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Advising Women Undergoing Treatment for Breast Cancer: A Narrative Review

Dawn Lemanne, MD, MPH,[1–3] and Victoria Maizes, MD[1]

Abstract

A majority of women undergoing conventional treatment for breast cancer also undertake complementary and integrative approaches. Practitioners knowledgeable about the evidence base behind common integrative approaches can help patients attain improved quality of life, and at times, improved survival. Evidence-based recommendations include the following: a plant-based diet for general health after diagnosis, and carbohydrate restriction for patients with estrogen receptor-positive postmenopausal breast cancer may be prudent. Other dietary recommendations include a 13-h daily overnight fast. Carefully selected patients may choose to fast the day before and the day of chemotherapy to decrease side effects. Specific food recommendations include avoidance or limitation of alcohol, and liberal culinary use of cruciferous vegetables, coffee, green tea, soy, and flaxseed. Promising supplements include diindolylmethane and melatonin. Omega 3 fatty acids may help with bone density in patients on aromatase inhibitors, but may increase chemotherapy resistance. Findings regarding the usefulness of multivitamins, vitamin D, vitamin C, and vitamin E are weak and/or mixed different exercise modalities may have different effects and thus play different roles in breast cancer therapy. Aerobic and resistance training combined during breast cancer chemotherapy may confer a survival benefit, while yoga may improve outcome in lymphedema patients. Current evidence suggests that meditation, yoga, breathing, music therapy, guided imagery, and hypnosis may improve mood and quality of life during breast cancer treatment. Acupuncture is useful for treating side effects of breast cancer therapies, including hot flushes, aromatase inhibitor-induced joint pain, chemotherapy-induced peripheral neuropathy, and vulvodynia. Vaginal moisturizers and vaginal rings supplying low-dose estrogen can be useful in the treatment of symptoms of estrogen-deprivation states caused by breast cancer treatments; such symptoms include vaginal dryness, dyspareunia, and sexual dysfunction. Carbon dioxide laser technology can rejuvenate atrophied vaginal mucosa and relieve dyspareunia, allowing avoidance of estrogen therapy. Tertiary sexual health centers are available for referral.

Keywords: cancer, integrative therapies, nutrition, dietary supplements, intermittent fasting, stress management

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Breast cancer is common. Lifetime risk of a breast cancer diagnosis is 12.4% for women living in the United States, and the disease accounts for 15% of new cancer diagnoses annually.[1] Use of integrative approaches as adjuncts to conventional care is extremely common, with as many as 84% of breast cancer patients using diet, supplements, exercise, and stress control interventions in hopes of improving survival and decreasing the side effects of conventional treatment.[2] Providers able to guide these patients toward evidence-based choices can be pivotal in helping them achieve their goals of improved physical and emotional well-being.[3] It has been the authors' experience that women respond with relief and gratitude at being able to discuss openly the use of integrative modalities during cancer therapy, with a knowledgeable health professional.

Providers can be confident that complementary interventions are effective adjuncts to conventional therapy. A trial of 275 breast cancer patients demonstrated that those

[1]The University of Arizona Center for Integrative Medicine, Tucson, Arizona.
[2]Oregon Integrative Oncology, Ashland, Oregon.
[3]National Institute of Integrative Medicine, Melbourne, Australia.

randomized to a personalized complementary program along with conventional care enjoyed a higher quality of life compared with similar patients given usual care only.[4]

In this article, the authors address many evidence-based integrative strategies that can enhance quality of life, and some that may extend life. What follows are the approaches they recommend most in their practices for patients on active conventional treatment for breast cancer.

Nutrition

Women often have questions about what they should eat; commonly women will change their diet after a breast cancer diagnosis.[5]Advice addresses whole food dietary patterns as well as pros and cons of specific foods. For general health purposes following a breast cancer diagnosis, the World Cancer Research Fund/American Institute for Cancer Research guidelines for cancer prevention are a starting point.[6] This is because following diagnosis, 35% of deaths in breast cancer patients are related not to breast cancer, but to cardiovascular disease.[7] An anti-inflammatory diet decreases overall mortality after a diagnosis of breast cancer, specifically by decreasing risk of death from cardiovascular disease.[8]

Carbohydrates

Following a diagnosis of breast cancer, the amount of dietary carbohydrate intake may influence prognosis. The Women's Healthy Eating and Lifestyle (WHELS) study found that failure to reduce carbohydrate intake after a postmenopausal breast cancer diagnosis was associated with a fivefold increase in recurrence. Confirmatory studies are needed; meanwhile, the lack of harm from moderating carbohydrate intake is reason to advise breast cancer patients to consider decreasing overall carbohydrate intake.[9]

Intermittent fasting

Animal studies show that short-term fasting, or the complete abstinence from dietary calories while taking water, rivals the anticancer effect of chemotherapy. For example, two 48-h fasting cycles alone arrested tumor progression in a mouse model of breast cancer.[10] Furthermore, combining fasting with chemotherapy resulted in long-term disease-free survival in animal models of usually incurable human tumors, a synergistic effect that neither fasting alone nor chemotherapy alone can approach. The authors of these studies concluded that fasting immediately before, during, and after a chemotherapy infusion potentiates the anticancer effects of the treatment while reducing side effects.[11–13]

A randomized controlled study of 13 women with HER2-negative breast cancer undergoing neoadjuvant treatment with docetaxel, doxorubicin, and cyclophosphamide found that fasting 24 h before and after each chemotherapy infusion was well tolerated and decreased hematologic toxicity.[14]

Patients with a variety of tumors, including breast cancer, who fasted for at least 48 h during platinum-based chemotherapy incurred less DNA damage in leukocytes than those fasting for shorter periods. No serious adverse effects occurred in patients fasting up to 72 h.[15]

An observational study found that patients with early-stage breast cancer fasting 13 or more hours overnight suffered fewer cancer relapses compared with those fasting 12 or fewer hours overnight.[16] This suggests that simply extending the daily overnight fast to 13 or more hours may decrease the risk of breast cancer recurrence. This was a single observational study; confirmatory studies are needed. However, in clinical experience, this is a safe and comfortable practice for many women.

Alcohol

In women with postmenopausal breast cancer, alcohol consumption is related to an increased risk of recurrence, but not mortality.[17,18] Therefore, women with postmenopausal breast cancer can be advised to minimize alcohol intake.

Medicinal mushrooms

The use of medicinal mushrooms in cancer therapy has ancient roots[19] and preclinical work reveals plausible anticancer mechanisms.[20] A few of these include Agaricus, maitake (*Grifola frondosa)*, shiitake (*Lentinula edodes*), reishi (*Ganoderma lucidum)*, turkey tail (*Trametes versicolor*), and *Cordyceps sinensis*. Clinical data on the efficacy of medicinal mushrooms, however, are sparse, and adequately controlled trials are lacking. Case studies exist but are often confounded by concurrent use of conventional therapy. More research is needed before use of medicinal mushrooms can be recommended during breast cancer treatment.[21–24]

Cruciferous vegetables

The WHELS intervention, which emphasized fat restriction with increased fruit and vegetable intake, failed to document a compelling association between dietary components and overall breast cancer survival.[25,26] However, the subgroup of breast cancer patients on tamoxifen experienced a reduction in recurrence risk with increased intake of vegetables, especially cruciferous vegetables.[27] Cruciferous vegetable intake can be enthusiastically encouraged for all women with breast cancer, especially those taking tamoxifen, because of the suggestion of synergy between cruciferous vegetables and tamoxifen in the WHELS trial.

Coffee

A study found that compared with low coffee intake, 0–1 cups daily, a moderate coffee intake of 2–4 cups daily was associated with fewer recurrences in breast cancer patients on tamoxifen.[28] Because two studies found an association between heavy coffee consumption, five or more cups daily, and increased mortality in those younger than 55 years, it would be prudent to advise those who enjoy coffee to drink it in moderation, especially before middle age.[29,30]

Green tea

Green tea consumption after a breast cancer diagnosis was associated in two Japanese observational studies with a decreased risk of recurrence. The minimum intake needed to see the association in one study was five cups per day; in the second study the amount needed was three cups per day. In both studies, the effect was strongest in those with stage I disease, still present but less evident in those with stage II disease, and not seen in patients with stage III or IV disease.[31,32]

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Soy

In Asian populations, observational work shows that soy ingestion may improve all-cause mortality after a breast cancer diagnosis.[33] The authors are still learning the complex ways in which soy isoflavones interact with the gut microbiome and human enzymes to influence steroid signaling pathways. The benefits of dietary soy are modulated by the presence or absence of commensal gut bacteria with the specific ability to metabolize the soy isoflavone daidzein to the nonsteroidal estradiol analogue (*S*)-equol.[34,35] The carriage of equol-producing commensals differs at the population level. Only 25%–30% of Westerners produce (*S*)-equol after soy intake, compared with 50%–60% of East Asians.[36]

A few preclinical studies document harm from soy isoflavones, including promotion of breast cancer metastasis.[37,38] This suggests biologically relevant differences between consuming whole soy foods and isolated soy isoflavones. Two large U.S. trials, the Life After Cancer Epidemiology and The Breast Cancer Family Registry, confirm safety of whole soy after a breast cancer diagnosis.[39,40] Women with breast cancer can be advised to enjoy a reasonable amount of whole soy foods, while avoiding supplemental soy protein and isoflavone isolates. A reasonable amount can be deduced from the average soy consumption in Asian populations, which provides 10–20 mg of soy isoflavones per person daily. This is the amount found in 30 g of whole soy products such as tofu.[41,42]

Flaxseed

Flaxseed provides fiber and enterolignans important for general health, and studies suggest that after a diagnosis of breast cancer, flaxseed may provide some antitumor activity. A prospective controlled trial of flaxseed intake in women newly diagnosed with primary breast cancer demonstrated downregulation of tumor expression of the c-erbB2 (HER2) growth pathway, a decreased tumor proliferation index, concomitant increase in apoptosis, and programmed cell death, with intake of flaxseed compared with placebo.[43] A prospective observational study of breast cancer patients found an association between women whose dietary recall reported high intake of enterolignans from either sesame seeds or flaxseeds and lower overall mortality.[44]

Dietary Supplements

The effect of dietary supplements in the breast cancer treatment setting is controversial and difficult to study. A comprehensive treatment of the topic is not possible here; the recommendation is that physicians obtain information on supplements from credible sources and individualize supplement recommendations.[45]

The finding of a connection between cruciferous vegetable intake and tamoxifen use in the WHELS cohort led to a randomized, placebo-controlled study of diindolylmethane (DIM), an active metabolite of indole-3-carbinol, found in cruciferous vegetables. This study confirmed that DIM, when given to breast cancer patients on tamoxifen, beneficially modulated levels of sex hormone binding globulin and endogenous estrogens.[46] Whether this results in improved breast cancer-specific or overall survival has not been studied.

Melatonin is well studied in breast cancer. A meta-analysis of eight randomized controlled trials of solid tumors evaluated 761 subjects who received 20 mg of melatonin at bedtime in conjunction with chemotherapy or radiation. It found near-doubling of complete or partial remission and increased 1-year survival in patients taking melatonin, along with decreases in treatment side effects.[47] Whether this translates to long-term survival benefits remains to be studied.

Omega 3 fatty acids are sometimes recommended for supplementation. High-dose docosahexaenoic acid and eicosapentaenoic acid (3 g per day) have been studied in women treated with aromatase inhibitors and shown to reduce bone resorption.[48] Obtaining omega 3 fatty acids through fish oil and even fish consumption has been shown in at least one study to increase production of drug resistance factors in patients undergoing platinum-based chemotherapy. Therefore, until more is learned about this interaction, omega 3 and fish oil supplementation should be avoided by breast cancer patients on chemotherapy.[49]

The Women's Health Initiative (WHI) trial, in which 7728 postmenopausal women were followed for an average of 7.1 years after the diagnosis of invasive breast cancer, found an association between enhanced survival and multivitamin use.[50] Other studies, however, have failed to replicate this result.[51,52]

Antioxidant supplements should not be considered benign; a review of four randomized clinical trials, evaluating the effects of supplementation with vitamin E and beta-carotene during radiation therapy for head and neck cancer, found that while the supplements decreased side effects from radiation therapy, recurrence and survival were worsened, especially in smokers.[45] This raises questions regarding the safety of using antioxidant supplements during breast cancer chemotherapy and radiation, questions that to date remain unanswered.

Finally, one retrospective study found vitamin D supplementation to be associated with decreased risk of breast cancer recurrence, but only in patients with estrogen receptor-expressing tumors. The same study found supplemental antioxidant use, in the form of vitamin C, vitamin E, or multivitamin formulas, to be associated with decreased overall mortality, but not cancer mortality, in all breast cancer subtypes.[53]

Exercise

Exercise modulates immune function, inflammation, angiogenesis, metabolism, sex steroid hormone production, endogenous antioxidant production, mood and autonomic function, and other systems involved in cancer recovery.[54]

Observational studies consistently demonstrate an association between exercise and enhanced quality of life during cancer treatment, and improved survival after a breast cancer diagnosis.[55] Controlled clinical trials suggest that vigorous exercise carried out during breast cancer chemotherapy improves cancer-specific survival.[56,57]

Early controlled trials suggest that breast cancer patients on chemotherapy should be prescribed exercise to improve cancer-specific survival. The three-armed Canadian START trial of women with early-stage breast cancer demonstrated improved survival with exercise at long-term follow-up (mean 89 months).[58,59] Those subjects enjoying the greatest

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exercise-related improvements in breast cancer survival had stage II/III disease, estrogen receptor-positive tumors and/or HER2-positive tumors, received taxane-based chemotherapies, completed at least 85% of recommended chemotherapy, or were overweight or obese. Although the findings did not reach statistical significance, the authors felt that the effects were meaningful, with a 7%–9% difference in absolute survival favoring the exercise interventions.[60]

A small pilot study randomized patients undergoing chemotherapy for breast cancer to aerobic plus resistance training, and a nonexercise control group, and showed the combination aerobic plus resistance training arm had improved cancer-related fatigue, pain, mood, and quality of life, with no adverse events related to exercise.[61]

A prospective three-armed trial of aerobic exercise in breast cancer chemotherapy patients receiving glucocorticoids showed that compared with subjects randomized to the nonexercise control groups, who suffered the expected severe loss of bone mineral density, those in the resistance training and aerobic training arms maintained bone mineral density.[62]

Two prospective controlled trials demonstrated that supervised resistance training lowered the incidence of lymphedema in high-risk breast cancer patients.[63,64] Two randomized trials found yoga improved arm circumference in patients with lymphedema.[65,66]

For patients undergoing breast cancer chemotherapy, supervised exercise programs have proved more effective than home-based or unsupervised programs in improving chemotherapy completion rates.[67] Referral to an exercise-based lifestyle program during adjuvant chemotherapy is well accepted by patients and oncologists, and results in increased physical activity levels and health-related quality of life that persist for at least 2 years following completion of the intervention.[68]

Stress Management

Animal models of breast cancer and other malignancies provide strong evidence that chronic stress and sympathetic activation can drive tumor invasion and metastasis via adrenergic upregulation of growth signaling pathways.[69,70] Whether stress reduction improves breast cancer survival is unknown; however, quality of life is improved with use of stress management interventions.[71]

Practices supported by the American Society of Clinical Oncology and the Society for Integrative Oncology for this purpose include meditation, yoga, music therapy, guided imagery, hypnosis, deep breathing, exercise, and massage.[72] A recent review found that after a breast cancer diagnosis, a formal mindfulness practice was associated with improvements in mood, anxiety, and physical symptoms.[73]

Acupuncture

Acupuncture can be helpful for a variety of side effects related to breast cancer treatment. A randomized, placebo-controlled trial found electroacupuncture to be slightly more effective than gabapentin in controlling hot flushes.[74] In another randomized, controlled trial, acupuncture was effective for joint pain due to aromatase inhibitor therapy[75] and chemotherapy-induced peripheral neuropathy. Acupuncture offers a nonpharmaceutical approach to pain from chemotherapy-induced peripheral neuropathy and is recommended for this use by the American Society of Clinical Oncology.[76]

Sexuality

As many as 90% of women have sexual problems after breast cancer treatment; in 50%, these problems are chronic. They include loss of sexual pleasure with breast stimulation following a mastectomy; vaginal dryness leading to painful intercourse due to treatment-induced menopause or selective estrogen receptor modulators; vulvodynia and decreased libido due to hormonal changes; and loss of interest due to focus on survival. Inquiring about changes in sexual function since diagnosis is part of a complete history. For providers uncomfortable with management, a number of programs in sexuality after cancer are available at tertiary care centers.[77]

Table 1. Evidence-Based Integrative Approaches for Patients Undergoing Treatment for Breast Cancer

Intervention class	*Details and study findings*	*Refs.*
Macronutrient ratio and fasting	• Carbohydrate restriction was associated with decreased recurrence in patients with postmenopausal, hormone receptor-expressing breast cancer	9
	• 13-h overnight fasting was associated with decreased breast cancer recurrence over 2 years	16
	• 48-h peri-chemotherapy water fasting decreased hematologic toxicity	15
Specific foods	• Alcohol may increase recurrence risk	17
	• Cruciferous vegetables may reduce recurrence risk in tamoxifen users	27
	• Coffee may decrease recurrence risk in tamoxifen users	28
	• Green tea may decrease recurrence risk in early breast cancer	31,32
Supplements	• Melatonin improved treatment response and 1-year survival	47
	• Vitamin D is associated with decreased recurrence in patients with estrogen receptor-positive breast cancer	54
Exercise	• Aerobic + resistance training during adjuvant chemotherapy: associated with improved long-term survival	61
	• Yoga: improvement in lymphedema outcome	66,67
Stress management	• Mindfulness may improve mood, anxiety, pain	74
Treatment side effect management	• Acupuncture may improve hot flushes and joint pain due to aromatase inhibitors	75,76
	• Improved pain from chemotherapy-induced peripheral neuropathy	77
Sexual health	• CO_2 laser vaginal mucosal microablation (MonaLisa Touch®): restores elasticity and moisture to vaginal tissues atrophied by lack of estrogen	82

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Table 2. Resources

Clinical practice guidelines	Society for integrative oncology	https://integrativeonc.org/integrativeoncology-guidelines
Environmental information	Environmental working group	https://www.ewg.org
Sexuality after cancer	University of Chicago Integrative Sexual Medicine (PRISM) for Women and Girls with Cancer	www.uchospitals.edu/specialties/obgyn/prism.html
Nutrition and cancer	University of Arizona Center for Integrative Medicine online course	https://integrativemedicine.arizona.edu/online_courses/nut_cancer.html
Supplements	Natural Medicines Comprehensive Database	http://naturaldatabase.therapeuticresearch.com/home.aspx?cs=&s=ND
Herbs and botanicals: information on safety and effectiveness	National Center for Complementary and Integrative Health	https://nccih.nih.gov/health/herbsataglance.htm
Herbs, botanicals, and alternative treatments: evidence-based reviews	Memorial Sloan Kettering Cancer Center	https://www.mskcc.org/cancer-care/diagnosis-treatment/symptom-management/integrative-medicine/herbs
Integrative approaches to breast cancer	University of Arizona Center for Integrative Medicine online course	https://integrativemedicine.arizona.edu/online_courses/breastcancer_integrativeapproach.html

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Vaginal dryness can be addressed with moisturizers (used regularly) or lubricants (used during intercourse). While systemic hormone therapy is contraindicated in women with estrogen receptor-positive breast cancer, short courses of vaginal estrogen can be considered. The lowest systemic absorption of vaginal estrogen is with the vaginal ring; at a dose of 5–10 μg/daily it does not increase serum estradiol levels.[78] Vaginal estrogen may be contraindicated for women on aromatase inhibitors (AIs) as one study suggested that this counteracts AI-induced estrogen suppression.[79] A pilot study suggests that for some women, vulvodynia may be addressed with acupuncture.[80]

Fractionated laser therapies for vulvovaginal atrophy, such as the MonaLisa Touch®, use a low-energy CO_2 laser to painlessly disrupt the vaginal mucosa. This results in a healing response that includes increased vascularity and collagen production, restoring elasticity to the vaginal mucosa and relieving symptoms of dryness and pain with intercourse, all while avoiding the use of estrogenic drugs. Such treatments have been found to enhance the Female Sexual Function Index score and reduce dyspareunia due to vulvovaginal atrophy in postmenopausal women.[81]

Conclusion

Integrative therapies can mitigate side effects of conventional breast cancer treatments, increasing the likelihood that women will complete therapy. Sufficient evidence of benefit is present for recommending specific foods, exercise, and acupuncture.

Whole foods should be chosen over supplements when possible. Alcohol, low-quality carbohydrates, soy protein isolates, and seed oils high in polyunsaturated fats should be avoided. Coffee can be taken in moderation, while green and cruciferous vegetables, culinary mushrooms, olive oil, seed nuts, and whole soy can be enjoyed *ad libitum*.

Medically supervised short fasts at the time of chemotherapy can be considered in otherwise healthy patients and may decrease the adverse effects of chemotherapy while increasing efficacy. A 13-h overnight fast may decrease risk of breast cancer recurrence.

Aerobic training, resistance (weight) training, and yoga have demonstrated measurable beneficial effects across the breast cancer spectrum, including decrease in breast cancer incidence, partial mitigation of chemotherapy side effects, reduction in the incidence and severity of lymphedema, and improvements in cancer-related survival. Supervised exercise is more likely than unsupervised exercise to result in lasting benefits. These are summarized in Table 1.

Many additional questions will arise when caring for women with breast cancer. It is highly recommended that providers continue to educate themselves. Credible resources are found in Table 2.

Author Disclosure Statement

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References

1. Howlader N, Noone AM, Krapcho M, et al. SEER Cancer Statistics Review, 1975–2014, National Cancer Institute. Bethesda, MD. 2017. Online document at: https://seer.cancer.gov/csr/1975_2014/, based on November 2016 SEER data submission, posted to the SEER web site, accessed March 1, 2018.
2. Morris K, Johnson N, Homer L, et al. A comparison of complementary therapy use between breast cancer patients and patients with other primary tumor sites. Am J Surg 2000;179:407–411.
3. Ben-Arye E, Dahly H, Keshet Y, et al. Providing integrative care in the pre-chemotherapy setting: A pragmatic controlled patient-centered trial with implications for supportive cancer care. J Cancer Res Clin Oncol 2018;144:1825–1833.
4. Witt CM, Außerer O, Baier S, et al. Effectiveness of an additional individualized multi-component complementary medicine treatment on health-related quality of life in

breast cancer patients: A pragmatic randomized trial. Breast Cancer Res Treat 2015;149:449–460.
5. Kaledkiewicz E, Szostak-Węgierek D. Dietary practices and nutritional status in survivors of breast cancer. Rocz Panstw Zakl Hig 2018;69:175–182.
6. World Cancer Research Fund/American Institute for Cancer Research. Continuous Update Project Expert Report 2018. London, UK: Diet, Nutrition, Physical Activity, and Breast Cancer Survivors. p. 32.
7. Schairer C, Mink PJ, Carroll L, Devesa SS. Probabilities of death from breast cancer and other causes among female breast cancer patients. J Natl Cancer Inst 2004;96:1311–1321.
8. Zheng J, Tabung FK, Zhang J, et al. Association between post-cancer diagnosis dietary inflammatory potential and mortality among invasive breast cancer survivors in the Women's Health Initiative. Cancer Epidemiol Biomarkers Prev 2018;27:454–463.
9. Emond JA, Pierce JP, Natarajan L, et al. Risk of breast cancer recurrence associated with carbohydrate intake and tissue expression of IGF-1 receptor. Cancer epidemiology, biomarkers and prevention: A publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 2014;23:1273–1279.
10. Lee C, Safdie FM, Raffaghello L, et al. Reduced IGF-I differentially protects normal and cancer cells and improves chemotherapeutic index in mice. Cancer Res 2010; 70:1564–1572.
11. Lee C, Raffaghello L, Brandhorst S, et al. Fasting cycles retard growth of tumors and sensitize a range of cancer cell types to chemotherapy. Sci Transl Med 2012;4:124ra27.
12. Shi Y, Felley-Bosco E, Marti TM, et al. Starvation-induced activation of ATM/Chk2/p53 signaling sensitizes cancer cells to cisplatin. BMC Cancer 2012;12:571.
13. Raffaghello L, Lee C, Safdie FM, et al. Starvation-dependent differential stress resistance protects normal but not cancer cells against high-dose chemotherapy. Proc Natl Acad Sci USA 2008;105:8215–8220.
14. De Groot S, Vreeswijk MP, Welters MJ, et al. The effects of short-term fasting on tolerance to (neo) adjuvant chemotherapy in HER2-negative breast cancer patients: A randomized pilot study. BMC Cancer 2015;15:652.
15. Dorff TB, Groshen S, Garcia A, et al. Safety and feasibility of fasting in combination with platinum-based chemotherapy. BMC Cancer 2016;16:360.
16. Marinac CR, Nelson SH, Breen CI, et al. Prolonged nightly fasting and breast cancer prognosis. JAMA Oncol 2016;2: 1049–1055.
17. Kwan ML, Chen WY, Flatt SW, et al. Post-diagnosis alcohol consumption and breast cancer prognosis in the after breast cancer pooling project. Cancer Epidemiol Biomarkers Prev 2013;22:32–41.
18. Frydenberg H, Flote VG, Larsson IM, et al. Alcohol consumption, endogenous estrogen and mammographic density among premenopausal women. Breast Cancer Res 2015;17: 103.
19. Guggenheim AG, Wright KM, Zwickey HL. Immune modulation from five major mushrooms: application to integrative oncology. Integr Med 2014;13:32–44.
20. Joseph TP, Chanda W, Padhiar AA, et al. A preclinical evaluation of the antitumor activities of edible and medicinal mushrooms: A molecular insight. Integr Cancer Ther 2018; 17:200–209.
21. Kodama N, Komuta K, Nanba H. Can maitake MD-fraction aid cancer patients? Altern Med Rev 2002;7:236–239.
22. Standish LJ, Wenner CA, Sweet ES, et al. Trametes versicolor mushroom immune therapy in breast cancer. J Soc Integr Oncol 2008;6:122–128.
23. Suárez-Arroyo IJ, Loperena-Alvarez Y, Rosario-Acevedo R, Martínez-Montemayor MM. Ganoderma spp.: A promising adjuvant treatment for breast cancer. Medicines 2017; 4:15.
24. Chang ST, Wasser SP. The role of culinary-medicinal mushrooms on human welfare with a pyramid model for human health. Int J Med Mushrooms 2012;14:95–134.
25. Pierce JP, Natarajan L, Caan BJ, et al. Influence of a diet very high in vegetables, fruit, and fiber and low in fat on prognosis following treatment for breast cancer: The women's healthy eating and living (WHEL) randomized trial. JAMA 2007;298:289–298.
26. Chlebowski RT, Blackburn GL, Thomson CA, et al. Dietary fat reduction and breast cancer outcome: Interim efficacy results from the women's intervention nutrition study. J Natl Cancer Inst 2006;98:1767–1776.
27. Thomson CA, Rock CL, Thompson PA, et al. Vegetable intake is associated with reduced breast cancer recurrence in tamoxifen users: A secondary analysis from the Women's Healthy Eating and Living Study. Breast Cancer Res Treat 2011;125:519.
28. Simonsson M, Söderlind V, Henningson M, et al. Coffee prevents early events in tamoxifen-treated breast cancer patients and modulates hormone receptor status. Cancer Causes Control 2013;24:929–940.
29. Liu J, Sui X, Lavie CJ, et al. Association of coffee consumption with all-cause and cardiovascular disease mortality. Mayo Clinic Proc 2013;88:1066–1074.
30. Löf M, Sandin S, Yin L, et al. Prospective study of coffee consumption and all-cause, cancer, and cardiovascular mortality in Swedish women. Eur J Epidemiol 2015;30: 1027–1034.
31. Inoue M, Tajima K, Mizutani M, et al. Regular consumption of green tea and the risk of breast cancer recurrence: Follow-up study from the Hospital-based Epidemiologic Research Program at Aichi Cancer Center (HERPACC), Japan. Cancer Lett 2001;167:175–182.
32. Nakachi K1, Suemasu K, Suga K, et al. Influence of drinking green tea on breast cancer malignancy among Japanese patients. Jpn J Cancer Res 1998;89:254–261.
33. Zhang FF, Haslam DE, Terry MB, et al. Dietary isoflavone intake and all-cause mortality in breast cancer survivors: The Breast Cancer Family Registry. Cancer 2017;123:2070–2079.
34. Ko KP. Isoflavones: Chemistry, analysis, functions and effects on health and cancer. Asian Pac J Cancer Prev 2014; 15:7001–7010.
35. Ko KP. Isoflavones: Chemistry, analysis, functions and effects on health and cancer. Asian Pac J Cancer Prev 2014; 15:7001-7010.
36. Song KB, Atkinson C, Frankenfeld CL, et al. Prevalence of daidzein-metabolizing phenotypes differs between Caucasian and Korean American women and girls. J Nutr 2006; 136:1347–1351.
37. Martínez-Montemayor MM, Otero-Franqui E, Martinez J, et al. Individual and combined soy isoflavones exert differential effects on metastatic cancer progression. Clin Exp Metastasis 2010;27:465–480.
38. Yang X, Belosay A, Hartman JA, et al. Dietary soy isoflavones increase metastasis to lungs in an experimental

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model of breast cancer with bone micro-tumors. Clin Exp Metastasis 2015;32:323–333.
39. Guha N, Kwan ML, Quesenberry CP Jr, et al. Soy isoflavones and risk of cancer recurrence in a cohort of breast cancer survivors: The Life After Cancer Epidemiology study. Breast Cancer Res Treat 2009;118:395–405.
40. Zhang FF, Haslam DE, Terry MB, et al. Dietary isoflavone intake and all-cause mortality in breast cancer survivors: The Breast Cancer Family Registry. Cancer 2017;123: 2070–2079.
41. Hui E, Henning SM, Park N, et al. Genistein and daidzein/glycitein content in tofu. J Food Comp Anal 2001;14:199–206.
42. Wu AH, Lee E, Vigen C. Soy isoflavones and breast cancer. Am Soc Clin Oncol Educ Book 2013;33:102–106.
43. Thompson LU, Chen JM, Li T, et al. Dietary flaxseed alters tumor biological markers in postmenopausal breast cancer. Clin Cancer Res 2005;11:3828–3835.
44. Buck K, Zaineddin AK, Vrieling A, et al. Estimated enterolignans, lignan-rich foods, and fibre in relation to survival after postmenopausal breast cancer. Br J Cancer 2011; 105:1151–1157.
45. Harvie M. Nutritional supplements and cancer: Potential benefits and proven harms. Am Soc Clin Oncol Educ Book 2014;34:e478–e486.
46. Thomson CA, Chow HHS, Wertheim BC et al. A randomized, placebo-controlled trial of diindolylmethane for breast cancer biomarker modulation in patients taking tamoxifen. Breast Cancer Res Treat 2017;165:97.
47. Wang YM, Jin BZ, Ai F, et al. The efficacy and safety of melatonin in concurrent chemotherapy or radiotherapy for solid tumors: A meta-analysis of randomized controlled trials. Cancer Chemother Pharmacol 2012;69: 1213–1220.
48. Hutchins-Wiese HL, Picho K, Watkins BA, et al. High-dose eicosapentaenoic acid and docosahexaenoic acid supplementation reduces bone resorption in postmenopausal breast cancer survivors on aromatase inhibitors: A pilot study. Nutr Cancer 2014;66:68–76.
49. Daenen LG, Cirkel GA, Houthuijzen JM, et al. Increased plasma levels of chemoresistance-inducing fatty acid 16: 4(n-3) after consumption of fish and fish oil. JAMA Oncol 2015;1:350–358.
50. Wassertheil-Smoller S, McGinn AP, Budrys N, et al. Multivitamin and mineral use and breast cancer mortality in older women with invasive breast cancer in the women's health initiative. Breast Cancer Res Treat 2013;141:495–505.
51. Ishitani K, Lin J, Manson JE, et al. A prospective study of multivitamin supplement use and risk of breast cancer. Am J Epidemiol 2008;167:1197–1206.
52. Larsson SC, Åkesson A, Bergkvist L, Wolk A. Multivitamin use and breast cancer incidence in a prospective cohort of Swedish women. Am J Clin Nutr 2010;91:1268–1272.
53. Poole EM, Shu X, Caan BJ, et al. Post-diagnosis supplement use and breast cancer prognosis in the After Breast Cancer Pooling Project. Breast Cancer Res Treat 2013;139: 529–537.
54. Thomas RJ, Kenfield SA, Jimenez A. Exercise-induced biochemical changes and their potential influence on cancer: A scientific review. Br J Sports Med 2017;51: 640–644.
55. Cormie P, Zopf EM, Zhang X, Schmitz KH. The impact of exercise on cancer mortality, recurrence, and treatment-related adverse effects. Epidemiol Rev 2017;391:71–92.
56. Rezende LFMD, Sá THD, Markozannes G, et al. Physical activity and cancer: An umbrella review of the literature including 22 major anatomical sites and 770,000 cancer cases. Br J Sports 2018;52:826–833.
57. Holmes MD, Chen WY, Feskanich D, et al. Physical activity and survival after breast cancer diagnosis. JAMA 2005;293:2479–2486.
58. Courneya KS, Segal RJ, Mackey JR, et al. Effects of aerobic and resistance exercise in breast cancer patients receiving adjuvant chemotherapy: A multicenter randomized controlled trial. J Clin Oncol 2007;25:4396–4404.
59. Courneya KS, Segal RJ, Gelmon K, et al. Six-month follow-up of patient-rated outcomes in a randomized controlled trial of exercise training during breast cancer chemotherapy. Cancer Epidemiol Biomarkers Prev 2007;16: 2572–2578.
60. Courneya KS, Segal RJ, McKenzie DC, et al. Effects of exercise during adjuvant chemotherapy on breast cancer outcomes. Med Sci Sports Exerc 2014;46:1744–1751.
61. Schulz SVW, Laszlo R, Otto S, et al. Feasibility and effects of a combined adjuvant high-intensity interval/strength training in breast cancer patients: A single-center pilot study. Disabil Rehabil 2017;21:1–8.
62. Schwartz AL, Winters-Stone K, Gallucci B. Exercise effects on bone mineral density in women with breast cancer receiving adjuvant chemotherapy. Oncol Nurs Forum 2007; 34:627–633.
63. Bloomquist K, Oturai P, Steele ML, et al. Heavy-load lifting: Acute response in breast cancer survivors at risk for lymphedema. Med Sci Sports Exerc 2018;50:187–195.
64. Schmitz KH, Ahmed RL, Troxel AB, et al. Weight lifting for women at risk for breast cancer-related lymphedema: A randomized trial. JAMA 2010;304:2699–2705.
65. Loudon A, Barnett T, Piller N, et al. Yoga management of breast cancer-related lymphoedema: A randomised controlled pilot-trial. BMC Complement Altern Med 2014;14: 214.
66. Fisher MI, Donahoe-Fillmore B, Leach L, et al. Effects of yoga on arm volume among women with breast cancer related lymphedema: A pilot study. J Bodyw Mov Ther 2014;18:559–565.
67. van Waart H, Stuiver MM, van Harten WH, et al. Effect of low-intensity physical activity and moderate- to high-intensity physical exercise during adjuvant chemotherapy on physical fitness, fatigue, and chemotherapy completion rates: Results of the PACES randomized clinical trial. J Clin Oncol 2015;33:1918–1927.
68. Kirkham AA, Van Patten CL, Gelmon KA, et al. Effectiveness of oncologist-referred exercise and healthy eating programming as a part of supportive adjuvant care for early breast cancer. Oncologist 2018;23:105–115.
69. Le CP, Nowell CJ, Kim-Fuchs C, et al. Chronic stress in mice remodels lymph vasculature to promote tumour cell dissemination. Nat Commun 2016;7:10634.
70. Sloan EK, Priceman SJ, Cox BF, et al. Sympathetic nervous system induces a metastatic switch in primary breast cancer. Cancer Res 2010;70:7042–7052.

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71. Lyman GH, Greenlee H, Bohlke K, et al. Integrative therapies during and after breast cancer treatment: ASCO endorsement of the SIO clinical practice guideline. J Clin Oncol 2018;14:495–499.
72. Greenlee H, Balneaves LG, Carlson LE, et al. Clinical practice guidelines on the use of integrative therapies as supportive care in patients treated for breast cancer. JNCI Monogr 2014;2014:346–358.
73. Modica C, Hoenig K. Mindfulness in follow-up care after breast cancer: Can it prevent recurrence? Breast Care (Basel) 2018;13:102–108.
74. Mao J, Bowman M, Xie S, et al. Electroacupuncture versus gabapentin for hot flashes among breast cancer survivors: A randomized placebo-controlled trial. J Clin Oncol 2015;33: 3615–3620.
75. Crew KD, Capodice JL, Greenlee H, et al. Pilot study of acupuncture for the treatment of joint symptoms related to adjuvant aromatase inhibitor therapy in postmenopausal breast cancer patients. J Cancer Surviv 2007;1: 283–291.
76. Lu W, Rosenthal DS. Acupuncture for chronic pain in cancer survivors: A reflection on the American Society of Clinical Oncology chronic pain guideline. Hematol Oncol Clin North Am 2018;32:519–533.
77. Lindau ST, Abramsohn EM, Baron SR, et al. Physical examination of the female cancer patient with sexual concerns: What oncologists and patients should expect from consultation with a specialist. CA Cancer J Clin 2016;66: 241–263.
78. Krause M, Wheeler TL, Richter HE, Snyder TE. Systemic effects of vaginally administered estrogen therapy: A review. Female Pelvic Med Reconstr Surg 2010;16: 188–195.
79. Kendall A, Dowsett M, Folkerd E, et al. Caution: Vaginal estradiol appears to be contraindicated in postmenopausal women on adjuvant aromatase inhibitors. Ann Oncol 2006; 17:584–587.
80. Schlaeger JM, Xu N, Mejta CL. Acupuncture for the treatment of vulvodynia: A randomized wait-list controlled pilot study. J Sex Med 2015;12:1019–1027.
81. Salvatore S, Pitsouni E, Del Deo F, et al. Sexual function in women suffering from genitourinary syndrome of menopause treated with fractionated CO2 Laser. Sex Med Rev 2017;5:486–494.

Address to correspondence:
Victoria Maizes, MD
The University of Arizona Center for Integrative Medicine
1249N. Mountain Avenue
PO Box 245153
Tucson, AZ 85724

E-mail: vmaizes@email.arizona.edu

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