

**ARTICLE TITLE: Clinical Practice Guidelines on the Evidence-Based Use of Integrative Therapies During and After Breast Cancer Treatment**

CME CNE

**CONTINUING MEDICAL EDUCATION ACCREDITATION AND DESIGNATION STATEMENT:**

Blackwell Futura Media Services is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education (CME) for physicians.

Blackwell Futura Media Services designates this enduring material for a maximum of 2.25 *AMA PRA Category 1 Credit*<sup>™</sup>. Physicians should only claim credit commensurate with the extent of their participation in the activity.

**CONTINUING NURSING EDUCATION ACCREDITATION AND DESIGNATION STATEMENT:**

The American Cancer Society (ACS) is accredited as a provider of continuing nursing education (CNE) by the American Nurses Credentialing Center's Commission on Accreditation.

Accredited status does not imply endorsement by the ACS or the American Nurses Credentialing Center of any commercial products displayed or discussed in conjunction with an educational activity. The ACS gratefully acknowledges the sponsorship provided by Wiley for hosting these CNE activities.

**EDUCATIONAL OBJECTIVES:**

After reading the article "Clinical Practice Guidelines on the Evidence-Based Use of Integrative Therapies During and After Breast Cancer Treatment," the learner should be able to:

1. Highlight current practice guidelines on the use of integrative therapies during and after breast cancer treatment.
2. Apply evidence-based gradings of the efficacy of integrative treatment modalities that balance potential benefits and harms in formulating treatment decisions and referrals for addressing the symptoms and side effects of breast cancer therapy.
3. Acknowledge the strengths and limitations of integrative therapies for treating breast cancer-related symptoms and side effects and future research needs in this area.

**ACTIVITY DISCLOSURES:**

No commercial support has been accepted related to the development or publication of this activity.

**ACS CONTINUING PROFESSIONAL EDUCATION COMMITTEE DISCLOSURES:**

Editor: Ted Gansler, MD, MBA, MPH, has no financial relationships or interests to disclose.

Associate Editor: Durado Brooks, MD, MPH, has no financial relationships or interests to disclose.

Lead Nurse Planner: Cathy Meade, PhD, RN, FAAN, has no financial relationships or interests to disclose.

Editorial Advisory Member: Richard C. Wender, MD, has no financial relationships or interests to disclose.

**NURSING ADVISORY BOARD DISCLOSURES:**

Maureen Berg, RN, has no financial relationships or interests to disclose.

Susan Jackson, RN, MPH, has no financial relationships or interests to disclose.

Barbara Lesser, BSN, MSN, has no financial relationships or interests to disclose.

**AUTHOR DISCLOSURES:**

Linda E. Carlson, PhD, reports royalties from New Harbinger Publications and American Psychological Association Books, outside the submitted work. Misha R. Cohen, OMD, LAc, reports royalties from Health Concerns Inc, outside the submitted work. Matthew Mumber, MD, reports ownership interest in the I Thrive cancer survivorship software company, outside the submitted work.

Heather Greenlee, ND, PhD, MPH, Melissa J. DuPont-Reyes, MPH, MPhil, Lynda G. Balneaves, RN, PhD, Gary Deng, MD, PhD, Jillian A. Johnson, PhD, Dugald Seely, ND, MSc, Suzanna Zick, ND, MPH, Lindsay M. Boyce, MLIS, and Debu Tripathy, MD, have no financial relationships or interests to disclose.

The peer reviewers disclose no conflicts of interest. Identities of the reviewers are not disclosed in line with the standard accepted practices of medical journal peer review.

**SCORING:**

A score of 70% or better is needed to pass a quiz containing 10 questions (7 correct answers), or 80% or better for 5 questions (4 correct answers).

**CME INSTRUCTIONS ON RECEIVING CME CREDIT:**

This activity is intended for physicians. For information concerning the applicability and acceptance of CME credit for this activity, please consult your professional licensing board.

This activity is designed to be completed within 2.25 hours; physicians should claim only those credits that reflect the time actually spent in the activity. To successfully earn credit, participants must complete the activity during the valid credit period, which is up to 2 years from the time of initial publication.

**CNE INSTRUCTIONS ON RECEIVING CNE CREDIT:**

This activity is intended for nurses. For information concerning the applicability and acceptance of CNE credit for this activity, please consult your professional licensing board.

This activity is designed to be completed within 2.25 hours; nurses should claim only those credits that reflect the time actually spent in the activity. To successfully earn credit, participants must complete the activity during the valid credit period, which is up to 2 years from the time of initial publication.

**FOLLOW THESE STEPS TO EARN CREDIT:**

- Log on to [acsjournals.com/ce](http://acsjournals.com/ce).
- Read the target audience, educational objectives, and activity disclosures.
- Read the activity contents in print or online format.
- Reflect on the activity contents.
- Access the examination, and choose the best answer to each question.
- Complete the required evaluation component of the activity.
- Claim your certificate.

This activity will be available for CME/CNE credit for 1 year following its launch date. At that time, it will be reviewed and potentially updated and extended for an additional 12 months.

All CME/CNE quizzes are offered online **FREE OF CHARGE**. Please log in at [acsjournals.com/ce](http://acsjournals.com/ce). New users can register for a **FREE** account. Registration will allow you to track your past and ongoing activities. After successfully completing each quiz, you may instantly print a certificate, and your online record of completed courses will be updated automatically.

# Clinical Practice Guidelines on the Evidence-Based Use of Integrative Therapies During and After Breast Cancer Treatment

Heather Greenlee, ND, PhD, MPH<sup>1,2</sup>; Melissa J. DuPont-Reyes, MPH, MPhil<sup>3</sup>; Lynda G. Balneaves, RN, PhD<sup>4</sup>; Linda E. Carlson, PhD<sup>5</sup>; Misha R. Cohen, OMD, LAc<sup>6,7</sup>; Gary Deng, MD, PhD<sup>8</sup>; Jillian A. Johnson, PhD<sup>9</sup>; Matthew Mumber, MD<sup>10</sup>; Dugald Seely, ND, MSc<sup>11,12</sup>; Suzanna M. Zick, ND, MPH<sup>13,14</sup>; Lindsay M. Boyce, MLIS<sup>15</sup>; Debu Tripathy, MD<sup>16</sup>

CME

CNE

<sup>1</sup>Assistant Professor, Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, NY; <sup>2</sup>Member, Herbert Irving Comprehensive Cancer Center, Columbia University, New York, NY; <sup>3</sup>Doctoral Fellow, Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, NY; <sup>4</sup>Associate Professor, College of Nursing, Rady Faculty of Health Sciences, Winnipeg, MB, Canada; <sup>5</sup>Professor, Department of Oncology, University of Calgary, Calgary, AB, Canada; <sup>6</sup>Adjunct Professor, American College of Traditional Chinese Medicine at California Institute of Integral Studies, San Francisco, CA; <sup>7</sup>Clinic Director, Chicken Soup Chinese Medicine, San Francisco, CA; <sup>8</sup>Medical Director, Integrative Oncology, Memorial Sloan Kettering Cancer Center, New York, NY; <sup>9</sup>Post-Doctoral Scholar, Department of Biobehavioral Health, The Pennsylvania State University, University Park, PA; <sup>10</sup>Radiation Oncologist, Harbin Clinic, Rome, GA; <sup>11</sup>Executive Director, Ottawa Integrative Cancer Center, Ottawa, ON, Canada; <sup>12</sup>Executive Director of Research, Canadian College of Naturopathic Medicine, Toronto, ON, Canada; <sup>13</sup>Research Associate Professor, Department of Family Medicine, Michigan Medicine, University of Michigan, Ann Arbor, MI; <sup>14</sup>Research Associate Professor, Department of Nutritional Sciences, School of Public Health, University of Michigan, Ann Arbor, MI; <sup>15</sup>Research Informationist, Memorial Sloan Kettering Library, Memorial Sloan Kettering Cancer Center, New York, NY; <sup>16</sup>Professor, Department of Breast Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX.

Additional supporting information may be found in the online version of this article.

**Corresponding author:** Heather Greenlee, ND, PhD, MPH, Department of Epidemiology, Mailman School of Public Health, Columbia University, 722 West 168th St, Seventh Fl, New York, NY 10032; hg2.120@columbia.edu

**DISCLOSURES:** Linda E. Carlson reports book royalties from New Harbinger and the American Psychological Association. Misha R. Cohen reports royalties from Health Concerns Inc., outside the submitted work. Matthew Mumber owns stock in I Thrive. All remaining authors report no conflicts of interest.

doi: 10.3322/caac.21397. Available online at [cancerjournal.com](http://cancerjournal.com)

**Abstract:** Patients with breast cancer commonly use complementary and integrative therapies as supportive care during cancer treatment and to manage treatment-related side effects. However, evidence supporting the use of such therapies in the oncology setting is limited. This report provides updated clinical practice guidelines from the Society for Integrative Oncology on the use of integrative therapies for specific clinical indications during and after breast cancer treatment, including anxiety/stress, depression/mood disorders, fatigue, quality of life/physical functioning, chemotherapy-induced nausea and vomiting, lymphedema, chemotherapy-induced peripheral neuropathy, pain, and sleep disturbance. Clinical practice guidelines are based on a systematic literature review from 1990 through 2015. Music therapy, meditation, stress management, and yoga are recommended for anxiety/stress reduction. Meditation, relaxation, yoga, massage, and music therapy are recommended for depression/mood disorders. Meditation and yoga are recommended to improve quality of life. Acupressure and acupuncture are recommended for reducing chemotherapy-induced nausea and vomiting. Acetyl-L-carnitine is not recommended to prevent chemotherapy-induced peripheral neuropathy due to a possibility of harm. No strong evidence supports the use of ingested dietary supplements to manage breast cancer treatment-related side effects. In summary, there is a growing body of evidence supporting the use of integrative therapies, especially mind-body therapies, as effective supportive care strategies during breast cancer treatment. Many integrative practices, however, remain understudied, with insufficient evidence to be definitively recommended or avoided. *CA Cancer J Clin* 2017;67:194-232. © 2017 American Cancer Society.

**Keywords:** acupressure, acupuncture, breast cancer, complementary therapies, integrative medicine, integrative oncology, massage, meditation, music therapy, stress management, yoga

## Practical Implications for Continuing Education

- > To make informed decisions on the use of integrative therapies in the oncology setting, clinicians and patients should understand the level of evidence of associated benefits and harms for each therapy.
- > Based on a systematic review of the literature, the Society for Integrative Oncology makes the following recommendations:
  - Use of music therapy, meditation, stress management and yoga for anxiety/stress reduction.
  - Use of meditation, relaxation, yoga, massage and music therapy for depression/mood disorders.
  - Use of meditation and yoga to improve quality of life.
  - Use of acupressure and acupuncture for reducing CINV.
  - There is a lack of strong evidence supporting the use of ingested dietary supplements or botanical agents as supportive care and/or to manage breast cancer treatment-related side effects.
- > Implementing integrative therapies in a clinical setting requires a coordinated team approach with well-trained providers. Training and credentialing for many integrative providers varies by jurisdictions. Best practices suggest that providers be trained to the highest standard of their profession and educated in other relevant disciplines.

## Introduction

Patients with breast cancer and breast cancer survivors are frequent users of complementary and integrative therapies, and there are growing numbers of formal, integrative oncology programs within cancer centers.<sup>1-6</sup> Various terms are used to describe such therapies, and it is helpful at the outset to define terms. *Complementary and alternative therapies* are generally defined as any medical system, practice, or product that is not part of conventional medical care.<sup>7,8</sup> Other relevant terminology includes *complementary medicine*, which comprises therapies used as a complement alongside conventional medicine; *alternative medicine*, which comprises therapies used in place of conventional medicine; and *integrative medicine*, which is the coordinated use of evidence-based complementary practices and conventional care. *Integrative oncology* refers to the use of complementary and integrative therapies in collaboration with conventional oncology care. In oncology, individuals use complementary and integrative therapies with the intent of enhancing wellness, improving quality of life (QOL), and relieving symptoms of disease and side effects of conventional treatments. However, the evidence supporting the use of complementary and integrative therapies in the oncology setting is limited.

In November 2014, the Society for Integrative Oncology (SIO) published clinical practice guidelines to inform both clinicians and patients on the use of integrative therapies during breast cancer treatment and to treat breast cancer treatment-related symptoms.<sup>9</sup> The SIO adapted methods established by the US Preventive Services Task Force<sup>10</sup> to develop graded recommendations on the use of specific integrative therapies for defined clinical indications based on the strength of available evidence concerning associated benefits and harms. The 2014 clinical practice guidelines were derived from a systematic review of randomized clinical trials published between 1990 and 2013 and organized by specific clinical conditions (eg, anxiety/stress, fatigue). This review provides an updated set of clinical practice guidelines based on a current, systematic literature review of randomized controlled trials (RCTs) published through December 2015 along with detailed definitions of integrative therapies and clinical outcomes of interest, a detailed summary of the literature upon which the clinical practice guidelines are based, and suggestions for how appropriate therapies may be integrated into clinical practice.

Of note, it is important to define the use of the term *recommendation* in these clinical practice guidelines. In many settings, a clinical guideline recommendation suggests that it should be used as the standard of care and is favorable or equal compared with all other options based on best clinical evidence for benefit/risk ratio. Here, in the setting of integrative oncology, we use the term recommendation to

conclude that the therapy should be considered as a viable but not singular option for the management of a specific symptom or side effect. Few studies have conducted a head-to-head comparison of a given integrative therapy against a conventional treatment, and most integrative therapies are used in conjunction with standard therapy and have been studied in this manner. Moreover, combination-based approaches and the interactions of the numerous permutations of integrative and conventional treatments have not been formally investigated, such that recommendations must account for this limitation of our knowledge. Despite these limitations to evaluating the use of integrative therapies in the oncology setting, there is a body of well conducted trials of specific therapies for specific conditions that provides sufficient evidence to warrant recommendations on the therapies as viable options for treating specific conditions.

In this review, we provide clinicians and patients with updated SIO clinical practice guidelines on the use of integrative therapies to manage symptoms and side effects during and after breast cancer treatment. The clinical practice guidelines do not address breast cancer recurrence or survival endpoints, because very few adequately powered RCTs have examined the effect of integrative therapies on these outcomes. We also provide a definition for each integrative therapy that had a sufficiently large body of evidence to formulate a specific recommendation. Information is also provided on how to implement the recommendations into the clinical setting, with caveats for specific clinical situations. In addition, this review summarizes pertinent meta-analyses and identifies promising areas for future investigation. The information that arose from other published reviews and meta-analyses did not change the interpretation of the findings or the quality of specific trials, but the information was used to influence the establishment of specific recommendation grades based on consistency, reproducibility, and assessment of potential harms and benefits. The goal of this current review is to provide clinicians and patients with practical information and tools to evaluate whether there is an evidence base to support the use of a defined integrative therapy for a specific clinical application in the context of breast cancer.

## Methods

### Systematic Review Methodology

To update the previously published clinical practice guidelines, which were based on a systematic review of the literature from January 1, 1990 through December 31, 2013,<sup>9</sup> we conducted a systematic review of published RCTs from January 1, 2014 through December 31, 2015, using the same search criteria and process. The process followed the methods set forth by the Institute of Medicine on clinical guideline development.<sup>11</sup> The following databases were searched: Embase, MEDLINE, PsychINFO, and CINAHL.

As previously reported,<sup>9</sup> trials were selected for inclusion in the systematic review if they met the following criteria: 1) peer-reviewed, published RCT; 2) available in English; 3) included  $\geq 50\%$  patients with breast cancer and/or reported results separately for patients with breast cancer; 4) used an integrative therapy as an intervention during standard treatment with surgery, chemotherapy, radiation therapy, and/or hormonal therapy or addressed symptoms and side effects resulting from diagnosis and/or treatment; and 5) addressed an endpoint of clinical relevance to patients with breast cancer and breast cancer survivors (see Supporting Information Table 1).<sup>9</sup> Several lifestyle and psychological interventions were excluded from current as well as previous guidelines, because they have already been well summarized by other groups (eg, diet<sup>12,13</sup> and physical activity<sup>12-14</sup> recommendations for cancer survivors) and/or because they have a strong evidence base and are often considered to be mainstream rather than integrative or complementary (eg, cognitive-behavioral therapy,<sup>15</sup> psychoeducation,<sup>16</sup> counseling,<sup>17</sup> and support groups<sup>16</sup>). Other interventions that were excluded were in early or pilot stages of research (eg, attention-restoration therapy) or were not considered to be an integrative oncology therapy for the purposes of the SIO guidelines (eg, prayer, spirituality). Each article was scored according to the quality of design and reporting based on the Jadad scoring scale and a modified scale adapted from the Delphi scoring system.<sup>18,19</sup> Finally, grades of evidence were determined for each therapy as applied to a specific clinical outcome using a modified version of the US Preventive Services Task Force grading system.<sup>10</sup> Grades were based on strength of evidence, determined by the number of trials, quality of trials, magnitude of effect, statistical significance, sample size, consistency of results across studies, and whether the outcomes were primary or secondary. The highest grades (A and B) indicate that a specific therapy is recommended for a particular clinical indication. Grade A indicates there is high certainty that the net benefit is substantial, while grade B indicates there is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial. Grade C indicates that the evidence is equivocal or that there is at least moderate certainty that the net benefit is small. The lowest grades (D, H, and I) indicate no demonstrated effect, suggest harm, or indicate that the current evidence is inconclusive, respectively.

According to the clinical guideline development process outlined by the Institute of Medicine,<sup>11</sup> drafts prepared by the SIO Guideline Working Group were distributed to an interdisciplinary group of SIO internal and external reviewers. Reviewer comments, suggestions, and critiques were incorporated into the final version of these guidelines.

It is important to note that, as we reviewed the literature, we recognized the difference between statistical and

clinical significance. The graded recommendations reflect our assessment of the clinical significance based on our assessment of the body of literature, including the importance of statistical significance with respect to the primary endpoint. We did not report on specific magnitudes of effect because of the range of outcome measures and statistical methods used across the trials, which made it difficult to describe detailed data on effect sizes across all trials. Although some of the trials with small sample sizes ( $n < 100$ ) may have been methodologically sound, we downplayed their contribution to the graded recommendation, because larger trials provided more information on generalizability of results to larger populations. Because of space limitations, *P* values are reported and citations are provided to reference the primary reports for additional details.

### Definitions of Complementary and Integrative Therapies

Below are definitions listed alphabetically for each of the complementary and integrative therapies that received a grade of A, B, C, D, or H in the updated clinical practice guidelines.<sup>20,21</sup> Table 1 displays the graded recommendations.<sup>10,22-151</sup> Table 2 provides background information on the specific training, licensure, and professional organizations associated with each therapy.<sup>152</sup> If a therapy is known to have a specific contraindication or caution, it is noted in the description. The descriptions include statements on how the therapies are often used by patients with cancer and by survivors but do not indicate the level of evidence supporting such use. The guideline recommendations provide a summary of the evidence on the use for specific conditions. In addition to the information provided below, there are continuously updated, well referenced websites that can provide additional details on the range of therapies, including Natural Medicines ([naturalmedicines.therapeuticresearch.com](http://naturalmedicines.therapeuticresearch.com)), Memorial Sloan Kettering Cancer Center's *About Herbs* website ([mskcc.org/cancer-care/treatments/symptom-management/integrative-medicine/herbs](http://mskcc.org/cancer-care/treatments/symptom-management/integrative-medicine/herbs)), and the National Cancer Institute (NCI) Office of Cancer Complementary and Alternative Medicine Therapies: A-Z website ([cam.cancer.gov/health\\_information/cam\\_therapies\\_a-z.htm](http://cam.cancer.gov/health_information/cam_therapies_a-z.htm)).

#### Acetyl-L-carnitine

Acetyl-L-carnitine is a dietary supplement that some patients use to treat cancer-related fatigue by enhancing energy and lowering inflammation in the body.<sup>153</sup> It has demonstrated effectiveness in preventing and treating diabetic neuropathy and thus was of interest to examine in the context of chemotherapy-induced peripheral neuropathy (CIPN). It is a substance made in muscle and liver tissue and is found in foods, including meats, poultry, fish, and some dairy products.

**TABLE 1. Graded Integrative Therapies for Use in Patients With Breast Cancer According to Clinical Outcomes<sup>a</sup>**

CLINICAL OUTCOMES	RECOMMENDED THERAPY	STRENGTH OF EVIDENCE GRADE <sup>b</sup>
Acute radiation skin reaction	Aloe vera <sup>22,23</sup> and hyaluronic acid cream <sup>24,25</sup> should not be recommended for improving acute radiation skin reaction.	D
Anxiety/stress reduction	Meditation is recommended for reducing anxiety. <sup>26-30</sup>	A
	Music therapy is recommended for reducing anxiety. <sup>31-35</sup>	B
	Stress management is recommended for reducing anxiety during treatment, but longer group programs are likely better than self-administered home programs or shorter programs. <sup>36-39</sup>	B
	Yoga is recommended for reducing anxiety. <sup>40-48</sup>	B
	Acupuncture, <sup>49-51</sup> massage, <sup>52-55</sup> and relaxation <sup>56-60</sup> can be considered for reducing anxiety.	C
Chemotherapy-induced nausea and vomiting	Acupressure can be considered as an addition to antiemetics drugs to control nausea and vomiting during chemotherapy. <sup>61-63</sup>	B
	Electroacupuncture can be considered as an addition to antiemetics drugs to control vomiting during chemotherapy. <sup>64,65</sup>	B
	Ginger <sup>66-68</sup> and relaxation <sup>59,69</sup> can be considered as additions to antiemetic drugs to control nausea and vomiting during chemotherapy.	C
	Glutamine <sup>70,71</sup> should not be recommended for improving nausea and vomiting during chemotherapy.	D
Depression/mood disturbance	Meditation, particularly MBSR, is recommended for treating mood disturbance and depressive symptoms. <sup>26-30,72-76</sup>	A
	Relaxation is recommended for improving mood disturbance and depressive symptoms. <sup>56,59,60,69,77,78</sup>	A
	Yoga is recommended for improving mood and depressive symptoms. <sup>40-43,45-48,79-85</sup>	B
	Massage is recommended for improving mood disturbance. <sup>53-55,86-88</sup>	B
	Music therapy is recommended for improving mood. <sup>33,35,89,90</sup>	B
	Acupuncture, <sup>49-51,91,92</sup> healing touch, <sup>93,94</sup> and stress management <sup>36-38,95,96</sup> can be considered for improving mood disturbance and depressive symptoms.	C
Fatigue	Hypnosis <sup>97,98</sup> and ginseng <sup>99,100</sup> can be considered for improving fatigue during treatment.	C
	Acupuncture <sup>51,101-103</sup> and yoga <sup>45,80,84,104-106</sup> can be considered for improving post-treatment fatigue.	C
	Acetyl-L-carnitine <sup>107</sup> and guarana <sup>108,109</sup> should not be recommended for improving fatigue during treatment.	D
Lymphedema	Low-level laser therapy, <sup>110,111</sup> manual lymphatic drainage, <sup>112-118</sup> and compression bandaging <sup>114-116</sup> can be considered for improving lymphedema.	C
Neuropathy	Acetyl-L-carnitine is not recommended for the prevention of chemotherapy-induced peripheral neuropathy in patients with BC due to potential harm. <sup>107</sup>	H
Pain	Acupuncture, <sup>119-124</sup> healing touch, <sup>93</sup> hypnosis, <sup>125,126</sup> and music therapy <sup>31,34</sup> can be considered for the management of pain.	C
Quality of life	Meditation is recommended for improving quality of life. <sup>27-29,73-75,127</sup>	A
	Yoga is recommended for improving quality of life. <sup>43,46-48,82-85,104-106,128</sup>	B
	Acupuncture, <sup>49,51,102,129,130</sup> mistletoe, <sup>131-134</sup> qigong, <sup>135,136</sup> reflexology, <sup>137-139</sup> and stress management <sup>36-38,95,96,140,141</sup> can be considered for improving quality of life.	C
Sleep disturbance	Gentle yoga <sup>45,48,79,84,142</sup> can be considered for improving sleep.	C
Vasomotor/hot flashes	Acupuncture <sup>49,91,92,143-148</sup> can be considered for improving hot flashes.	C
	Soy <sup>149-151</sup> is not recommended for hot flashes in patients with BC due to lack of effect.	D

Abbreviations: BC, breast cancer; MBSR, mindfulness-based stress reduction. <sup>a</sup>The clinical population is patients with BC during treatment, including surgery, chemotherapy, hormonal/biological therapy, and radiation therapy. The clinical question is “What integrative therapies can be used to prevent, treat and manage symptoms and side effects encountered during breast cancer treatment?” <sup>b</sup>Definitions of the grade of recommendations are as follows<sup>10</sup>: Grade A recommends the modality (there is high certainty that the net benefit is substantial: offer/provide this modality). Grade B recommends the modality (there is high certainty that the net benefit is moderate, or there is moderate certainty that the net benefit is moderate to substantial: offer/provide this modality). Grade C recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences (there is at least moderate certainty that the net benefit is small: offer/provide this modality for selected patients, depending on individual circumstances). Grade D recommends against the service (there is moderate or high certainty that the modality has no net benefit: discourage the use of this modality). Grade H recommends against the service (there is moderate or high certainty that the harms outweigh the benefits: discourage the use of this modality).

**TABLE 2. Training and Licensure Information for A-Grade and B-Grade Integrative Therapies**

MODALITY OR THERAPY	TRAINING	LICENSURE AND REGULATION	PROFESSIONAL SOCIETIES AND ORGANIZATIONS
Acupuncture, electro-acupuncture, and acupressure	<p>Licensed acupuncturists generally have attended formal schools of Asian medicine and have passed national certification examinations in order to sit for state or provincial licensing examinations. The Accreditation Commission for Acupuncture and Oriental Medicine (ACAOM) accredits schools of Asian medicine in the United States. Degrees include the Masters of Acupuncture, requiring a minimum of 3 y and 1900 h of training, and the Masters of Acupuncture and Oriental Medicine, requiring a 3-4 y program, averaging 2700-3465 h of training.</p> <p>Advanced degrees include Doctor of Acupuncture and Oriental Medicine (DAOM), Oriental Medicine Doctor (OMD), Doctor of Acupuncture and Chinese Medicine (DACM), and Doctor of Oriental Medicine (DOM), who provide advanced evaluations, integrative medicine, as well as acupuncture and herbal therapy and can provide access to the whole breadth of Chinese medicine. Advanced degrees require a Masters-level degree with additional 1000+ h of training. NCCAOM offers acupuncture and herbal and Oriental medicine certifications on a national level.<sup>152</sup></p>	<p>UNITED STATES: Acupuncture, Chinese herbology, and Oriental medicine are regulated via state licensing bodies. The National Certification Commission for Acupuncture and Oriental Medicine (NCCAOM) reports that 44 states plus the District of Columbia have acupuncture practice acts. Forty-three states currently require passage of NCCAOM national examinations for initial licensure. The NCCAOM certifies acupuncture, Chinese herbology, and Oriental medicine. Currently, California requires passage of its own state examinations for licensure and does not accept the NCCAOM certification. A subset of states regulates acupressure under acupuncture or massage regulations.</p> <p>CANADA: Acupuncture is regulated via provincial licensing bodies in the provinces of British Columbia, Alberta, Ontario, Quebec, and Newfoundland. Chinese medicine is currently only regulated in British Columbia and Ontario.</p>	<p>ACAOM, <a href="http://acaom.org">acaom.org</a>; NCCAOM, <a href="http://mx.nccaom.org">mx.nccaom.org</a></p> <p>College of Traditional Chinese Medicine Practitioners and Acupuncturists of British Columbia (CTCMA), <a href="http://ctcma.bc.ca">ctcma.bc.ca</a>; College of Traditional Chinese Medicine Practitioners and Acupuncturists of Ontario (CTCMPAO), <a href="http://ctcmapao.on.ca/">ctcmapao.on.ca/</a>; College and Association of Acupuncturists of Alberta (CAAA), <a href="http://acupuncturealberta.ca/">acupuncturealberta.ca/</a>; Association of Acupuncturists of Quebec (AAQ), <a href="http://acupuncture-quebec.com/en/home.html">acupuncture-quebec.com/en/home.html</a>; Newfoundland and Labrador Council of Health Professionals (NLCHP), <a href="http://nlchp.ca/">nlchp.ca/</a></p>
Hypnosis	<p>Mental health and medical professionals typically practice hypnosis as a specialty or subspecialty. Certified hypno-therapists, in general, hold a graduate-level or bachelor's-level degree in a broad range of specialties, including MD, registered nurse, dentist, social worker, licensed counselor or psychologist, pastoral counselor, ordained minister, and chiropractor, among many others, prior to obtaining training in hypnosis.</p> <p>Currently, there are no accredited schools offering standard college or university degrees in hypnosis; therefore, training in one of the above professions is typically required before acceptance into one of many training or certification programs. These programs have a wide range of training requirements but in general require anywhere from 50 to 200 h of classroom and clinical training before certification.</p>	<p>UNITED STATES: To be certified as a clinical hypnotherapist, applicants typically require anywhere from 50 to 200 h of training and often y of experience. There are a number of certification programs with a range of requirements (see links). Regulations for the practice of hypnosis vary on a state-by-state basis (<a href="http://ahcp.org/hypnosis-regulation.htm">ahcp.org/hypnosis-regulation.htm</a>). Typically, clinical hypnotherapists must renew their certification every 2 to 4 y and must have completed 20+ h of approved training during that time.</p> <p>CANADA: Certification is similar to the United States; however, requirements are much higher, between 225 and 1100 h (<a href="http://archanada.ca/">archanada.ca/</a>).</p> <p>The Council of Professional Hypnosis encompasses many professional societies and organizations listed (<a href="http://copho.com/org.htm">copho.com/org.htm</a>).</p>	<p>Association of Registered Clinical Hypnotherapists (ARCH), <a href="http://archcanada.ca/">archcanada.ca/</a>; American College of Hypnotherapy at the American Institute of Health Care Professionals, <a href="http://ahcp.net/american-college-of-hypnotherapy/">ahcp.net/american-college-of-hypnotherapy/</a>; American Society of Clinical Hypnosis (ASCH), <a href="http://asch.net/">asch.net/</a>; Hypnosis Motivation Institute (HMI), <a href="http://hypnosis.edu">hypnosis.edu</a>; National Board for Certified Clinical Hypnotherapists (NBCCH), <a href="http://naboard.com">naboard.com</a>; The International Society of Hypnosis (ISH), <a href="http://ishypnosis.org/">ishypnosis.org/</a>; Society for Clinical and Experimental Hypnosis (SCEH), <a href="http://sceh.us/">sceh.us/</a>; The Milton H. Erickson Foundation, <a href="http://erickson-foundation.org/">erickson-foundation.org/</a></p>
Massage	<p>Associated Bodywork and Massage Professional (ABMP) members at the certified or professional levels must possess a valid massage license from a regulated state/province/territory, must have completed 500 approved educational h or be certified through the National Certification Board for Therapeutic Massage and Bodywork (NCTMB). Licensed nurse and physical therapists may qualify for membership at either the certified or professional level with a minimum of 50 h of additional massage therapy training. Board certification is the highest voluntary credential attainable to massage therapists and bodyworkers in the profession today (for the requirements of board certification, see <a href="http://nctmb.org">nctmb.org</a> board-certification).</p>	<p>UNITED STATES: Massage therapy is regulated by some US states. See link for state-by-state massage licensure information (<a href="http://massagetherapy.com/careers/stateboards.php">massagetherapy.com/careers/stateboards.php</a>).</p> <p>CANADA: Massage therapists can only be registered, not licensed, in Canada. Currently, only 4 provinces regulate massage therapists: Ontario, British Columbia, New Brunswick, and Newfoundland. The Web site for the Ontario Massage Therapists has links to the 4 provinces' registration procedures and links to other provincial massage organizations.</p>	<p>American Massage Therapy Association, <a href="http://amtamassage.org">amtamassage.org</a>; ABMP, <a href="http://abmp.com">abmp.com</a>; NCTMB, <a href="http://nctmb.org/">nctmb.org/</a>; Society for Oncology Massage, <a href="http://s4om.org">s4om.org</a></p> <p>Massage Therapists' Association of Ontario, <a href="http://secure.rmtao.com/message_therapy/regulation_of_mt/massage_therapy_in_canada.htm">secure.rmtao.com/message_therapy/regulation_of_mt/massage_therapy_in_canada.htm</a></p>

TABLE 2. Continued

MODALITY OR THERAPY	TRAINING	LICENSURE AND REGULATION	PROFESSIONAL SOCIETIES AND ORGANIZATIONS
Meditation	<p>Mindfulness-Based Stress Reduction: The Center for Mindfulness in Massachusetts provides meditation specialist training (umassmed.edu/cfm/training/detailed-training-information/teacher-certification-review/).</p> <p>The University of California at San Diego Center for Mindfulness provides extensive training (mbpti.org).</p> <p>The University of Bangor in Wales awards a Masters in Mindfulness and also has a range of teacher training programs (bangor.ac.uk/mindfulness/courses.php/en)</p> <p>The Centre for Mindfulness Studies in Toronto, Ontario, Canada, offers 1-d workshops as well as intensive professional training in Mindfulness-Based Cognitive Therapy (mindfulnessstudies.com/).</p>	<p>In both the United States and Canada, board certification is the highest credential attainable for meditation teachers in the health care profession today. There is no registration or licensure currently available.</p> <p>Completing mindfulness teacher training courses at one of the recognized training programs, in addition to professional certification, would be the optimal level of training for providing these interventions.</p>	<p>American Mindfulness Research Association, goamma.org/</p>
Music therapy	<p>A professional music therapist holds a bachelor's degree or higher in music therapy from one of over 70 American Music Therapy Association-approved college and university programs. Music therapists who currently hold professional designation are listed on the National Music Therapy Registry and are qualified to practice music therapy.</p>	<p>Music therapists are regulated by some US states (eg, North Dakota, Nevada; for state-by-state massage licensure information, see cbmt.org/examination/state-licensure/).</p> <p>Currently no Canadian provinces/territories license or regulate music therapists.</p>	<p>The Certification Board for Music Therapists (CBMT), cbmt.org/ Canadian Association for Music Therapy (CAMT), musictherapy.ca/</p>
Relaxation and stress management	<p>Relaxation and stress management are usually provided by trained mental health professionals, such as registered/chartered/counseling psychologists, psychiatrists, marital and family counselors, clinical social workers, and nurses. Any of these professions could have specific training in these 2 modalities.</p>	<p>Typically, the aforementioned professionals would take courses in relaxation training or stress management as part of their training.</p>	<p>Every jurisdiction has a college of psychologists and social workers. American Psychological Association (APA), apa.org/ Canadian Psychological Association (CPA), cpa.ca</p>
Yoga	<p>There are very stringent criteria to be a yoga instructor, and most jurisdictions have their own requirements. Most jurisdictions have criteria in place to become a "certified yoga instructor." There are also requirements for specific genres of yoga, such as Bikram, Iyengar, Ashtanga, restorative yoga, etc. Most states and provinces/territories have a designation as a certified yoga instructor. In the United States and Canada, the Yoga Alliance is the biggest body that registers teachers (yogaalliance.org/Credentialing/Credentials_for_Teachers, yogaalliance.org/Credentialing/CredentialsforSchools, and canadianyogicalliance.com).</p>	<p>There are currently no states or Canadian provinces/territories that regulate or license yoga.</p>	<p>Most states and provinces have a professional association (or more than one) for certified yoga instructors.</p>

### Acupuncture

Acupuncture involves the stimulation of specific points, (ie, acupoints) by penetrating the skin with thin, solid, metallic needles.<sup>154,155</sup> A variation of acupuncture includes electroacupuncture, in which a small electric current is passed along acupuncture needles to provide a stronger stimulus than acupuncture alone, with distinct effects suggested by functional magnetic resonance imaging.<sup>156,157</sup> Acupuncture has been practiced in Asia for thousands of years as a component of traditional medicine systems (eg, traditional forms of Chinese, Japanese, and Korean medicine) and is thought to stimulate the flow of a form of energy called *qi* (chee) throughout the body. Traditional Chinese acupuncture, which is commonly used in North America, requires needle manipulation to produce a *de qi* sensation (a soreness, fullness, heaviness, or local area distension<sup>157,158</sup>), along with a period of rest with the needles in place.<sup>159</sup> It is posited that this removes energetic blockages, thus reestablishing homeostasis. The mechanisms for acupuncture's effects are not well understood but are thought to function in part through modulation of specific neuronal/cortical pathways.<sup>160</sup> Acupuncture practice typically requires formal education through schools, training programs, and certifications (Table 2). Acupuncture is often used in the oncology setting for chemotherapy-induced nausea/vomiting (CINV), pain management, musculoskeletal complaints, hot flashes, fatigue, stress, anxiety, and sleep disorders. The practice of acupuncture in North America is regulated by some US states and Canadian provinces and territories (Table 2).

### Acupressure

Acupressure draws on the same knowledge and philosophical system as acupuncture. A trained therapist or the patient uses his/her hands and fingers, or possibly a device, to apply pressure to specific points on the body (acupoints), in contrast to metallic needles.<sup>161</sup> Practices can range from stimulating a single point or a combination of points to achieve the intended outcome. In the oncology setting, acupressure is often used for CINV pain, stress management, and fatigue.

### Aloe vera

Aloe vera gel is derived from the leaves of the perennial succulent plant, *Aloe vera* (Liliaceae). Typically, it is applied topically or ingested in the form of a clear, thick gel.<sup>153</sup> Aloe vera gel is found in multiple skin products, such as lotions, creams, and sunblock, and is used as a topical ointment to heal wounds, sunburn, insect bites, and skin conditions, including psoriasis and frostbite.<sup>162</sup> In oncology, it is typically used with the goal of healing surgical wounds or preventing or treating radiation-induced dermatitis.

### Ginger

Ginger (*Zingiber officinale*) comes from the rhizome or root of a tropical plant with green-purple flowers and an aromatic stem.<sup>153,163</sup> Ginger can be used as a food in cooking and for medicinal purposes. In Asian medicine, ginger is used to treat stomach aches, nausea, and diarrhea. For patients with cancer, it has been studied for the treatment of CINV. Ginger is available in capsule form, fresh as a root, as a tea, as a candy, or at highly diluted quantities in ginger ale. Ginger supplementation should not be used in perioperative settings or in patients with bleeding disorders due to a potential risk of increased bleeding.<sup>162</sup>

### Ginseng

Ginseng is derived from a plant root and has been used to treat certain medical problems.<sup>153</sup> Two common types of ginseng are used: Asian ginseng (*Panax ginseng*) and American ginseng (*Panax quinquefolius*). Another herb called Siberian ginseng or eleuthero is not a true ginseng.<sup>162</sup> Asian and American ginsengs are used to boost the immune system and promote well being and stamina. Ginseng comes in capsule form made of ground ginseng, extracts, and teas and in creams and other products for topical use. Taken as an herbal supplement, ginseng is often used to treat cancer-related fatigue.<sup>162</sup> Side effects of taking ginseng may include headaches, breast tenderness and menstrual irregularities, sleep problems, restlessness, rapid heart rate, low blood sugar, allergic reactions, and gastrointestinal problems.<sup>162</sup>

### Glutamine

Glutamine is a nonessential amino acid used in the biosynthesis of proteins and is primarily synthesized in skeletal muscle.<sup>162</sup> Most of the glutamine synthesized in the body is used by the intestinal tract. Glutamine has numerous biologic functions, including protein and lipid synthesis and the regulation of acid-base balance in the kidney, and it is an important mitochondrial cellular energy source. Normally, the body can synthesize its own glutamine; however, during a critical illness like cancer, not enough glutamine is made, leading to problems such as fatigue and muscle wasting. Glutamine has been used as an oral supplement in patients with cancer to reverse cachexia in those who have advanced disease. It has also been used for CINV in patients with cancer. Glutamine can be obtained from food or supplements, and important food sources include beef, pork, chicken, fish, eggs, milk, dairy products, wheat, cabbage, beets, beans, spinach, and parsley.<sup>162</sup>

### Guarana

Guarana is an herbal supplement from the guarana plant (*Paullinia cupana*), which is native to the Amazon basin.<sup>162</sup> Guarana supplements contain various phytochemicals, including caffeine, theobromine, theophylline, tannins, saponins, catechins, epicatechins, proanthocyanidols, and other

compounds, in minor concentrations. Guarana has been used as a stimulant since pre-Columbian times.<sup>162</sup> In the oncology setting, guarana is often used to decrease fatigue.

### **Healing touch**

Healing touch (also known as therapeutic touch) is based on the belief that vital energy flows through and around the human body and may be transferred or modified.<sup>93,94</sup> A healing touch practitioner (often a nurse trained in the practice) passes his/her hands over, or gently touches, a patient's body to balance or increase their energy. Healing touch is often used in patients with cancer to improve QOL, pain, fatigue, and depression.

### **Hyaluronic acid cream**

Hyaluronic acid cream is a topical cream containing hyaluronic acid that is used to heal wounds through repair-promoting, skin-moisturizing, and potential radioprotective properties.<sup>153</sup> When the cream is applied, the hyaluronic acid adheres to injured tissue, provides hydration to the skin, and protects against dehydration and chemical and mechanical irritation. Hyaluronic acid cream is often used by patients with cancer to prevent and treat radiation-induced dermatitis.

### **Hypnosis**

Hypnosis is facilitated by a specially trained therapist or is practiced on one's own (self-hypnosis). It is characterized by a trance-like state, which allows a patient to be more aware, focused, and open to suggestion. A person in a hypnotic state can concentrate more clearly on specific feelings, thoughts, images, sensations, or behaviors without distraction.<sup>164</sup> The hypnotic state is obtained by first relaxing the body and then shifting attention toward a narrow range of objects or ideas given by the hypnotist or hypnotherapist. A person under hypnosis may feel more calm and relaxed. In patients with cancer, hypnosis is often used to help relieve stress, anxiety, and pain.

### **Laser therapy**

Low-level laser therapy has been cleared by the FDA to treat lymphedema after breast cancer surgery<sup>165</sup> and should be administered by trained users. It is believed that low-level laser therapy stimulates macrophages and the immune system and breaks down scar tissue, thus improving lymphatic flow.<sup>166</sup>

### **Manual lymphatic drainage and compression bandaging**

Manual lymphatic drainage and compression bandaging are used individually and in combination for the treatment of lymphedema after breast cancer surgery.<sup>166</sup> Manual lymph drainage is a specific type of therapeutic massage that ideally is delivered by a health professional who is certified in the technique. Manual lymph drainage can decrease lymphedema when administered early, before symptoms advance.<sup>166</sup>

Compression bandages or garments, including sleeves, stockings, bras, compression shorts, gloves, bandages, or neck compression wraps, are also used to treat lymphedema and can be worn during the day or night, depending on the garment and the individual.<sup>166</sup>

### **Massage**

There are many different forms of this type of physical therapy, which involves a therapist stroking, kneading, applying friction, and stretching specific muscles and other connective tissues at an even tempo with various levels of pressure.<sup>167</sup> In patients with cancer, the goal of massage is to promote relaxation, address muscle stiffness and pain, and resolve musculoskeletal complaints. There are multiple forms of massage, including, but not limited to, Swedish, Shiatsu, and deep-tissue massage. Massage therapists should take precautions with all patients who have cancer and to avoid massaging specific vulnerable areas of the body, including open wounds, bruises, skin breakdown, a blood clot in a vein, a tumor site, areas near a medical device (eg, drain), or sensitive skin after radiation therapy.<sup>168</sup> In addition, certain patients with multiple bone metastases may be at risk for fracture during deep massage. The practice of massage therapy in North America is regulated by some US states and Canadian provinces and territories (Table 2).

### **Meditation**

Meditation is a group of self-regulation practices focused on training attention and awareness to bring mental processes under greater voluntary control.<sup>169</sup> In patients with cancer, these practices are intended to foster general mental well being, calmness, clarity, and concentration. The ultimate goal of meditation varies, depending on the type of practice, its history, and its application. Most meditation practices have 4 elements in common: a quiet location with few distractions; a specific, comfortable posture achieved by sitting or lying down; a focus of attention; and an open attitude of letting thoughts come and go naturally without judgment.<sup>170</sup> The focus of attention may be on a specific target, such as the breath or a repeated sound or mantra (known as *concentration meditation*); on all experiences that enter the field of awareness (called *open awareness* or *mindfulness meditation*); or a combination of both. There has been growing interest in cancer care on the practice of a secular form of mindfulness meditation called *mindfulness-based stress reduction* (MBSR), which is based on the work of Jon Kabat-Zinn.<sup>171</sup> MBSR is typically delivered in an 8-week, structured group program consisting of a range of meditation practices, including a sensate focus body scan, sitting meditation, walking meditation, loving-kindness practice, and gentle Hatha yoga postures. All formal practices are designed to cultivate increasing levels of mindfulness in day-to-day life. Participants engage in home practice daily

throughout the program, and each session involves teaching relevant concepts, discussions of progress and barriers to practice, and introduction and practice of new meditation modalities. Several recent articles and meta-analyses have reviewed the literature on the use of MBSR in the oncology setting, and some are specific to breast cancer.<sup>172-175</sup>

### **Mistletoe**

The use of mistletoe in cancer care is based on the premise that injections of specially prepared extracts of the plant during chemotherapy and radiation therapy can create a host response that is immune-stimulatory, preferentially cytotoxic to cancer cells, and protective of host cells.<sup>176</sup> Mistletoe is a parasitic plant from the Santalaceae family that attaches to and penetrates the branches of a tree or shrub to absorb water and nutrients from the host plant. The use of mistletoe as a medicine extends back centuries, whereas its modern use for cancer care was promoted in Europe, and particularly in Germany, in the early part of the 20th century.<sup>177</sup> There are 3 main types of mistletoe: European mistletoe (*Viscum album*), Korean mistletoe (*Viscum album var. coloratum*), and American mistletoe (*Phoradendron leucarpum*), but multiple methods of preparation and formulation exist. Preparations from European mistletoe are some of the most common internationally prescribed substances in outpatient clinics for cancer, where they are delivered most often as a subcutaneous injection or occasionally as an intravenous infusion.<sup>178</sup> While this therapy is often used clinically for its antineoplastic potential, clinical trial evidence on the use of mistletoe is based on trials in which it is coadministered with conventional treatments to improve QOL.<sup>178</sup>

### **Music therapy**

Music therapy is the clinical use of music to accomplish individualized goals within a therapeutic relationship by a credentialed professional.<sup>179</sup> In cancer care, music therapy is used to address various physical, emotional, cognitive, and social needs. Qualified music therapists assess patients' strengths and needs and provide indicated treatment, such as creating, singing, moving to, and listening to music. Music therapy interventions can be described as either *passive* (eg, listening to music before a medical intervention) or *active* (eg, a therapist instructing a patient to engage in the creation of live music), depending on the level of engagement required. Although the exact mechanisms by which music therapy works are not well understood, the most commonly accepted theories are through neurologic, psychological, behavioral, and physiologic pathways.<sup>180,181</sup> The practice of music therapy in North America is regulated by some US states (Table 2).

### **Reflexology**

In reflexology, a trained practitioner applies pressure to the feet, hands, ears, and face using specific thumb, finger, and

hand techniques with the goal of stimulating the reflex areas to promote physiologic changes in the body. The theory behind reflexology states that specific areas on the feet and hands correspond to specific glands, organs, and other parts of the body, which are stimulated to help numerous health problems.<sup>182</sup> Reflexology is used to cause relaxation and healing in those specific stimulated parts of the body. In oncology, reflexology is often used to promote relaxation and improve QOL.

### **Relaxation techniques**

Various techniques are used to promote relaxation in patients with cancer. The NCI defines relaxation techniques as including progressive muscle relaxation (PMR), guided imagery, autogenic training, biofeedback, self-hypnosis, and deep breathing exercises.<sup>183</sup> PMR focuses on the tightening and relaxation of specific, successive muscle groups and is usually combined with breathing and imagery exercises.<sup>183</sup> Guided imagery can be self-directed or led by a practitioner or a recording and often involves focusing on pleasant imagery to replace negative or stressful feelings.<sup>183</sup> Autogenic training involves concentrating on physical sensations of warmth, heaviness, and relaxation in different parts of the body.<sup>183</sup> Biofeedback uses electronic devices to monitor and teach control of certain bodily functions, such as breathing or heart rate, to facilitate relaxation.<sup>183</sup> Self-hypnosis refers to training patients to induce a hypnotic state, which is a natural state of aroused, attentive, focal concentration along with a relative suspension of peripheral awareness, either on their own or when prompted by a phrase or a cue.<sup>183</sup> Deep breathing exercises involve the use of slow, deep, and even breaths, sometimes called diaphragmatic or belly breathing.<sup>183</sup>

### **Qigong**

The word qigong consists of 2 Chinese words: *qi* (chee), meaning life force or vital energy that flows through all things in the universe, and *gong* (gung), meaning accomplishment or skill that is cultivated through steady practice.<sup>184</sup> Qigong is a form of ancient and traditional Chinese medicine that integrates movement (physical postures), meditation (focused attention), and controlled breathing. Qigong aims to enhance vital energy or life force that balances a patient's spiritual, emotional, mental, and physical health. Qigong practices are used to increase the qi, circulate it, use it to cleanse and heal the body, store it, or emit qi to help heal others. Practices range in intensity from the gentle movements of tai chi to the more vigorous practice of kung fu.<sup>184</sup> In patients with cancer, qigong is often used to reduce anxiety, fatigue, and pain; to support the immune system; and to improve physical and emotional balance.

### **Stress management**

Acute stress is a normal physical and emotional reaction that people experience as they encounter changes in life,<sup>185</sup>

including after a cancer diagnosis, during cancer treatment, and throughout cancer survivorship. Long-term chronic stress may contribute to or worsen a range of health problems, including digestive disorders, headaches, sleep disorders, depression, anxiety, and other mental health problems.<sup>185</sup> To address stress and induce the relaxation response, stress-management programs teach techniques like PMR, guided imagery, and breathing exercises. Stress management also typically incorporates elements of cognitive-behavioral therapy, such as understanding the effects of appraisal and perception on the experience of subjective stress.<sup>186,187</sup> Participants are taught coping skills and practice various techniques for cognitive reappraisal. One common structured group stress-reduction program studied in oncology is called *cognitive-behavioral stress management*.<sup>140,188</sup> There are overlaps in some techniques used in stress management, relaxation, and meditation therapies. For example, meditation, guided imagery, and yoga may be practiced as techniques in isolation or combined. In this review, we distinguish between stress-management, relaxation, and meditation interventions. Stress-management interventions include psychoeducation on stress and coping and emphasize cognitive-behavioral therapy and coping skills training; relaxation interventions typically consist of PMR and guided imagery; and meditation interventions use some form of meditation practice as the focal point of the training.

### Soy

Soy is a plant in the pea family that has been common in Asian diets for thousands of years and more recently in the American diet.<sup>162</sup> Soybeans are the seeds of the soy plant and contain isoflavones and soy protein. Soy is available as a dietary supplement in tablet or capsule form and contains isoflavones and/or soy protein. Soybeans can be cooked or eaten or may be used to make tofu, soy milk, and other food products. Soy is also used as an additive to other processed foods, such as baked goods. Soy is used to treat menopausal symptoms, osteoporosis, memory problems, high blood pressure, and high cholesterol levels.<sup>162</sup> In patients with cancer, soy is often used to treat hot flashes.

### Yoga

Yoga is a mind-body practice with origins in ancient South Asian philosophy and practice.<sup>189</sup> The term yoga is derived from the Sanskrit word *yug*, meaning “yoke” or “union.”<sup>190</sup> This, according to traditional yoga philosophy, is the ultimate intent of a yoga practice—to unite the individual with the totality of the universe. The techniques of yoga include ethical daily living (*yamas* and *niyamas*), physical postures (*asanas*), breathing techniques (*pranayama*), and meditation training (*dhyana*). There is a wide range of yoga forms and styles. The most commonly practiced form of yoga in the United States and Canada is Hatha yoga, which emphasizes

postures (*asanas*) and often breathing exercises (*pranayama*). In patients with cancer, yoga is used for a variety of conditions, including stress, anxiety, depression, and fatigue, and as a method to increase physical activity.

## Literature Review on the Use of Complementary and Integrative Therapies for Clinical Outcomes in Patients With Breast Cancer

The clinical outcomes addressed here are common symptoms and side effects experienced by patients with breast cancer during treatment or as sequelae of treatment. The outcomes of interest include: anxiety/stress, pain, depression/mood, fatigue, sleep disturbances, QOL and physical functioning, CINV, radiation dermatitis, vasomotor outcomes, lymphedema, CIPN, pain, and sleep disturbance. Guidelines outlining conventional approaches to managing these symptoms and outcomes have been issued by national organizations like the National Comprehensive Cancer Network and the American Society of Clinical Oncology, but many of the prior guidelines and reviews did not include thorough reviews of complementary and integrative medicine approaches.<sup>191-197</sup> This review fills that gap for patients with breast cancer.

Below, for each therapy and clinical outcome of interest that received a grade of A or B, we summarize the trials that contributed to the graded recommendation to give the reader an understanding of the specific interventions that were tested. To provide additional context, there is a brief review of the literature on the use of each integrative therapy for conditions other than breast cancer. We also provide a risk/benefit assessment of each therapy as well as suggestions for future research. For therapies and clinical outcomes of interest that received grades of C, D, or H, we provide a brief overview of the rationale for the graded recommendation. The supporting tables provide detailed information on each trial that informed an A-graded or B-graded recommendation (see Supporting Information Table 2,<sup>26-48</sup> Supporting Information Table 3,<sup>26-30,33,35,40-43,45-48,53-56,59,60,69,72-90</sup> Supporting Information Table 4,<sup>27-29,43,46-48,73-75,82-85,104-106,127,128</sup> and Supporting Information Table 5<sup>61-65</sup>). Table 3 lists the clinical outcomes and integrative therapy combinations that had insufficient evidence to make a grade A, B, C, D, or H recommendation.<sup>26,33,36,37,40,43,45-50,52,69,72,73,76,77,79,83,84,87-89,94,97,104,108,111,113,129,130,133-135,138,139,149,198-301</sup>

### Updated Recommendations

Although the majority of graded recommendations remain the same as those in the previously published guidelines,<sup>9</sup> there are 5 noteworthy changes. For the outcome of anxiety and stress reduction, the use of meditation moved from grade B to grade A because of results from a fifth trial,<sup>26</sup> in

addition to the previously published 4 trials,<sup>27-30</sup> showing beneficial effects. The use of yoga for depression and mood disturbance was downgraded from grade A to grade B because of 4 new published studies demonstrating conflicting results.<sup>40,79-81</sup> The use of yoga for improving QOL changed from grade C to grade B, because 2 additional trials demonstrated beneficial effects.<sup>104,128</sup> Finally, new trials on the use of yoga<sup>40,80,104</sup> and hypnosis<sup>97,98</sup> for fatigue upgraded previous recommendations from grade I to grade C.

## Use of Integrative Therapies for Anxiety/Stress Reduction

### *Description of anxiety/stress*

Patients with cancer may experience stress related to the life changes associated with a cancer diagnosis, both during and after treatment. Under the NCI's Common Terminology Criteria for Adverse Event (CTCAE) psychiatric disorders, anxiety is categorized from grade 1 (mild symptoms and no intervention required) to grade 4 (life-threatening). Stress is often the result of life challenges that exceed the individual's perceived ability to cope and is a common and normal reaction during cancer diagnosis and treatment. This stress is associated with symptoms of anxiety and somatic complaints that can significantly diminish QOL.<sup>302</sup> Patients with anxiety may worry more frequently, have difficulty relaxing, or feel tense. Patients with cancer-related anxiety also may have elevated heart rate, myalgias, headaches, sleep disturbances, changes in appetite, nausea, diarrhea, and difficulty concentrating. The percentage of patients with breast cancer who report anxiety ranges from 12% to 47%, and approximately 11% to 16% of patients experience combined symptoms of anxiety and depression.<sup>303-305</sup> Evidence suggests that effective anxiety management is associated with improvements in QOL, psychological adjustment, understanding of the disease, decision making, and adherence to treatment.<sup>306-308</sup>

### *Meditation (A grade)*

**Overview of meditation interventions for anxiety/stress reduction.** Meditation is recommended for reducing anxiety in patients with breast cancer, including during radiation therapy (grade A). Many uncontrolled trials have been published, but this recommendation is based on 5 RCTs completed between 2009 and 2013 that used meditation to reduce anxiety symptoms (see Supporting Information Table 2).<sup>26-30</sup> Anxiety was the primary outcome for 4 of those trials. In all 5 studies, a meditation intervention was compared with a usual-care control condition. Study participants included women undergoing radiation or chemotherapy, breast cancer survivors who had completed treatment, and older adult breast cancer survivors ages 50 years and older. The study sample sizes ranged from 49 to 336 participants. Among these trials, 3 types of meditation

interventions were tested. Three trials implemented an intensive, integrated MBSR program customized for patients with breast cancer in which participants were trained in mindfulness meditation and gentle yoga for body awareness.<sup>26,29,30</sup> A fourth intervention was called the Mindful Movement Program and was also an intensive, integrated program customized for patients with breast cancer that included mindful walking/moving, group discussion, exploration of body parts, specific and deliberate movements, moving with intentional effort, active energetic movement, and partner work.<sup>27</sup> The fifth trial assessed a brain wave vibration meditation<sup>28</sup> or a mind/body training technique that combined simple, rhythmic movements with music, action, and positive messages.<sup>26</sup>

A systematic review and meta-analysis examined meditation in terms of its ability to reduce general psychological distress and stress-related health problems in adult clinical populations with a variety of health conditions; that analysis included 47 trials with 3515 participants.<sup>309</sup> Overall, mindfulness meditation programs demonstrated moderate evidence of improved anxiety at 8 weeks and at 3 to 6 months and showed low evidence of improved stress/distress and mental health-related QOL. The findings of these reviews across other patient populations and disease types support our recommendations.

The earliest work in MBSR interventions specifically demonstrated sustained benefits for individuals with anxiety disorders, and more recent research has continued to show a benefit for generalized anxiety.<sup>310-312</sup> The first study conducted in patients with cancer, an RCT of 89 patients with a variety of cancer types, found substantial decreases in anxiety for the group that received MBSR compared with results for a usual-care control group; results for the MBSR interventions were maintained at 6-month follow-up.<sup>313,314</sup> The reduction in anxiety observed in the above-described trials, specifically those that used more traditional forms of MBSR, provide support for the recommendation that meditation can be beneficial for the management of anxiety in women with breast cancer.

A recent systematic review and meta-analysis of 22 studies examined the effect of mindfulness-based therapy specifically on symptoms of anxiety and depression in adult patients with cancer and cancer survivors; of those 22 studies, 21 included either a substantial percentage of patients with breast cancer or only patients with breast cancer.<sup>315</sup> Overall, that review included 12 nonrandomized studies and RCTs. In the nonrandomized studies, mindfulness-based therapy was associated with significantly reduced symptoms of anxiety postintervention with a moderate effect size, while the pooled effects sizes of RCTs, including that discussed above,<sup>29</sup> resulted in a larger effect size ( $P < .001$ ). Although the review reported that overall study quality

**TABLE 3. Clinical Outcomes and Integrative Therapies With Insufficient Evidence to Form a Clinical Recommendation (I-Statement)<sup>a</sup>**

OUTCOME	INTEGRATIVE THERAPIES
Adherence	Acupressure, <sup>198</sup> multimodal <sup>199</sup>
Anemia	LCS101 combination botanical, <sup>200</sup> RG-CMH combination botanical, <sup>201</sup> shenqi fuzheng injection <sup>202</sup>
Anxiety/stress reduction	Art therapy, <sup>203,204</sup> comprehensive coping strategy, <sup>205</sup> electrical nerve stimulation, <sup>206</sup> healing touch, <sup>94,207</sup> hypnosis, <sup>208</sup> myofascial release, <sup>209</sup> multimodal, <sup>210,211</sup> reflexology, <sup>138,139,212</sup> reiki, <sup>213</sup> tai chi <sup>214</sup>
Cardiomyopathy	N-acetylcysteine <sup>215</sup>
Chemotherapy-induced nausea and vomiting	Acupressure, <sup>216</sup> aromatherapy, <sup>217</sup> <i>Agaricus sylvaticus</i> , <sup>218</sup> Cocculine (complex homeopathic Rx), <sup>219</sup> comprehensive coping strategy, <sup>205</sup> massage, <sup>52</sup> Nevasic audio program, <sup>220</sup> yoga <sup>43</sup>
Cognition	Natural environment, <sup>221</sup> <i>Ginkgo biloba</i> , <sup>222</sup> meditation, <sup>72</sup> yoga <sup>223</sup>
Constipation	Self-management program <sup>224</sup>
Depression/mood	Art therapy, <sup>203</sup> Biofield Healing, <sup>225</sup> comprehensive coping strategy, <sup>205</sup> CoQ10, <sup>226</sup> electrical nerve stimulation, <sup>206</sup> <i>Gandoderma lucidium</i> , <sup>227</sup> guarana, <sup>108</sup> hypnosis, <sup>228</sup> multimodal, <sup>199,210,229,230</sup> myofascial release, <sup>209</sup> qigong, <sup>135</sup> reflexology, <sup>138,139</sup> tai chi <sup>214</sup>
Fatigue	Acupressure, <sup>198</sup> acupuncture, <sup>50,231,232</sup> Biofield Healing, <sup>225</sup> comprehensive coping strategy, <sup>205</sup> CoQ10, <sup>226</sup> <i>Gandoderma lucidium</i> , <sup>227</sup> light treatment, <sup>233</sup> massage, <sup>87</sup> meditation, <sup>72,76</sup> mind-body cognitive therapy, <sup>234</sup> movement, <sup>235</sup> multimodal, <sup>230,236,237</sup> multivitamin, <sup>238</sup> polarity therapy, <sup>239,240</sup> stress management, <sup>241</sup> qigong, <sup>135</sup> reflexology, <sup>139</sup> relaxation, <sup>242,243</sup> stress management, <sup>36</sup> yoga <sup>40,46-48,79,83</sup>
Lymphedema	CYCLO 3 FORT, <sup>244</sup> electrotherapy, <sup>245</sup> ginkgo forte, <sup>246</sup> pentoxifyline and vitamin E, <sup>247,248</sup> yoga <sup>249</sup>
Neuropathy	Omega 3 fatty acids, <sup>250</sup> vitamin E, <sup>251,252</sup> acupuncture <sup>130</sup>
Neutropenia/leukopenia	Cat's claw, <sup>253</sup> LCS101 combination botanical, <sup>200</sup> RG-CMH combination botanical, <sup>201</sup> mistletoe, <sup>133,134</sup> shenqi fuzheng injection <sup>202</sup>
Pain	Comprehensive coping strategy, <sup>205</sup> stress management, <sup>36</sup> vitamin D2, <sup>254</sup> electrical nerve stimulation, <sup>206</sup> cognitive and behavioral therapy, <sup>255</sup> hypnosis, <sup>256</sup> massage, <sup>88</sup> myofascial release, <sup>209</sup> reflexology <sup>139,212</sup>
Quality of life	Acupressure, <sup>216</sup> Biofield Healing, <sup>225</sup> calendula cream, <sup>257</sup> cannabis, <sup>258</sup> chlorella extract, <sup>259</sup> CoQ10, <sup>226</sup> curcuminoids, <sup>260</sup> electrical nerve stimulation, <sup>206</sup> electrotherapy, <sup>245</sup> flaxseed, <sup>261</sup> <i>Gandoderma lucidium</i> , <sup>227</sup> ginkgo forte, <sup>246</sup> guided imagery, <sup>262</sup> healing touch, <sup>94</sup> homeopathy, <sup>263-265</sup> hypnosis, <sup>97</sup> laser therapy, <sup>111</sup> manual lymphatic draining, <sup>113</sup> massage, <sup>87</sup> meditation, <sup>26,72</sup> movement, <sup>235,264</sup> music therapy, <sup>89</sup> multimodal, <sup>199,210,230,236,237,267</sup> multivitamin, <sup>238</sup> polarity therapy, <sup>239,240</sup> relaxation, <sup>69,77</sup> shenqi fuzheng, <sup>202</sup> shark cartilage, <sup>268</sup> soy, <sup>149</sup> supportive-expressive group therapy, <sup>269</sup> tai chi <sup>214,270-272</sup>
Physical functioning	Mind-body cognitive therapy, <sup>234</sup> music therapy, <sup>33</sup> multimodal, <sup>199</sup> myofascial release, <sup>209</sup> reflexology, <sup>139</sup> stress management, <sup>37</sup> tai chi, <sup>270,272</sup> yoga <sup>45,79,84,273</sup>
Radiation therapy-induced toxicity outcomes	Adlay bran extract, <sup>274</sup> alpha ointment with henna, <sup>275</sup> Aquaphor-Biafine-Radiacare, <sup>276b</sup> boswellia cream, <sup>277</sup> calendula cream, <sup>257,278</sup> chamomile, <sup>279</sup> curcumin, <sup>280</sup> glutamine, <sup>281</sup> homeopathic pills, <sup>282</sup> honey, <sup>283,284</sup> hydration, <sup>285</sup> massage, <sup>286</sup> oil-in-water emulsion, <sup>287</sup> glutathione and anthocyanin gel, <sup>288c</sup> wheat grass extract, <sup>289</sup> pentoxifyline and vitamin E <sup>290,291</sup>
Sleep disturbance	Acupuncture, <sup>49,50,129</sup> calendula cream, <sup>257</sup> meditation, <sup>72,292-294</sup> qigong, <sup>135</sup> stress-management techniques <sup>36</sup>
Vasomotor outcomes	Black cohosh, <sup>295,296</sup> flaxseed, <sup>261</sup> homeopathy, <sup>264,265</sup> hypnosis, <sup>297</sup> magnetic therapy, <sup>298</sup> meditation, <sup>73</sup> peppermint, <sup>299</sup> vitamin E, <sup>300</sup> yoga <sup>104,301</sup>

Abbreviations: CoQ10, coenzyme 10Q; CYCLO 3 FORT, fluid extract of *Ruscus aculeatus*, hesperidin methyl chalcone, and vitamin C; LCS101, a botanical compound mixture; RG-CMH, a Chinese medicinal herb complex. <sup>a</sup>Definition of the I Statement: Concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined. Read the Clinical Considerations section of the US Preventive Services Task Force Recommendation Statement. If the service is offered, then patients should understand the uncertainty about the balance of benefits and harms. <sup>b</sup>Suppliers for these topicals are as follows: Aquaphor (Beiersdorf AG, Hamburg, Germany), Biafine (Laboratoire Medix, Houdan, France), and RadiaCare (Medline Industries, Inc., Northfield, IL). <sup>c</sup>RayGel is a proprietary glutathione and anthocyanin gel.

varied among the studies included, there appears to be sound evidence from carefully conducted RCTs (n = 9) supporting the use of mindfulness-based therapies for the management of anxiety in patients with breast cancer and in breast cancer survivors. Another review of 9 studies (including 2 RCTs, a quasi-experimental case-control study, and 6 single-group pre/post-intervention studies) investigated the efficacy of MBSR

on mental health specifically in patients with breast cancer and found an overall decrease in anxiety scores after MBSR (P < .01).<sup>174</sup> That review provides further support for the use of MBSR to manage anxiety, specifically in women with breast cancer. Many other reviews reached similar conclusions, reporting positive, moderate effect sizes of mind-body interventions (MBIs) on anxiety and distress in cancer.<sup>174,175,316</sup>

**Risk/benefit assessment of meditation interventions.** Meditation therapies pose very little risk to participants in this type of intervention. Few adverse events have been reported in any trials, but there has been recent interest within the meditation research community in exploring adverse reactions to intensive meditation practice, particularly in vulnerable individuals.<sup>317,318</sup> Typically, potential participants are screened through individual orientation interviews before joining meditation group programs, and participants who have serious mental health issues are often redirected to individual counseling or psychiatric intervention before or concomitant with MBI participation. Group facilitators are typically mental health care professionals trained to identify and manage psychological symptoms and reactions that may occur during the training.

Participants in these meditation therapy groups typically report that the sessions are enjoyable, and dropout rates are often low and are comparable to the rates in other psychosocial group programs. Because they are offered in group settings, meditation interventions are more cost effective than traditional individual counseling or psychotherapy and can often achieve similar results. However, the literature on meditation therapy is lacking in head-to-head comparisons with other forms of therapy, including individual counseling, cognitive-behavioral therapy, or other MBIs. Hence, the specificity of meditation therapy is not yet known. With the exception of the trial reported by Carlson et al,<sup>26</sup> studies have not compared MBIs with other effective interventions. Other research suggests that the benefit is related to the degree of the participant's engagement in and commitment to the practice,<sup>313,319</sup> in that participants who practice more at home often benefit more, but this area is still being investigated.<sup>320</sup> Drawbacks of these types of group interventions are the requirement for highly trained facilitators and the need for and ability of participants to attend in person, usually in large cities with tertiary cancer centers. In response to these issues, online and home-based adaptations of MBIs are being developed. For example, Zernicke et al<sup>321</sup> demonstrated that an online, live MBI group in which rural and remotely located patients who had cancer participated weekly over 8 weeks had similar benefit to the on-site, in-person version; and patients were highly satisfied with the remote MBI adaptations.

**Future research in meditation interventions for anxiety reduction.** Future research on the use of meditation interventions for anxiety can similarly test novel interventions in populations that may not have ready access to in-person meditation programs.

#### **Music therapy (B grade)**

**Overview of music therapy interventions for anxiety/stress reduction.** Passive music therapy is recommended to

reduce anxiety during radiation therapy, chemotherapy sessions, and postsurgery (grade B) based on results from 5 RCTs comparing music therapy interventions with standard care (see Supporting Information Table 2).<sup>31-35</sup> Study participants included patients with breast cancer who were undergoing mastectomy, chemotherapy, and/or radiation therapy. The sample sizes of these studies ranged from 30 to 170 participants. The music therapy interventions were described as either *passive* or *active* music therapy, depending on the level of engagement required by the individual. Four trials examined the effect of passive music therapy, which was found to decrease anxiety scores in the intervention group,<sup>31,32,34,35</sup> including reducing sedation requirements during radiation therapy (measured as a secondary outcome).<sup>31,32,34</sup> The fifth trial, which was conducted by Hanser et al,<sup>33</sup> examined active music therapy (which required active engagement of the participant) and yielded substantially different results from the 4 trials of passive music therapy. In that study, active music therapy did not result in decreases in anxiety. The discrepancy in trial results between passive and active music therapy might have occurred because the participant engagement required for active therapy does not include the potential relaxing components of passive music therapy (eg, listening to music).

A recent systematic review and meta-analysis by Boehm et al<sup>322</sup> assessed the effect of different expressive therapies, including passive and active music therapy, on improving anxiety, depression, and QOL in patients with breast cancer. The review included 3 of the RCTs that formed the basis for our recommendation of passive music therapy for anxiety/stress reduction, of which 2 trials tested passive music therapy,<sup>31,34</sup> and the other tested active music therapy.<sup>33</sup> Another recent meta-analysis included an additional RCT evaluating art therapy.<sup>204</sup> Boehm et al found a clinically and statistically significant mean difference ( $P < .01$ ) in the anxiety scores of patients who received music therapy compared with the control group,<sup>322</sup> thus further supporting our recommendation of passive music therapy for reducing anxiety. Passive music therapy has also been shown to reduce anxiety among patients undergoing mammographic screening, indicating that the recommendation may apply broadly to adult women in a clinical cancer setting.<sup>323</sup>

**Risk/benefit assessment of music therapy.** Passive music therapy is noninvasive, does not interfere with a patient's privacy, and has no reported deleterious effects. Furthermore, it does not require costly, technologically advanced equipment and can be implemented in a variety of locations. As such, passive music therapy can be safely and effectively implemented in clinical settings for patients with breast cancer to help reduce short-term anxiety associated with receiving medical care for their cancer.

**Future research in music therapy for anxiety reduction.**

Future research should assess the long-term effects of passive music therapy on anxiety, because the trials reviewed here only assessed short-term reductions in anxiety. Although active music therapy may also have benefit, more than one existing trial will be needed for a comprehensive risk/benefit assessment. Trials that directly compare the effect of passive versus active music therapy on anxiety are needed to clarify whether the benefit is because of listening to music in a relaxed state or participating in the creation of music.

**Stress management (B grade)**

**Overview of stress-management interventions for anxiety/stress reduction.** Stress management is recommended to reduce anxiety in patients during breast cancer treatment (grade B), but long-term stress-management group programs appear to be better than self-administered home programs. This recommendation is based on 4 RCTs, which were completed between 2008 and 2013 among patients with breast cancer, testing a stress-management intervention compared with usual care using an improvement in anxiety as the primary outcome.<sup>36-39</sup> Study participants included only patients who had breast cancer in 2 of the 4 trials<sup>36,39</sup> and a mixed group of patients with cancer that included a significant proportion of women who had breast cancer in the other 2 trials.<sup>37,38</sup> In all 4 trials, patients with breast cancer were included from defined periods along the continuum of care, including before surgery, during chemotherapy, and after cancer treatment. Patients thus were either undergoing or had undergone surgery, chemotherapy, or radiation therapy, either alone or in combination. The study sample sizes for these trials ranged from 85 to 286 participants. Of the 4 trials, 2 indicated that the improvement was statistically significantly different compared with the control group.<sup>37,39</sup> One trial found a similar improvement in both the intervention and control groups with no statistically significant differences across groups,<sup>36</sup> and the fourth trial found no improvement<sup>38</sup> (see Supporting Information Table 2, Stress Management).

Stress-management interventions varied among the studies (see Supporting Information Table 2).<sup>36-39</sup> One trial<sup>38</sup> implemented a self-administered stress-management intervention before patients received chemotherapy. The intervention included video and booklet information specific to stress management and exercise and was delivered by a doctoral-level psychologist.<sup>38</sup> A second trial<sup>36</sup> offered stress-management modalities that included guided imagery techniques, relaxation, meditative exercises, and counseling that aimed to promote active coping, alert relaxation, and a positive attitude toward change. Instruction was given in person and was complemented by audio CDs for use at home. Face-to-face sessions lasted from 45 to 60 minutes each and

took place in the hospital.<sup>36</sup> The stress-management portion included information, demonstrations and instructions for paced breathing, PMR with guided imagery, and the use of coping strategies to manage stress. A third trial,<sup>37</sup> which took place at a multicenter community clinical oncology program involving 20 clinical sites, was designed to determine whether a self-administered stress-management intervention that was previously identified as beneficial for patients with cancer would improve QOL and decrease psychological distress (including anxiety and depression) in patients receiving chemotherapy at community clinical centers. The study used a factorial design to test stress-management training, exercise training, combined stress-management and exercise training, and usual care. Patients assigned to stress-management training were provided written materials and videos on 3 techniques, including PMR and guided imagery, abdominal breathing, and coping skills training.<sup>37</sup> A fourth trial<sup>39</sup> examined the effects of a cognitive-behavioral stress-management intervention (comprised of relaxation training, including meditation, guided imagery, PMR and breathing techniques, cognitive restructuring, and coping skills training) on late-afternoon serum cortisol and relaxation indicators in women undergoing treatment for nonmetastatic breast cancer.

A systematic review by Trijsburg et al evaluated the effects of stress-management techniques on mental health outcomes, including anxiety, across 22 studies using samples from heterogeneous cancer populations that included 6 studies of breast cancer-only samples.<sup>324</sup> The interventions assessed were all structured and included counseling and coping components in addition to some interventions, including PMR, guided imagery, self-hypnosis, and deep breathing. Overall, the review found positive effects for mental health outcomes, including anxiety scores.

**Risk/benefit assessment of stress-management interventions.**

Stress-management therapy is noninvasive, nontoxic, and has no appreciable risk to patients. Stress management does not require specialized equipment and can be implemented in a variety of locations. Resources for providing instruction on self-management practices are broadly available. Because the majority of trials discussed above tested long-term interventions, the guideline recommendation is specific to long-term stress-management programs. However, this may be complicated by other factors, including a potential increase in the cost of delivery for providers/facilitators as a result of the implementation of longer term programs, and it also could present a barrier to patients who have access-to-care and other health care disparity issues. Overall, it is recommended that stress-management therapy can be safely and effectively implemented in clinical settings for patients with breast cancer.

**Future research in stress-management interventions for anxiety reduction.** Future research in this area should compare in-person, professionally led stress-management group programs versus home-based, self-study, and internet-based stress-management intervention options, which are less costly and more broadly accessible. Research should also examine long-term outcomes for each type of delivery modality.

### Yoga (B grade)

**Overview of yoga interventions for anxiety/stress reduction.** Yoga is recommended for reducing anxiety in patients with breast cancer (grade B). This recommendation is based on 9 RCTs, completed between 2007 and 2014, in which a yoga intervention was implemented to reduce physical symptoms and psychological distress, including anxiety, which was assessed as the primary outcome in 4 of the studies (see Supporting Information Table 2).<sup>40-48</sup> Those 9 trials tested 5 different yoga interventions. The first intervention was an intensive, integrated yoga program customized for patients with breast cancer, in which participants were led through slow stretching and loosening exercises, various postures (*asanas*), guided imagery specific to cancer, positive thought provocation, chanting exercises, various breathing exercises (*pranayama*), and soothing sound vibrations and guided imagery (*yoga nidra*).<sup>41-44</sup> A second intervention implemented Iyengar yoga, a traditional form of Hatha yoga emphasizing postures and breathing techniques that target symptom-specific concerns using passive inversions (upside-down postures with the head lower than the heart) and passive backbends (supported spinal extensions).<sup>45</sup> A third intervention used Patanjali's yoga sutras, which included warm-up movements synchronized with breathing, selected postures, deep relaxation techniques, alternate-nostril breathing (*pranayama*), and meditation.<sup>48</sup> The fourth intervention implemented meditation and breathing exercises that focused attention on internal body sensations as well as yoga exercises (modified *asanas*) composed of gentle stretching and strengthening exercises.<sup>40</sup> Pranayama or yoga breathing practices were tested in the remaining trials.<sup>46,47</sup> Study participants included women who had been recently diagnosed with breast cancer, those who were currently receiving radiation or chemotherapy or a combination of both, and those who were experiencing significant fatigue post-treatment. The study sample sizes ranged from 23 to 98 participants.

Several recent reviews of yoga interventions for individuals with cancer have been published.<sup>325-328</sup> The first meta-analysis investigating the impact of yoga interventions on psychological health outcomes<sup>329</sup> identified 10 articles that examined outcomes in patients with breast cancer ( $n = 7$  articles), patients with lymphoma ( $n = 1$ ), and mixed cancer

populations ( $n = 2$ ). Analyses involving 8 trials that assessed anxiety found that lower anxiety was associated with the yoga groups relative to controls ( $P = .009$ ); and similar results with yoga interventions were observed for distress ( $P = .003$ ) and stress ( $P = .006$ ). However, because this was a heterogeneous sample of patients, it was unclear whether the results could be generalized specifically to patients with breast cancer. More recently, a systematic review and meta-analysis assessing the impact of yoga interventions on QOL and psychological health specifically in patients with breast cancer and survivors was conducted.<sup>330</sup> Overall, 12 RCTs were included in the analysis with a total of 742 participants. Analyses revealed short-term positive effects of yoga interventions on improved psychological health, including anxiety ( $P < .01$ ), perceived stress ( $P = .03$ ), and psychological distress ( $P < .01$ ). However, it is notable that these effects were applicable only to those who engaged in yoga during active cancer treatment and not in the post-treatment period. The authors stated that, based on these positive preliminary results, a wide variety of yoga practices could be recommended for this population.<sup>330</sup> Finally, although the methodological quality across the trials varied, it has been demonstrated that yoga is beneficial for reducing psychological distress in a wide variety of non-cancer clinical populations, including adult patients with anxiety and depression.<sup>331,332</sup>

**Risk/benefit assessment of yoga interventions.** Yoga interventions are noninvasive and, with proper instruction, can be adapted to people who have functional and other impairments without harm. Yoga interventions are low cost and can be practiced at home with instructional videos; however, in the context of breast cancer, they are best undertaken under the guidance of certified yoga instructors who have specific training in teaching patients with cancer and cancer survivors. Such programs also have the ability to be adapted and modified for people with medical conditions or limited mobility.<sup>333</sup> Older adults, individuals with limited mobility, and those with chronic medical conditions should proceed with yoga therapy only under the guidance of a certified instructor to minimize the potential risk of harms such as strained muscles and dizziness if yoga postures are attempted incorrectly or prematurely.

**Future research in yoga interventions for anxiety reduction.** Many of the studies investigating the impact of yoga on psychological outcomes in individuals with cancer should be interpreted with caution, because many of these studies are small and preliminary. Furthermore, the studies summarized above have some inconsistency of results; the trials from India<sup>41-44</sup> reported consistently positive results, while the trials from North America<sup>40,45-48</sup> reported less consistent positive results. Nevertheless, many of the

studies and reviews that examined yoga interventions reported overall positive outcomes in several physical, psychological, and QOL measures. Future trials of yoga interventions for anxiety/stress reduction should focus on testing forms of yoga that can be more easily applied and, to improve the generalizability of the results, should test the interventions in larger sample size and in minority and underserved populations that may not have easy access to yoga programs.

#### **C-graded therapies for anxiety and stress reduction**

Acupuncture,<sup>49-51</sup> massage,<sup>52-55</sup> and relaxation<sup>56-60</sup> can be considered for reducing anxiety and stress (grade C). Three high-quality trials assessed acupuncture for anxiety and stress reduction, which were secondary outcomes; 2 of the 3 positive trials were small,<sup>49,50</sup> and the other demonstrated no effect.<sup>51</sup> However, of 4 studies that examined massage for anxiety, 3 with positive findings included fewer than 40 participants,<sup>52-54</sup> and the other demonstrated no effect.<sup>55</sup> Results were inconclusive regarding relaxation for anxiety and stress reduction because of inconsistencies and small sample sizes. Future directions in research can focus on evaluating these modalities in a large, high-quality trial assessing anxiety as the primary outcome.

### **Use of Integrative Therapies for Depression/Mood Disturbances**

#### **Description of depression/mood disturbances**

Both during and after cancer therapy, patients may experience symptoms of depression, as they often feel a sense of loss of health and the life they had before their cancer diagnosis.<sup>302</sup> The CTCAE categorizes depression as a psychiatric disorder on a scale from 1 (mild) to 5 (death). Symptoms of depression in patients with cancer may include persistent feelings of sadness, numbness, nervousness, guilt, worthlessness, helplessness or hopelessness, difficulty concentrating or behavior that includes being short-tempered or moody, crying for long periods of time or many times each day, lacking interest or pleasure in performing activities, and having suicidal thoughts. Other symptoms may include weight change, sleep disturbances, tachycardia, dry mouth, increased perspiration, gastrointestinal symptoms, diarrhea, changes in energy level, persistent fatigue, headaches, or myalgias. The percentage of patients with breast cancer reporting depression ranges from 3% to 34%, and 11% to 16% of patients experience combined depression and anxiety symptoms, depending on the population studied.<sup>303-305</sup> Effectively managing depression may improve QOL, psychological adjustment, understanding of the disease, decision making, adherence with cancer treatment, and response to cancer treatment.<sup>306-308</sup>

#### **Meditation (A grade)**

**Overview of meditation interventions for depression/mood disturbances.** Meditation, particularly MBSR, is recommended for treating mood disturbance and depressive symptoms in patients with breast cancer (grade A). This recommendation is based on 10 RCTs, completed between 2009 and 2015, that used meditation to help reduce depressive symptoms (see Supporting Information Table 3).<sup>26-30,72-76</sup> Depression was the primary or secondary outcome for all of these trials. In 8 of the 10 trials,<sup>27-30,72-74,76</sup> a meditation intervention was compared with a usual care group, a waitlist control group, or another active intervention; 2 other trials used a 3-arm trial design.<sup>26,75</sup> Study participants included women undergoing current radiation therapy or chemotherapy for breast cancer, breast cancer survivors who had completed treatment, and adult breast cancer survivors ages 55 years and older. The study sample sizes ranged from 33 to 336 participants and tested 6 different types of meditation interventions, including an intensive, integrated MBSR program customized for patients with breast cancer<sup>26,29,30,73,75</sup>; the Mindful Movement Program<sup>73</sup>; brain wave vibration meditation<sup>28</sup>; Tibetan sound meditation<sup>72</sup>; cognitively based compassion training<sup>76</sup>; and Transcendental Meditation.<sup>74</sup>

In the meta-analysis examining the effect of mindfulness-based therapy on psychological outcomes in adult cancer populations,<sup>315</sup> compared with results in controls, mindfulness-based therapy was associated with significantly reduced depression postintervention, with a moderate effect size in the nonrandomized studies and RCTs, including one trial listed above<sup>29</sup> ( $P < .001$ ). By using evidence from 9 well conducted studies, the review and meta-analysis by Zainal et al confirmed the use of mindfulness-based therapies for the management of depression in patients with breast cancer and survivors despite the heterogeneity in the reviewed studies; the results of the meta-analysis identified a significant pooled effect size for MBSR on depression scores (effect size, 0.575; 95% confidence interval, 0.429-0.722 [ $P < .01$ ]).<sup>174</sup> In their study, Teasdale et al<sup>334</sup> modified traditional MBSR by combining it with principles of cognitive behavioral therapy to create mindfulness-based cognitive therapy, which was designed specifically to prevent recurrence of depressive symptoms in individuals with relapsed major depression.<sup>335</sup> The intervention proved effective for preventing depression relapse<sup>334</sup> and has since been widely applied and adapted to treat depression symptoms in a range of clinical samples.<sup>336</sup> In patients with cancer, other RCTs of meditative interventions resulted in decreased depressive symptoms,<sup>313</sup> with results maintained after 6 months of follow-up.<sup>314</sup> The reduction in depressive symptoms observed in the above-described trials comprising these reviews and meta-analyses provide further support for

the recommendation that meditation can be beneficial for the management of depressive symptoms in women with breast cancer.

**Risk/benefit assessment of meditation interventions.**

The risk/benefit assessment of the effects of meditation intervention on depression and mood disturbance outcomes is similar to the assessment of anxiety outcomes. Despite these limitations, the evidence suggests that meditation and MBSR could be added to treatment plans or in the post-treatment period, provided that these interventions are facilitated by appropriately trained instructors and can be adapted and modified if needed for individuals with cancer.

**Future research in meditation interventions for depression/mood.** Future research on meditation interventions to improve mood disturbances/depression should focus on understanding the type, duration, and lasting effects of specific meditation techniques on specific mental health outcomes.

**Relaxation (A grade)**

**Overview of relaxation interventions for depression/mood disturbances.** Relaxation therapy is recommended for improving mood disturbances and depressive symptoms when added to standard care (grade A). The recommendation put forth in the guidelines is based on results from 6 RCTs, completed between 1999 and 2007, which implemented a relaxation program with or without guided imagery as an intervention to improve mood disturbances and treat depression (see Supporting Information Table 3).<sup>56,59,60,69,77,78</sup> Five of the 6 trials measured depression as the primary outcome. In all 6 trials, a relaxation therapy intervention group was compared with a standard care group. The interventions comprised some form of relaxation therapy that included PMR and guided imagery or visualization techniques. One trial<sup>56</sup> assessed autogenic training, which provided training in relaxation meant to induce heaviness and warmth of limbs, calming of the heart and breathing, abdominal warmth, and cooling of the forehead. Limitations of all of these trials included the potential for expectation bias attributable to the inability to blind participants and a lack of attention control groups, although one study used a health education attention control.<sup>78</sup> Participants in these studies included patients with breast cancer who had undergone or were currently undergoing surgery, chemotherapy, or radiation therapy. The study sample sizes ranged from 31 to 183 participants.

The majority of pertinent systematic reviews combine relaxation techniques with stress-management, psychosocial, and psychological interventions for patients with breast cancer. Thus, a review specific to relaxation interventions that includes PMR and guided imagery for depression/mood or other psychological outcomes in patients with breast cancer

and survivors is warranted. A review of studies of guided imagery as adjuvant cancer therapy broadly assessed 6 RCTs and found the methodological quality inconsistent.<sup>337</sup> Across trials, the results provided few details, and the studies were implemented with heterogeneous cancer populations, interventions, and outcome measures, which ultimately precluded statistical pooling of the results. Despite these limitations, the results indicated that guided imagery as a sole adjuvant cancer therapy was supportive and increased comfort in patients and had few risks.

Beyond decreasing depression, relaxation therapy may also have a beneficial impact on other symptoms important to women with breast cancer. For instance, PMR was effective in ameliorating sleep problems and fatigue in women undergoing chemotherapy for breast cancer.<sup>338</sup> Other likely benefits attributable to this therapy in breast cancer populations include reduced nausea and anxiety.<sup>339-342</sup>

**Risk/benefit assessment of relaxation interventions.**

Relaxation therapy is noninvasive and positively engages the patient with very little potential for harm. The goal of this treatment approach is to use principles of psychoneuroimmunology to better regulate the hypothalamic-pituitary-adrenal axis, modulate cortisol production, and decrease stress, which may have other health benefits, including psychological outcomes that may be affected by stress and distress (such as anxiety and depression/mood disturbances). Some of the appeal of relaxation therapy includes its low cost, safety, and portability. With adequate training, patients themselves can apply this therapy when and where they want without the need for supervision. However, the durability of relaxation therapy and the frequency required to sustain a long-term positive effect on depression remain unclear. It seems that relaxation therapy is not only applicable for those with breast cancer and depression but also has been shown to be beneficial in other contexts, including the ability to decrease depression in adults<sup>343,344</sup> and depression associated with cardiac disease.<sup>345</sup> The minimal cost and low potential for harm with relaxation therapy, in conjunction with its evidence of benefit, support an A grade recommendation for depression.

**Future research in relaxation interventions for depression/mood.** In addition to the gaps in the literature described above, future research on the use of relaxation interventions to improve mood disturbances should focus on how to use novel electronic communication strategies to deliver low-cost relaxation techniques to diverse patient populations.

**Yoga (B grade)**

**Overview of yoga interventions for depression/mood disturbances.** Yoga is recommended for improving mood disturbances and depressive symptoms in women with breast

cancer (grade B). This recommendation is based on the results from 15 RCTs, completed between 2006 and 2015, that used a yoga intervention to reduce physical symptoms and psychological distress, including depression (see Supporting Information Table 3).<sup>40-43,45-48,79-85</sup> Depression or depressive symptoms were the primary or secondary outcome for all studies included in this review. Study participants included women recently diagnosed with or having a recurrence of breast cancer; women who were receiving radiation therapy, chemotherapy, or a combination of both; an ethnically diverse and underserved sample of female patients; and women who had completed breast cancer treatment. Five different yoga interventions were tested in study samples ranging in size from 23 to 200 participants. Five trials assessed an intensive, integrated yoga program that was customized for patients with breast cancer, including asanas, pranayama, and yoga nidra.<sup>41-43,81,85</sup> Five trials implemented Iyengar yoga, a traditional form of Hatha yoga, and passive backbends.<sup>45,80,82-84</sup> Two trials assessed Patanjali's yoga sutras, which included warm-up movements synchronized with breathing, selected postures, deep relaxation techniques, meditation, and alternate-nostril breathing (pranayama)<sup>48,79</sup>; while 2 trials evaluated only the pranayama practices.<sup>46,47</sup> Finally, a yoga exercise intervention implemented meditation and breathing exercises that focused attention on internal body sensations as well as yoga exercises (modified asanas) composed of gentle stretching and strengthening exercises.<sup>40</sup>

It has been shown that yoga is beneficial for reducing depression in a wide variety of clinical populations,<sup>332,346-348</sup> and specifically among individuals with cancer.<sup>325-328</sup> One meta-analysis investigating the impact of yoga interventions on psychological health outcomes<sup>329</sup> analyzed 8 trials of yoga interventions for depression and showed improvement in depressive symptoms in the yoga groups compared with the control groups ( $P = .002$ ) among a heterogeneous sample of patients. Specifically in patients with breast cancer and in breast cancer survivors, a meta-analysis<sup>330</sup> of 12 RCTs, representing a total of 742 participants, revealed short-term effects of yoga interventions on improved psychological health, including depression ( $P < .01$ ). A caveat was that the observed efficacy was only applicable for yoga practiced during active cancer treatment and not necessarily in the post-treatment period. Overall, the authors stated that, based on these positive preliminary results, yoga therapy should be used in this population.

**Risk/benefit assessment of yoga interventions.** The risk/benefit assessment of the effects of yoga on depression and mood disturbance outcomes is similar to the assessment for anxiety outcomes. Studies assessing yoga for psychological outcomes in individuals with cancer are typically small, not well controlled, and preliminary in nature.

Furthermore, comparability across studies is difficult, because findings differ between populations from India<sup>41-43,85</sup> and North America.<sup>45,46,48,82-84</sup> Despite these limitations, the evidence suggests that yoga interventions could be added to treatment plans or in the post-treatment period, provided these interventions are facilitated by appropriately trained yoga instructors and can be adapted and modified for people with medical conditions or limited mobility.<sup>333</sup>

**Future research in yoga interventions for depression/mood.** Future trials of yoga interventions to improve mood disturbances/depression should test the effects of different types, doses, and durations of yoga on patient populations with various degrees and types of mood disturbances and depression in addition to including larger sample sizes and testing across active controls.

#### **Massage (B grade)**

**Overview of massage therapy interventions for depression/mood disturbances.** Massage therapy is recommended to improve mood disturbance in breast cancer survivors after active treatment (ie, surgery, chemotherapy, radiation; grade B). This recommendation is based on results from 6 trials completed between 2004 and 2012.<sup>53-55,86-88</sup> In the trial reported by Listing et al,<sup>87</sup> the primary outcomes focused on physical discomfort and fatigue, with mood disturbance as a secondary outcome. The other 5 trials assessed depression as the primary outcome and had other secondary outcomes, including perceived stress, QOL, pain, heart rate variability, and emesis. In the 5 trials, the effect of massage therapy was compared with the effect of standard care. The studies, which took place in the United States,<sup>53</sup> Germany,<sup>54,86,87</sup> England,<sup>55</sup> and Spain,<sup>88</sup> all included breast cancer survivors who had completed active cancer treatment at least 3 months before study enrollment. The study sample sizes ranged from 20 to 288 participants. In 3 of the 6 trials, the massage therapy intervention was a variation of classic massage involving rhythmic stroking, kneading, and acupressure at select areas on the body.<sup>54,86,87</sup> The study by Fernandez-Lao used an experienced and trained physical therapist to administer manual massage therapy.<sup>88</sup> Wilkinson et al<sup>55</sup> included aromatherapy as part of the massage therapy, which was individualized across study participants. Hernandez-Reif et al<sup>53</sup> combined massage with acupressure and Trager, which uses hundreds of small, rocking, and elongating movements that release muscle tension. The number and frequency of massage therapy sessions varied across the studies.

All of the trials assessing classic massage therapy used the same protocol of biweekly, 30-minute massages for 5 weeks,<sup>54,86,87</sup> with the exception of the trial by Fernandez-Lao et al, in which a one-time, 40-minute massage session was assessed.<sup>88</sup> Across these studies, compared with control

groups, women in the intervention groups reported significant improvement in mental health outcomes, including reduced depression and mood disturbance scores particularly in relation to anxious depression, anger, and tiredness. These differences between groups, however, were not consistently sustained across all studies. For example, in the study by Fernandez-Lao et al, the improvements in depression outcomes with a single-session massage intervention depended on the participant's individual level of enthusiasm for that intervention. The classic massage studies<sup>54,86,87</sup> and one trial that combined massage with aromatherapy<sup>55</sup> found that the massage interventions significantly decreased depression only immediately after the intervention but not long term. The remaining study that combined massage therapy with acupressure and Trager<sup>53</sup> demonstrated a positive effect of the interventions on anxiety and depression, with these effects sustained at long-term follow-up.

A systematic review and meta-analysis examined the role of massage interventions in the management of treatment-related side effects associated with breast cancer in terms of improvement in overall QOL, including measures of depression.<sup>349</sup> In total, 18 RCTs were included in this review. Overall regular massage therapy was shown to have positive effects on other outcomes, such as anger and fatigue symptoms, but the meta-analysis of 8 trials, 3 of which are summarized in this section,<sup>53,54,87</sup> did not find significant beneficial effects of massage therapy for depression. However, that meta-analysis was limited by significant heterogeneity across the studies that assessed depression as the outcome ( $P = .002$ ) as well as by small and possibly underpowered sample sizes, which may have accounted for the nonsignificant results. An earlier systematic review of massage therapy in breast cancer populations that found no positive effect of massage on depression also concluded that few rigorous trials have been conducted and that the risk of bias in such trials is high.<sup>350</sup>

**Risk/benefit assessment of massage therapy interventions.** Classic massage is a noninvasive therapy that has limited adverse effects. For patients with cancer, massage therapy by a trained massage professional appears to have few risks and may reduce pain, promote relaxation, and boost mood, at least in the short term.<sup>351</sup> Since trained, licensed therapists delivered the interventions tested in these studies, the recommendation of massage for depression applies specifically to massage by trained therapists.<sup>352,353</sup> Some caution is needed, however, for individuals receiving anticoagulation therapy because of their risk of bruising. Women with breast cancer who have undergone radiation therapy or surgery or have implanted medical devices also may need to be cautious in having massage to the affected regions. In addition, some women may be reluctant to disrobe because of altered body image, modesty, or

ethnocultural issues. Thus, important considerations include appropriate draping of the individual and ensuring that the massage therapist is sensitive to the treatment experiences of women with breast cancer and develops a therapeutic relationship with the individual. Ensuring that the massage therapist is the same gender as the patient is considered best practice in the massage profession and may also increase an individual's comfort with receiving massage therapy. However, this practice was not tested in the studies included in this review.

**Future research in massage interventions for depression/mood.** A 2008 systematic review of massage therapy for depression in the general public concluded that evidence to support massage as an effective treatment for this indication and population was lacking.<sup>354</sup> However, a more recent (2010) meta-analysis of 17 RCTs concluded that massage therapy had a positive effect on individuals suffering from depression.<sup>355</sup> That meta-analysis also highlighted the heterogeneity across massage therapy trials in terms of therapy protocols, outcomes measurement, and populations and underscored the need for standardization across future massage therapy trials. These issues are also true for the trials assessing massage interventions for depression/mood in patients with breast cancer. Future research on massage therapy interventions to improve depression/mood disturbances should focus on understanding how best to disseminate cost-effective massage interventions in routine clinical settings.

### **Music therapy (B grade)**

**Overview of music therapy interventions for depression/mood disturbances.** Passive music therapy is recommended to improve depression/mood disturbances in patients with newly diagnosed breast cancer (grade B). This recommendation is based on 4 RCTs, completed between 2000 and 2011, that tested a music therapy intervention to improve mood/depression (see Supporting Information Table 3).<sup>33,35,89,90</sup> Depression/mood disturbances were assessed either as the primary outcome or as a secondary outcome to anxiety. In all 4 trials, a music therapy intervention group was compared with either a waitlist or a standard care control group. Study participants included women with a breast cancer diagnosis who had completed mastectomy, chemotherapy, or radiation therapy or who had metastatic disease. The study sample sizes ranged from 8 to 170 participants. Three trials examined the effect of passive music therapy, which was found to decrease depression scores compared with controls,<sup>35,89,90</sup> and the fourth trial examining active music therapy<sup>33</sup> yielded no clinically meaningful, long-term effects between groups or over time. Active music therapy resulted in immediate effects on happiness within the intervention group that were not sustained over time.

Therefore, the guideline recommendation is specific to passive music therapy.

Of the 5 studies combined in the meta-analysis described above that assessed multiple types of art therapies for improving anxiety, depression, and QOL among patients with breast cancer<sup>322</sup> (4 music therapy interventions, including 2 trials identified in our review,<sup>33,204</sup> and an art therapy trial), a clinically and statistically significant mean difference ( $P = .05$ ) was observed across all depression scores in the music therapy intervention groups compared with control groups. Furthermore, a systematic review of music therapy specifically for depression in the *Cochrane Database of Systematic Reviews* found that, although only 5 RCTs have tested music therapy interventions for depression and have met the review study inclusion criteria, this therapy is widely accepted and beneficial to a broad range of individuals with depression and is associated with improvements in mood disturbances.<sup>356</sup> Taken together, this literature supports our recommendation of passive music therapy for reducing depression and improving mood.

#### **Risk/benefit assessment of music therapy interventions.**

The risk/benefit assessment of passive and active music therapy interventions for depression/mood among patients with breast cancer is the same as that for anxiety depression (see above).

**Future research in music therapy interventions for depression/mood.** Future research in this area should assess long-term effects of passive music therapy on mood disturbances/depression, because the reviewed trials were limited to assessing short-term improvement of mood/depression after breast cancer treatments or during metastatic cancer diagnosis. In addition, studies should attempt to replicate the null findings of active music therapy interventions to formulate a comprehensive risk assessment regarding active music therapy. Suggestions for future research in music therapy for improving depression/mood are similar to those for anxiety, as stated above (see Use of Integrative Therapies for Anxiety/Stress Reduction).

#### **C-graded therapies for depression/mood**

Acupuncture,<sup>49-51,91,92</sup> healing touch,<sup>93,94</sup> and stress management<sup>36-38,95,96</sup> can be considered for improving mood and depressive symptoms (grade C). Five trials assessed acupuncture as a treatment for depression/mood (but as a secondary outcome), and only one trial was large,<sup>51</sup> with mixed findings in terms of effect. Two studies assessed the effect of healing touch on depression as a primary outcome, with one small study showing no effect<sup>94</sup> and a larger study showing a positive effect.<sup>93</sup> Although 5 large studies were reviewed for the effect of stress management on depression/mood, the findings were inconclusive because of inconsistent results across trials. Future research directions should

include conducting trials with larger samples sizes and replicating trials with these modalities to examine their impact on depression symptoms and improving mood as the primary outcome.

## **Use of Integrative Therapies for Fatigue**

### **Description of fatigue**

Among patients with cancer, fatigue is commonly referred to as cancer-related fatigue. Fatigue is a multifactorial condition marked by extreme tiredness and an inability to function because of lack of energy.<sup>357</sup> According to National Comprehensive Cancer Network guidelines, ratings of fatigue of 4 or higher on a scale from 0 to 10 (where 10 is very severe fatigue) are further evaluated for known contributing factors, such as pain, emotional distress, anemia, sleep, nutrition, and level of activity. These comorbidities are then treated. The CTCAE measures fatigue from grade 1 (relieved by rest) to grade 3 (not relieved by rest, limiting activities of daily living). Fatigue is the most frequent and distressing side effect of common antineoplastic therapies, including chemotherapy, radiation therapy, surgery, and selected biologic response modifiers.<sup>196</sup> Although cancer-related fatigue typically improves upon the conclusion of treatment, it can last for months or years in up to one-third of patients and may become a chronic condition that leads to a variety of physical and psychological effects long into survivorship. Symptoms of fatigue include feeling tired, weak, worn-out, heavy, slow, or having “no energy or get-up-and-go.” Cancer-related fatigue is different from common tiredness in both its magnitude and quality. Cancer-related fatigue is not typically relieved by rest and is much more profound than simply feeling tired. About 33% of patients with breast cancer experience moderate to severe fatigue.<sup>358-360</sup> Fatigue has disruptive consequences and can have a negative impact on a patient’s QOL, mood, and self-esteem.<sup>192</sup> Cancer-related fatigue can prevent patients from taking part in daily activities, relationships, social events, community activities, as well as work or school, which can have financial consequences, such as loss of employment and health insurance.

### **C-graded and D-graded therapies for fatigue**

There are no A-graded or B-graded therapies to report for fatigue. Trials evaluating hypnosis,<sup>97,98</sup> ginseng,<sup>99,100</sup> acetyl-L-carnitine,<sup>107</sup> and guarana<sup>108,109</sup> have examined their effects on fatigue during treatment. Two trials from a single research group reported beneficial effects of hypnosis on fatigue during treatment; therefore, hypnosis can be considered for fatigue during treatment (grade C). Neither acetyl-L-carnitine nor guarana is recommended for improving fatigue during treatment because of a lack of effect in clinical trials among patients with cancer (grade D for both). Ginseng received a grade C for fatigue during treatment

based on a single, high-quality trial with a large sample size.<sup>99</sup> A previous large, high-quality, dose-finding study by the same group indicated that a higher dose was more effective.<sup>100</sup> In subset analyses in the subsequent trial, which tested the receipt of ginseng by patients who reported fatigue either during or after treatment, the results showed that ginseng was more effective in patients undergoing active treatment. Trials testing the effects of acupuncture<sup>51,101-103</sup> and yoga<sup>45,80,84,104-106</sup> for post-treatment fatigue yielded modest results (grade C). Four high-quality acupuncture trials assessed fatigue as the primary outcome; 3 of those 4 trials included a large sample size.<sup>51,101-103</sup> Acupuncture for post-treatment fatigue received a grade of C mainly because of inconsistent comparison groups across the trials, including sham acupuncture,<sup>101,103</sup> standard of care,<sup>51,102</sup> self-administered acupuncture,<sup>102</sup> and wait-list control.<sup>103</sup> Three trials evaluated yoga for post-treatment fatigue as a primary outcome<sup>45,80,106</sup>; only one study had a large sample size<sup>80</sup> and the other 2 reported contrasting results.<sup>45,106</sup>

## Use of Integrative Therapies for QOL

### *Description of QOL*

QOL is a multidimensional construct that typically measures the functioning of emotional, physical, role, and social domains using validated questionnaires.<sup>361</sup> The majority of patients with breast cancer report some level of diminished QOL during cancer treatment and/or survivorship.<sup>362</sup> The physical domain includes common physical side effects of cancer and cancer treatment, including constipation and diarrhea, fatigue, hair loss, fever, hot flashes and night sweats, lymphedema, nausea and vomiting, poor nutrition, oral complications, pain, and skin changes, as well as the ability to function physically in everyday life. The emotional domain includes psychological functioning with indicators of anxiety, depression, distress, confusion, and memory problems. The sexual functioning domain refers to patients' perception of sexuality and sexual functioning, attractiveness, and fertility. Finally, the social domain refers to the patients' social functioning, their social role, and level of social support. Each of the domains, either individually or in combination, influences a patient's QOL.<sup>302,363-365</sup> Decrements in QOL may persist upon the conclusion of treatment, during chronic/long-term hormonal and biotherapies, and into survivorship.<sup>366</sup>

### *Meditation (A grade)*

**Overview of meditation interventions for QOL.** Meditation is recommended for improving QOL in patients with breast cancer (grade A). This recommendation is based on 7 RCTs, completed between 2009 and 2013, which used meditation for this indication (see Supporting Information Table 4).<sup>27-29,73-75,127</sup> QOL was the primary outcome in 4

of those 7 trials.<sup>73-75,127</sup> In 4 trials,<sup>27-29,74</sup> a meditation intervention group was compared with a usual care or waitlist control condition group, and 3 other trials<sup>73,75,127</sup> used a 3-arm design. Study participants included women undergoing radiation therapy for breast cancer, patients with newly diagnosed stage 0 through IV breast cancer, breast cancer survivors who had completed treatment, and older adult breast cancer survivors aged 55 years and older. The study sample sizes ranged from 47 to 180 participants. These trials overlap with the trials described under meditation interventions for anxiety/stress reduction and depression outcomes (see above).

Previous research has supported the role of MBSR interventions for improved QOL in heterogeneous samples of patients with cancer and survivors, with effect sizes ranging from small to large on QOL scales.<sup>319,367,368</sup> One review in particular assessed the impact of MBSR on QOL in patients with breast cancer.<sup>175</sup> In that review, the authors identified only 3 studies that met their criteria and also measured QOL as an outcome.<sup>29,127,292</sup> Of the 3 studies that measured QOL, only one (also included in our review) reported significant improvements after MBSR intervention<sup>29</sup> relative to results in control or comparator groups. The other 2 trials reported no significant improvements in QOL after MBSR intervention or at follow-up. A second systematic review and meta-analysis was conducted to investigate the effect of MBSR in the cancer care setting on several psychological outcomes, including QOL.<sup>316</sup> The analyses specific to the QOL outcome included 248 patients in 6 studies and reported a small effect size ( $P < .01$ ). The authors suggest that, although these findings support the use of MBSR for improving QOL, more well conducted RCTs are required that implement adequate controls, longer follow-up periods, larger sample sizes, and obtainment of patients' psychological profiles.

### *Risk/benefit assessment of meditation interventions*

There is very little risk to participants who use meditation therapies to improve QOL and/or physical functioning. Few adverse events have been reported in any trials involving meditation, with participants typically reporting positive feedback about meditation, resulting in low dropout rates from the programs. Group meditation formats and online and home-based adaptations of MBIs<sup>321</sup> are cost-effective and beneficial therapies that can be used as adjuncts to traditional individual counseling or psychotherapy.

**Future research in meditation interventions for QOL.** To improve specificity of the effective components of meditation and to compare meditation interventions with other MBIs, research assessing meditation as a treatment for improved QOL and/or physical functioning should be extended to directly compare meditation with other forms of therapy, including individual counseling, cognitive

behavioral therapy, and other MBIs, similar to the therapies compared in the trial by Carlson et al.<sup>26</sup>

### *Yoga (B grade)*

**Overview of yoga interventions for QOL.** Yoga is recommended for improving QOL in patients with breast cancer (grade B). This recommendation is based on 12 RCTs, completed between 2006 and 2015, which tested a variety of yoga programs (see Supporting Information Table 4).<sup>43,46-48,82-85,104-106,128</sup> QOL was the primary outcome for 6 of those 12 trials.<sup>47,82,83,105,106,128</sup> In 10 trials, a yoga intervention group was compared with a usual care or waitlist control condition group, and 2 other trials used brief supportive therapy as a comparison group.<sup>43,85</sup> Study participants included women undergoing radiation therapy or chemotherapy for breast cancer, patients with newly diagnosed breast cancer, and breast cancer survivors who had completed treatment. The study sample sizes ranged from 15 to 128 participants. Several of these trials overlap with those described under yoga interventions for anxiety and depression outcomes (see above). In total, 4 different types of yoga interventions were investigated, including: Iyengar or Hatha yoga,<sup>82-84,104-106</sup> an integrated yoga program,<sup>43,85,128</sup> pranayama or yoga breathing,<sup>46,47</sup> and Patanjali's yoga sutras.<sup>48</sup>

Another systematic review and meta-analysis assessed the impact of yoga interventions on QOL and psychological health specifically in patients with breast cancer and survivors.<sup>330</sup> Overall, 12 RCTs were included in that analysis with a total of 742 participants. Analyses revealed short-term effects on improved psychological health, including anxiety ( $P < .01$ ), perceived stress ( $P = .03$ ), and psychological distress ( $P < .01$ ). However, it is notable that these effects were only applicable to those who engaged in yoga during active cancer treatment and not in the post-treatment period. The authors state that, with these positive preliminary results, yoga should be used in this population.

**Risk/benefit assessment of yoga interventions.** As stated above regarding yoga for anxiety/stress and for depression/mood disturbances, yoga can be adapted and modified for use in this population with low risk to the patient. Overall, yoga has shown preliminary efficacy in improving QOL and is recommended for use in patients with breast cancer.

**Future research in yoga interventions for QOL.** As also stated above, future trials of yoga to improve QOL/physical functioning should examine the effects of different types, doses, and durations of yoga on QOL outcomes. Higher quality trials, including trials with larger and more diverse samples, should be conducted.

### *C-graded and D-graded therapies for QOL*

Trials in acupuncture,<sup>49,51,102,129,130</sup> mistletoe,<sup>131-134</sup> qigong,<sup>135,136</sup> reflexology,<sup>137-139</sup> and stress management<sup>36-38,95,96,140,141</sup> have assessed the effect of these

therapies on QOL and received a grade of C, indicating that they can be considered for use. The 5 trials evaluating acupuncture had mixed findings and small sample sizes; future studies should replicate the trials of acupuncture that compared real versus sham acupuncture, which were the study designs that produced no effect.<sup>49,102</sup> Two trials<sup>135,136</sup> found that qigong had beneficial effects on QOL; however, those studies were fairly small and should be replicated in larger and more diverse patient populations. Three large, high-quality trials<sup>137-139</sup> of reflexology for improving QOL reported mixed findings. The trials of stress management had conflicting results and used a broad range of control groups.<sup>36-38,95,96,140,141</sup>

There is some evidence that mistletoe may improve QOL in patients with breast cancer.<sup>131-134</sup> However, although the trials have study quality and sample sizes that could merit a grade of B, the final decision to assign a grade of C is because of 2 areas of uncertainty. First, while several different preparations and formulations have been found to be effective in trials of moderate size, the assessment does not result in a higher grade because of the nonspecificity and variability in formulations of the agents tested. Second, mistletoe is an injected bioactive compound with a potential for a differential risk/benefit ratio because of toxicities and drug interaction with standard cancer therapies that may not be detected in smaller studies; a similar stringency need not to be applied to MBIs, because they have lower risk profiles. The grade C recommendation is based on 4 RCTs, completed between 2004 and 2014, which tested the use of mistletoe for improving QOL.<sup>131-134</sup> QOL was the primary outcome in all 4 trials in which a mistletoe product group was compared with a placebo<sup>131,132</sup> or standard care<sup>133,134</sup> control group. The mistletoe products tested, all of which injected subcutaneously, included PS76A2,<sup>131,132</sup> Helixor A,<sup>134</sup> and Iscador.<sup>133</sup> Study participants included women who were receiving chemotherapy for breast cancer, and sample sizes ranged from 61 to 352 participants. To improve specificity of the effectiveness of mistletoe as a treatment for improved QOL in patients with breast cancer, double-blind trials need to directly evaluate and compare the different products available and also should assess long-term benefit and safety from the use of mistletoe products. Trials of bioactive agents carry the additional requirement of adequate size and statistical power to exclude drug interactions and attenuation of cancer outcome benefits of concurrently administered, adjuvant treatments. Two systematic literature reviews<sup>178,369</sup> of controlled clinical trials of mistletoe, including a Cochrane database analysis, did find an improvement in survival in the adjuvant setting. Although this outcome was outside the scope of this current review, the 2 reviews suggested a QOL benefit and called for further confirmatory trials.<sup>178,369</sup>

## Use of Integrative Therapies for CINV

### Description of CINV

CINV is experienced by some patients with cancer after they receive chemotherapy.<sup>197,370,371</sup> Acute CINV is typically defined as occurring during the first 24-hour period after chemotherapy administration. It is believed that delayed or late CINV is mediated by different mechanisms compared with acute CINV<sup>372</sup> and occurs more than 24 hours after chemotherapy administration. In a large, prospective study of patients with breast cancer who were receiving chemotherapy, 37% reported any nausea, and 13% reported any vomiting during the first 24-hour period.<sup>373</sup> In the 2 to 5 days after chemotherapy administration, 70% reported any nausea, and 15% reported any vomiting.<sup>195,373</sup> The consequences of CINV include dehydration, serious metabolic derangements, nutritional depletion and anorexia, deterioration of physical and mental status, withdrawal from potentially useful and curative antineoplastic treatment, and decreases in self-care and functional ability. CINV is considered to be one of the most severe and feared adverse effects of cancer treatment by patients and can have a significant impact on QOL.<sup>370,374-376</sup> Standard of care antiemetics for managing CINV have changed considerably in the last 5 years, thus many of the trials evaluating integrative approaches are not tested with the newest and most effective standard treatment regimen.<sup>197,371</sup> Most contemporary studies use as the endpoint the proportion of patients achieving a complete response, defined as no emesis or use of rescue medication. In addition, antiemetics themselves have side effects, such as headaches, constipation, and neuropsychiatric effects, and thus merit study designs that replace medications with integrative approaches and use equivalence or nonsuperiority designs for the CINV and medication side-effect endpoints.

### Acupressure (B grade)

**Overview of acupressure interventions for CINV.** For patients with breast cancer who are receiving chemotherapy, acupressure can be considered as an addition to antiemetics to help control nausea and vomiting (grade B). This recommendation is based on results from 3 RCTs, reported between 2000 and 2007, of an acupressure intervention used in conjunction with antiemetics to treat CINV (see Supporting Information Table 5).<sup>61-63</sup> Acute and delayed nausea and vomiting were the primary outcomes for all 3 trials. In 2 trials,<sup>61,63</sup> the acupressure plus usual care intervention group was compared with a usual care group. The third trial<sup>62</sup> was a 3-arm trial comparing: 1) true acupressure at the P6 and SI3 points in addition to usual care; 2) sham acupressure, or placebo acupressure on a different acupressure point, in addition to usual care; and 3) usual care only. (Of note, the use of sham controls in acupressure and

acupuncture studies is an attempt to control for the experience of receiving the treatment; if it is implemented well, participants will not be able to discern between the true and sham techniques.) Study participants included patients with breast cancer undergoing the first, second, or third cycle of chemotherapy. The study sample sizes in the trials ranged from 17 to 160 participants. The acupressure interventions included self-acupressure<sup>61,62</sup> using a finger and wearing acupressure wristbands.<sup>63</sup> Across the 3 trials, acupressure therapy produced significant decreases in nausea, retching, and vomiting ( $P < .05$  for multiple outcomes assessing CINV) (for details, see Supporting Information Table 5).

A review assessing acupressure as a nonpharmacologic adjunctive intervention for CINV control across all cancers concluded that acupressure should be strongly recommended as an effective intervention along with standard care for CINV control.<sup>377</sup> Other studies of acupressure to reduce nausea and vomiting have shown efficacy in other populations, including pregnant women and postoperative patients, including after thyroidectomy.<sup>378</sup> All of these studies were conducted with acupressure wristbands placed on both the patient's arms at the PC6 acupoint.<sup>379</sup> A review of acupuncture and acupressure for CINV control among patients with breast cancer concluded that the therapies are both safe and effective.<sup>380</sup> A secondary data analysis of the multicenter study by Dibble et al<sup>62</sup> concluded that patients with breast cancer whose nausea intensity started higher from the acute phase continued to experience higher symptom intensity during the 11 days after chemotherapy administration and required more frequent acupressure on acupressure point PC6 even after the peak of nausea.<sup>381</sup> However, a recent publication by Molassiotis, a lead author of one of the included trials in our review, and colleagues<sup>382</sup> suggests an overall placebo effect in the study of acupressure for control of CINV, although this interpretation included a mix of cancer populations and was not limited to patients with breast cancer.

### Risk/benefit assessment of acupressure interventions.

Self-administered acupressure is easy to perform, safe, cost effective, noninvasive, does not interfere with a patient's privacy, and has no deleterious effects on patients. Acupressure can be performed anywhere with little or no equipment.

### Future research in acupressure interventions for CINV.

Future research in this area could assess how to identify the best patients who can be instructed to perform self-administered acupressure, when acupressure can be performed, and whether additional points can be administered along with PC6 to increase the effectiveness of self-administered acupressure to reduce nausea and vomiting.

**Electroacupuncture (B grade)****Overview of electroacupuncture interventions for CINV.**

Electroacupuncture or acustimulation can be considered as an addition to antiemetics to control CINV in patients with breast cancer during chemotherapy (grade B). This recommendation is based on 2 RCTs, published in 2000 and 2012 (see Supporting Information Table 5),<sup>64,65</sup> as well as the 1997 National Institutes of Health Consensus Conference on acupuncture.<sup>383</sup> However, most of those trials predated the use of newer agents, including, 5-hydroxytryptamine type 3 (5-HT<sub>3</sub>) and neurokinin-1 (NK1) receptor antagonists, which have become standard antiemetic therapies for patients who receive highly emetogenic chemotherapy. We do not have a body of evidence to evaluate whether the addition of acupuncture to contemporary antiemetics yields added benefit. Participants in the trials in this analysis included patients with breast cancer who had received moderately high or highly emetogenic chemotherapy without a 5-HT<sub>3</sub> or NK1 receptor antagonist.<sup>197</sup> Both trials used PC6 and ST36 acupoints and sham controls, and both trials evaluated the effects of these acupoints on acute and delayed CINV. One trial also used acupoint LI4 and found that electroacupuncture was no better than sham electroacupuncture and that a likely contributor to the lack of effect of electroacupuncture in CINV was the that the study evaluated only feasibility with a minimal electroacupuncture intervention and without a no-acupuncture arm.<sup>64</sup> The second trial indicated that the patients receiving electroacupuncture experienced significantly fewer emesis episodes over the 5 days of the acupressure intervention than the patients receiving mock therapy or antiemetics alone ( $P < .001$ ).<sup>65</sup> Between-group differences in the number of emesis episodes were also significant for electroacupuncture versus minimal needling ( $P < .001$ ) and for minimal needling versus antiemetics alone ( $P = .01$ ).

A multicenter study by Yang et al<sup>384</sup> that compared ST36 electroacupuncture plus antiemetics with antiemetics alone in 246 patients with heterogeneous cancers indicated an additive effect with the use of electroacupuncture ( $P < .01$ ), with greater decreases in nausea and vomiting scores ( $P < .001$ ) compared with the use of antiemetics alone. Two early studies by Dundee and colleagues<sup>385,386</sup> reported significantly less CINV with a PC6 electroacupuncture intervention, although the investigators noted that the brevity of emetic action was a major problem. In a recent review of acupuncture studies, including those that evaluated CINV, investigators concluded that only the electroacupuncture study by Shen et al<sup>65</sup> had a low risk of bias.<sup>160</sup> In addition, an earlier meta-analysis by Ezzo et al<sup>387</sup> determined that electroacupuncture, but not manual acupuncture, was beneficial for first-day vomiting and that needle insertion as part of manual and electroacupuncture provides greater intensity

of stimulation and produces more beneficial effects than surface electrostimulation.

**Risk/benefit assessment of electroacupuncture interventions for CINV.** With proper administration, electroacupuncture has been shown to be both safe and effective.<sup>119,388-392</sup> In addition to possibly reducing CINV, PC6 stimulation has been associated with other positive benefits, including analgesic,<sup>119</sup> sedative,<sup>393</sup> and anxiolytic effects.<sup>394</sup> Furthermore, because CINV is drug-specific rather than disease-specific, these benefits should extend to CINV in other cancer patient populations, as suggested in the study by Yang et al,<sup>384</sup> with participants who had a variety of cancers. Practical issues to consider are that electroacupuncture should not be used in patients with a pacemaker or implantable defibrillators and that special attention is required when treating patients who are pregnant, have seizure disorders, or are disoriented.<sup>160</sup>

**Future research in electroacupuncture interventions for CINV.**

Future trials on the use of electroacupuncture interventions for CINV in patients with breast cancer can focus on testing the use of electroacupuncture with new standard-of-care treatment regimens as well as the dissemination and implementation of this technique in the clinical setting. In addition, nausea that is unrelated to chemotherapy is also a common problem in patients with cancer, and this modality could be tested and compared with less potent antiemetics or best supportive care when other therapies are ineffective.

**C-graded and D-graded therapies for CINV**

Three trials of ginger<sup>66-68</sup> and 2 trials of relaxation<sup>59,69</sup> have examined their effects on CINV as a primary outcome. Although the number of trials was limited, the results suggested enough of an effect to result in a grade C recommendation stating that ginger and relaxation can be considered as an addition to antiemetics for the control of acute CINV. Future directions in research should focus on replicating trials of these modalities for CINV as the primary outcome. Glutamine is not recommended for improving CINV because of a lack of effect from 2 trials<sup>70,71</sup> in which CINV was assessed as a secondary outcome (grade D).

**Use of Integrative Therapies for Acute Radiation Dermatitis**

Because radiation is a localized, targeted therapy, side effects are most often locoregional within the targeted area. However, damage to normal local tissues and adjacent organs at risk can result in fatigue as the body expends energy in normal tissue repair. The most common side effect in patients with breast cancer is acute skin irritation. Late changes to normal tissue can occur years after therapy and can include soft tissue fibrosis, lymphedema, lung, and heart and chest wall damage.<sup>395</sup> Not all patients experience one or all of the

side effects of radiation, but patients who do experience acute side effects of radiation typically see the effects go away several weeks after treatment.<sup>395</sup> Acute radiation dermatitis can occur with radiation therapy and may result in reactions ranging from faint erythema; to dry, itchy, and peeling skin; and ultimately to moist desquamation and ulceration.<sup>396</sup> The Cooperative Group Common Toxicity Criteria (CGCTC) is the most common scale to measure acute radiation skin toxicity that is used by cooperative groups during cancer clinical trials and grades skin reactions from 0 to 4 with, grade 1 indicating erythema and grade 4 indicating ulceration. Most patients with breast cancer develop mild-to-moderate acute skin reactions of grade 1 through 3 during and shortly after a course of radiation therapy. These reactions usually resolve quickly but can cause significant symptoms, especially with higher grade toxicity.<sup>396</sup>

#### ***D-graded therapies for acute radiation dermatitis***

There are no therapies graded A, B, or C to report for acute radiation dermatitis after treatment. Aloe vera gel and hyaluronic cream are not recommended as a standard therapy to prevent or treat acute radiation dermatitis simply because of lack of effect (grade D). Our review consisted of 2 quality studies for each product with large sample sizes for both the aloe vera<sup>22,23</sup> and hyaluronic cream<sup>24,25</sup> trials. Each trial assessed the acute skin reaction from radiation therapy as its primary outcome.

#### **Use of Integrative Therapies for Vasomotor Outcomes**

Vasomotor symptoms are common in patients with breast cancer and include hot flashes, intense sweating, and flushing on the face and chest, and they may come with heart palpitations and anxiety.<sup>397</sup> These symptoms occur episodically, including nocturnally, when night sweats can significantly disrupt women's sleep. According to the NCI, about two-thirds of postmenopausal women with a history of breast cancer experience hot flashes. These symptoms may occur naturally or as a consequence of surgery, chemotherapy, or endocrine therapy.<sup>398</sup> While vasomotor symptoms may resolve on their own, 20% of affected women suffer from persistent hot flashes 4 years after their last menses.<sup>397</sup> Together, vasomotor symptoms can significantly impact women's QOL.<sup>398</sup>

#### ***C-graded and D-graded therapies for vasomotor outcomes***

There are no A-graded or B-graded therapies to recommend for vasomotor outcomes. Acupuncture can be considered as a therapy for hot flashes based on 9 trials that assessed acupuncture for hot flashes (grade C).<sup>49,91,92,143-148</sup> Seven of those trials assessed hot flashes as the primary outcome,<sup>91,92,143-146,148</sup> and only one trial<sup>148</sup> had more than

100 participants. Overall, the literature showed mixed findings; however, the single, large trial demonstrated significant reductions in hot flashes in their electroacupuncture group compared with sham and control groups. The use of soy as a therapy for hot flashes is not recommended because of lack of effect (grade D). Three large trials<sup>149-151</sup> assessed soy for the treatment of hot flashes as the primary outcome and showed a lack of effect.

#### **Use of Integrative Therapies for Lymphedema**

##### ***Lymphedema***

Lymphedema is a condition after treatment, such as surgery or radiation therapy, in which parts of the lymph system become damaged or blocked, leading to an accumulation of lymph fluid that does not drain properly, builds up in tissues, and causes swelling.<sup>166</sup> The CTCAE grades edema of the limbs from grade 1 (5%-10% interlimb discrepancy) up to grade 3 (>30% interlimb discrepancy). Lymphedema commonly affects the arm or leg but can also impact other parts of the body. For patients with breast cancer and survivors, lymphedema is most common in the upper extremities and sometimes in the breast and/or chest wall, and it can occur up to 30 years after treatment. Because of differences in diagnosis, characteristics of the patients studied, and inadequate follow-up, the overall incidence of arm lymphedema after breast cancer reportedly ranges from 8% to 56%.<sup>399</sup> Breast cancer survivors with arm lymphedema in particular have been found to have decreased QOL and increased psychological distress and disability compared with survivors without lymphedema.<sup>399-401</sup>

##### ***C-graded therapies for lymphedema***

There are no A-graded or B-graded therapies to report for lymphedema. Two trials assessed low-level laser therapy,<sup>110,111</sup> and 7 trials assessed manual lymphatic drainage<sup>112-118</sup> for the treatment of lymphedema as a primary outcome. The 2 trials that evaluated low-level laser therapy were small in sample size and showed mixed findings. Only 2 of the 7 trials that assessed manual lymphatic drainage had a sample size greater than 100 participants.<sup>113,118</sup> Overall, the literature suggests that manual lymphatic drainage and compression bandaging are equivalent.<sup>114-116</sup> Thus, either therapy can be considered as treatment options for lymphedema, with manual lymphatic drainage being considered for those who have sensitivity to bandaging (grade C).

#### **Use of Integrative Therapies for CIPN**

##### ***CIPN***

Cancer treatments, including chemotherapy, may cause damage to the peripheral nerves, resulting

in neuropathy.<sup>402</sup> The CGCTC categorizes neuropathy under neurologic-sensory and grades it from 0 to 3, with 3 indicating severe objective sensory loss or paresthesias that interfere with function. Sensory neuropathy can include symptoms of pain, tingling, numbness, or a pins-and-needles feeling, the inability to feel a hot or cold sensation, or the inability to feel pain. Motor neuropathy can include problems with balance, weak or achy muscles, twitching, cramping or wasting muscles, and swallowing or breathing difficulties. Autonomic nerve damage can cause dizziness or faintness and digestive, sexual, sweating, and urination problems.<sup>402</sup>

#### ***H-graded therapies for CIPN***

There are no A-graded or B-graded therapies to report for the prevention or treatment of CIPN. Acetyl-L-carnitine is not recommended as a standard therapy to prevent or treat CIPN because of harm (grade H). A single, large, high-quality study<sup>107</sup> assessing the use of acetyl-L-carnitine capsules to prevent CIPN after taxane therapy as a primary outcome found that acetyl-L-carnitine administered during taxane chemotherapy was associated with worse CIPN symptoms.

### **Use of Integrative Therapies for Pain**

#### ***Pain***

According to the International Association for the Study of Pain, pain can be defined as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage.”<sup>403</sup> The CTCAE grades pain from 1 (mild) to 3 (severe, limiting self-care). Pain can be caused by cancer therapies, including surgery, radiation therapy, chemotherapy, targeted therapy, supportive care therapies, and/or diagnostic procedures.<sup>404</sup> Pain is commonly experienced by patients who have breast cancer with a prevalence ranging from 40% to 89%.<sup>403</sup> Pain management requires proper assessment, including measurement of intensity.<sup>404</sup> It is also important to evaluate the impact of pain on the patient’s physical, mental, and social health, because pain can negatively impact their functional status and QOL. Pain management can include both pharmacologic and nonpharmacologic modalities. Proper education about treatment and longitudinal follow-up are essential.

#### ***C-graded therapies for pain***

There are no A-graded or B-graded therapies to report for pain. Healing touch<sup>93</sup> for pain after chemotherapy; music therapy,<sup>31,34</sup> hypnosis,<sup>125,126</sup> and acupuncture<sup>119</sup> for pain after surgery; and acupuncture<sup>120-124</sup> for pain related to aromatase inhibitor-associated musculoskeletal symptoms were examined, and each received a grade of C, indicating that they can be considered as a therapy for pain. A single, large trial assessed healing touch<sup>93</sup> for pain after chemotherapy as

a secondary outcome and demonstrated small positive effects favoring the therapy. Similarly, trials that assessed music therapy,<sup>31,34</sup> hypnosis,<sup>125,126</sup> and acupuncture<sup>119</sup> for pain after surgery as a primary outcome demonstrated small positive effects favoring the therapy. However, there is a lack of multiple, large trials to support each therapy. Finally, 5 trials evaluated acupuncture for pain related to aromatase inhibitor-associated musculoskeletal symptoms as the primary outcome.<sup>120-124</sup> All of those trials had small sample sizes and reported mixed findings.

### **Use of Integrative Therapies for Sleep Disturbance**

#### ***Sleep disturbances***

Studies have shown that nearly one-half of all patients with breast cancer have sleep-related problems from a range of causes, including side effects of antineoplastic medications, long hospital stays, or stress.<sup>405,406</sup> In addition, growing numbers of patients with breast cancer are obese,<sup>407</sup> which increases the incidence of sleep apnea, a major cause for insomnia. Insomnia, a specific sleep disorder of initiating and maintaining sleep, is most common in patients with cancer and often occurs along with anxiety and depression.<sup>408</sup> The CTCAE measures insomnia under psychiatric disorders from grade 1 through grade 3, with grade 3 indicating severe difficulty falling asleep, staying asleep, or waking up early.

#### ***C-graded therapies for sleep disturbance***

There are no A-graded or B-graded therapies to report for sleep disturbance. Yoga can be considered for sleep disturbance (grade C). Five trials assessed yoga for sleep disturbance<sup>45,48,79,84,172</sup>; and, in 4 of those trials, sleep was a secondary outcome. Two trials were of high quality, with more than 100 participants.<sup>79,142</sup> Overall, the body of literature showed no greater effect on sleep quality for health education classes, stretching groups, and wait-list controls.

### **Conclusion**

In this review, we closely examined and described the RCTs that provide support for the highest graded therapy recommendations for the use of integrative therapies during the patient experience of breast cancer and for side effects related to breast cancer treatment. High levels of evidence support the routine use of mind-body practices, such as yoga, meditation, relaxation techniques, and passive music therapy, to address common mental health concerns among patients with breast cancer, including anxiety, stress, depression, and mood disturbances. In addition, it has been demonstrated that meditation improves QOL and physical functioning; yoga improves QOL and fatigue; massage improves mood; and acupressure and electroacupuncture decrease CIN. Given the high level of evidence of benefit

coupled with the relatively low level of risk, these therapies can be incorporated as an option into patient care, especially when there is poor symptom control. As is the case with many standard therapies, the impact of integrative approaches on symptom management is highly individualized. Therefore, a patient-centered trial and evaluation approach may be needed and can be guided by the grade of recommendations and altered as needed along with the incorporation of patient preferences. In addition to the modalities discussed in this review that were given a lower grade (C or D), patients are using many other forms of integrative therapies with little or no supporting evidence; this serves as a compelling call for further research to support patients and health care providers in making more informed decisions that avoid harm. In the meantime, while further clinical evaluation is underway, clinicians and patients need to be cautious about the use of therapies that received a grade of C or D and need to fully understand the potential risks and benefits of use, including the risk associated with not using a conventional therapy that may effectively prevent or treat the condition. For example, in a patient with incurable disease who has marked symptoms not adequately managed with conventional therapies, carefully monitored use of a grade-C therapy could be medically reasonable, although more research clearly would be needed to apply this broadly across a patient population. This review and others support referral or provision of clinical services to include both evidence-based conventional and integrative therapy options.

The limited numbers of integrative modalities with grades of A or B emphasize the need for all cancer care providers to initiate a dialogue early in their relationship with patients to develop a framework for how evidence forms the basis for all clinical decisions. Patients and clinicians should engage in shared decision making based on the best available evidence on the benefits and harms while reflecting patient values and preferences. A careful appraisal of the evidence base for integrative therapies can help allay a patient's concern that their care team is informed and is not overlooking options that may be of interest to them. In addition, such an appraisal of the evidence will offer those modalities that do merit consideration and allow for better personalization of care and shared decision making.

This systematic review with grades of evidence adds to a growing literature base that includes reviews of integrative therapy for patients with breast cancer and other cancer populations. For example, numerous reviews support the use of integrative therapies, including passive music therapy,<sup>322</sup> stress-management programs,<sup>324</sup> various yoga practices,<sup>329</sup> meditation and MBSR,<sup>315</sup> massage,<sup>349</sup> and relaxation techniques,<sup>337</sup> as adjunctive therapies for psychological outcomes, specifically the anxiety/stress and

depression/mood outcomes assessed in this review. Acupressure for CINV is also well supported in the review literature across all populations of patients with cancer.<sup>377</sup> There are mixed findings in the areas of meditation and MBSR for QOL<sup>175,316</sup> and electroacupuncture for CINV,<sup>160</sup> which suggests overall low quality or too few studies. Thus, future research on the impact of these integrative therapies on the relevant clinical outcomes is warranted. A limitation to the generalizability of our findings is that the majority of participants in the clinical trials we evaluated were non-Hispanic white women with high socioeconomic status relative to the general population. In addition, none of the trials examined age-related responses and or differential responses in premenopausal versus postmenopausal women. There is a clear need to design well powered, controlled trials using the best standard treatment control or an appropriate placebo.

### Challenges of Implementing Integrative Therapies in Breast Oncology

Patients with cancer face several psychological and physical challenges as they move through cancer diagnosis, treatment, and survivorship. According to National Comprehensive Cancer Network guidelines, comprehensive clinical programs should systematically screen for cancer-related symptoms and side effects in the process of mandated screening for distress. This review and others support subsequent referral or provision of clinical services to include both evidence-based conventional and integrative therapy options.<sup>194,409</sup>

On the basis of recent estimates from the US National Health Interview Survey, 75% of individuals with a history of cancer use one or more complementary and integrative therapies.<sup>410</sup> Many North American cancer centers now operate formal integrative oncology programs. Because most of these services are not reimbursable by insurance, the methods and models of funding and implementing these programs vary; some programs and services are fully funded and are provided free of charge to patients, some are entirely paid for out-of-pocket by patients, and some are a combination of both. Often, mind-body therapies already are available from trained clinical staff at cancer centers, such as oncology nurses or social workers, and hence are more readily accessible at low or no cost. Others, such as massage therapy and acupuncture, may be covered by some forms of insurance, varying by country, province/territory, and state.

Implementing complementary and integrative therapies in a clinical setting requires not only funding and infrastructure but also well trained, knowledgeable providers. Many of the integrative therapies do not have a one-size-fits-all approach and need to be provided and administered by appropriately trained practitioners who can evaluate which are the best forms and techniques to use with a specific patient. Although training and credentialing for many

integrative providers varies by jurisdictions, best practices suggest that providers be trained to the highest standard of their profession, even if that exceeds the state-based or province-based standards, such as a requirement for institutional credentialing that may include proctoring. As the fields of integrative therapies are expanding, there are now new professional associations that specialize in oncology, for example, the Society for Oncology Massage and the Oncology Association of Naturopathic Physicians.<sup>411,412</sup>

### Future Research

Rigorous clinical research that appropriately reflects integrative care as it is used in the community and at integrative cancer centers is needed to responsibly move this field forward. Integrative modalities can be tested in addition to standard supportive treatments, or even in place of them, if the standard therapy is associated with side effects or significant costs and the trial design allows for early discontinuation in the event of futility. Clinical trials designed to test efficacy in tightly controlled, academic research settings are often testing protocols that are not realistically implementable in the community setting. Implementation and dissemination research designs to consider include pragmatic trials that involve multimodal therapies applied in the manner in which they are typically offered in clinical settings. This approach, while unable to pinpoint clear causal relationships between specific interventions and outcomes, allows an exploration and evaluation of clinical impact that is more truly generalizable. Head-to-head comparisons of different integrative therapies and conventional symptom-management therapies would help provide some specificity and direction for health care providers making recommendations to patients. Comparative-effectiveness research testing integrative modalities in relationship to pharmacological and other approaches would also be informative in providing options as well as comparisons of toxicities and cost effectiveness. Studies that examine mechanism of action are also needed; however, the emphasis here is on trials of agents that are actively in use, unlike novel pharmacological therapies. Importantly, interventions need to be tested in economically and culturally diverse patient populations to understand the applicability of an intervention to the growing population of cancer survivors.

Future studies need to include systematic assessments of treatment toxicities, including toxicities from both the integrative and the conventional therapies. In this review, when possible, the NCI CTCAE are used to describe cancer treatment side effects. However, many of the trials did not report toxicities or adverse events; and, among the trials that did, the majority did not assess toxicities and adverse events systematically. The CTCAE are a set of criteria for the standard grading and classifications of adverse effects of drugs used in

cancer therapy and the US Food and Drug Administration is increasingly using CTCAE patient-reported outcomes (CTCAE-PROs) to monitor treatment side effects.<sup>413,414</sup> Ideally, trials will include systematic evaluation of both provider (ie, CTCAE) and patient (ie, CTCAE-PROs) assessments of adverse events. If future trials do not use these methods, at minimum, validated measurement tools need to be used to allow for ongoing quantitative assessments of adverse events using robust statistical analyses.

Ongoing challenges include the inability to blind participants to most of the integrative modalities studied, because most measures are subjective and thus are susceptible to suggestive biases in which patients perceive benefit to an intervention simply because they are receiving it. By using a mixed-methods model of research, including both qualitative inquiry that explores the patient's experience of their treatments and quantitative data, will be helpful to validate and better justify the use of integrative therapies. In addition, the use of both subjective and objective patient-reported outcomes should be used within a mixed-methods model. This approach can be used in both clinical trials and in prospective observational studies. To better enable real clinical uptake and change, knowledge translation experts, patients with cancer, policy makers, and decision makers should be involved in both study design and interpretation to better enable integration of these therapies into clinical practice.

In conclusion, awareness of the base of evidence for complementary and integrative therapies based on the recently published SIO guidelines and the emerging literature should be a core competence for the cancer care provider and should be applied in decision making for patients with breast cancer who require supportive care. Billions of dollars are spent each year on complementary and integrative health therapies with unknown benefits and on those that have thus far been shown to be ineffective.<sup>410</sup> Research in this area could save large amounts of health care dollars and resources and, more importantly, can redirect patients to treatments with known benefits and better safety profiles. This article provides greater depth of discussion of these interventions, such that clinicians and patients can begin the process of integration based on patient needs in their specific setting and context. ■

**Acknowledgements:** We thank the following internal and external reviewers for their insightful comments and critiques: Internal reviewers: Executive Committee of the Society for Integrative Oncology; Board of Trustees of the Society for Integrative Oncology; Donald Abrams, MD (University of California at San Francisco), Ting Bao, MD (Memorial Sloan Kettering Cancer Center), Gustav Dobos, MD (Duisberg-Essen University), Petra Klose, MD (Duisberg-Essen University), Omer Kucuk, MD (Emory University), Jodi MacLeod (University of Pennsylvania), Gregory Plotnikoff, MD (Minnesota Personalized Medicine), and Santosh Rao, MD (Banner MD Anderson Cancer Center). External Society for Integrative Oncology reviewers included Gabriel Hortobagyi, MD (The University of Texas MD Anderson Cancer Center), Shelley Hwang, MD (Duke University), and Anna Wu, PhD (University of Southern California).

## References

- Boon HS, Olatunde F, Zick SM. Trends in complementary/alternative medicine use by breast cancer survivors: comparing survey data from 1998 and 2005 [serial online]. *BMC Womens Health*. 2007;7:4.
- Greenlee H, Kwan ML, Ergas IJ, et al. Changes in vitamin and mineral supplement use after breast cancer diagnosis in the pathways study: a prospective cohort study [serial online]. *BMC Cancer*. 2014;14:382-397.
- Link AR, Gammon MD, Jacobson JS, et al. Use of self-care and practitioner-based forms of complementary and alternative medicine before and after a diagnosis of breast cancer [serial online]. *Evid Based Complement Alternat Med*. 2013;2013:301549.
- Matsuno RK, Pagano IS, Maskarinec G, Issell BF, Gotay CC. Complementary and alternative medicine use and breast cancer prognosis: a pooled analysis of four population-based studies of breast cancer survivors. *J Womens Health (Larchmt)*. 2012;21:1252-1258.
- Greenlee H, Kwan ML, Ergas IJ, et al. Complementary and alternative therapy use before and after breast cancer diagnosis: the Pathways study. *Breast Cancer Res Treat*. 2009;117:653-665.
- Bright-Ghebry M, Makambi KH, Rohan JP, et al. Use of multivitamins, folic acid and herbal supplements among breast cancer survivors: the Black Women's Health Study [serial online]. *BMC Complement Alternat Med*. 2011;11:30-35.
- Office of Cancer Complementary and Alternative Medicine. CAM Definitions. [cam.cancer.gov/health\\_information/cam\\_definitions.htm](http://cam.cancer.gov/health_information/cam_definitions.htm). Accessed June 18, 2015.
- National Center for Complementary and Integrative Health. Complementary, Alternative, or Integrative Health: What's In a Name? [nccam.nih.gov/health/whatiscam](http://nccam.nih.gov/health/whatiscam). Accessed June 18, 2015.
- 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. *J Natl Cancer Inst Monogr*. 2014;2014:346-358.
- US Preventive Services Task Force. Grade Definitions. [uspsf/grades.htm](http://uspsf/grades.htm). Accessed May 10, 2014.
- Institute of Medicine, Committee on Standard for Developing Trustworthy Clinical Practice Guidelines. *Clinical Practice Guidelines We Can Trust*. Washington DC: The National Academies Press; 2011.
- World Cancer Research Fund/American Institute for Cancer Research (AICR). Food, Nutrition, Physical Activity, and the Prevention of Cancer: A Global Perspective. Washington, DC: AICR; 2007.
- Rock CL, Doyle C, Demark-Wahnefried W, et al. Nutrition and physical activity guidelines for cancer survivors. *CA Cancer J Clin*. 2012;62:243-274.
- Schmitz KH, Courneya KS, Matthews C, et al. American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. *Med Sci Sports Exerc*. 2010;42:1409-1426.
- Duijts SF, Faber MM, Oldenburg HS, van Beurden M, Aaronson NK. Effectiveness of behavioral techniques and physical exercise on psychosocial functioning and health-related quality of life in breast cancer patients and survivors—a meta-analysis. *Psychooncology*. 2011;20:115-126.
- Faller H, Schuler M, Richard M, Heckl U, Weis J, Kuffner R. Effects of psychosocial interventions on emotional distress and quality of life in adult patients with cancer: systematic review and meta-analysis. *J Clin Oncol*. 2013;31:782-793.
- Galway K, Black A, Cantwell M, Cardwell CR, Mills M, Donnelly M. Psychosocial interventions to improve quality of life and emotional wellbeing for recently diagnosed cancer patients [serial online]. *Cochrane Database Syst Rev*. 2012;11:CD007064.
- Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials*. 1996;17:1-12.
- Verhagen AP, de Vet HC, de Bie RA, et al. The Delphi list: a criteria list for quality assessment of randomized clinical trials for conducting systematic reviews developed by Delphi consensus. *J Clin Epidemiol*. 1998;51:1235-1241.
- National Center for Complementary and Integrative Health. Health Topics A-Z. [nccih.nih.gov/health/atoz.htm](http://nccih.nih.gov/health/atoz.htm). Accessed June 18, 2015.
- National Cancer Institute. Complementary and Alternative Medicine. [cancer.gov/cancer-topics/cam](http://cancer.gov/cancer-topics/cam). Accessed June 18, 2015.
- Heggie S, Bryant GP, Tripcony L, et al. A phase III study on the efficacy of topical aloe vera gel on irradiated breast tissue. *Cancer Nurs*. 2002;25:442-451.
- Williams MS, Burk M, Loprinzi CL, et al. Phase III double-blind evaluation of an aloe vera gel as a prophylactic agent for radiation-induced skin toxicity. *Int J Radiat Oncol Biol Phys*. 1996;36:345-349.
- Kirova YM, Fromantin I, De Rycke Y, et al. Can we decrease the skin reaction in breast cancer patients using hyaluronic acid during radiation therapy? Results of phase III randomised trial. *Radiother Oncol*. 2011;100:205-209.
- Pinnix C, Perkins GH, Strom EA, et al. Topical hyaluronic acid vs. standard of care for the prevention of radiation dermatitis after adjuvant radiotherapy for breast cancer: single-blind randomized phase III clinical trial. *Int J Radiat Oncol Biol Phys*. 2012;83:1089-1094.
- Carlson LE, Doll R, Stephen J, et al. Randomized controlled trial of mindfulness-based cancer recovery versus supportive expressive group therapy for distressed survivors of breast cancer. *J Clin Oncol*. 2013;31:3119-3126.
- Crane-Okada R, Kiger H, Sugerman F, et al. Mindful movement program for older breast cancer survivors: a pilot study. *Cancer Nurs*. 2012;35:E1-E13.
- Kim YH, Kim HJ, Ahn SD, Seo YJ, Kim SH. Effects of meditation on anxiety, depression, fatigue, and quality of life of women undergoing radiation therapy for breast cancer. *Complement Ther Med*. 2013;21:379-387.
- Lengacher CA, Johnson-Mallard V, Post-White J, et al. Randomized controlled trial of mindfulness-based stress reduction (MBSR) for survivors of breast cancer. *Psychooncology*. 2009;18:1261-1272.
- Wurtzen H, Dalton SO, Elsass P, et al. Mindfulness significantly reduces self-reported levels of anxiety and depression: results of a randomised controlled trial among 336 Danish women treated for stage I-III breast cancer. *Eur J Cancer*. 2013;49:1365-1373.
- Binns-Turner PG, Wilson LL, Pryor ER, Boyd GL, Prickett CA. Perioperative music and its effects on anxiety, hemodynamics, and pain in women undergoing mastectomy. *AANA Journal*. 2011;79(4 suppl):S21-S27.
- Bulfone T, Quattrin R, Zanotti R, Regattin L, Brusaferrero S. Effectiveness of music therapy for anxiety reduction in women with breast cancer in chemotherapy treatment. *Holist Nurs Pract*. 2009;23:238-242.
- Hanser SB, Bauer-Wu S, Kubicek L, et al. Effects of a music therapy intervention on quality of life and distress in women with metastatic breast cancer. *J Soc Integr Oncol*. 2006;4:116-124.
- Li XM, Zhou KN, Yan H, Wang DL, Zhang YP. Effects of music therapy on anxiety of patients with breast cancer after radical mastectomy: a randomized clinical trial. *J Adv Nurs*. 2012;68:1145-1155.
- Zhou K, Li X, Li J, et al. A clinical randomized controlled trial of music therapy and progressive muscle relaxation training in female breast cancer patients after radical mastectomy: results on depression, anxiety and length of hospital stay. *Eur J Oncol Nurs*. 2015;19:54-59.
- Garssen B, Boomsma MF, Meezenbroek Ede J, et al. Stress management training for breast cancer surgery patients. *Psychooncology*. 2013;22:572-580.
- Jacobsen PB, Phillips KM, Jim HS, et al. Effects of self-directed stress management training and home-based exercise on quality of life in cancer patients receiving chemotherapy: a randomized controlled trial. *Psychooncology*. 2013;22:1229-1235.
- Aguado Loi CX, Taylor TR, McMillan S, et al. Use and helpfulness of self-administered stress management therapy in patients undergoing cancer chemotherapy in community clinical settings. *J Psychosoc Oncol*. 2012;30:57-80.
- Phillips KM, Antoni MH, Lechner SC, et al. Stress management intervention reduces serum cortisol and increases relaxation during treatment for nonmetastatic breast cancer. *Psychosom Med*. 2008;70:1044-1049.
- Taso CJ, Lin HS, Lin WL, Chen SM, Huang WT, Chen SW. The effect of yoga exercise on improving depression, anxiety, and fatigue in women with breast cancer: a randomized controlled trial. *J Nurs Res*. 2014;22:155-164.
- Banerjee B, Vadiraj H, Ram A, et al. Effects of an integrated yoga program in modulating psychological stress and radiation-induced genotoxic stress in breast cancer patients undergoing radiotherapy. *Integr Cancer Ther*. 2007;6:242-250.
- Vadiraja HS, Raghavendra RM, Nagarathna R, et al. Effects of a yoga program on cortisol rhythm and mood states

- in early breast cancer patients undergoing adjuvant radiotherapy: a randomized controlled trial. *Integr Cancer Ther.* 2009;8:37-46.
43. Raghavendra R, Nagarathna R, Nagendra H, et al. Effects of an integrated yoga programme on chemotherapy-induced nausea and emesis in breast cancer patients. *Eur J Cancer Care.* 2007;16:462-474.
  44. Rao MR, Raghuram N, Nagendra HR, et al. Anxiolytic effects of a yoga program in early breast cancer patients undergoing conventional treatment: a randomized controlled trial. *Complement Ther Med.* 2009;17:1-8.
  45. Bower JE, Garet D, Sternlieb B, et al. Yoga for persistent fatigue in breast cancer survivors: a randomized controlled trial. *Cancer.* 2012;118:3766-3775.
  46. Dhruva A, Miaskowski C, Abrams D, et al. Yoga breathing for cancer chemotherapy-associated symptoms and quality of life: results of a pilot randomized controlled trial. *J Alternat Complement Med.* 2012;18:473-479.
  47. Pruthi S, Stan DL, Jenkins SM, et al. A randomized controlled pilot study assessing feasibility and impact of yoga practice on quality of life, mood, and perceived stress in women with newly diagnosed breast cancer. *Glob Adv Health Med.* 2012;1:30-35.
  48. Chandwani KD, Thornton B, Perkins GH, et al. Yoga improves quality of life and benefit finding in women undergoing radiotherapy for breast cancer. *J Soc Integr Oncol.* 2010;8:43-55.
  49. Bao T, Cai L, Snyder C, et al. Patient-reported outcomes in women with breast cancer enrolled in a dual-center, double-blind, randomized controlled trial assessing the effect of acupuncture in reducing aromatase inhibitor-induced musculoskeletal symptoms. *Cancer.* 2014;120:381-389.
  50. Mao JJ, Farrar JT, Bruner D, et al. Electroacupuncture for fatigue, sleep, and psychological distress in breast cancer patients with aromatase inhibitor-related arthralgia: a randomized trial. *Cancer.* 2014;120:3744-3751.
  51. Molassiotis A, Bardy J, Finnegan-John J, et al. Acupuncture for cancer-related fatigue in patients with breast cancer: a pragmatic randomized controlled trial. *J Clin Oncol.* 2012;30:4470-4476.
  52. Billhult A, Bergbom I, Stener-Victorin E. Massage relieves nausea in women with breast cancer who are undergoing chemotherapy. *J Alternat Complement Med.* 2007;13:53-57.
  53. Hernandez-Reif M, Ironson G, Field T, et al. Breast cancer patients have improved immune and neuroendocrine functions following massage therapy. *J Psychosom Res.* 2004;57:45-52.
  54. Listing M, Krohn M, Liezmann C, et al. The efficacy of classical massage on stress perception and cortisol following primary treatment of breast cancer. *Arch Womens Ment Health.* 2010;13:165-173.
  55. Wilkinson SM, Love SB, Westcombe AM, et al. Effectiveness of aromatherapy massage in the management of anxiety and depression in patients with cancer: a multicenter randomized controlled trial. *J Clin Oncol.* 2007;25:532-539.
  56. Hilderley M, Holt M. A pilot randomized trial assessing the effects of autogenic training in early stage cancer patients in relation to psychological status and immune system responses. *Eur J Oncol Nurs.* 2004;8:61-65.
  57. Kovacic T, Kovacic M. Impact of relaxation training according to Yoga In Daily Life(R) system on perceived stress after breast cancer surgery. *Integr Cancer Ther.* 2011;10:16-26.
  58. Kovacic T, Zagoricnik M, Kovacic M. Impact of relaxation training according to the Yoga In Daily Life(R) system on anxiety after breast cancer surgery. *J Complement Integr Med.* 2013;10:153-164.
  59. Molassiotis A, Yung HP, Yam BM, Chan FY, Mok TS. The effectiveness of progressive muscle relaxation training in managing chemotherapy-induced nausea and vomiting in Chinese breast cancer patients: a randomised controlled trial. *Support Care Cancer.* 2002;10:237-246.
  60. Nunes DF, Rodriguez AL, da Silva Hoffmann F, et al. Relaxation and guided imagery program in patients with breast cancer undergoing radiotherapy is not associated with neuroimmunomodulatory effects. *J Psychosom Res.* 2007;63:647-655.
  61. Dibble SL, Chapman J, Mack KA, Shih AS. Acupressure for nausea: results of a pilot study. *Oncol Nurs Forum.* 2000;27:41-47.
  62. Dibble SL, Luce J, Cooper BA, et al. Acupressure for chemotherapy-induced nausea and vomiting: a randomized clinical trial. *Oncol Nurs Forum.* 2007;34:813-820.
  63. Molassiotis A, Helin AM, Dabbour R, Hummerston S. The effects of P6 acupressure in the prophylaxis of chemotherapy-related nausea and vomiting in breast cancer patients. *Complement Ther Med.* 2007;15:3-12.
  64. Beith JM, Oh B, Chatfield MD, Davis E, Venkateswaran R. Electroacupuncture for nausea, vomiting, and myelosuppression in women receiving adjuvant chemotherapy for early breast cancer: a randomized controlled pilot trial. *Med Acupunct.* 2012;24:241-248.
  65. Shen J, Wenger N, Glaspy J, et al. Electroacupuncture for control of myeloablative chemotherapy-induced emesis: a randomized controlled trial. *JAMA.* 2000;284:2755-2761.
  66. Arslan M, Ozdemir L. Oral intake of ginger for chemotherapy-induced nausea and vomiting among women with breast cancer. *Clin J Oncol Nurs.* 2015;19:E92-E97.
  67. Panahi Y, Saadat A, Sahebkar A, Hashemian F, Taghikhani M, Abolhasani E. Effect of ginger on acute and delayed chemotherapy-induced nausea and vomiting: a pilot, randomized, open-label clinical trial. *Integr Cancer Ther.* 2012;11:204-211.
  68. Ryan JL, Heckler CE, Roscoe JA, et al. Ginger (*Zingiber officinale*) reduces acute chemotherapy-induced nausea: a URCC CCOP study of 576 patients. *Support Care Cancer.* 2012;20:1479-1489.
  69. Yoo HJ, Ahn SH, Kim SB, Kim WK, Han OS. Efficacy of progressive muscle relaxation training and guided imagery in reducing chemotherapy side effects in patients with breast cancer and in improving their quality of life. *Support Care Cancer.* 2005;13:826-833.
  70. Bozzetti F, Biganzoli L, Gavazzi C, et al. Glutamine supplementation in cancer patients receiving chemotherapy: a double-blind randomized study. *Nutrition.* 1997;13:748-751.
  71. Peterson DE, Jones JB, Petit li RG. Randomized, placebo-controlled trial of Saforis for prevention and treatment of oral mucositis in breast cancer patients receiving anthracycline-based chemotherapy. *Cancer.* 2007;109:322-331.
  72. Milbury K, Chaoul A, Biegler K, et al. Tibetan sound meditation for cognitive dysfunction: results of a randomized controlled pilot trial. *Psychooncology.* 2013;22:2354-2363.
  73. Hoffman CJ, Ersser SJ, Hopkinson JB, Nicholls PG, Harrington JE, Thomas PW. Effectiveness of mindfulness-based stress reduction in mood, breast- and endocrine-related quality of life, and well-being in stage 0 to III breast cancer: a randomized, controlled trial. *J Clin Oncol.* 2012;30:1335-1342.
  74. Nidich SI, Fields JZ, Rainforth MV, et al. A randomized controlled trial of the effects of transcendental meditation on quality of life in older breast cancer patients. *Integr Cancer Ther.* 2009;8:228-234.
  75. Henderson VP, Massion AO, Clemow L, Hurley TG, Druker S, Hebert JR. A randomized controlled trial of mindfulness-based stress reduction for women with early stage breast cancer receiving radiotherapy. *Integr Cancer Ther.* 2013;12:404-413.
  76. Dodds SE, Pace TW, Bell ML, et al. Feasibility of Cognitively Based Compassion Training (CBCT) for breast cancer survivors: a randomized, wait list controlled pilot study. *Support Care Cancer.* 2015;23:3599-3608.
  77. Walker LG, Walker MB, Ogston K, et al. Psychological, clinical and pathological effects of relaxation training and guided imagery during primary chemotherapy. *Br J Cancer.* 1999;80:262-268.
  78. Gudenkauf LM, Antoni MH, Stagl JM, et al. Brief cognitive-behavioral and relaxation training interventions for breast cancer: a randomized controlled trial. *J Consult Clin Psychol.* 2015;83:677-688.
  79. Chandwani KD, Perkins G, Nagendra HR, et al. Randomized, controlled trial of yoga in women with breast cancer undergoing radiotherapy. *J Clin Oncol.* 2014;32:1058-1065.
  80. Kiecolt-Glaser JK, Bennett JM, Andridge R, et al. Yoga's impact on inflammation, mood, and fatigue in breast cancer survivors: a randomized controlled trial. *J Clin Oncol.* 2014;32:1040-1049.
  81. Rao RM, Raghuram N, Nagendra HR, et al. Effects of an integrated yoga program on self-reported depression scores in breast cancer patients undergoing conventional treatment: a randomized controlled trial. *Indian J Palliat Care.* 2015;21:174-181.
  82. Culos-Reed SN, Carlson LE, Daroux LM, Hatley-Aldous S. A pilot study of yoga for breast cancer survivors: physical and psychological benefits. *Psychooncology.* 2006;15:891-897.

83. Moadel AB, Shah C, Wylie-Rosett J, et al. Randomized controlled trial of yoga among a multiethnic sample of breast cancer patients: effects on quality of life. *J Clin Oncol*. 2007;25:4387-4395.
84. Danhauer SC, Mihalko SL, Russell GB, et al. Restorative yoga for women with breast cancer: findings from a randomized pilot study. *Psychooncology*. 2009;18:360-368.
85. Vadiraja H, Rao MR, Nagarathna R, et al. Effects of yoga program on quality of life and affect in early breast cancer patients undergoing adjuvant radiotherapy: a randomized controlled trial. *Complement Ther Med*. 2009;17:274-280.
86. Krohn M, Listing M, Tjahjono G, et al. Depression, mood, stress, and Th1/Th2 immune balance in primary breast cancer patients undergoing classical massage therapy. *Support Care Cancer*. 2011;19:1303-1311.
87. Listing M, Reissauer A, Krohn M, et al. Massage therapy reduces physical discomfort and improves mood disturbances in women with breast cancer. *Psychooncology*. 2009;18:1290-1299.
88. Fernandez-Lao C, Cantarero-Villanueva I, Diaz-Rodriguez L, Cuesta-Vargas AI, Fernandez-Delas-Penas C, Arroyo-Morales M. Attitudes towards massage modify effects of manual therapy in breast cancer survivors: a randomised clinical trial with crossover design. *Eur J Cancer Care*. 2012;21:233-241.
89. Burns DS. The effect of the Bonny method of guided imagery and music on the mood and life quality of cancer patients. *J Music Ther*. 2001;38:51-65.
90. Zhou KN, Li XM, Yan H, Dang SN, Wang DL. Effects of music therapy on depression and duration of hospital stay of breast cancer patients after radical mastectomy. *Chin Med J (Engl)*. 2011;124:2321-2327.
91. Nedstrand E, Wijma K, Wyon Y, Hammar M. Vasomotor symptoms decrease in women with breast cancer randomized to treatment with applied relaxation or electro-acupuncture: a preliminary study. *Climacteric*. 2005;8:243-250.
92. Walker EM, Rodriguez AI, Kohn B, et al. Acupuncture versus venlafaxine for the management of vasomotor symptoms in patients with hormone receptor-positive breast cancer: a randomized controlled trial. *J Clin Oncol*. 2010;28:634-640.
93. Post-White J, Kinney ME, Savik K, Gau JB, Wilcox C, Lerner I. Therapeutic massage and healing touch improve symptoms in cancer. *Integr Cancer Ther*. 2003;2:332-344.
94. FitzHenry F, Wells N, Slater V, Dietrich MS, Wisawatapnimit P, Chakravarthy AB. A randomized placebo-controlled pilot study of the impact of healing touch on fatigue in breast cancer patients undergoing radiation therapy. *Integr Cancer Ther*. 2014;13:105-113.
95. Lechner SC, Whitehead NE, Vargas S, et al. Does a community-based stress management intervention affect psychological adaptation among underserved black breast cancer survivors? *J Natl Cancer Inst Monogr*. 2014;2014:315-322.
96. Stagl JM, Bouchard LC, Lechner SC, et al. Long-term psychological benefits of cognitive-behavioral stress management for women with breast cancer: 11-year follow-up of a randomized controlled trial. *Cancer*. 2015;121:1873-1881.
97. Montgomery GH, David D, Kangas M, et al. Randomized controlled trial of a cognitive-behavioral therapy plus hypnosis intervention to control fatigue in patients undergoing radiotherapy for breast cancer. *J Clin Oncol*. 2014;32:557-563.
98. Montgomery GH, Kangas M, David D, et al. Fatigue during breast cancer radiotherapy: an initial randomized study of cognitive-behavioral therapy plus hypnosis. *Health Psychol*. 2009;28:317-322.
99. Barton DL, Liu H, Dakhlil SR, et al. Wisconsin ginseng (*Panax quinquefolius*) to improve cancer-related fatigue: a randomized, double-blind trial, N07C2. *J Natl Cancer Inst*. 2013;105:1230-1238.
100. Barton DL, Soori GS, Bauer BA, et al. Pilot study of *Panax quinquefolius* (American ginseng) to improve cancer-related fatigue: a randomized, double-blind, dose-finding evaluation: NCCCTG trial N03CA. *Support Care Cancer*. 2010;18:179-187.
101. Deng G, Chan Y, Sjoberg D, et al. Acupuncture for the treatment of post-chemotherapy chronic fatigue: a randomized, blinded, sham-controlled trial. *Support Care Cancer*. 2013;21:1735-1741.
102. Molassiotis A, Bardy J, Finnegan-John J, et al. A randomized, controlled trial of acupuncture self-needling as maintenance therapy for cancer-related fatigue after therapist-delivered acupuncture. *Ann Oncol*. 2013;24:1645-1652.
103. Smith C, Carmady B, Thornton C, Perz J, Ussher JM. The effect of acupuncture on post-cancer fatigue and well-being for women recovering from breast cancer: a pilot randomised controlled trial. *Acupunct Med*. 2013;31:9-15.
104. Cramer H, Rabsilber S, Lauche R, Kummel S, Dobos G. Yoga and meditation for menopausal symptoms in breast cancer survivors—a randomized controlled trial. *Cancer*. 2015;121:2175-2184.
105. Banasik J, Williams H, Haberman M, Blank SE, Bendel R. Effect of Iyengar yoga practice on fatigue and diurnal salivary cortisol concentration in breast cancer survivors. *J Am Acad Nurs Pract*. 2011;23:135-142.
106. Littman AJ, Bertram LC, Ceballos R, et al. Randomized controlled pilot trial of yoga in overweight and obese breast cancer survivors: effects on quality of life and anthropometric measures. *Support Care Cancer*. 2012;20:267-277.
107. Hershman DL, Unger JM, Crew KD, et al. Randomized double-blind placebo-controlled trial of acetyl-L-carnitine for the prevention of taxane-induced neuropathy in women undergoing adjuvant breast cancer therapy. *J Clin Oncol*. 2013;31:2627-2633.
108. da Costa Miranda V, Truffelli DC, Santos J, et al. Effectiveness of guarana (*Paullinia cupana*) for postradiation fatigue and depression: results of a pilot double-blind randomized study. *J Alternat Complement Med*. 2009;15:431-433.
109. de Oliveira Campos MP, Riechelmann R, Martins LC, Hassan BJ, Casa FBA, Giglio AD. Guarana (*Paullinia cupana*) improves fatigue in breast cancer patients undergoing systemic chemotherapy. *J Alternat Complement Med*. 2011;17:505-512.
110. Ahmed Omar MT, Abd-El-Gayed Ebid A, El Morsy AM. Treatment of post-mastectomy lymphedema with laser therapy: double blind placebo control randomized study. *J Surg Res*. 2011;165:82-90.
111. Ridner SH, Poage-Hooper E, Kanar C, Doersam JK, Bond SM, Dietrich MS. A pilot randomized trial evaluating low-level laser therapy as an alternative treatment to manual lymphatic drainage for breast cancer-related lymphedema. *Oncol Nurs Forum*. 2013;40:383-393.
112. Andersen L, Hojris I, Erlandsen M, Andersen J. Treatment of breast-cancer-related lymphedema with or without manual lymphatic drainage: a randomized study. *Acta Oncol*. 2000;39:399-405.
113. Devoogdt N, Christiaens MR, Geraerts I, et al. Effect of manual lymph drainage in addition to guidelines and exercise therapy on arm lymphoedema related to breast cancer: randomised controlled trial [serial online]. *BMJ*. 2011;343:d5326.
114. Gurdal SO, Kostanoglu A, Cavdar I, et al. Comparison of intermittent pneumatic compression with manual lymphatic drainage for treatment of breast cancer-related lymphedema. *Lymphat Res Biol*. 2012;10:129-135.
115. Maher J, Refshauge K, Ward L, Paterson R, Kilbreath S. Change in extracellular fluid and arm volumes as a consequence of a single session of lymphatic massage followed by rest with or without compression. *Support Care Cancer*. 2012;20:3079-3086.
116. McNeely ML, Magee DJ, Lees AW, Bagnall KM, Haykowsky M, Hanson J. The addition of manual lymph drainage to compression therapy for breast cancer related lymphedema: a randomized controlled trial. *Breast Cancer Res Treat*. 2004;86:95-106.
117. Williams AF, Vadgama A, Franks PJ, Mortimer PS. A randomized controlled crossover study of manual lymphatic drainage therapy in women with breast cancer-related lymphoedema. *Eur J Cancer Care (Engl)*. 2002;11:254-261.
118. Dayes IS, Whelan TJ, Julian JA, et al. Randomized trial of decongestive lymphatic therapy for the treatment of lymphedema in women with breast cancer. *J Clin Oncol*. 2013;31:3758-3763.
119. Gan TJ, Jiao KR, Zenn M, Georgiade G. A randomized controlled comparison of electro-acupoint stimulation or ondansetron versus placebo for the prevention of postoperative nausea and vomiting. *Anesth Analg*. 2004;99:1070-1075.
120. Bao T, Cai L, Giles JT, et al. A dual-center randomized controlled double blind trial assessing the effect of acupuncture in reducing musculoskeletal symptoms in breast cancer patients taking aromatase inhibitors. *Breast Cancer Res Treat*. 2013;138:167-174.
121. 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.

122. Crew KD, Capodice JL, Greenlee H, et al. Randomized, blinded, sham-controlled trial of acupuncture for the management of aromatase inhibitor-associated joint symptoms in women with early stage breast cancer. *J Clin Oncol*. 2010;28:1154-1160.
123. Oh B, Kimble B, Costa DS, et al. Acupuncture for treatment of arthralgia secondary to aromatase inhibitor therapy in women with early breast cancer: pilot study. *Acupunct Med*. 2013;31:264-271.
124. Mao JJ, Xie SX, Farrar JT, et al. A randomized trial of electro-acupuncture for arthralgia related to aromatase inhibitor use. *Eur J Cancer*. 2014;50:267-276.
125. Montgomery GH, Bovbjerg DH, Schnur JB, et al. A randomized clinical trial of a brief hypnosis intervention to control side effects in breast surgery patients. *J Natl Cancer Inst*. 2007;99:1304-1312.
126. Montgomery GH, Weltz CR, Seltz M, Bovbjerg DH. Brief presurgery hypnosis reduces distress and pain in excisional breast biopsy patients. *Int J Clin Exp Hypn*. 2002;50:17-32.
127. Henderson VP, Clemow L, Massion AO, Hurley TG, Druker S, Hebert JR. The effects of mindfulness-based stress reduction on psychosocial outcomes and quality of life in early stage breast cancer patients: a randomized trial. *Breast Cancer Res Treat*. 2012;131:99-109.
128. Siedentopf F, Utz-Billing I, Gairing S, Schoenegg W, Kantenich H, Kollak I. Yoga for patients with early breast cancer and its impact on quality of life—a randomized controlled trial. *Geburtshilfe Frauenheilkd*. 2013;73:311-317.
129. Frisk J, Kallstrom AC, Wall N, Fredrikson M, Hammar M. Acupuncture improves health-related quality-of-life (HRQoL) and sleep in women with breast cancer and hot flashes. *Support Care Cancer*. 2012;20:715-724.
130. Rostock M, Jaroslowski K, Guethlin C, Ludtke R, Schroder S, Bartsch HH. Chemotherapy-induced peripheral neuropathy in cancer patients: a four-arm randomized trial on the effectiveness of electroacupuncture [serial online]. *Evid Based Complement Alternat Med*. 2013;2013:349653.
131. Semiglazov VF, Stepula VV, Dudov A, Lehmacher W, Mengs U. The standardised mistletoe extract PS76A2 improves QoL in patients with breast cancer receiving adjuvant CMF chemotherapy: a randomised, placebo-controlled, double-blind, multicentre clinical trial. *Anticancer Res*. 2004;24:1293-1302.
132. Semiglazov VF, Stepula VV, Dudov A, Schmitker J, Mengs U. Quality of life is improved in breast cancer patients by standardised mistletoe extract PS76A2 during chemotherapy and follow-up: a randomised, placebo-controlled, double-blind, multicentre clinical trial. *Anticancer Res*. 2006;26:1519-1529.
133. Troger W, Jezdic S, Zdravle Z, Tisma N, Hamre HJ, Matijasevic M. Quality of life and neutropenia in patients with early stage breast cancer: a randomized pilot study comparing additional treatment with mistletoe extract to chemotherapy alone. *Breast Cancer (Auckl)*. 2009;3:35-45.
134. Troger W, Zdravle Z, Tisma N, Matijasevic M. Additional therapy with a mistletoe product during adjuvant chemotherapy of breast cancer patients improves quality of life: an open randomized clinical pilot trial. *Evid Based Complement Alternat Med*. 2014;2014:430518.
135. Chen Z, Meng Z, Milbury K, et al. Qigong improves quality of life in women undergoing radiotherapy for breast cancer: results of a randomized controlled trial. *Cancer*. 2013;119:1690-1698.
136. Oh B, Butow PN, Mullan BA, et al. Effect of medical qigong on cognitive function, quality of life, and a biomarker of inflammation in cancer patients: a randomized controlled trial. *Support Care Cancer*. 2012;20:1235-1242.
137. Dyer J, Thomas K, Sandsund C, Shaw C. Is reflexology as effective as aromatherapy massage for symptom relief in an adult outpatient oncology population? *Complement Ther Clin Pract*. 2013;19:139-146.
138. Sharp DM, Walker MB, Chaturvedi A, et al. A randomised, controlled trial of the psychological effects of reflexology in early breast cancer. *Eur J Cancer*. 2010;46:312-322.
139. Wyatt G, Sikorskii A, Rahbar MH, Victorson D, You M. Health-related quality-of-life outcomes: a reflexology trial with patients with advanced-stage breast cancer. *Oncol Nurs Forum*. 2012;39:568-577.
140. Antoni MH, Lechner SC, Kazi A, et al. How stress management improves quality of life after treatment for breast cancer. *J Consult Clin Psychol*. 2006;74:1143-1152.
141. Lerman R, Jarski R, Rea H, Gellish R, Vicini F. Improving symptoms and quality of life of female cancer survivors: a randomized controlled study. *Ann Surg Oncol*. 2012;19:373-378.
142. Mustian K, Sprod L, Janelsins M, et al. Multicenter, randomized controlled trial of yoga for sleep quality among cancer survivors. *J Clin Oncol*. 2013;31:3233-3241.
143. Bokmand S, Flyger H. Acupuncture relieves menopausal discomfort in breast cancer patients: a prospective, double blinded, randomized study. *Breast*. 2013;22:320-323.
144. Deng G, Vickers A, Yeung S, et al. Randomized, controlled trial of acupuncture for the treatment of hot flashes in breast cancer patients. *J Clin Oncol*. 2007;25:5584-5590.
145. Frisk J, Carlhall S, Kallstrom AC, Lindh-Astrand L, Malmstrom A, Hammar M. Long-term follow-up of acupuncture and hormone therapy on hot flashes in women with breast cancer: a prospective, randomized, controlled multicenter trial. *Climacteric*. 2008;11:166-174.
146. Hervik J, Mjaland O. Quality of life of breast cancer patients medicated with anti-estrogens, 2 years after acupuncture treatment: a qualitative study. *Int J Womens Health*. 2010;2:319-325.
147. Liljegren A, Gunnarsson P, Landgren BM, Robeus N, Johansson H, Rotstein S. Reducing vasomotor symptoms with acupuncture in breast cancer patients treated with adjuvant tamoxifen: a randomized controlled trial. *Breast Cancer Res Treat*. 2012;135:791-798.
148. Mao J, Bowman M, Xie S, Bruner D, De Michele A, Farrar J. Electroacupuncture versus gabapentin for hot flashes among breast cancer survivors: a randomized placebo-controlled trial. *J Clin Oncol*. 2015;33:3615-3620.
149. MacGregor CA, Canney PA, Patterson G, McDonald R, Paul J. A randomised double-blind controlled trial of oral soy supplements versus placebo for treatment of menopausal symptoms in patients with early breast cancer. *Eur J Cancer*. 2005;41:708-714.
150. Quella SK, Loprinzi CL, Barton DL, et al. Evaluation of soy phytoestrogens for the treatment of hot flashes in breast cancer survivors: a North Central Cancer Treatment Group trial. *J Clin Oncol*. 2000;18:1068-1074.
151. Van Patten CL, Olivotto IA, Chambers GK, et al. Effect of soy phytoestrogens on hot flashes in postmenopausal women with breast cancer: a randomized, controlled clinical trial. *J Clin Oncol*. 2002;20:1449-1455.
152. Cohen MR. The New Chinese Medicine Handbook: An Innovative Guide to Integrating Eastern Wisdom with Western Practice for Modern Healing. Beverly, MA: Fairwinds Press; 2015.
153. National Cancer Institute. NCI Dictionary of Cancer Terms. cancer.gov/publications/dictionaries/cancer-terms. Accessed June 27, 2016.
154. National Center for Complementary and Integrative Health. Acupuncture. nccih.nih.gov/health/acupuncture. Accessed June 18, 2015.
155. Shen Y, Liu L, Chiang JS, et al. Randomized, placebo-controlled trial of K1 acupoint acupoint stimulation to prevent cisplatin-induced or oxaliplatin-induced nausea. *Cancer*. 2015;121:84-92.
156. Napadow V, Makris N, Liu J, Kettner NW, Kwong KK, Hui KK. Effects of electroacupuncture versus manual acupuncture on the human brain as measured by fMRI. *Hum Brain Mapp*. 2005;24:193-205.
157. Gottschling S, Reindl TK, Meyer S, et al. Acupuncture to alleviate chemotherapy-induced nausea and vomiting in pediatric oncology—a randomized multicenter crossover pilot trial. *Klin Padiatr*. 2008;220:365-370.
158. Rithirangraroj K, Manchana T, Akkayagorn L. Efficacy of acupuncture in prevention of delayed chemotherapy induced nausea and vomiting in gynecologic cancer patients. *Gynecol Oncol*. 2015;136:82-86.
159. Melchart D, Ihbe-Heffinger A, Leps B, von Schilling C, Linde K. Acupuncture and acupressure for the prevention of chemotherapy-induced nausea—a randomised cross-over pilot study. *Support Care Cancer*. 2006;14:878-882.
160. Garcia MK, McQuade J, Haddad R, et al. Systematic review of acupuncture in cancer care: a synthesis of the evidence. *J Clin Oncol*. 2013;31:952-960.
161. Zick SM, Sen A, Wyatt GK, Murphy SL, Arnedt JT, Harris RE. Investigation of 2 types of self-administered acupressure for persistent cancer-related fatigue in breast cancer survivors: a randomized clinical trial. *JAMA Oncol*. 2016;2:1470-1476.

162. Memorial Sloan Kettering Cancer Center. Integrative Medicine: About Herbs, Botanicals and Other Products. [mskcc.org/cancer-care/treatments/symptom-management/integrative-medicine/herbs](http://mskcc.org/cancer-care/treatments/symptom-management/integrative-medicine/herbs). Accessed June 27, 2016.
163. National Center for Complementary and Integrative Health. Ginger. [nccih.nih.gov/health/ginger](http://nccih.nih.gov/health/ginger). Accessed June 27, 2016.
164. National Cancer Institute. Topics in Integrative, Alternative, and Complementary Therapies (PDQ)-Patient Version. [cancer.gov/about-cancer/treatment/cam/patient/cam-topics-pdq](http://cancer.gov/about-cancer/treatment/cam/patient/cam-topics-pdq). Accessed November 29, 2016.
165. U.S Food and Drug Administration Product Classification. [accessdata.fda.gov/scripts/cdrh/cfdocs/cfPCD/classification.cfm?ID=3639](http://accessdata.fda.gov/scripts/cdrh/cfdocs/cfPCD/classification.cfm?ID=3639). Accessed April 3, 2017.
166. National Cancer Institute. Lymphedema (PDQ)-Health Professional Version. [cancer.gov/about-cancer/treatment/side-effects/lymphedema/lymphedema-hp-pdq](http://cancer.gov/about-cancer/treatment/side-effects/lymphedema/lymphedema-hp-pdq). Accessed June 27, 2016.
167. National Center for Complementary and Integrative Health. Massage Therapy for Health Purposes. [nccih.nih.gov/health/massage/massageintroduction.htm](http://nccih.nih.gov/health/massage/massageintroduction.htm). Accessed June 18, 2015.
168. Gecsedí RA. Massage therapy for patients with cancer. *Clin J Oncol Nurs*. 2002;6:52-54.
169. Walsh R, Shapiro SL. The meeting of meditative disciplines and Western psychology—a mutually enriching dialogue. *Am Psychol*. 2006;61:227-239.
170. Bond K, Ospina MB, Hooton N, et al. Defining a complex intervention: the development of demarcation criteria for “meditation.” *Psychol Religion Spirituality*. 2009;1:129-137.
171. Kabat-Zinn J. *Full Catastrophe Living*. New York: Bantam Dell; 1990.
172. Shennan C, Payne S, Fenlon D. What is the evidence for the use of mindfulness-based interventions in cancer care? A review. *Psychooncology*. 2011;20:681-697.
173. Matchim Y, Armer JM, Stewart BR. Mindfulness-based stress reduction among breast cancer survivors: a literature review and discussion. *Oncol Nurs Forum*. 2011;38:E61-E71.
174. Zainal NZ, Booth S, Huppert FA. The efficacy of mindfulness-based stress reduction on mental health of breast cancer patients: a meta-analysis. *Psychooncology*. 2013;22:1457-1465.
175. Cramer H, Lauche R, Paul A, Dobos G. Mindfulness-based stress reduction for breast cancer—a systematic review and meta-analysis. *Curr Oncol*. 2012;19:e343-352.
176. Marvibaigi M, Supriyanto E, Amini N, Abdul Majid FA, Jaganathan SK. Preclinical and clinical effects of mistletoe against breast cancer [serial online]. *Biomed Res Int*. 2014;2014:785479.
177. Bussing A. *Mistletoe: The Genus Viscum*. The Netherlands: CRC Press; 2000.
178. Horneber MA, Bueschel G, Huber R, Linde K, Rostock M. Mistletoe therapy in oncology [serial online]. *Cochrane Database Syst Rev*. 2008;2:CD003297.
179. American Music Therapy Association. What Is Music Therapy? [musictherapy.org/about/musictherapy/](http://musictherapy.org/about/musictherapy/). Accessed June 22, 2015.
180. Nilsson U. The anxiety- and pain-reducing effects of music interventions: a systematic review. *AORN J*. 2008;87:780-807.
181. Guetin S, Charras K, Berard A, et al. An overview of the use of music therapy in the context of Alzheimer’s disease: a report of a French expert group. *Dementia (London)*. 2013;12:619-634.
182. National Center for Complementary and Integrative Health. Reflexology. [nccih.nih.gov/health/reflexology](http://nccih.nih.gov/health/reflexology). Accessed June 27, 2016.
183. National Center for Complementary and Integrative Health. Relaxation Techniques for Health: What you need to know. [nccih.nih.gov/health/stress/relaxation.htm](http://nccih.nih.gov/health/stress/relaxation.htm). Accessed June 18, 2015.
184. National Center for Complementary and Integrative Health. Tai Chi and Qi Gong: In Depth. [nccih.nih.gov/health/taichi/introduction.htm](http://nccih.nih.gov/health/taichi/introduction.htm). Accessed June 27, 2016.
185. National Center for Complementary and Integrative Health. Stress. [nccih.nih.gov/health/stress](http://nccih.nih.gov/health/stress). Accessed June 18, 2015.
186. National Cancer Institute. Depression (PDQ)-Health Professional Version. [cancer.gov/about-cancer/coping/feelings/depression-hp-pdq](http://cancer.gov/about-cancer/coping/feelings/depression-hp-pdq). Accessed August 10, 2015.
187. National Cancer Institute. Cancer-Related Post-Traumatic Stress (PDQ)-Health Professional Version. [cancer.gov/about-cancer/coping/survivorship/new-normal/ptsd-hp-pdq](http://cancer.gov/about-cancer/coping/survivorship/new-normal/ptsd-hp-pdq). Accessed August 8, 2015.
188. Antoni MH, Lehman JM, Kilbourn KM, et al. Cognitive-behavioral stress management intervention decreases the prevalence of depression and enhances benefit finding among women under treatment for early stage breast cancer. *Health Psychol*. 2001;20:20-32.
189. National Center for Complementary and Integrative Health. Yoga. [nccih.nih.gov/health/yoga](http://nccih.nih.gov/health/yoga). Accessed June 18, 2015.
190. Iyengar B. *Light on Pranayama: The Yogic Art of Breathing*. Chestnut Ridge, NY: Crossroad Publishing Company; 2005.
191. Andersen BL, DeRubeis RJ, Berman BS, et al. Screening, assessment, and care of anxiety and depressive symptoms in adults with cancer: an American Society of Clinical Oncology guideline adaptation. *J Clin Oncol*. 2014;32:1605-1619.
192. Bower JE, Bak K, Berger A, et al. Screening, assessment, and management of fatigue in adult survivors of cancer: an American Society of Clinical oncology clinical practice guideline adaptation. *J Clin Oncol*. 2014;32:1840-1850.
193. Hershman DL, Lacchetti C, Dworkin RH, et al. Prevention and management of chemotherapy-induced peripheral neuropathy in survivors of adult cancers: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol*. 2014;32:1941-1967.
194. Runowicz CD, Leach CR, Henry NL, et al. American Cancer Society/American Society of Clinical Oncology breast cancer survivorship care guideline. *J Clin Oncol*. 2016;34:611-635.
195. Jordan K, Jahn F, Aapro M. Recent developments in the prevention of chemotherapy-induced nausea and vomiting (CINV): a comprehensive review. *Ann Oncol*. 2015;26:1081-1090.
196. Berger AM, Abernethy AP, Atkinson A, et al. NCCN Clinical Practice Guidelines cancer-related fatigue. *J Natl Compr Canc Netw*. 2010;8:904-931.
197. Hesketh PJ, Bohlke K, Lyman GH, et al. Antiemetics: American Society of Clinical Oncology focused guideline update. *J Clin Oncol*. 2016;34:381-386.
198. Zick SM, Alrawi S, Merel G, et al. Relaxation acupressure reduces persistent cancer-related fatigue [serial online]. *Evid Based Complement Alternat Med*. 2011; 2011. pii: 142913.
199. Targ EF, Levine EG. The efficacy of a mind-body-spirit group for women with breast cancer: a randomized controlled trial. *Gen Hosp Psychiatry*. 2002;24:238-248.
200. Yaal-Hahoshen N, Maimon Y, Siegelmann-Danieli N, et al. A prospective, controlled study of the botanical compound mixture LCS101 for chemotherapy-induced hematological complications in breast cancer. *Oncologist*. 2011;16:1197-1202.
201. Zhuang SR, Chiu HF, Chen SL, et al. Effects of a Chinese medical herbs complex on cellular immunity and toxicity-related conditions of breast cancer patients. *Br J Nutr*. 2012;107:712-718.
202. Bo Y, Li HS, Qi YC, Lu MY. Clinical study on treatment of mammary cancer by Shenqi Fuzheng injection in cooperation with chemotherapy. *Chin J Integr Med*. 2007;13:37-40.
203. Thyme KE, Sundin EC, Wiberg B, Oster I, Astrom S, Lindh J. Individual brief art therapy can be helpful for women with breast cancer: a randomized controlled clinical study. *Palliat Support Care*. 2009; 7:87-95.
204. Monti DA, Kash KM, Kunkel EJ, et al. Changes in cerebral blood flow and anxiety associated with an 8-week mindfulness programme in women with breast cancer. *Stress Health*. 2012;28:397-407.
205. Gaston-Johansson F, Fall-Dickson JM, Nanda J, et al. The effectiveness of the comprehensive coping strategy program on clinical outcomes in breast cancer autologous bone marrow transplantation. *Cancer Nurs*. 2000;23:277-285.
206. Robb KA, Newham DJ, Williams JE. Transcutaneous electrical nerve stimulation vs. transcutaneous spinal electroanalgesia for chronic pain associated with breast cancer treatments. *J Pain Symptom Manage*. 2007;33:410-419.
207. Frank LS, Frank JL, March D, Makari-Judson G, Barham RB, Mertens WC. Does therapeutic touch ease the discomfort or distress of patients undergoing stereotactic core breast biopsy? A randomized clinical trial. *Pain Med*. 2007;8:419-424.
208. Schnur JB, Bovbjerg DH, David D, et al. Hypnosis decreases presurgical distress in excisional breast biopsy patients. *Anesth Analg*. 2008;106:440-444.

209. Marshall-Mckenna R, Paul L, McFadyen AK, et al. Myofascial release for women undergoing radiotherapy for breast cancer: a pilot study. *Eur J Physiother* 2014; 16:58-64.
210. Baker BS, Harrington JE, Choi BS, Kropf P, Muller I, Hoffman CJ. A randomised controlled pilot feasibility study of the physical and psychological effects of an integrated support programme in breast cancer. *Complement Ther Clin Pract*. 2012; 18:182-189.
211. Liu CJ, Hsiung PC, Chang KJ, et al. A study on the efficacy of body-mind-spirit group therapy for patients with breast cancer. *J Clin Nurs*. 2008;17:2539-2549.
212. Stephenson NL, Weinrich SP, Tavakoli AS. The effects of foot reflexology on anxiety and pain in patients with breast and lung cancer. *Oncol Nurs Forum*. 2000;27: 67-72.
213. Potter PJ. Breast biopsy and distress: feasibility of testing a reiki intervention. *J Holist Nurs*. 2007;25:238-251.
214. Robins JL, McCain NL, Elswick RK Jr, Walter JM, Gray DP, Tuck I. Psychoneuro-immunology-based stress management during adjuvant chemotherapy for early breast cancer [serial online]. *Evid Based Complement Alternat Med*. 2013;2013: 372908.
215. Jo SH, Kim LS, Kim SA, et al. Evaluation of short-term use of N-acetylcysteine as a strategy for prevention of anthracycline-induced cardiomyopathy: EPOCH trial—a prospective randomized study. *Korean Circ J*. 2013;43:174-181.
216. Roscoe JA, Matteson SE, Morrow GR, et al. Acustimulation wrist bands are not effective for the control of chemotherapy-induced nausea in women with breast cancer. *J Pain Symptom Manage*. 2005;29: 376-384.
217. Lua PL, Salihah N, Mazlan N. Effects of inhaled ginger aromatherapy on chemotherapy-induced nausea and vomiting and health-related quality of life in women with breast cancer. *Complement Ther Med*. 2015;23:396-404.
218. Valadares F, Novaes MR, Canete R. Effect of *Agaricus sylvaticus* supplementation on nutritional status and adverse events of chemotherapy of breast cancer: a randomized, placebo-controlled, double-blind clinical trial. *Indian J Pharmacol*. 2013;45: 217-222.
219. Perol D, Provençal J, Hardy-Bessard AC, et al. Can treatment with *Cocculine* improve the control of chemotherapy-induced emesis in early breast cancer patients? A randomized, multi-centered, double-blind, placebo-controlled phase III trial [serial online]. *BMC Cancer*. 2012;12: 603.
220. Moradian S, Walshe C, Shahidsales S, Ghavam Nasiri MR, Pilling M, Molassiotis A. Nevasic audio program for the prevention of chemotherapy induced nausea and vomiting: a feasibility study using a randomized controlled trial design. *Eur J Oncol Nurs*. 2015;19:282-291.
221. Cimprich B, Ronis DL. An environmental intervention to restore attention in women with newly diagnosed breast cancer. *Cancer Nurs*. 2003;26:284-292.
222. Barton DL, Burger K, Novotny PJ, et al. The use of *Ginkgo biloba* for the prevention of chemotherapy-related cognitive dysfunction in women receiving adjuvant treatment for breast cancer, N00C9. *Support Care Cancer*. 2013;21:1185-1192.
223. Derry HM, Jaremka LM, Bennett JM, et al. Yoga and self-reported cognitive problems: a randomized controlled trial for breast cancer survivors. *Psychooncology*. 2015;24:958-966
224. Hanai A, Ishiguro H, Sozu T, et al. Effects of a self-management program on antiemetic-induced constipation during chemotherapy among breast cancer patients: a randomized controlled clinical trial. *Breast Cancer Res Treat*. 2016;155: 99-107.
225. Jain S, Pavlik D, Distefan J, et al. Complementary medicine for fatigue and cortisol variability in breast cancer survivors. *Cancer*. 2012;118:777-787.
226. Lesser GJ, Case D, Stark N, et al. A randomized, double-blind, placebo-controlled study of oral coenzyme Q10 to relieve self-reported treatment-related fatigue in newly diagnosed patients with breast cancer. *J Support Oncol*. 2013;11:31-42.
227. Zhao H, Zhang Q, Zhao L, Huang X, Wang J, Kang X. Spore powder of *Ganoderma lucidum* improves cancer-related fatigue in breast cancer patients undergoing endocrine therapy: a pilot clinical trial [serial online]. *Evid Based Complement Alternat Med*. 2012;2012:89614.
228. Schnur JB, David D, Kangas M, Green S, Bovbjerg DH, Montgomery GH. A randomized trial of a cognitive-behavioral therapy and hypnosis intervention on positive and negative affect during breast cancer radiotherapy. *J Clin Psychol*. 2009;65: 443-455.
229. Andersen BL, Farrar WB, Golden-Kreutz DM, et al. Psychological, behavioral, and immune changes after a psychological intervention: a clinical trial. *J Clin Oncol*. 2004;22:3570-3580.
230. Spahn G, Choi KE, Kennemann C, et al. Can a multimodal mind-body program enhance the treatment effects of physical activity in breast cancer survivors with chronic tumor-associated fatigue? A randomized controlled trial. *Integr Cancer Ther*. 2013;12:291-300.
231. Balk J, Day R, Rosenzweig M, Beriwal S. Pilot, randomized, modified, double-blind, placebo-controlled trial of acupuncture for cancer-related fatigue. *J Soc Integr Oncol*. 2009;7:4-11.
232. Johnston MF, Hays RD, Subramanian SK, et al. Patient education integrated with acupuncture for relief of cancer-related fatigue randomized controlled feasibility study [serial online]. *BMC Complement Alternat Med*. 2011;11:49.
233. Ancoli-Israel S, Rissling M, Neikrug A, et al. Light treatment prevents fatigue in women undergoing chemotherapy for breast cancer. *Support Care Cancer*. 2012; 20:1211-1219.
234. van der Lee ML, Garssen B. Mindfulness-based cognitive therapy reduces chronic cancer-related fatigue: a treatment study. *Psychooncology*. 2012;21:264-272.
235. Reis D, Walsh ME, Young-McCaughan S, Jones T. Effects of Nia exercise in women receiving radiation therapy for breast cancer. *Oncol Nurs Forum*. 2013;40:E374-E381.
236. Adamsen L, Quist M, Andersen C, et al. Effect of a multimodal high intensity exercise intervention in cancer patients undergoing chemotherapy: randomised controlled trial [serial online]. *BMJ*. 2009; 339:b3410.
237. Bjorneklett HG, Lindemalm C, Rosenblad A, et al. A randomised controlled trial of support group intervention after breast cancer treatment: results on anxiety and depression. *Acta Oncol*. 2012;51:198-207.
238. de Souza Fede AB, Bensi CG, Trufelli DC, et al. Multivitamins do not improve radiation therapy-related fatigue: results of a double-blind randomized crossover trial. *Am J Clin Oncol*. 2007;30:432-436.
239. Roscoe J, Matteson S, Mustian K, Padmanaban D, Morrow G. Treatment of radiotherapy-induced fatigue through a nonpharmacological approach. *Integr Cancer Ther*. 2005;4:8-13.
240. Mustian KM, Roscoe JA, Palesh OG, et al. Polarity therapy for cancer-related fatigue in patients with breast cancer receiving radiation therapy: a randomized controlled pilot study. *Integr Cancer Ther*. 2011;10:27-37.
241. Rissanen R, Arving C, Ahlgren J, Nordin K. Group versus individual stress management intervention in breast cancer patients for fatigue and emotional reactivity: a randomised intervention study. *Acta Oncol*. 2014;53:1221-1229.
242. Steindorf K, Schmidt ME, Klassen O, et al. Randomized, controlled trial of resistance training in breast cancer patients receiving adjuvant radiotherapy: results on cancer-related fatigue and quality of life. *Ann Oncol*. 2014;25:2237-2243.
243. Schmidt ME, Wiskemann J, Armbrust P, Schneeweiss A, Ulrich CM, Steindorf K. Effects of resistance exercise on fatigue and quality of life in breast cancer patients undergoing adjuvant chemotherapy: a randomized controlled trial. *Int J Cancer*. 2015;137:471-480.
244. Cluzan RV, Alliot F, Ghabboun S, Pascot M. Treatment of secondary lymphedema of the upper limb with CYCLO 3 FORT. *Lymphology*. 1996;29:29-35.
245. Belmonte R, Tejero M, Ferrer M, et al. Efficacy of low-frequency low-intensity electrotherapy in the treatment of breast cancer-related lymphoedema: a cross-over randomized trial. *Clin Rehabil*. 2012;26: 607-618.
246. Cluzan RV, Pecking AP, Mathieux-Fortunet H, Leger Picherit E. Efficacy of BN165 (Ginkor Fort) in breast cancer related upper limb lymphedema: a preliminary study. *Lymphology*. 2004;37:47-52.
247. Gothard L, Cornes P, Earl J, et al. Double-blind placebo-controlled randomised trial of vitamin E and pentoxifylline in patients with chronic arm lymphoedema and fibrosis after surgery and radiotherapy for breast cancer. *Radiother Oncol*. 2004;73: 133-139.
248. Magnusson M, Hoglund P, Johansson K, et al. Pentoxifylline and vitamin E treatment for prevention of radiation-induced side-effects in women with breast cancer: a phase two, double-blind, placebo-controlled randomised clinical trial (Ptx-5). *Eur J Cancer*. 2009;45:2488-2495.
249. Loudon A, Barnett T, Piller N, Immink MA, Williams AD. Yoga management of

- breast cancer-related lymphoedema: a randomised controlled pilot-trial [serial online]. *BMC Complement Alternat Med*. 2014;14:214.
250. Ghoreishi Z, Esfahani A, Djazayeri A, et al. Omega-3 fatty acids are protective against paclitaxel-induced peripheral neuropathy: a randomized double-blind placebo controlled trial [serial online]. *BMC Cancer*. 2012;12:355.
251. Argyriou AA, Chroni E, Koutras A, et al. Preventing paclitaxel-induced peripheral neuropathy: a phase II trial of vitamin E supplementation. *J Pain Symptom Manage*. 2006;32:237-244.
252. Pace A, Giannarelli D, Galie E, et al. Vitamin E neuroprotection for cisplatin neuropathy: a randomized, placebo-controlled trial. *Neurology*. 2010;74:762-766.
253. Santos Araujo Mdo C, Farias IL, Gutierrez J, et al. Uncaria tomentosa—adjuvant treatment for breast cancer: clinical trial [serial online]. *Evid Based Complement Alternat Med*. 2012;2012:676984
254. Rastelli AL, Taylor ME, Gao F, et al. Vitamin D and aromatase inhibitor-induced musculoskeletal symptoms (AIMSS): a phase II, double-blind, placebo-controlled, randomized trial. *Breast Cancer Res Treat*. 2011;129:107-116.
255. Arathuzik D. Effects of cognitive-behavioral strategies on pain in cancer patients. *Cancer Nurs*. 1994;17:207-214.
256. Butler LD, Koopman C, Neri E, et al. Effects of supportive-expressive group therapy on pain in women with metastatic breast cancer. *Health Psychol*. 2009;28:579-587.
257. Sharp L, Finnila K, Johansson H, Abrahamsson M, Hatschek T, Bergenmar M. No differences between Calendula cream and aqueous cream in the prevention of acute radiation skin reactions—results from a randomised blinded trial. *Eur J Oncol Nurs*. 2013;17:429-435.
258. Brisbois TD, de Kock IH, Watanabe SM, et al. Delta-9-tetrahydrocannabinol may palliate altered chemosensory perception in cancer patients: results of a randomized, double-blind, placebo-controlled pilot trial. *Ann Oncol*. 2011;22:2086-2093.
259. Noguchi N, Maruyama I, Yamada A. The influence of chlorella and its hot water extract supplementation on quality of life in patients with breast cancer [serial online]. *Evid Based Complement Alternat Med*. 2014;2014:704619.
260. Panahi Y, Saadat A, Beiraghdar F, Sahebkar A. Adjuvant therapy with bioavailability-boosted curcuminoids suppresses systemic inflammation and improves quality of life in patients with solid tumors: a randomized double-blind placebo-controlled trial. *Phytother Res*. 2014;28:1461-1467.
261. Pruthi S, Qin R, Terstreip SA, et al. A phase III, randomized, placebo-controlled, double-blind trial of flaxseed for the treatment of hot flashes: North Central Cancer Treatment Group N08C7. *Menopause*. 2012;19:48-53.
262. Richardson M, Post-White J, Grimm E, Moye L, Singletary S, Justice B. Coping, life attitudes, and immune responses to imagery and group support after breast cancer treatment. *Alternat Ther Health Med*. 1997;3:62-70.
263. Frass M, Friehs H, Thallinger C, et al. Influence of adjunctive classical homeopathy on global health status and subjective wellbeing in cancer patients—a pragmatic randomized controlled trial. *Complement Ther Med*. 2015;23:309-317.
264. Jacobs J, Herman P, Heron K, Olsen S, Vaughters L. Homeopathy for menopausal symptoms in breast cancer survivors: A preliminary randomized controlled trial. *J Alternat Complement Med*. 2005;11:21-27.
265. Thompson EA, Oxon BA, Montgomery A, Douglas D, Reilly D. A pilot, randomized, double-blinded, placebo-controlled trial of individualized homeopathy for symptoms of estrogen withdrawal in breast-cancer survivors. *J Alternat Complement Med*. 2005;11:13-20.
266. Sandel SL, Judge JO, Landry N, Faria L, Ouellette R, Majczak M. Dance and movement program improves quality-of-life measures in breast cancer survivors. *Cancer Nurs*. 2005;28:301-309.
267. 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.
268. Loprinzi CL, Levitt R, Barton DL, et al. Evaluation of shark cartilage in patients with advanced cancer: a North Central Cancer Treatment Group trial. *Cancer*. 2005;104:176-182.
269. Kissane DW, Grabsch B, Clarke DM, et al. Supportive-expressive group therapy for women with metastatic breast cancer: survival and psychosocial outcome from a randomized controlled trial. *Psycho-Oncology*. 2007;16:277-286.
270. Campo RA, O'Connor K, Light KC, et al. Feasibility and acceptability of a tai chi chih randomized controlled trial in senior female cancer survivors. *Integr Cancer Ther*. 2013;12:464-474.
271. Mustian KM, Katula JA, Gill DL, Roscoe JA, Lang D, Murphy K. Tai chi chuan, health-related quality of life and self-esteem: a randomized trial with breast cancer survivors. *Support Care Cancer*. 2004;12:871-876.
272. Sprod LK, Janelsins MC, Palesh OG, et al. Health-related quality of life and biomarkers in breast cancer survivors participating in tai chi chuan. *J Cancer Surviv*. 2012;6:146-154.
273. Harder H, Langridge C, Solis-Trapala I, et al. Post-operative exercises after breast cancer surgery: results of a RCT evaluating standard care versus standard care plus additional yoga exercise. *Eur J Integr Med*. 2015;7:202-210.
274. Huang C, Hou M, Kan J, et al. Prophylactic treatment with Adlay bran extract reduces the risk of severe acute radiation dermatitis: a prospective, randomized, double-blind study [serial online]. *Evid Based Complement Alternat Med*. 2015;2015:312072.
275. Ansari M, Dehsara F, Mosalaei A, Omidvari S, Ahmadloo N, Mohammadianpanah M. Efficacy of topical alpha ointment (containing natural henna) compared to topical hydrocortisone (1%) in the healing of radiation-induced dermatitis in patients with breast cancer: a randomized controlled clinical trial. *Iran J Med Sci*. 2013;38:293-300.
276. Gosselin TK, Schneider SM, Plambeck MA, Rowe K. A prospective randomized, placebo-controlled skin care study in women diagnosed with breast cancer undergoing radiation therapy. *Oncol Nurs Forum*. 2010;37:619-626.
277. Togni S, Maramaldi G, Bonetta A, Giacomelli L, Di Pierro F. Clinical evaluation of safety and efficacy of Boswellia-based cream for prevention of adjuvant radiotherapy skin damage in mammary carcinoma: a randomized placebo controlled trial. *Eur Rev Med Pharmacol Sci*. 2015;19:1338-1344.
278. Pommier P, Gomez F, Sunyach MP, D'Hombres A, Carrie C, Montbarbon X. Phase III randomized trial of Calendula officinalis compared with trolamine for the prevention of acute dermatitis during irradiation for breast cancer. *J Clin Oncol*. 2004;22:1447-1453.
279. Maiche AG, Grohn P, Maki-Hokkonen H. Effect of chamomile cream and almond ointment on acute radiation skin reaction. *Acta Oncol*. 1991;30:395-396.
280. Ryan JL, Heckler CE, Ling M, et al. Curcumin for radiation dermatitis: a randomized, double-blind, placebo-controlled clinical trial of thirty breast cancer patients. *Radiat Res*. 2013;180:34-43.
281. Rubio I, Suva LJ, Todorova V, et al. Oral glutamine reduces radiation morbidity in breast conservation surgery. *JPEN J Parenter Enteral Nutr*. 2013;37:623-630.
282. Balzarini A, Felisi E, Martini A, De Conno F. Efficacy of homeopathic treatment of skin reactions during radiotherapy for breast cancer: a randomised, double-blind clinical trial. *Br Homeopath J*. 2000;89:8-12.
283. Moolenaar M, Poorter RL, van der Toorn PP, Lenderink AW, Poortmans P, Egberts AC. The effect of honey compared to conventional treatment on healing of radiotherapy-induced skin toxicity in breast cancer patients. *Acta Oncol*. 2006;45:623-624.
284. Shoma A, Eldars W, Noman N, et al. Pentoxifylline and local honey for radiation-induced burn following breast conservative surgery. *Curr Clin Pharmacol*. 2010;5:251-256.
285. Kunos CA, Abdallah RR, Lyons JA. Hydration during breast radiotherapy may lower skin toxicity. *Breast J*. 2014;20:679-681.
286. Bourgeois JF, Gourgou S, Kramar A, Lagarde JM, Guillot B. A randomized, prospective study using the LPG technique in treating radiation-induced skin fibrosis: clinical and profilometric analysis. *Skin Res Technol*. 2008;14:71-76.
287. Jensen JM, Gau T, Schultze J, et al. Treatment of acute radiodermatitis with an oil-in-water emulsion following radiation therapy for breast cancer: a controlled, randomized trial. *Strahlenther Onkol*. 2011;187:378-384.
288. Enomoto TM, Johnson T, Peterson N, et al. Combination glutathione and anthocyanins as an alternative for skin care during external-beam radiation. *Am J Surg*. 2005;189:627-631.

289. Wheat J, Currie G, Coulter K. Wheatgrass extract as a topical skin agent for acute radiation skin toxicity in breast radiation therapy: a randomized controlled trial. *J Aust Tradit Med Soc.* 2006;12:135-137.
290. Jacobson G, Bhatia S, Smith BJ, Button AM, Bodeker K, Buatti J. Randomized trial of pentoxifylline and vitamin E vs standard follow-up after breast irradiation to prevent breast fibrosis, evaluated by tissue compliance meter. *Int J Radiat Oncol Biol Phys.* 2013;85:604-608.
291. Delanian S, Porcher R, Balla-Mekias S, Lefaix JL. Randomized, placebo-controlled trial of combined pentoxifylline and tocopherol for regression of superficial radiation-induced fibrosis. *J Clin Oncol.* 2003;21:2545-2550.
292. Shapiro SL, Bootzin RR, Figueredo AJ, Lopez AM, Schwartz GE. The efficacy of mindfulness-based stress reduction in the treatment of sleep disturbance in women with breast cancer: an exploratory study. *J Psychosom Res.* 2003;54:85-91.
293. Andersen SR, Wurtzen H, Steding-Jessen M, et al. Effect of mindfulness-based stress reduction on sleep quality: results of a randomized trial among Danish breast cancer patients. *Acta Oncol.* 2013;52:336-344.
294. Lengacher CA, Reich RR, Paterson CL, et al. The effects of mindfulness-based stress reduction on objective and subjective sleep parameters in women with breast cancer: a randomized controlled trial. *Psychooncology.* 2015;24:424-432.
295. Hernandez Munoz G, Pluchino S. Cimicifuga racemosa for the treatment of hot flashes in women surviving breast cancer. *Maturitas.* 2003;44(suppl 1):S59-S65.
296. Jacobson JS, Troxel AB, Evans J, et al. Randomized trial of black cohosh for the treatment of hot flashes among women with a history of breast cancer. *J Clin Oncol.* 2001;19:2739-2745.
297. Elkins G, Marcus J, Stearns V, et al. Randomized trial of a hypnosis intervention for treatment of hot flashes among breast cancer survivors. *J Clin Oncol.* 2008;26:5022-5026.
298. Carpenter JS, Wells N, Lambert B, et al. A pilot study of magnetic therapy for hot flashes after breast cancer. *Cancer Nurs.* 2002;25:104-109.
299. Dyer J, Ashley S, Shaw C. A study to look at the effects of a hydrolat spray on hot flashes in women being treated for breast cancer. *Complement Ther Clin Pract.* 2008;14:273-279.
300. Barton DL, Loprinzi CL, Quella SK, et al. Prospective evaluation of vitamin E for hot flashes in breast cancer survivors. *J Clin Oncol.* 1998;16:495-500.
301. Carson JW, Carson KM, Porter LS, Keefe FJ, Seewaldt VL. Yoga of Awareness program for menopausal symptoms in breast cancer survivors: results from a randomized trial. *Support Care Cancer.* 2009;17:1301-1309.
302. National Cancer Institute. Feelings and Cancer. cancer.gov/cancertopics/coping/feelings. Accessed June 18, 2015.
303. Brintzenhofe-Szoc KM, Levin TT, Li YL, Kissane DW, Zabora JR. Mixed anxiety/depression symptoms in a large cancer cohort: prevalence by cancer type. *Psychosomatics.* 2009;50:383-391.
304. Eskelinen M, Ollonen P. Assessment of general anxiety in patients with breast disease and breast cancer using the Spielberger STAI self evaluation test: a prospective case-control study in Finland. *Anticancer Res.* 2011;31:1801-1806.
305. Ollonen P, Lehtonen J, Eskelinen M. Anxiety, depression, and the history of psychiatric symptoms in patients with breast disease: a prospective case-control study in Kuopio, Finland. *Anticancer Res.* 2005;25:2527-2533.
306. Institute of Medicine. Cancer Care for the Whole Patient: Meeting Psychosocial Health Needs. Washington, DC: The National Academic Press; 2007.
307. Valentine A. Mood disorders. In: Duffy JD, Valentine AD, eds. *The MD Anderson Manual of Psychosocial Oncology.* New York: McGraw-Hill, Inc.; 2011:271-288.
308. Rashid A. Anxiety in cancer patients. In: Duffy JD, Valentine AD, eds. *The MD Anderson Manual of Psychosocial Oncology.* New York: McGraw-Hill, Inc.; 2010:271-288.
309. Goyal M, Singh S, Sibinga EM, et al. Meditation programs for psychological stress and well-being: a systematic review and meta-analysis. *JAMA Intern Med.* 2014;174:357-368.
310. Miller JJ, Fletcher K, Kabat-Zinn J. Three-year follow-up and clinical implications of a mindfulness meditation-based stress reduction intervention in the treatment of anxiety disorders. *Gen Hosp Psychiatry.* 1995;17:192-200.
311. Kabat-Zinn J, Massion AO, Kristeller J, et al. Effectiveness of a meditation-based stress reduction program in the treatment of anxiety disorders. *Am J Psychiatry.* 1992;149:936-943.
312. Hoge EA, Bui E, Marques L, et al. Randomized controlled trial of mindfulness meditation for generalized anxiety disorder: effects on anxiety and stress reactivity. *J Clin Psychiatry.* 2013;74:786-792.
313. Specia M, Carlson LE, Goodey E, Angen M. A randomized, wait-list controlled clinical trial: the effect of a mindfulness meditation-based stress reduction program on mood and symptoms of stress in cancer outpatients. *Psychosom Med.* 2000;62:613-622.
314. Carlson LE, Ursuliak Z, Goodey E, Angen M, Specia M. The effects of a mindfulness meditation-based stress reduction program on mood and symptoms of stress in cancer outpatients: 6-month follow-up. *Support Care Cancer.* 2001;9:112-123.
315. Piet J, Wurtzen H, Zachariae R. The effect of mindfulness-based therapy on symptoms of anxiety and depression in adult cancer patients and survivors: a systematic review and meta-analysis. *J Consult Clin Psychol.* 2012;80:1007-1020.
316. Musial F, Bussing A, Heusser P, Choi K-E, Ostermann T. Mindfulness-based stress reduction for integrative cancer care: a summary of evidence. *Forsch Komplementmed.* 2011;18:192-202.
317. Rocha T. The Dark Knight of the Soul. *The Atlantic.* June 25, 2014:25.
318. Lomas T, Cartwright T, Edginton T, Ridge D. A qualitative analysis of experiential challenges associated with meditation practice. *Mindfulness.* 2015;6:848-860.
319. Lengacher CA, Kip KE, Barta M, et al. A pilot study evaluating the effect of mindfulness-based stress reduction on psychological status, physical status, salivary cortisol, and interleukin-6 among advanced-stage cancer patients and their caregivers. *J Holist Nurs.* 2012;30:170-185.
320. Tamagawa R, Specia M, Stephen J, Pickering B, Lawlor-Savage L, Carlson LE. Predictors and effects of class attendance and home practice of yoga and meditation among breast cancer survivors in a mindfulness-based cancer recovery (MBCR) program. *Mindfulness.* 2015;6:1201-1210.
321. Zernicke KA, Campbell TS, Specia M, McCabe-Ruff K, Flowers S, Carlson LE. A randomized wait-list controlled trial of feasibility and efficacy of an online mindfulness-based cancer recovery program: the eTherapy for Cancer Applying Mindfulness trial. *Psychosom Med.* 2014;76:257-267.
322. Boehm K, Cramer H, Staroszyński T, Ostermann T. Arts therapies for anxiety, depression, and quality of life in breast cancer patients: a systematic review and meta-analysis [serial online]. *Evid Based Complement Alternat Med.* 2014;2014:103297.
323. Zavotsky KE, Banavage A, James P, Easter K, Pontieri-Lewis V, Lutwin L. The effects of music on pain and anxiety during screening mammography. *Clin J Oncol Nurs.* 2014;18:E45-E49.
324. Trijsburg RW, van Knippenberg FC, Rijpma SE. Effects of psychological treatment on cancer patients: a critical review. *Psychosom Med.* 1992;54:489-517.
325. Smith KB, Pukall CF. An evidence-based review of yoga as a complementary intervention for patients with cancer. *Psychooncology.* 2009;18:465-475.
326. Culos-Reed SN, Mackenzie MJ, Sohl SJ, Jesse MT, Zahavich AN, Danhauer SC. Yoga & cancer interventions: a review of the clinical significance of patient reported outcomes for cancer survivors [serial online]. *Evid Based Complement Alternat Med.* 2012;2012:642576.
327. Buffart LM, Van Uffelen JG, Riphagen II, et al. Physical and psychosocial benefits of yoga in cancer patients and survivors, a systematic review and meta-analysis of randomized controlled trials [serial online]. *BMC Cancer.* 2012;12:559.
328. Sada J, Mills PJ. Effects of yoga interventions on fatigue in cancer patients and survivors: a systematic review of randomized controlled trials. *Explore (NY).* 2013;9:232-243.
329. Lin KY, Hu YT, Chang KJ, Lin HF, Tsao JY. Effects of yoga on psychological health, quality of life, and physical health of patients with cancer: a meta-analysis. *Evid Based Complement Alternat Med.* 2011;2011:659876.
330. Cramer H, Lange S, Klose P, Paul A, Dobos G. Yoga for breast cancer patients and survivors: a systematic review and meta-analysis [serial online]. *BMC Cancer.* 2012;12:412.
331. Kirkwood G, Ramples H, Tuffrey V, Richardson J, Pilkington K. Yoga for anxiety: a systematic review of the research

- evidence. *Br J Sports Med.* 2005;39:884-891.
332. Woolery A, Myers H, Sternlieb B, Zeltzer L. A yoga intervention for young adults with elevated symptoms of depression. *Alternat Ther Health Med.* 2004;10:60-63.
333. Cramer H, Krucoff C, Dobos G. Adverse events associated with yoga: a systematic review of published case reports and case series [serial online]. *PLoS One.* 2013;8:e75515.
334. Teasdale JD, Segal ZV, Williams JM, Ridgeway VA, Soulsby JM, Lau MA. Prevention of relapse/recurrence in major depression by mindfulness-based cognitive therapy. *J Consult Clin Psychol.* 2000;68:615-623.
335. Zindel V, Segal J, Williams MG, Teasdale JD. *Mindfulness-based cognitive therapy for depression (Second Ed.)*. New York, NY: The Guilford Press. 2012.
336. Hofmann SG, Sawyer AT, Witt AA, Oh D. The effect of mindfulness-based therapy on anxiety and depression: a meta-analytic review. *J Consult Clin Psychol.* 2010;78:169.
337. Roffe L, Schmidt K, Ernst E. A systematic review of guided imagery as an adjuvant cancer therapy. *Psychooncology.* 2005;14:607-617.
338. Demiralp M, Oflaz F, Komurcu S. Effects of relaxation training on sleep quality and fatigue in patients with breast cancer undergoing adjuvant chemotherapy. *J Clin Nurs.* 2010;19:1073-1083.
339. Goerling U, Jaeger C, Walz A, Stickel A, Mangler M, van der Meer E. The efficacy of short-term psycho-oncological interventions for women with gynaecological cancer: a randomized study. *Oncology.* 2014;87:114-124.
340. Park ER, Traeger L, Willett J, et al. A relaxation response training for women undergoing breast biopsy: exploring integrated care. *Breast.* 2013;22:799-805.
341. Song QH, Xu RM, Zhang QH, Ma M, Zhao XP. Relaxation training during chemotherapy for breast cancer improves mental health and lessens adverse events. *Int J Clin Exp Med.* 2013;6:979-984.
342. Yilmaz SG, Arslan S. Effects of progressive relaxation exercises on anxiety and comfort of Turkish breast cancer patients receiving chemotherapy. *Asian Pac J Cancer Prev.* 2015;16:217-220.
343. Tanyi RA, Berk LS, Lee JW, Boyd K, Arechiga A. The effects of a psychoneuro-immunology (PNI) based lifestyle intervention in modifying the progression of depression in clinically depressed adults. *Int J Psychiatry Med.* 2011;42:151-166.
344. Klainin-Yobas P, Oo WN, Suzanne Yew PY, Lau Y. Effects of relaxation interventions on depression and anxiety among older adults: a systematic review. *Aging Ment Health.* 2015;19:1043-1055.
345. Younge JO, Gotink RA, Baena CP, Roos-Hesselink JW, Hunink MG. Mind-body practices for patients with cardiac disease: a systematic review and meta-analysis. *Eur J Prev Cardiol.* 2015;22:1385-1398.
346. Pilkington K, Kirkwood G, Rampes H, Richardson J. Yoga for depression: the research evidence. *J Affect Disord.* 2005;89:13-24.
347. Shapiro D, Cook IA, Davydov DM, Ottaviani C, Leuchter AF, Abrams M. Yoga as a complementary treatment of depression: effects of traits and moods on treatment outcome. *Evid Based Complement Alternat Med.* 2007;4:493-502.
348. Uebelacker LA, Epstein-Lubow G, Gaudio BA, Tremont G, Battle CL, Miller IW. Hatha yoga for depression: critical review of the evidence for efficacy, plausible mechanisms of action, and directions for future research. *J Psychiatr Pract.* 2010;16:22-33.
349. Pan YQ, Yang KH, Wang YL, Zhang LP, Liang HQ. Massage interventions and treatment-related side effects of breast cancer: a systematic review and meta-analysis. *Int J Clin Oncol.* 2014;19:829-841.
350. Lee MS, Lee EN, Ernst E. Massage therapy for breast cancer patients: a systematic review. *Ann Oncol.* 2011;22:1459-1461.
351. Kutner JS, Smith MC, Corbin L, et al. Massage therapy versus simple touch to improve pain and mood in patients with advanced cancer: a randomized trial. *Ann Intern Med.* 2008;149:369-379.
352. Ernst E. The safety of massage therapy. *Rheumatology (Oxford).* 2003;42:1101-1106.
353. Wilkinson S, Barnes K, Storey L. Massage for symptom relief in patients with cancer: systematic review. *J Adv Nurs.* 2008;63:430-439.
354. Coelho HF, Boddy K, Ernst E. Massage therapy for the treatment of depression: a systematic review. *Int J Clin Pract.* 2008;62:325-333.
355. Hou WH, Chiang PT, Hsu TY, Chiu SY, Yen YC. Treatment effects of massage therapy in depressed people: a meta-analysis. *J Clin Psychiatry.* 2010;71:894-901.
356. Maratos AS, Gold C, Wang X, Crawford MJ. Music therapy for depression [serial online]. *Cochrane Database Syst Rev.* 2008;1:CD004517.
357. National Cancer Institute. Fatigue (PDQ)-Health Professional Version. cancer.gov/cancertopics/pdq/supportivecare/fatigue/HealthProfessional. Accessed June 18, 2015.
358. Minton O, Stone P. How common is fatigue in disease-free breast cancer survivors? A systematic review of the literature. *Breast Cancer Res Treat.* 2008;112:5-13.
359. Bower JE, Ganz PA, Desmond KA, et al. Fatigue in long-term breast carcinoma survivors—a longitudinal investigation. *Cancer.* 2006;106:751-758.
360. Stone P, Richardson A, Ream E, et al. Cancer-related fatigue: inevitable, unimportant and untreatable? Results of a multi-centre patient survey. *Ann Oncol.* 2000;11:971-975.
361. Victorson D, Cella D, Wagner L, Kramer L, Smith ML. Measuring quality of life in cancer survivors. In: Feuerstein M, ed. *Handbook of Cancer Survivorship*. New York: Springer; 2007:79-110.
362. Ganz PA, Rowland JH, Desmond K, Meyerowitz BE, Wyatt GE. Life after breast cancer: understanding women's health-related quality of life and sexual functioning. *J Clin Oncol.* 1998;16:501-514.
363. National Cancer Institute. Cancer Treatment: Side Effects. cancer.gov/cancertopics/about-cancer/treatment/side-effects. Accessed June 18, 2015.
364. Ganz PA, Guadagnoli E, Landrum MB, Lash TL, Rakowski W, Silliman RA. Breast cancer in older women: quality of life and psychosocial adjustment in the 15 months after diagnosis. *J Clin Oncol.* 2003;21:4027-4033.
365. Weitzner MA, Meyers CA, Stuebing KK, Saleeba AK. Relationship between quality of life and mood in long-term survivors of breast cancer treated with mastectomy. *Support Care Cancer.* 1997;5:241-248.
366. Montazeri A, Vahdaninia M, Harirchi I, Ebrahimi M, Khaleghi F, Jarvandi S. Quality of life in patients with breast cancer before and after diagnosis: an eighteen months follow-up study [serial online]. *BMC Cancer.* 2008;8:330.
367. Foley E, Baillie A, Huxter M, Price M, Sinclair E. Mindfulness-based cognitive therapy for individuals whose lives have been affected by cancer: a randomized controlled trial. *J Consult Clin Psychol.* 2010;78:72-79.
368. Kieviet-Stijnen A, Visser A, Garssen B, Hudig W. Mindfulness-based stress reduction training for oncology patients: Patients' appraisal and changes in well-being. *Patient Educ Couns.* 2008;72:436-442.
369. Ostermann T, Raak C, Bussing A. Survival of cancer patients treated with mistletoe extract (Iscaдор): a systematic literature review [serial online]. *BMC Cancer.* 2009;9:451.
370. National Cancer Institute. Nausea and Vomiting (PDQ)-Health Professional Version. cancer.gov/cancertopics/pdq/supportivecare/nausea/HealthProfessional. Accessed June 22, 2015.
371. Roila F, Ruggeri B, Ballatori E, Del Favero A, Tonato M. Aprepitant versus dexamethasone for preventing chemotherapy-induced delayed emesis in patients with breast cancer: a randomized double-blind study. *J Clin Oncol.* 2014;32:101-106.
372. Rojas C, Rajé M, Tsukamoto T, Slusher BS. Molecular mechanisms of 5-HT(3) and NK(1) receptor antagonists in prevention of emesis. *Eur J Pharmacol.* 2014;722:26-37.
373. Booth CM, Clemons M, Dranitsaris G, et al. Chemotherapy-induced nausea and vomiting in breast cancer patients: a prospective observational study. *J Support Oncol.* 2007;5:374-380.
374. Lindley CM, Hirsch JD. Nausea and vomiting and cancer patients' quality of life—a discussion of Professor Selby's paper. *Br J Cancer Suppl.* 1992;19:S26-S29.
375. Fabi A, Barduagni M, Lauro S, et al. Is delayed chemotherapy-induced emesis well managed in oncological clinical practice? An observational study. *Support Care Cancer.* 2003;11:156-161.
376. Carlotto A, Hogsett VL, Maiorini EM, Razulis JG, Sonis ST. The economic burden of toxicities associated with cancer treatment: review of the literature and analysis of nausea and vomiting, diarrhoea, oral mucositis and fatigue. *Pharmacoeconomics.* 2013;31:753-766.

377. Lee J, Dodd M, Dibble S, Abrams D. Review of acupressure studies for chemotherapy-induced nausea and vomiting control. *J Pain Symptom Manage*. 2008;36:529-544.
378. Kwon JH, Shin Y, Juon HS. Effects of Nei-Guan (P6) acupressure wristband: on nausea, vomiting, and retching in women after thyroidectomy. *Cancer Nurs*. 2016;39:61-66.
379. Noroozinia H, Mahoori A, Hasani E, Gerami-Fahim M, Sepehrvand N. The effect of acupressure on nausea and vomiting after cesarean section under spinal anesthesia. *Acta Med Iran*. 2013;51:163-167.
380. Collins KB, Thomas DJ. Acupuncture and acupressure for the management of chemotherapy-induced nausea and vomiting. *J Am Acad Nurse Pract*. 2004;16:76-80.
381. Lee J, Dibble S, Dodd M, Abrams D, Burns B. The relationship of chemotherapy-induced nausea to the frequency of pericardium 6 digital acupressure. *Oncol Nurs Forum*. 2010;37:E419-E425.
382. Molassiotis A, Russell W, Hughes J, et al. The effectiveness and cost-effectiveness of acupressure for the control and management of chemotherapy-related acute and delayed nausea: Assessment of Nausea in Chemotherapy Research (ANChOR), a randomised controlled trial. *Health Technol Assess*. 2013;17:1-114.
383. NIH Consensus Conference. Acupuncture. *JAMA*. 1998;280:1518-1524.
384. Yang Y, Zhang Y, Jing NC, et al. Electroacupuncture at Zusanli (ST 36) for treatment of nausea and vomiting caused by the chemotherapy of the malignant tumor: a multicenter randomized controlled trial [article in Chinese]. *Zhongguo Zhen Jiu*. 2009;29:955-958.
385. Dundee JW, Ghaly RG, Fitzpatrick KT, Abram WP, Lynch GA. Acupuncture prophylaxis of cancer chemotherapy-induced sickness. *J R Soc Med*. 1989;82:268-271.
386. Dundee JW, Ghaly RG, Fitzpatrick KT, Lynch GA, Abram WP. Acupuncture to prevent cisplatin-associated vomiting [letter]. *Lancet*. 1987;1:1083.
387. Ezzo J, Vickers A, Richardson MA, et al. Acupuncture-point stimulation for chemotherapy-induced nausea and vomiting. *J Clin Oncol*. 2005;23:7188-7198.
388. Wang XQ, Yu JL, Du ZY, Xu R, Jiang CC, Gao X. Electroacupoint stimulation for postoperative nausea and vomiting in patients undergoing supratentorial craniotomy. *J Neurosurg Anesthesiol*. 2010;22:128-131.
389. El-Deeb AM, Ahmady MS. Effect of acupuncture on nausea and/or vomiting during and after cesarean section in comparison with ondansetron. *J Anesth*. 2011;25:698-703.
390. Rusy LM, Hoffman GM, Weisman SJ. Electroacupuncture prophylaxis of postoperative nausea and vomiting following pediatric tonsillectomy with or without adenoidectomy. *Anesthesiology*. 2002;96:300-305.
391. Lee S, Lee MS, Choi DH, Lee SK. Electroacupuncture on PC6 prevents opioid-induced nausea and vomiting after laparoscopic surgery. *Chin J Integr Med*. 2013;19:277-281.
392. Zhang H, Wang L, Zhang M, et al. Effects of electroacupuncture on postoperative functional recovery in patients with gynaecological laparoscopic surgery [article in Chinese]. *Zhongguo Zhen Jiu*. 2014;34:273-278.
393. White PF, Issioui T, Hu J, et al. Comparative efficacy of acustimulation (Relief-Band) versus ondansetron (Zofran) in combination with droperidol for preventing nausea and vomiting. *Anesthesiology*. 2002;97:1075-1081.
394. Genc F, Tan M. The effect of acupressure application on chemotherapy-induced nausea, vomiting, and anxiety in patients with breast cancer. *Palliat Support Care*. 2015;13:275-284.
395. National Cancer Institute. Radiation Therapy. cancer.gov/about-cancer/treatment/types/radiation-therapy. Accessed June 27, 2016.
396. National Cancer Institute. Skin and Nail Changes. cancer.gov/about-cancer/treatment/side-effects/skin-nail-changes. Accessed June 27, 2016.
397. National Cancer Institute. Hot Flashes and Night Sweats (PDQ)-Health Professional Version. cancer.gov/about-cancer/treatment/side-effects/sexuality-fertility-women/hot-flashes-hp-pdq. Accessed December 19, 2016.
398. Vincent A. Management of menopause in women with breast cancer. *Climacteric*. 2014;8:690-701.
399. Paskett ED, Naughton MJ, McCoy TP, Case LD, Abbott JM. The epidemiology of arm and hand swelling in premenopausal breast cancer survivors. *Cancer Epidemiol Biomarkers Prev*. 2007;16:775-782.
400. Ridner SH. Quality of life and a symptom cluster associated with breast cancer treatment-related lymphedema. *Support Care Cancer*. 2005;13:904-911.
401. Pyszel A, Malyszczak K, Pyszel K, Andrzejak R, Szuba A. Disability, psychological distress and quality of life in breast cancer survivors with arm lymphedema. *Lymphology*. 2006;39:185-192.
402. National Cancer Institute. Nerve Problems (Peripheral Neuropathy). cancer.gov/about-cancer/treatment/side-effects/nerve-problems. Accessed November 27, 2016.
403. International Association for the Study of Pain. Epidemiology of Cancer Pain. iaspain.org/AM/Template.cfm?Section=Home&Template=/CM/ContentDisplay.cfm&ContentID=7395. Accessed June 6, 2016.
404. National Cancer Institute. Cancer Pain (PDQ)-Health Professional Version. cancer.gov/about-cancer/treatment/side-effects/pain/pain-hp-pdq. Accessed June 27, 2016.
405. Savard J, Morin CM. Insomnia in the context of cancer: a review of a neglected problem. *J Clin Oncol*. 2001;19:895-908.
406. National Cancer Institute. Sleep Disorders (PDQ)-Health Professional Version. cancer.gov/about-cancer/treatment/side-effects/sleep-disorders-hp-pdq. Accessed June 27, 2016.
407. Greenlee H, Shi Z, Sardo Molmenti CL, Rundle A, Tsai WY. Trends in obesity prevalence in adults with a history of cancer: results from the US National Health Interview Survey, 1997 to 2014. *J Clin Oncol*. 2016;34:3133-3140.
408. Bardwell WA, Profant J, Casden DR, et al. The relative importance of specific risk factors for insomnia in women treated for early stage breast cancer. *Psychooncology*. 2008;17:9-18.
409. Witt CM, Cardoso MJ. Complementary and integrative medicine for breast cancer patients—evidence based practical recommendations. *Breast*. 2016;28:37-44.
410. John GM, Hershman DL, Falci L, Shi Z, Tsai WY, Greenlee H. Complementary and alternative medicine use among US cancer survivors. *J Cancer Surviv*. 2016;10:850-864.
411. Society for Oncology Massage. S4OM. Society for Oncology Massage. s4om.org/. Accessed June 18, 2015.
412. Oncology Association of Naturopathic Physicians (OncANP). Oncology Association of Naturopathic Physicians. oncanp.org. Accessed December 14, 2016.
413. Kluetz PG, Chingos DT, Basch EM, Mitchell SA. Patient-reported outcomes in cancer clinical trials: measuring symptomatic adverse events with the National Cancer Institute's patient-reported outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). *Am Soc Clin Oncol Educ Book*. 2016;35:67-73.
414. National Cancer Institute (NCI). NCI Common Terminology Criteria for Adverse Events (CTCAE) v.4 data files. evs.nci.nih.gov/ftp1/CTCAE/About.html. Accessed October 26, 2016.