to the assigned nutritious diet. More studies with larger groups are needed.[79]

EXERCISE

GENERAL EXERCISE

Exercise may play a significant role in breast cancer prevention and recurrence. A recent meta-analysis (study of multiple studies) found that study participants with the highest level of physical activity had the lowest risk of premenopausal breast cancer,[80] though others have found no association.[81,82,83,84,85] According to researchers, evidence showing that total physical activity decreases premenopausal breast cancer risk is limited, though not absent.[86]

Regarding post menopausal risk, the evidence is much more consistent. In a meta-analysis of 8 studies comparing levels of physical activity to breast cancer risk, the highest level of physical activity showed a 13% decreased risk of post menopausal breast cancer, as compared to the lowest level of physical activity. This result was considered statistically significant.[80] Other risk factors such as age, BMI, hormone therapy and alcohol intake were accounted for in all of the meta-analyses. Researchers concluded that total physical activity is most likely protective against post menopausal breast cancer.[86]

VIGOROUS EXERCISE

One meta-analysis of 6 studies examined the link between vigorous exercise and premenopausal cancer, While the highest level of vigorous exercise was associated with a 17% decrease in risk of premenopausal breast cancer compared to the lowest level, dose-response studies showed no significant association between increments of 30 minutes vigorous exercise daily and the risk of premenopausal breast cancer.[86]

Regarding post menopausal breast cancer, a meta-analysis examining 12 studies comparing the highest with the lowest levels of vigorous exercise found a 10% decrease in post menopausal breast cancer risk. This result was considered to be statistically significant.[86] Researchers concluded that vigorous physical activity probably protects against both premenopausal and post menopausal breast cancer.[86]

SURVIVOR BENEFITS

Exercise is also beneficial to breast cancer survivors. Twelve months or more after breast cancer diagnosis, there is evidence that higher levels of exercise are associated with a decreased risk of death, though randomized controlled trials are needed.[87]

One meta-analysis showed that exercise decreases inflammatory markers, with a combination of aerobic and resistance training having the greatest effect.[88] Another meta-analysis included 11 randomized controlled trials with 458 breast cancer patients. Four of the studies measured arm circumference and found a statistically significant decrease in breast-cancer related lymphedema (BCRL), with moderate, dynamic, and high-frequency exercise being the most beneficial.[89] Another meta-analysis indicated that a combination of physical and mind-body exercise resulted in statistically significant improvements in sleep quality, with no differences between breast cancer patients undergoing current treatment and breast cancer survivors who had completed treatment.[90]

TYPES OF EXERCISE

Dragon boating as physical therapy for breast cancer survivors was founded by sports medicine specialist Don McKenzi in 1996. It has since become a worldwide movement. Dragon boating is an engaging way for breast cancer survivors to undergo strenuous upper-body activity in a socially supportive environment. While there are few randomized controlled trials on this form of exercise, it has been shown to contribute to social support, develop social relationships, and support post-traumatic growth.[91] Other studies have shown improvements in cancer related fatigue, health-related quality of life, and improved well-being in multiple dimensions (physical, emotional, spiritual, and functional).[92] One study examined myocardial function in a 4-year followup of 55 breast cancer survivors. Researchers concluded that breast cancer survivors had significantly improved diastolic heart function after 4 years of dragon boating.[93] An observational study examined the effectiveness of dragon boating in reducing lymphedema, a common complication of breast cancer after surgery and/or radiation therapy. There were two groups of women, one who participated in dragon boating for at least 6 months, and the other who participated in other forms of exercise for the same amount of time. Arm circumference was measured to estimate lymphedema. Lymphedema in the dragon boating group was only 4%, compared to 26% of the regular exercise group.[94] A retrospective observational study with 64 participants concluded that dragon boating is helpful in reducing late arm impairment following surgery for breast cancer.[95]

Yoga is a healing art and a popular form of exercise that may be of benefit to breast cancer patients. One meta-analysis of randomized controlled trials included 13 studies, all with cancer patients and most with breast cancer. Researchers found significant improvements in emotional distress, depression and anxiety, as well as moderate improvements in emotional and social function, fatigue, and overall quality of life.[96] Another meta-analysis examined fatigue in both breast cancer patients and survivors. Ten studies with a total of 583 participants were included. There was a statistically significant decrease in fatigue among those doing yoga, with some studies reporting an increased benefit for those attending more classes. Researchers concluded that yoga may be helpful in reducing cancer-related fatigue, but that more studies are needed.[97] Other meta-analyses revealed significant improvements in gastrointestinal symptoms, depression, and anxiety, though the anxiety benefit was seen only after 3 months of practice.[98] Another meta-analysis included 17 studies with 2,183 breast cancer patients, 1112 assigned to the yoga group and 1,071 to the control group. They found that supervised yoga significantly decreased chemotherapy related fatigue after treatment had concluded, but only mildly decreased it during ongoing treatment. They also found that yoga moderately improved physical and cognitive fatigue, and mildly improved mental fatigue. Programs ran from 6 to 8 weeks, with greater benefits to fatigue in the 8-week program.[99]

Tai Chi & Qigong are healing arts with therapeutic effects, as shown is several recent meta-analyses. One meta-analysis examined the role of qigong or tai chi in cancer care. Those in the qigong or tai chi groups had statistically significant improvements in fatigue and sleep quality. While there were also improvements in depression, anxiety, stress, and overall quality of life, these were not considered statistically significant.[100] Another meta-analysis including 22 randomized controlled trials examined the impact of tai chi on quality of life in cancer survivors. They found moderate evidence that tai chi reduces cortisol (a stress hormone) and low-level evidence suggesting that physical and mental quality of life, as well as sleep, may be improved from tai chi practice.[101] Another meta-analysis specifically examined fatigue levels in breast cancer patients, including 16 randomized controlled trials and a total of 1,268 participants. While they initially found that the benefits of tai chi were the same as supportive conventional care at 3 or 6 months in terms of fatigue, quality of sleep, and depression, they did find a statistically significant improvement in overall quality of life at 3 months. When the tai chi intervention was given in conjunction with supportive conventional care, there was a significant improvement in fatigue and quality of life.[102]

FOODS

FRUITS

Blueberry *(Vaccinium spp.)* contains pterostilbene, which in laboratory studies, has been shown be suppress cell growth in ER+ MCF-7 and triple-negative MDA-MB-231 breast cancer cells.[103] Both fermented and non-fermented enriched blueberry juice suppressed cancer growth, with fermented being more effective.[104] Whole blueberry powder has inhibited triple-negative MDAMB-231 breast cancer cells in the laboratory, and mice fed a 5% blueberry diet had 70% fewer metastases to lymph nodes and liver than the control mice.[105] Another mouse study showed inhibition of lung metastases.[104] In additional mouse studies, a diet supplemented with 5% blueberry powder was shown to inhibit tumor growth.[106,107] In a prospective human study using data from the Nurses' Health Study, a higher intake of berries was associated with a lower risk of ER(-) breast cancer in postmenopausal women.[108]

Goji berry *(Lycium barbarum)*, sometimes called wolfberry, is usually consumed in dried or powdered form and can be found in the health food section. It is often considered a super food due to its impressive micronutrient content. In laboratory studies, goji berry extract was found to inhibit proliferation (growth) of ER+ MCF-7 breast cancer cells.[109]

Tart cherry juice *(Prunus cerasus)* has been found in laboratory studies to cause apoptosis (cell death) in ER+ MCF-7 breast cancer cells, attributed to the anthocyanin content.[110]

VEGETABLES

Cruciferous vegetables *(Brassica spp.)* include broccoli, cauliflower, cabbage, brussels sprouts, bok choy, and kale, among others. A meta-analysis on cruciferous vegetables and breast cancer risk examined 11 case control studies and 2 cohort studies. In this meta-analysis, high cruciferous vegetable intake was significantly associated with a decreased risk of breast cancer, which was even more pronounced in post menopausal women. The authors acknowledge that more studies with uniform parameters are needed.[111]

Indole-3-carbinol (I3C) is a natural component found in cruciferous vegetables that is available in supplement form. In a study of I3C for breast cancer prevention, 60 high risk women (both pre- and post menopausal) were assigned to I3C or placebo for 4 weeks. Doses of I3C ranged from 50-400 mg/day. Researchers concluded that 300 mg/day is the

minimum effective dose for breast cancer prevention, though more studies are needed.[112] Another study included 17 women at high risk for breast cancer, 16 pre- and 1 post-menopausal. The study began with 4 weeks of placebo followed by 4 weeks of 400 mg I3C daily, then concluded with 4 additional weeks of 800 mg I3C daily. The biochemical changes considered preventive for breast cancer were the same at both dosages (400 mg and 800 mg), leading the researchers to conclude that 400 mg/day of I3C is enough to exert a maximum protective effect.[113]

Sulforaphane is another natural component found in cruciferous vegetables. Laboratory studies have shown sulforaphane to inhibit cell growth of triple-negative MDA-MB-231, triple-negative MDA-MB-468, ER+ MCF-7, and ER+ T-47D breast cancer cells, as well as cause apoptosis (cell death).[114] Laboratory studies have shown it to inhibit growth by interfering with the cell cycle,[115,116] without harming normal breast cells,[117] and to inhibit the expression of estrogen receptor alpha protein in ER+ MCF-7 breast cancer cells.[117]

Beets *(Beta vulgaris)* may also have anticancer effects. One laboratory study compared the effects of beetroot extract and the chemotherapy doxorubicin in ER+ MCF-7 breast cancer cells. Both had cytotoxic effects, though doxorubicin was stronger, as expected. Researchers concluded that the compound betanin was likely responsible for beetroot's cytotoxic effects, that there may be a future role for beetroot extract used in combination with doxorubicin to help mitigate side effects, and that far more studies are needed.[118] Another laboratory study investigated the synergistic cytotoxicity of beetroot extract combined with doxorubicin in ER+ MCF-7 breast cancer cells. The synergistic effect was greatest at one part beetroot extract to 5 parts doxorubicin.[119] Animal and especially human studies are needed.

Beetroot extract is approved by both the FDA and EU as a food coloring, and both beets and doxorubicin share a chemical similarity that makes them red.[118] Doxorubicin is known to have cardiac side effects. In the most recent laboratory study, triple-negative MDA-MB-231 breast cancer cells and rat cardiomyocytes (heart cells) were used. Co-treatment with beetroot juice and doxorubicin led to increased cell death in cancer cells but decreased cell death in heart cells, having a protective effect.[120] Swiss chard is a subspecies of beets, and has been shown in laboratory studies to inhibit proliferation (tumor growth) in ER+ MCF-7 human breast cancer cells.121 More studies are needed in both animals and humans.

NUTS & SEEDS

Walnuts *(Juglans spp.)* may have a protective effect against breast cancer. In a laboratory study, walnut oil extract, purified walnut compounds such as alpha-linolenic acid (ALA) and beta-sitosterol, and postprandial serum (a component of blood plasma, after eating walnuts) were each tested with ER+ MCF-7 breast cancer cells. The walnut oil extract, ALA and betasitosterol all decreased proliferation of the ER+ MCF-7 breast cancer cells. Strangely enough, when serum from people who had eaten walnuts was applied to the cells, the serum from those with a lower BMI was more effective than from those with a higher BMI. Multiple gene targets were affected, and more studies are needed.[122] In another laboratory study, an alcohol extract of walnut was tested on MCF-7 ER+ breast cancer cells, MDA-MB-231 triple-negative breast cancer cells, and HeLa cervical cancer cells. The walnut extract was cytotoxic to all of the cells tested, reducing mitochondrial function (the cell's energy source) and causing apoptosis (cancer cell death).[123]

A human case-control study examined the protective effect of nut consumption (peanut, walnut and almond) on the risk of breast cancer. The participants included 97 patients with breast cancer and 104 healthy controls. While researchers concluded that lifelong high intake of nuts appeared to significantly reduce the risk of developing breast cancer, randomized controlled trials are needed to accurately determine the role of nuts, specifically walnuts, in breast cancer risk.[124] Lastly, a randomized controlled trial examined the relationship between dietary walnut consumption and tumor-related gene expression. In this 2-armed pilot clinical trial, ten women with breast lumps were randomly assigned to either the walnut consuming group or the control group. Immediately after biopsy, the five women in the walnut group began consuming 2 ounces of walnuts per day until their surgery. All breast lumps were confirmed by biopsy to be cancerous. At the time of surgery, the cancer was again biopsied, with results compared to the original biopsy. The genetic expression of 456 genes within the tumors were significantly altered in the walnut consuming group. Many of these beneficial changes favored apoptosis (cell death) and inhibited both tumor growth and tumor spread. Researchers concluded that walnut consumption may help to suppress breast cancer growth and increase survival.[125]

Flaxseed *(Linum usitatissimum)* is a plant source of phytoestrogens as well as healthful omega-3 fatty acids. A randomized double blind placebo-controlled trial examined the impact of dietary flaxseed on tumor markers in post menopausal breast cancer. In this study, 32 patients with newly diagnosed breast cancer were randomly assigned to a flaxseed muffin (25 g/day flaxseed) group or the placebo muffin group. Participants ate a daily muffin for approximately one month (32 days flaxseed, 29 days placebo) with no difference in dietary calories or micro nutrients between groups. Tumor markers were improved and apoptosis (cell death) increased in the flaxseed group but not the placebo group. Researchers concluded that dietary flaxseed has the potential to decrease tumor growth in patients with breast cancer.[126]

Another randomized controlled trial examined the effects of ground flaxseed on hormone levels. The study consisted of 99 postmenopausal women aged 57-64 who were randomly assigned to either treatment or control group. The treatment group was instructed to include 2 tbsp ground flaxseed in their diet daily. Flaxseed affected the levels of circulating sex hormones, particularly estrogens, which may be protective against breast cancer.[127] Another randomized controlled trial in 24 postmenopausal women with newly diagnosed ER+ breast cancer compared the effects of flaxseed, an aromatase inhibitor (medication that blocks some estrogen production), and a combination of both. The study took place between biopsy and breast cancer surgery, with the intervention lasting from 13-16 days. The women were randomly assigned to one of four groups: 25 g/day ground flaxseed + 1 placebo pill, 1 mg/day anastrozole, 25 g/day ground flaxseed + 1 mg anastrozole, or 1 placebo control pill. Researchers found flaxseed + anastrozole to be the most effective in reducing levels of a specific estrogen, though the effects were not statistically

significant. Researchers concluded that flaxseed may have a role in breast cancer prevention, though more studies are needed.[128]

PROTEIN

Fish, specifically fatty fish, can be a good source of omega-3 fatty acids. Fatty fish and other marine sources of omega-3s include herring, salmon, sardines, oysters, crab, trout, and tuna.[129] In a randomized controlled trial of 25 women at high risk for breast cancer with an average age of 51.9 years, participants were randomly assigned to either 4 six-ounce servings of fish weekly (such as canned salmon with albacore) or 2 one-gram capsules of omega-3 daily, for 3 months. Measurements such as BMI and waist-hip circumference were taken at baseline and at the end of the 3-month study. EPA and DHA increased in both groups, though women in the dietary fish group had a greater increase in EPA. Changes in DHA and omega-3/omega-6 ratio were the same between groups. Tissue EPA and DHA increased in both groups, without significant differences. Researchers concluded that both strategies worked to increase omega-3s in breast tissue, which may be a starting point for future breast cancer prevention trials.[130] A 2019 meta-analysis examined the protective effect of dietary omega-3 fatty fish on breast cancer risk, including 11 studies and 130,365 patients. Researchers concluded that the consumption of fatty fish rich in omega 3s was protective against breast cancer, with uncertain significance to a diverse population as the study only included Asian participants.[131]

Omega-3 fatty acids, specifically EPA and DHA, are the primary beneficial compounds in fatty fish. Plant foods high in omega-3 fatty acids also include flaxseed, chia seed, and walnuts.[129] A meta-analysis of 21 prospective cohort studies including 883,585 participants and 20,905 cases of breast cancer found that the risk of breast cancer decreased by 5% per 0.1 g/day of supplemental marine omega-3 intake, though they found no correlation between dietary fish intake and decreased risk.[132] In one meta-analysis, 6 prospective nested case-control and 5 cohort studies were examined, including 274,135 adult females from several countries and 8,331 cases of breast cancer. This meta-analysis concluded that higher omega-3 intake is associated with decreased breast cancer risk across the study populations, though the number of US studies was limited.[133] Another meta-analysis examined the dietary intake of higher omega-3 to omega-6 fatty acids and breast cancer risk in both western and Asian countries, including 913 studies with 275,264 patients. They, too, concluded that increasing the dietary intake of omega 3 to omega 6 fatty acids helps in breast cancer/ prevention.[134]

Soy *(Glycine max)* may help decrease the risk of breast cancer, though studies have been conflicting. There is significant research examining the potential protective effect of soy, and consequently many meta-analyses (studies of multiple studies) to examine. Some studies found a link between soy consumption and a decreased risk of breast cancer in both pre- and postmenopausal women; however, this was seen in Asian but not in Western women.[135,136] In other meta-analyses, each 10 g/day of tofu intake was associated with a 3%137 or a 10% decrease in breast cancer risk, respectively.[138] Each 10 g/day of tofu was associated with a 7% decrease in overall cancer death and a 9% decrease in breast cancer death.[137] One meta-analysis found a protective benefit of pre-diagnosis soy consumption on both overall survival and breast cancer survival, but no benefit of increased post-diagnosis soy consumption.[139] Another meta-analysis found evidence that high but not moderate soy consumption decreases breast cancer risk.[140] Yet another meta-analysis found that high soy intake was associated with reduced breast cancer mortality and risk of recurrence, specifically in ER(-), E+/PR+, and post-menopausal patients, though this was an Asian study and may only be applicable to Asian populations.

Some studies examined specific isoflavones from soy, such as genistein, daidzein, and biochanin. One laboratory study found that genistein was the most effective isoflavone at inhibiting angiogenesis (blood vessel formation to nourish tumor cells).[141] However, other studies have shown that soy isoflavones are not well-absorbed in humans. In a clinical trial with healthy adults, participants were assigned to consume one of the following: 50 mg of genistein, 50 mg of daidzein, or 250 mL of soymilk containing glycoside isoflavones. After 8 hours, there were no trace of genistein or daidzein isoflavones in blood plasma for any of the groups, showing that soy isoflavones are not well-absorbed.[142]

It is hypothesized that isoflavones from fermented soy products are more bioavailable and easier to absorb. Mouse studies have shown that some but not all *Lactobacillus spp.* probiotics used in fermentation have their own tumor suppressive effects, through activation of dendritic immune cells.[142] A laboratory study showed that soy milk fermented with *Lactobacillus acidophilus, Lactobacillus bulgaricus, Streptococcus lactis,* and *Bifidobacterium spp*. inhibited growth in ER+ MCF-7 and triple-negative MDA-MB- 453 breast cancer cells. This study also found the water-soluble portion of the fermented soy milk to be most effective, vs. the lipid-soluble portion with genistein and daidzein. The fermented soy milk induced apoptosis (cell death), particularly in the ER+ MCF-7 breast cancer cells.[143] Another laboratory and animal study used *Lactobacillus helveticus* in their fermentation process due to its antitumor properties, finding it particularly effective in a mouse model of ER+ breast cancer.[144]

One laboratory study found that *Lactobacillus casei Shirota* enhanced cytotoxicity by activating natural killer immune cells, which slowed tumor growth in mice with mammary (breast) cancer,[145] and a rat study showed that fermentation with Lactobacillus casei Shirota enhanced the breast cancer prevention of soymilk.[146] Human studies, however, have proven a bit more complicated. A few human clinical trials have examined the effect of soy consumed with a probiotic supplement containing *Lactobacillus acidophilus, Bifidobacterium spp*., and fructooligosaccharide, which did not increase the effectiveness of soy isoflavones.[147,148]

One randomized controlled trial examined the effects of soy isoflavones plus *Lactobacillus sporogenes* probiotic in post menopausal women. The goal of this study was to examine the safety of soy isoflavones, with their potentially phytoestrogenic effects, on the endometrium (uterus) and breast, in addition to liver function. The trial included 130 healthy post menopausal women with menopausal symptoms. They were randomly assigned to either the treatment group (60 mg soy isoflavones + *Lactobacillus sporogenes* 1 billion spores) or the control group (calcium + vitamin D3). Safety of the soy and probiotic treatment was evaluated at baseline and after 1 year;

menopausal symptoms were measured at baseline and every 3 months. After a year, there were no significant differences in breast density or liver function, though menopausal symptoms decreased in both severity and frequency.[149] Researchers concluded that soy isoflavones + *Lactobacillus sporogenes* is safe for the endometrium and breasts, as well as liver function.

It is good to know that soy isoflavones may be protective against breast cancer and effective against menopausal symptoms, without increasing risk of breast or endometrial cancers, or negatively impacting liver function. It should be kept in mind that fermentation with probiotic species may increase the protective benefits of soy.

FIBER

A meta-analysis (study of multiple studies) showed that increased dietary fiber may lead to a decreased risk of breast cancer. A total of 24 studies with 3,662,421 participants were included. For every 10g/day of fiber intake, there was a 4% decrease in breast cancer risk. Researchers concluded that dietary fiber intake was significantly associated with breast cancer risk, particularly in post-menopausal women.[150]

Another meta-analysis included 11 total studies, 4 cohort and 7 case control. These high-quality studies included a total of 131,151 participants, 11,589 of whom had breast cancer. Fiber-rich whole grain intake was associated with a decreased risk of breast cancer in both case cohort and case control studies, but the difference was only statistically significant in the case control studies. Researchers concluded that additional, larger cohort studies are needed to explore the association.[151]

OILS

Extra-virgin olive oil (EVOO) has been mentioned previously in the context of Mediterranean diets. Both Mediterranean diet groups had a decreased risk of breast cancer compared to control, but the decrease was greatest in the group supplemented with EVOO (vs. mixed nuts).[77] In an 2010 update of epidemiological findings on olive oil and cancer risk, there was a five-fold difference in risk between those consuming most dietary fats in the form of olive oil and those consuming most dietary fats in the form of butter, with olive oil protective.[152] A meta-analysis of 19 observational studies including 13,000 patients and 23,340 controls examined the protective properties of olive oil. The highest intake of olive oil was associated with the lowest risk of cancer in general and breast cancer in particular. It is unclear whether the protective effect is due to olive oil's mono-unsatured fatty acid (MUFA) content or its antioxidant content.[153] Another meta-analysis examining vegetable oil intake and breast cancer risk included five prospective cohort studies and 11 retrospective case control studies, for a total of 16 studies involving more than 150,000 women. While there wasn't an association between vegetable oils and breast cancer in general, there was an association between olive oil and breast cancer in particular. A higher intake of olive oil was associated with a reduced risk of breast cancer, though the difference was only statistically significant in the case control studies.[154]

HERBS & SPICES

Garlic *(Allium sativum)* has many health benefits. One of its active components is allicin, which needs to be processed carefully to remain stable in supplement form. One laboratory study found that 7 out of 22 stabilized allicin compounds showed antiproliferative (growth-inhibiting) effects against ER+ MCF-7 breast cancer cells.[155] Another component, diallyl trisulfide, has been shown to inhibit growth in ER+ MCF- 7 breast cancer cells and to suppress metastasis of triple-negative MDA-MB-231 breast cancer cells.[156,157] One laboratory study found that oil-soluble garlic compounds such as diallyl trisulfide are more effective than water-soluble compounds at suppressing breast cancer.[158] Another laboratory study exposed ER+ MCF-7 breast cancer cells to a mixture of the garlic compound S-allyl-L-cysteine sulfoxide (alliin) and paclitaxel. The alliin and paclitaxel worked synergistically to trigger apoptosis in ER+ MCF-7 cells.[159] In a mouse study with triple-negative MDAMB- 231 breast cancer cells, diallyl disulfide increased apoptosis (cell death), significantly reducing tumor volume and weight.[160]

Thyme *(Thymus vulgaris)* has been tested in laboratory studies, where it decreased cell survival in both ER+ MCF-7 and triple negative MDA-MB-231 breast cancer cells, decreasing cell growth and causing apoptosis (cell death). In mouse studies, tested doses of thyme decreased tumor volume by 84-85%, compared to control.[161]

Rosemary *(Rosmarinus officinalis/Salvia rosmarinus)* has inhibited the growth of several cancers in laboratory studies. The carnosic acid compound has been tested against ER+ MCF-7 cells and triple-negative MDA-MB-468 cells, suppressing cell growth and increasing apoptosis (cell death).[162,163,164,165]

Oregano *(Origanum spp.)* has been examined in both laboratory and animal studies. In ER+ MCF-7, triple-negative MDA-MB-231, and triple-negative MDAMB-468 breast cancer cells, it inhibited growth and spread. At high doses, it triggered apoptosis (cell death).[166,167] Compared to control, oregano extract decreased tumor volume in one rat study by 41%[167] and in another rat study by 44.5%.[168]

Parsley *(Petroselinum crispum)* extract has been shown in laboratory studies to inhibit proliferation (growth) and spread of ER+ MCF-7 breast cancer cells while protecting normal cells from damage.[169] Parsley extract also stimulates apoptosis (cell death).[170] Apiole and apigenin, specific compounds within parsley, have been studied in triple negative MDA-MB-231 breast cancer cells. Apiole caused cell cycle arrest (preventing tumor growth) and apigenin has antiinflammatory activity.[171,172]

Basil *(Ocimum basilicum)* and its components lupeol and eugenol have been shown in laboratory studies to have cytotoxic effects in ER+ MCF-7 and triple negative MDA-MB-231 breast cancer cells.[173] The water extract of the herb has also been shown to decrease cell survival and inhibit proliferation (spread) of ER+ MCF-7 breast cancer cells.[174]

Ginger *(Zingiber officinale)* has been shown to inhibit proliferation (growth) and cause apoptosis (cell death) in laboratory studies with ER+ MCF-7 and triple-negative MDAMB- 231 breast cancer cells.[175,176] The component 6-shogaol inhibits metastasis in triple-negative MDA-MB-231 breast cancer cells.[177,178,179] The components 6-gingerol and 10 gingerol also inhibit metastasis in triple-negative MDA-MB-231 breast cancer cells.[180,181]

Black pepper *(Piper nigrum)* has several medicinal components. Kusunokinin and piperloguminine had cytotoxic effects on triple-negative MDA-MB-468 breast cancer cells in a laboratory study. These compounds interfere with the cell cycle (inhibiting tumor growth) and trigger apoptosis (cell death).[182] Black pepper also inhibits growth of ER+ MCF-7 breast cancer cells in laboratory studies.[183] An alcohol extract rich in piperamides causes oxidative damage to DNA, leading to cell cycle arrest and apoptosis of ER+ MCF-7 cells.[184] Piperine, another medicinal component, has been shown in laboratory studies to have anti-tumor effects in HER2+ over expressing breast cancer cells, inhibiting growth and stimulating apoptosis (cell death).[185] In a rat study, rats with mammary tumors were treated with piperine-free black pepper extract. Cancer cells were harmed while normal cells were not, and the growth rate of mammary tumors was much slower than control.[186]

Turmeric *(Curcuma longa)* has also been studied in the laboratory. Curcumin, considered its active constituent, has been shown to inhibit migration (spread) and cause apoptosis (cell death) in triple negative MDA-MB-231 breast cancer cells.[187,188] Curcumin has synergistic effects with paclitaxel chemotherapy on ER+ MCF- 7 breast cancer cells, and to a lesser extent, on triple-negative MDA-MB-234 breast cancer cells.[189] In other laboratory studies, it has been shown to reverse resistance to doxorubicin in both ER+ MCF-7 and triple negative MDA-MB-231 breast cancer cells.[190]

BEVERAGES

Green tea *(Camellia sinensis)* has been associated with many health benefits, including the potential for cancer prevention. One meta-analysis of case control studies examined the relationship between green tea consumption and breast cancer risk. Fourteen studies were included in the meta-analysis, with 14,058 breast cancer patients and 15,043 healthy controls. Those who habitually consumed green tea were found to have a lower risk of breast cancer, and this association persisted in the subgroup analysis. Researchers acknowledge that better, more well-designed trials are needed to further examine this relationship.[191] Another meta-analysis examined the relationship between green tea, breast cancer, and breast cancer recurrence. This meta-analysis included 13 studies, 8 cohort and 5 case-control, including 163,810 people. There was a statistically significant relationship between green tea consumption and decreased breast cancer risk, especially for breast cancer recurrence.[192]

VITAMINS

VITAMIN D

Vitamin D can be found in fatty fish such as mackerel, salmon, and sardines, or in fortified foods such as milk and cereal.[193] In a re-analysis of the randomized controlled Women's Health Initiative, those not previously taking supplements and assigned 1 g Ca/400 IU vitamin D daily were at a decreased risk for total, breast, and colorectal cancers, though the risk of fractures was surprisingly unchanged.[194] Vitamin D appears to be protective in some studies but not in others. In the Women's Healthy Eating and Living (WHEL) randomized controlled prospective trial, researchers found no relationship between vitamin D intake and recurrent breast cancer.[195] A later randomized controlled trial with 233 women with breast cancer and 466 healthy controls suggested that the discrepancy in previous studies may be due to the interference of obesity and/or alcohol intake with vitamin D's protective effects.[196]

One meta-analysis concluded that the protective benefits of vitamin D are mostly relevant to pre-menopausal women,[197] though a later randomized controlled trial showed that supplementation in high risk pre-menopausal women did not change either breast density (a risk factor for breast cancer) or overall breast cancer risk.[198] It is well known that many people, including but not limited to breast cancer patients, are vitamin D deficient, and that vitamin D deficiency may have negative effects on gene expression that favor cancer progression.[199] Genetics may also play a part in the effectiveness of vitamin D supplementation.[200] A 2019 meta-analysis of observational studies found an increased risk of breast cancer in vitamin D deficiency and a decreased risk of breast cancer in higher vitamin D intakes.[201] However, a 2019 randomized controlled trial examining high dose vitamin D in the pre-operative window between breast cancer diagnosis and surgery found no change in proliferation (growth) or apoptosis (cell death) between treatment and control groups.[202] Regardless, it seems prudent to identify and rectify any deficiency that exists.

VITAMIN A & CAROTENES

Foods high in vitamin A and carotenes include beef liver, cod liver oil, egg, butter, whole milk, sweet potato, carrot, pumpkin, mango, spinach, broccoli, butternut, and leafy greens.[203] A met-analysis examining vitamin A intake and breast cancer survival included 10 studies with 19,450 patients with breast cancer. They found a correlation between dietary beta carotene and overall breast cancer survival, though not with the other carotenes such as alpha carotene or lycopene.[204] The best sources of beta carotene are the plant sources listed above. Supplemental vitamin A is toxic in high doses, so it is important to stay within the Recommended Dietary Allowance (RDA) of 700 mcg in women and 900 mcg in men.[205] It is safer to obtain additional vitamin A from food than from supplements.

FOLIC ACID

Folic Acid and Folate are different forms of the same B vitamin. Folate is the active form. The body converts folic acid into folate for use, though the efficiency of this may depend on one's genetics. Foods high in folate or folic acid include beef liver, spinach, black-eyed peas, rice, and brussels sprouts. Folic acid can also be found in fortified foods such as breakfast cereals or anything made with fortified wheat flour.[206] One meta-analysis showed no association between low-dose folic acid and breast cancer, though surprisingly found there might be an increased risk of breast cancer with high-dose folic acid.[207] Two other meta-analyses, including 34,602 and 1,836,566 participants respectively, found no association between folate intake and breast cancer.[208,209] Another meta-analysis with 5,924 participants found that dietary folate intake between 153 and 400 mcg had a significant reduction in breast cancer risk, though this relationship did not persist for those with <153 mcg or with >400 mcg of intake. Researchers concluded that folate within the range of 153-400 mcg may decrease risk of breast cancer, especially in those with higher alcohol consumption, but that more studies are needed.[210] The most recent meta-analysis, including 23 prospective studies with 1,171,048 individuals and 41,516 cases of breast cancer, found that 100 mcg per day was associated

with a decreased risk of ER(-) and ER(-)/PR(-) breast cancer.[211]

VITAMIN C

Foods high in vitamin C include sweet peppers,citrus fruit, kiwi, strawberries, broccoli, and brussels sprouts.[212] In a randomized controlled five-month study, participants were assigned to chemotherapy alone (with fluoruracil, doxorubicin, or cyclophosphamide) or chemotherapy plus vitamins C and E (500 mg C, 400 mg E). The chemo plus vitamins C and E group had better antioxidant status as well as reduced DNA damage. Researchers concluded that vitamins C and E may be helpful in preventing chemotherapy-related side effects and that more clinical trials are needed.[213] A meta-analysis included randomized controlled trials and highquality prospective studies, 6 on vitamin C supplement use and 7 on dietary intake. In this group of 17,696, there were 2,791 total deaths, 1,558 of which were from breast cancer. Upon analyzing the data, researchers found a statistically significant decrease in breast cancer deaths in those who were taking post-diagnosis vitamin C compared to those who weren't. Researchers concluded that post-diagnosis vitamin C supplementation may be associated with a decreased risk of breast cancer mortality.[214]

VITAMIN E

Foods high in vitamin E include oils (wheat germ, sunflower, safflower, corn), nuts (almonds, hazelnuts, peanuts), sunflower seeds, spinach, and broccoli. There are no significant studies examining a potential relationship between vitamin E and breast cancer risk except for the one listed previously that studied vitamins C and E together.[213]

MINERALS

SELENIUM

Foods high in selenium include Brazil nuts, certain fish (tuna, halibut, sardines), ham, and shrimp.[215] There are two meta-analyses on the relationship between selenium and breast cancer risk. One meta-analysis found that high serum (blood) selenium had a protective effect on breast cancer risk, though there was no correlation with selenium supplementation.[216] The other meta-analysis examined both randomized controlled trials and longitudinal observational studies. While researchers found no significant relationship between selenium supplementation and breast cancer risk, they suggested that genetic factors, nutritional status, and different forms of supplemental selenium should be explored to better understand any potential link between adequate selenium levels and breast cancer risk.[217] Supplemental selenium is toxic in high doses, so it is important to stay within the Recommended Dietary Allowance (RDA) of 55 mcg in adults.[218] It is safer to obtain additional selenium from food than from supplements.

OTHER NUTRIENTS

RESVERATROL

Foods high in resveratrol are grapes, grape products, peanuts, and soy.[219] Laboratory studies have shown that resveratrol may inhibit proliferation (growth) and cause apoptosis (cell death). In animal studies, antiproliferative effects have been seen in ER+ MCF-7 but not triple-negative MDAMB- 231 breast cancer cells, though apoptosis was seen in both.[220] There is one randomized controlled trial in humans. In this trial, 39 women at high risk of breast cancer were randomly assigned to placebo, 5 mg resveratrol, or 50 mg resveratrol for 12 weeks. Researchers found protective changes in a particular tumor-suppressor gene, RASSF-1alpha, and acknowledge that larger studies are needed.[221]

QUERCETIN

Foods high in quercetin include onions and apples.[222] Only laboratory studies currently exist for the potential role of quercetin in breast cancer prevention. One showed that quercetin may have a beneficial effect in ER+ MCF-7 breast cancer cells, regulating gene expression that controls proliferation and metastasis.[223] The other laboratory study showed that quercetin had a synergistic effect with lonidamine, a medication that sensitizes tumors to chemotherapy, in ER+ MCF-7 breast cancer cells.[224]

HERBS

Human studies are the highest level of evidence as to whether something is effective in humans. Animal studies are promising but may or may not be applicable to humans. Laboratory studies (also known as *in vitro* studies) are the lowest level of useful evidence and cannot be assumed to apply to animals or humans without additional animal or human studies. The myriad of biochemical reactions that occur in a living being are far more complicated than what occurs in a simple laboratory study.

HUMAN STUDIES

Black Cohosh *(Actaea racemosa/Cimicifuga racemosa)* is well known for its use in menopause. There are laboratory, mouse, and human studies regarding its use in breast cancer. Laboratory studies have shown that black cohosh alcohol extract inhibits proliferation (growth) by inducing apoptosis (cell death) in both ER+ MCF-7 and triple-negative MDA-MB-231 breast cancer cells.[225,226] It also inhibits proliferation in ER(-) T-47D and MDA-MB-453 breast cancer cells.[227,228] The active constituent in black cohosh is thought to be actein, which causes apoptosis.[228,229] In mouse studies, actein has been shown to decrease tumor size and help prevent liver and lung metastases.[229]

A prospective observational study examined the effects of black cohosh in women with breast cancer taking tamoxifen. Each of the 50 participants had undergone surgery, most had undergone radiation therapy, and 50% had undergone chemotherapy. The starting dose of black cohosh was 40 mg, though after the initial 4 weeks, patients were allowed to decrease the dose to 20 mg or increase the dose to 60 or 80 mg, depending on symptoms. Participants were asked to rate their menopausal symptoms at baseline and again after 1, 3 and 6 months of black cohosh treatment. Participants experienced a statistically significant improvement in menopausal symptoms such as hot flashes, sweats, anxiety and sleep, though there were no changes in urogenital or musculoskeletal symptoms.[230]

A 2019 randomized controlled trial examined the effects of black cohosh on menopausal symptoms in pre- and perimenopausal breast cancer patients taking LHRHa (luteinizing hormone-releasing hormone agonist) medication. LHRHa medication prevents the ovaries from making estrogen, causing temporary

menopause. This trial included 85 women with breast cancer who were prescribed LHRHa medication. They were randomly assigned to either LHRHa plus black cohosh or LHRHa alone. There were 42 in the black cohosh group and 43 in the control group. Menopausal symptoms were recorded at baseline, 4 weeks, 8 weeks, and 12 weeks. While hormone levels were similar between groups at the end of 12 weeks, menopausal symptoms were significantly lower in the black cohosh group. While cervical cysts were higher in the black cohosh group than control, there were no other significant differences between groups. Researchers concluded that black cohosh is effective and safe for the treatment of LHRHa-induced menopausal symptoms and appears to be safe in cancer, without direct hormonal effects.[231]

Milk Thistle *(Silybum marianum)* and its components silymarin and silybin have been examined in laboratory settings as well as in multiple human trials, for a variety of health conditions. Silibinin, a compound extracted from the seed, inhibits spread and causes apoptosis (cell death) in laboratory studies in ER+ MCF-7 and triple-negative MDA-MB- 231 breast cancer cells.[232,233,234] Researchers in one laboratory study concluded that silibinin may be worth developing into an adjuvant drug to better help prevent cancer.[235] Another laboratory study found that the silymarin administered with doxorubicin to ER+ MCF-7 breast cancer cells can increase the therapeutic effects of doxorubicin and decrease its side effects.[236]

A human comparative study explored the use of topical silymarin to help prevent radiation-induced dermatitis, which 80% of breast cancer patients undergoing radiation experience. This study included 101 patients, with 51 of these treated with the silymarin cream. The remaining 50 were given the standard-of-care cream containing panthenol, a B vitamin. In the silymarin group, only 8% of patients experienced grade 2 skin toxicity compared to the control group, of which 52% had grade 2 skin toxicity. Researchers concluded that larger studies are needed to confirm these results.[237] In a randomized double-blind placebo-controlled trial, topical silymarin 1% gel was studied vs. placebo. Forty breast cancer patients were randomly assigned to either treatment or placebo, to be applied once daily for 5 weeks. Again, there was a significant delay in and progression of radiation-induced dermatitis in the silymarin group.[238]

Guarana *(Paullinia cupana)* has several human trials in addition to laboratory studies. Four different concentrations of guarana were tested along with caffeine, which is considered its active component. The guarana extracts performed better than caffeine alone at inhibiting cell growth in ER+ MCF-7 cells.[239] One double-blind randomized placebo-controlled crossover study examined the effects of guarana on depression and radiation-induced fatigue. A total of 36 patients who were undergoing radiation therapy for breast cancer were randomly assigned to 75 mg/day guarana or placebo, then switched to the other arm. There were no significant differences in fatigue or depression between the groups.[240] A randomized double-blind placebo controlled trial examining chemotherapy related fatigue, however, found a statistically significant difference between groups. In this study, 75 patients were randomly assigned to 50 mg/day guarana or placebo for three weeks, after which the patients were switched to the other treatment. Researchers concluded that guarana was effective in treating short-term fatigue in patients receiving chemotherapy, but suggested that more studies are needed to determine if it may be of help in chronic chemotherapy-related fatigue.[241] A clinical trial on chemotherapy-related fatigue in breast cancer involved 40 patients who were given a purified dry extract of guarana (PC-18) 37.5 mg twice daily. The intervention began one week after chemotherapy and continued for three weeks. Those whose fatigue remained stable or improved were then randomly assigned to either the same dose of PC-18 or placebo. While fatigue had improved in 36 of the 40 patients during the first part of the study, there were no significant differences between treatment or placebo groups during the second part of the study. Researchers wondered if the lack of statistical difference between groups during the second phase could have been due to a "conditioning effect," meaning that because they had felt significantly better initially, they expected to continue feeling better.[242]

Two recent randomized controlled trials continued to explore the effects of purified guarana extract (PC-18) on chemotherapy induced fatigue. Early breast cancer patients who experienced fatigue after their first cycle of chemo were enrolled. The first study compared 37.5 mg PC-18 twice daily to placebo; the second study compared 7.5 mg or 12.5 mg PC-18 twice daily to placebo. All participants experienced an anti-fatigue effect, though there were no statistically significant differences between groups. Researchers noted that all capsules (all doses of PC-18 as well as placebo) contained 100 mg of magnesium silicate and wondered if the lack of difference between groups may have been due to an energizing effect from magnesium. Authors concluded that more studies on magnesium may be warranted.[243]

A prospective phase II pilot study explored whether guarana could help to decrease the number and severity of hot flashes in breast cancer survivors. Patients who had finished breast cancer treatment 3 months previously and experienced at least 14 hot flashes a week were enrolled and treated with 50 mg guarana, twice daily, for 6 weeks. Ten of the 15 patients who completed the study experienced a ≥ 50% improvement in their hot flashes. Researchers concluded that there was a statistically significant decrease in both number and severity of hot flashes.[244]

Antrodia *(Antrodia cinnamomea)* is a mushroom with potentially beneficial effects. Laboratory studies have shown that it inhibits metastasis in both ER+ MCF-7 and triple-negative MDA-MB-231 breast cancer cells,[245,246] and inhibits proliferation (growth) in T-47D breast cancer cells.[247] A laboratory study with ER+ MCF-7 tamoxifen-resistant breast cancer cells showed that antrodia extract, when coadministered with tamoxifen, can overcome tamoxifen resistance and cause apoptosis (cell death).[248] The active constituent is thought to be antcin-A.[246] Laboratory studies have also shown antrodia extract to sensitize breast cancer cells to radiation while protecting normal cells.[249]

In mice with T-47D tumors, antrodia extract was seen to attack not only tumor cells, causing apoptosis (cell death), but also the tumor's blood supply. Also in mice, antrodia was equivalent to tamoxifen in antiestrogenic activity, with dehydroeburicoic acid considered to be the active component.[250]

In a randomized controlled trial, 37 patients with various forms of advanced cancer, including breast cancer, were randomly assigned to either antrodia

extract 20 ml/day or placebo for 30 days. Researchers measured 6-month overall survival. Death from disease progression occurred for 4 in the treatment group and 8 in the placebo group. The treatment group also had significantly improved sleep, though overall quality of life was the same between groups. More randomized controlled trials are needed, as the study size was considered too small for the outcomes to be statistically significant.[251]

Ashwagandha *(Withania somnifera)* is an Ayurvedic herb that has been studied in the laboratory, in animals, and in humans. In laboratory studies involving ER+ MCF-7 and triple-negative MDA-MB-231 human breast cancer cells, ashwagandha inhibited growth by causing apoptosis (cell death).[252,253,254] It also sensitized MDA-MB- 231 and SUM-159 triple-negative breast cancer cells to cisplatin chemotherapy.[255] A mouse study found that the root extract, specifically the withaferin A component, inhibits proliferation (growth) and lung metastasis in mammary cancer.[256] A controlled clinical trial in humans examined the effects of ashwagandha extract on chemotherapy-induced fatigue and quality of life. This was an open-label, non-randomized trial. There were two groups: the control group with chemotherapy alone, and the treatment group with chemotherapy plus ashwagandha. (Chemotherapy regimens were either paclitaxel + doxorubicin + cyclophosphamide or 5-fluorouracil + epirubicin + cyclophosphamide.) Patients in the control group (chemotherapy alone) had significantly greater fatigue scores. Survival at 24 months was 72% in the treatment group with ashwagandha vs. 56% in the control group, though this was not considered statistically significant. Larger randomized studies are needed.[257]

Frankincense *(Boswellia spp.)* consists of many species, though *Boswellia serrata* is perhaps the most well-known. It has been studied in the lab as well as in humans. One laboratory study compared 9 species of frankincense and found *Boswellia sacra* to have the greatest cytotoxic effects against triple-negative MDA-MB-231 breast cancer cells.[258] An alcohol extract of the leaves from *Boswellia ovalifoliolata* caused cytotoxicity in triple-negative breast cancer cell lines MDA-MB-231 and MDA-MB- 453, having a synergistic effect with and increasing cancer cell sensitivity to doxorubicin and cisplatin.[259] In another laboratory study, the essential oil of *Boswellia sacra* increased apoptosis in ER+ MCF-7, triple-negative MDA-MB-231, and T-47D breast cancer cells. A higher temperature distillation of the essential oil (100°C vs. 78°C) had greater cytotoxic effects.[260] Another laboratory study showed that an extract of *Boswellia frereana* inhibited migration (spread) though not proliferation (growth) in triple-negative MDA-MB-231 and triple-negative BT-549 breast cancer cells.[261] One laboratory study examined the cytotoxicity of specific compounds in frankincense, finding that supplements with >30% boswellic and lupeolic acids were the most active against the triple-negative MDA-MB-231 breast cancer cell line.[262]

In the one randomized controlled trial regarding *Boswellia serrata* and breast cancer, a boswellia cream was used to help prevent skin damage from radiation therapy for breast cancer. Frankincense is known for its anti-inflammatory properties, and this study found that the cream was effective in decreasing skin inflammation, skin damage, and the need for topical corticosteroids. Researchers concluded that more studies are needed to compare a variety of topical preparations to see which may be the most effective.[263]

Red Clover *(Trifolium pratense)* has been studied in humans for breast cancer prevention. In laboratory studies, it has been found to inhibit proliferation (growth) and cause apoptosis (cell death) in ER+ MCF-7 and triple-negative MDA-MB-231 breast cancer cells.[264,265] Researchers also found that the combination of red clover extract and tamoxifen had synergistic cytotoxic effects.[264] Researchers concluded that red clover sprouts, particularly when fermented, were a significant source of phytoestrogens.[265] In a three-year randomized controlled trial, 401 women with a family history of breast cancer in at least one first-degree relative were randomly assigned to treatment with 40 mg of red clover isoflavones or placebo. There were no significant differences between groups regarding breast density, endometrial (uterine) density, hormone levels, or bone density. However, when only the post menopausal women were considered, there were beneficial changes in bone density. The study authors concluded that red clover isoflavones are safe in women with a family history of breast cancer, though more studies are needed to determine if they are effective in decreasing breast cancer risk.[266] In a prospective double-blind randomized trial, 81 premenopausal women with ER+ breast cancer were randomly assigned to 80 mg red clover extract or placebo for two years. Both treatment and placebo groups were encouraged to follow a Mediterranean diet and pursue regular physical activity. Menopausal symptom scores were significantly improved from baseline, though the difference was not statistically significant between groups. There was a statistically significant decrease in waist circumference and BMI in the treatment group, however. The original purpose of the study was to potentially help with tamoxifen-induced menopausal symptoms. Because menopausal symptoms improved in both the treatment and placebo groups, researchers concluded that the improvements may have been from the Mediterranean diet rather than the red clover extract.[267]

Mistletoe *(Viscum album)* and its constituents have been studied in various types of human cancer. In a 2008 Cochrane review, researchers concluded that mistletoe therapy is usually well-tolerated without significant adverse effects, though more studies are needed. The data supporting mistletoe in increasing survival is considered weak, though there is moderate evidence that it may improve quality of life during chemotherapy for breast cancer. More studies are needed.[268] A 2018 randomized controlled trial evaluated the safety and benefits of using mistletoe during treatment with chemotherapy. In this trial, 95 breast cancer patients who were undergoing six cycles of chemotherapy with cyclophosphamide, doxorubicin, and 5- fluorouracil were randomly assigned to one of three groups: chemotherapy plus Helixor A brand mistletoe, chemotherapy plus Iscador M Spez brand mistletoe, and chemotherapy alone. While the mistletoe groups had decreased pain, increased appetite, and slightly less neutropenia (low white blood cell counts) than the control group, there were no significant differences between groups in rates of relapse or metastasis.[269]

Ginkgo *(Ginkgo biloba)* is well known for its effects on cognitive function. In a randomized controlled trial in people aged 75 years and older, 3,069 participants were randomly assigned to 120 mg ginkgo extract twice daily or placebo and followed for 6 years. The primary goal was to track memory, with a secondary

goal of cancer prevention. In this study, while treatment with ginkgo reduced risk of prostate cancer, it seemed to increase the risk of breast and colorectal cancers.[270] Another randomized controlled trial examined the use of ginkgo for preventing chemotherapy-related impaired cognition in women with breast cancer. The study included 166 women randomly assigned to either 60 mg ginkgo or a placebo, twice daily, beginning before the second cycle of chemotherapy and continuing for 30 days after the final chemotherapy cycle. When cognitive evaluations were performed after 12 months, researchers found no cognitive differences between the treatment and placebo groups, though the treatment group had less chemotherapy-related nausea.[271] Lastly, a randomized controlled trial examined the effect of ginkgo supplementation on cardiotoxicity in patients with breast cancer. In this study, women with breast cancer were randomly assigned to the treatment group with doxorubicin plus ginkgo, or the control group with doxorubicin alone. The rate of abnormal ECGs was much lower in the treatment group (6.7%) than in the control group (30.0%). More studies are needed to examine the relationship between ginkgo and doxorubicin-induced acute or chronic cardiotoxicity.[272]

Ginger *(Zingiber officinale)* has been discussed earlier under herbs and spices. Previously, we discussed the ability of ginger and its constituents 6-shaogol, 6-gingerol, and 10-gingerol to inhibit proliferation and cause apoptosis (cell death) in laboratory studies with ER+ MCF-7 and triple-negative MDA-MB-231 breast cancer cells, though the effects are more pronounced in triple-negative MDA-MB-231 cells.[175,176,177,178,179,180,181] In humans, a meta-analysis found that ginger may help to reduce chemotherapy-induced nausea. The doses of powdered encapsulated ginger used in studies were 250-500 mg every 12 hours, or 500 mg every 8 hours. Treatment with ginger capsules ranged from 4 to 6 days in length, generally beginning before and extending after the chemotherapy treatment. This meta-analysis also included ginger aromatherapy studies which are covered separately in the aromatherapy section.[273]

Turmeric *(Curcuma Longa)* was mentioned previously under herbs and spices. In laboratory studies with ER+ MCF-7 and triple-negative MDA-MB-231 breast cancer cells, curcumin has been shown to cause apoptosis (cell death).[187] It has synergistic effects with paclitaxel on both cell lines, though more so in ER+ MCF-7 cells.[189] It has also decreased doxorubicin resistance in both cell lines.[190] In a human pilot study, curcumin was used to help prevent capecitabine-induced hand-foot syndrome, which occurs in approximately 40-50% of patients who use this chemotherapy. Before starting treatment, at 3 weeks, and again at 6 weeks, skin toxicity was evaluated, blood was tested for inflammatory markers, and patients were asked to fill out quality-of-life questionnaires. There were 40 patients, 52% of whom had breast cancer, with the remainder having GI cancer. Patients were given 2 grams curcumin twice daily, 12 hours apart, starting at the beginning of chemotherapy treatment and lasting for 6 weeks. Researchers concluded that turmeric combined with capecitabine seems to produce a lower rate of hand-foot syndrome, particularly severe hand-foot syndrome.[274]

ANIMAL STUDIES

While animal studies are of limited use as human studies are needed, they may help provide direction for future research.

Reishi *(Ganoderma lucidum)* has been examined in both laboratory and animal studies. In laboratory studies, it has been shown to inhibit proliferation (growth) and cause apoptosis (cell death). In ER+ MCF-7 and triple-negative MDA-MB-231 breast cancer cells, reishi inhibits proliferation and metastasis in addition to having antiinflammatory effects.[275,276,277] The antiproliferative effects were found to be due to its effects on estrogen receptors and NFkappaB signals. (NF-kappa B is a protein involved in cell survival.) [278] Reishi has been shown to act as an antioxidant, reducing cancer spread that is caused by oxidative stress.[279] Another laboratory study concluded that the alcohol extract has multiple anti-tumor effects.[280] In mouse studies, reishi inhibited growth of triple negative MDA-MB-231 breast cancer tumors, decreasing tumor weight by 50%.[281] Other mouse studies showed that it increases apoptosis (cell death) and inhibits breast to lung metastasis.[282,283]

Curry tree *(Murraya koenigii)* has been examined in both laboratory and animal studies. An alkaloid extract from the leaves, when studied with triple-negative MDAMB- 231 breast cancer cells, reduced cancer cell survival, inhibited the cell cycle, and caused apoptosis (cell death).[284] In a laboratory study with both triple-negative MDA-MB-231 and ER+ MCF-7 cells, only the cancerous cells were harmed while the healthy cells were spared.[285] A specific component of the leaves, koenimbine, also inhibited ER+ MCF-7 breast cancer cells. Researchers concluded that it may reduce cancer recurrence and treatment resistance.[286] In one rat study, the water extract reduced tumor size and lung metastases.[287] In another rat study, the leaf extract selectively targeted cancer cells and made them more susceptible to chemotherapy, without toxicity to normal cells. The flavonoids also inhibited cell survival and proliferation (cell growth).[288] In rats, it caused apoptosis (cell death).[288] In another rat study, the alkaloid mahanine was found to decrease tumor volume.[289]

Jin batu *(Strobilanthes crispus*) is a Malaysian shrub whose leaves have medicinal effects. It helps to inhibit proliferation (growth) and metastasis (spread) in both ER+ MCF-7 and triple negative MDA-MB-231 breast cancer cells.[290,291,292] Another laboratory study examined the mechanism for apoptosis (cell death) in ER+ MCF-7 cells.[293] Another examined coadministration of the herb with tamoxifen to ER+ MCF-7 and triple negative MDA-MB-231 breast cancer cells. The resulting inhibition suggested that lower doses of tamoxifen might be used if the herb was given in conjunction, resulting in reduced side effects and toxicity.[294] Lutein seems to be the primary constituent. In rats with ER+ breast cancer treated for 8 weeks with F3 (a pharmacological fraction of the dichloromethane extract), tumors regressed significantly in 75% of the rats, with partial tumor regression from other fractions of the herb. Tumors did not regress at all in the untreated control group.[295]

Stinging nettle *(Urtica dioica)* has been studied in the laboratory and in mice. In one laboratory study with ER+ MCF-7 and triple-negative MDA-MB-231 breast cancer cells, stinging nettle decreased proliferation (growth) and caused apoptosis (cell death) in both lines.[296,297] There were additional changes in the genetic expression of ER+ MCF-7 breast cancer cells, attributed to stinging nettle's phytoestrogenic qualities.[296] The dichloromethane extract sensitized cancer cells to paclitaxel chemotherapy in triple-

negative MDA-MB-468 breast cancer cells. It also inhibited proliferation and metastasis without damaging normal cells.[298,299] In mice, it changed genetic expression in genes promoting metastasis.[297]

Ginseng *(Panax ginseng)*, also known as Asian ginseng, has been studied in the laboratory, it inhibited proliferation (growth), inhibited metastasis (spread) and caused apoptosis (cell death). It showed these effects in all breast cancer cell lines studied – triple-negative MDA-MB-231, T- 47D, regular ER+ MCF-7, and doxorubicinresistant ER+ MCF-7 breast cancer cells.[300,301] A new compound in panax ginseng, 20(S)-Rh2, decreases cell survival in ER+ MCF-7 breast cancer cells.[302] The component ginsenoside Rg3 may help to increase the effectiveness of paclitaxel, which is the most effective for triple negative breast cancers such as MDA-MB- 231, MDA-MB-453, and BT-549. Ginsenoside Rg3 appears to sensitize the cancer cells to paclitaxel, as seen in laboratory studies and in mice.[303]

Lemon balm *(Melissa officinalis)* has been studied in the laboratory and in rats. In a laboratory study with ER+ MCF-7 cells, the alcohol extract reduced cell survival to 33% (from 100%) and inhibited cancer growth by an average of 86.7%.[304] In another study with triple-negative MDA-MB-231 and triple-negative MDA-MB-468 as well as ER+ MCF-7 breast cancer cells, lemon balm was cytotoxic to all of the included cells,[305] though strongest against the ER+ MCF-7 cells.304 In one rat study, the alcohol extract decreased the tumor volume by an average of 40%.[305] In another rat study, lemon balm was found to increase the effectiveness of doxorubicin while decreasing cardiotoxicity. Researchers concluded that co-administration of both may be safer than doxorubicin alone, though more studies, specifically human studies, are needed.[306]

Flame-of-the-forest *(Butea monosperma)* is a traditional herb in Ayurvedic medicine with anti-estrogenic activity. The alcohol extract of the flower has been studied in ER+ MCF-7, triple-negative MDA-MB-231, and HER2+ MDA-MB-453 breast cancer cells, and most strongly inhibited the ER+ MCF-7 cells, being more active against ER+ positive cancer. In ER+ MCF-7 breast cancer cells, it inhibited metastasis and stimulated apoptosis (cell death). It was selectively cytotoxic, meaning it stimulated apoptosis in cancer cells but not in regular cells.[307] The flower extract also helped to decrease proliferation of cancer cells in rat mammary tumors, attributed to its action on estrogen and progesterone receptors.[307] Butein is considered one of the active components of the flower extract and has bene shown to decrease the genetic expression of COX2 inflammation in both cancerous and non-cancerous cells.[308]

Lotus *(Nelumbo nucifera)* has long been used in traditional Chinese medicine. Its alkaloids isoliensinine, liensinine, and neferine have potential anti-cancer activity and the leaf extract has been shown in laboratory studies to block proliferation (growth), migration (spread), and angiogenesis (blood vessel formation). It has also been shown to induce apoptosis in triple-negative MDA-MB-231 breast cancer cells.[309,310,311,312] In a single mouse study, it has been shown to decrease tumor volume.[313]

Acacia *(Acacia seyal)* has been studied in the laboratory as well as in rats. In one study, the alcohol extract of the stem bark helped to cause apoptosis (cell death) in triple-negative MDA-MB-231 but not in ER+ MCF-7 breast cancer cells. It also inhibited metastasis.[314] In another laboratory study, it was effective against ER+ MCF-7 cells.[315] In rat studies, it inhibited tumor formation and growth.[315]

LABORATORY STUDIES

<u>While laboratory studies are not applicable to human use, they are promising for the development of future therapies. Further testing in animal and then human studies is needed.</u>

Thale cress *(Arabidopsis thaliana)* has been in the news recently, in reference to breast cancer. BRCA1 and BARD1, genes for tumor suppressor proteins, can influence cancer predisposition in humans. There are similar analogous genes in plants. By better understanding the plant version of BARD1 protein in thale cress (previously thought to be a non-medicinal plant), hopefully, we will learn more about how this gene functions in humans.[316,317] In a laboratory study, incubating thale cress leaves treated with jasmonate (a plant hormone) with human breast cancer cells not only inhibited the cancer cells by interfering with the cell cycle, but also left the non-cancerous cells undamaged. Further research is needed, and may lead to advances in breast cancer treatment.[318]

Cat's claw *(Uncaria tomentosa)* has been used in laboratory studies with breast cancer cells. The alcohol extract had anti-tumor effects on triple-negative MDA-MB-231 breast cancer cells and had a synergistic effect with doxorubicin.[319] Extracts have also been shown to inhibit growth and genetic mutations in ER+ MCF-7 breast cancer cells.[320] Mitraphylline, a chemical from cat's claw, has been shown to inhibit triple-negative MT-3 breast cancer cells.[321]

Danshen *(Salvia miltiorrhiza)* has been used in Traditional Chinese Medicine for centuries. Laboratory studies have shown antiproliferative effects in both regular ER+ MCF-7 cells as well as those over expressing HER2+.[322] The constituent tanshinone IIA has anti-estrogenic, antiandrogenic, and antiproliferative actions in ER+ T-47D breast cancer cells.[323] Tanshinone IIA has also been studied in doxorubicin-resistant ER+ MCF-7 breast cancer cells. Researchers concluded that it helped increase the sensitivity of the cancer cells to doxorubicin and may be cardio protective.[324]

Indian trumpet flower *(Oroxylum indicum)* has been studied in both ER+ MCF-7 and triple-negative MDA-MB-231 cells, with antiproliferative effects.[325] Extracts are cytotoxic to ER+ MCF-7 cells and triple-negative MDA-MB-231 breast cancer cells without harming normal cells.[326] Oroxin A, an active component, interferes with the cell cycle and inhibits growth in both ER+ MCF- 7 and triple-negative MDA-MB-231 breast cancer cells.[327]

Drumstick Tree *(Moringa oleifera)* leaf extracts have been shown to decrease survival of ER+ MCF-7 breast cancer cells.[328] Extracts of leaves and bark have been shown to have anti-cancer effects while the seed extract has not. The leaf and bark extracts have been studied in triple-negative MDA-MB-231 and shown to decrease cell survival and increase apoptosis (cell death).[329] The alcohol seed extract did have antiproliferative effects in ER+ MCF-7 breast cancer cells, however.[330]

Simpoh ayer *(Dillenia suffruticosa)* root extract causes

apoptosis (cell death) in triple-negative MDA-MB-231 breast cancer cells.[331] The extract has also caused apoptosis in ER+ MCF-7 breast cancer cells.[332] Three anti-cancer compounds have been isolated from this plant, of which betulinic acid appears the strongest.[331]

Toosendanin *(Melia toosendan)* has been studied in triple-negative MDA-MB-231, triple-negative MDA-MB-468, and ER+ MCF-7 breast cancer cells, both regular and doxorubicin-resistant. Preliminary laboratory studies have shown that it may help reduce doxorubicin resistance.[333]

Hibiscus *(Hibiscus syriacus)* has been used in Traditional Chinese Medicine for centuries, and the root bark is known as mu jin pi. Of the discovered compounds, betulin and betulinic acid had the greatest anticancer effects in triple-negative breast cancer cells, interfering with the cell cycle and causing apoptosis (cell death).[334]

MIND-BODY THERAPIES

AROMATHERAPY

There have been several studies with aromatherapy in cancer patients. One randomized controlled trial compared the effect of ginger essential oil to placebo synthetic ginger fragrance oil. The essential oil or fragrance was contained in a necklace, and the intervention continued for five days. While there was a significant decrease in nausea after ginger essential oil inhalation compared to control, the benefits did not last, and there was no change in vomiting. There was, however, a statistically significant decrease in appetite loss.[335] One randomized controlled trial examined the impact of lavender essential oil on presurgical anxiety. Eighty patients were randomly assigned to either the treatment or control group. While the treatment group experienced decreased anxiety, this was not statistically significant compared to control. It may have been an issue that in this study, like the last one, the "placebo" control was a synthetic fragrance oil; maybe it doesn't matter to the brain whether a pleasant fragrance is botanically derived in this context.[336] Another randomized controlled trial examined the impact of aromatherapy on mood, physical symptoms, and quality of life in breast cancer patients about to undergo surgery. Patients were allowed to choose between ylang-ylang, orange, and lavender oils. There were 162 total patients, 110 randomly assigned to aromatherapy and 52 assigned to control (usual care). While there were no statistically significant improvements in quality of life, vital signs or sleep, patients reported the aromatherapy as a positive experience and researchers concluded that it may be used during the perioperative period to meet patient expectations.[337] In one other randomized controlled trial, 75 participants were randomly assigned to aromatherapy inhalation, massage, or control. The essential oil used was a combination of mint, bergamot, and cardamom, and inhalation lasted for 3 minutes prior to the 2nd, 3rd, and 4th chemotherapy cycles. The massage intervention consisted of a 20-minute foot massage. The severity of nausea and retching was lower in both inhalation and massage groups, compared to placebo, with the massage intervention more effective than aromatherapy.[338]

MASSAGE

Massage can be helpful for lymphedema, chronic musculoskeletal pain, anxiety and fatigue. Four meta-analyses have studied the impact of manual lymphatic drainage (MLD) on lymphedema alone. One evaluated 6 trials of massage for lymphedema, comparing MLD plus physiotherapy to physiotherapy alone, and MLD plus compression to compression alone. Researchers concluded that MLD is safe and may offer additional benefit to compression bandaging for swelling, noting that those with mild to moderate lymphedema benefited the most.[339] Another meta-analysis showed that combining MLD with physical exercise prevented upper limb edema, examining studies including 1,000 total patients (500 MLD plus exercise, 500 exercise only). Patients were also trained to perform self-MLD on the incision for 10 minutes, three times daily. Upper limb and shoulder abduction were evaluated the day before surgery, at one week, and at 1, 3, 6, and 12 months after surgery. Researchers concluded that Self-MLD plus physical exercise is beneficial in preventing lymphedema, scar formation, and shoulder joint problems.[340] One meta-analysis including 45 trials found that complex decongestive therapy (CDT), a combination of MLD, compression, skin care, and lymph-reducing exercises reduced lymphedema and increased quality of life in early-stage breast cancer. They also noted that liposuction may be an effective and safe treatment for moderate to severe lymphedema.[341] Another meta-analysis examined self-lymphatic drainage over a period of 6 months. Patients were taught to perform a 10-minute daily routine of gentle calisthenics and self-lymphatic drainage with moisturizing care. After 6 months of daily self-treatment, edema volume and compression resistance were reduced.[342] One meta-analysis included studies on myofascial therapy, classic massage, and trigger point compression. Researchers found that these various forms of manual therapy helped to decrease musculoskeletal pain.[343] Another meta-analysis found that breast cancer patients receiving regular massage had statistically significant decreases in fatigue and anger, though not in depression or anxiety.[344] One meta-analysis examined the effects of partner-delivered reflexology on pain in various types of 3 metastatic cancer. Patient partner pairs were randomly assigned to either reflexology or usual care with attention. In the treatment group, the patient received a 30-minute foot reflexology session from the partner, vs. a 30-minute reading session from the partner in the control group. Patients experienced a significant decrease in pain and anxiety after the reflexology intervention, while the reading session control group had only minimal changes.[345]

DETOXIFICATION

Organic foods were discussed previously in the diet section. Minimizing environmental contaminants such as pesticides in food is a good idea. For where to start, consult the Environmental Working Group's "Dirty Dozen/Clean fifteen" list.[73]

Cosmetics can be a source of significant exposure to carcinogens, xenoestrogens and other hormone disruptors. For information on safer cosmetics, consult the Environmental Working Group's "Skin Deep" database.[17]

Sauna is an age-old method of detoxification and health-building. It has been shown to help excrete heavy metals such as lead, mercury, cadmium and arsenic[346] as well as other potentially carcinogenic compounds.[347,348] A 2019 observational study with Finnish men examined the frequency of sauna use with cancer risk. The study included 2,173 men aged 42-61

without a personal history of cancer. Followup lasted for an average of 24.3 years. While there was a slight decrease in the risk of some cancers, it was below the level of statistical significance.[349] While sauna may have a role in cancer prevention, more studies are needed.

Be sure to discuss sauna therapy with your oncologist before trying it to determine whether it may be appropriate for your individual circumstance. In one randomized, controlled trial examining 30 potential risk factors for lymphedema following breast cancer surgery, sauna was the only risk factor associated with lymphedema.[350] The timing may matter, as another study found infrared sauna therapy to be helpful in treating lymphedema persisting 5 years after mastectomy. Study researchers concluded that it was safe and feasible in breast cancer survivors to help decrease lymphedema without elevating tumor markers or increasing rates of recurrence or metastasis.[351]

Chelation Therapy may have a role in decreasing cancer risk as heavy metals are known carcinogens when present in excess. However, more research is needed. In one laboratory study, deferasirox (an iron chelator) had synergistic effects with chemotherapy medicines doxorubicin, cisplatin and carboplatin to inhibit proliferation (growth) and cause apoptosis in triple-negative breast cancer.[352] This was a laboratory study, so much more research both in animals and in humans is necessary to draw any conclusions for cancer treatment.

REIKI, HEALING TOUCH & THERAPEUTIC TOUCH

Reiki, Healing Touch, and Therapeutic Touch are types of energy medicine, mostly conducted with hands a short distance from the body. While science does not currently understand how energy medicine works, it appears to be helpful for some people. One randomized controlled trial evaluated the effects of healing touch on fatigue in breast cancer patients receiving radiation therapy. Healing touch (3-6 inches from the body) was compared to sham healing touch (>12 inches from the body), and patients were unable to see what was happening because of a drape. Patients usually fell asleep, but there were no statistically significant differences in anxiety, depression, fatigue, or quality of life.[353] Another randomized controlled trial examined the effects of reiki therapy compared to companionship, specifically on mood, symptom distress, and quality of life during chemotherapy. There were 36 breast cancer patients with stages IIII breast cancer. Patients were randomly assigned to reiki, a companion, or usual care. Reiki and companion sessions were 30 minutes each, during chemo. Patients described reiki as relaxing, and both reiki and companion groups resulted in improvements in mood and quality of life. Surprisingly, quality of life was higher with companionship than with reiki. There were no significant differences between reiki and companion groups in depression, anxiety, anger, or fatigue, and no differences in nausea or other symptoms between any of the three groups.[354] Another randomized controlled trial evaluated the effect of therapeutic touch on nausea in breast cancer patients receiving chemotherapy. In this study, 108 patients were randomly assigned to therapeutic touch, placebo (sham therapeutic touch) or control groups. As with previous trials, the sham group was a similar intervention but with hands further from the body. Both the intensity and duration of nausea were significantly lower in the treatment group than in the placebo or control groups.[355]

ACUPUNCTURE

Acupuncture is often used to help control side effects from chemotherapy such as nausea and vomiting. While there aren't currently any randomized controlled trials on acupuncture for nausea or vomiting from chemotherapy in breast cancer specifically, one study in pediatric cancer patients has shown it to help chemotherapy-induced nausea and vomiting (CINV). Of a group of 23 children receiving chemotherapy known to cause nausea, patients were randomly assigned to acupuncture treatment during either the 2nd or 3rd chemotherapy treatment, together with the standard anti-emetic (antivomiting) medication. Researchers measured the number of vomiting episodes and the amount of additional anti-emetic medication needed. Both the number of vomiting episodes and the amount of antiemetic medication needed were significantly lower in the acupuncture treatment group.[356] Another randomized controlled trial explored post-operative acupuncture for pain, tension, and anxiety. This was an open label trial. Twenty adult breast cancer patients having mastectomy and/or breast reconstruction were offered daily acupuncture beginning on postop day 1 and continuing throughout their hospital stay. There was a statistically significant decrease in anxiety, tension/muscular discomfort, and pain. Researchers concluded that this intervention was feasible and that more studies are needed.[357] A meta-analysis examined the effect of acupuncture treatment on hot flashes in breast cancer patients in 18 different studies. Hot flashes significantly decreased during the treatment, but there was no statistically significant difference following the treatment or at follow up. Researchers concluded that there was still a significant benefit for breast cancer patients suffering from hot flashes, and that more studies are needed.[358] The most recent meta-analysis examined 6 trials with a total of 178 breast cancer patients. All trials included were high-quality randomized controlled trials. This meta-analysis of acupuncture trials did not show significant improvement in lymphedema as there was no change in arm circumference, though it did show a trend of symptom improvement. Researchers concluded that more studies are needed with both subjective and objective measures of improvement.[359]

ART THERAPY

Art therapy combines visual arts for self-expression with psychotherapy. Comparing art therapy groups with weekly sessions to control groups without art therapy, randomized controlled trials have shown an improvement in coping, stress levels, and quality of life.[360,361,362] In another randomized controlled trial, 24 breast cancer patients were assigned to the treatment group or control. The treatment group was given a series of 12 mindfulness-based art therapy sessions. The art therapy group had significant decreases in anxiety and depression, with a significant improvement in quality of life. Researchers concluded that mindfulness-based art therapy can improve psychological stability in patients with breast cancer.[363] Another randomized controlled trial examined emotional processing via art therapy in breast cancer patients. This study included 20 women who had completed primary treatment for breast cancer, randomly assigned to either a treatment (art therapy) group or a control (mandala-coloring) group. There were statistically significant improvements in increased emotional awareness and acceptance of emotions in the

art therapy group.[364]

COGNITIVE BEHAVIORAL THERAPY

Cognitive behavioral therapy is a type of psychotherapy that works with thoughts, emotions, and behaviors. In a 2015 randomized controlled trial, researchers compared 2 interventions (CBT or relaxation training) to a control group (health education) for 5 weeks. Women with stage 0 to III breast cancer were randomly assigned to one of the three groups, and psychosocial measurements were evaluated at baseline and after 5 weeks. Both of the treatment groups reported less depression, and the CBT group reported an increase in quality of life. There were no changes in the control group.[365] In another randomized controlled trial, internet-delivered CBT was studied for insomnia in breast cancer survivors. (Insomnia is 2-3x more common in breast cancer survivors than in the general population.) Breast cancer survivors were randomly assigned to either treatment (122) or wait list control (133) groups. Insomnia, sleep quality, and fatigue were measured at the beginning, 9 weeks, and 15 weeks. Researchers concluded that internet delivered CBT is an effective therapy for insomnia in breast cancer survivors, with the added benefit of decreased fatigue.[366] Another randomized controlled trial examined CBT plus hypnosis on emotional distress in women undergoing radiation therapy for breast cancer. Participants were randomly assigned to either CBT plus hypnosis (50) or attention control (50) groups. Emotional distress was significantly decreased in the CBT plus hypnosis group at midpoint, conclusion, and 4 weeks after conclusion.[367]

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