

# Evidence-Based Clinical Practice Guidelines for Integrative Oncology: Complementary Therapies and Botanicals

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The Society for Integrative Oncology (SIO) is an international organization dedicated to encouraging scientific evaluation, dissemination of evidence-based information, and appropriate clinical integration of complementary therapies.

Practice guidelines have been developed by the authors and endorsed by the Executive Committee of the SIO. Guidelines are a work in progress; they will be updated as needed and are available on the SIO Web site (<<http://www.IntegrativeOnc.org>>).

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## Executive Summary

In recent years, the term *integrative medicine* has gained acceptance in medical academia. The Consortium of Academic Health Centers for Integrative Medicine defines this term as “the practice of medicine that reaffirms the importance of the relationship between practitioner and patient, focuses on the whole person, is informed by evidence, and makes use of all appropriate therapeutic approaches, healthcare professionals, and disciplines to achieve optimal health and healing.”<sup>1</sup> *Integrative oncology* has been specifically described as both a science and a philosophy that focuses on the complex health of people with cancer and proposes an array of approaches to accompany the conventional therapies of surgery, chemotherapy, molecular therapeutics, and radiotherapy to facilitate health.<sup>2</sup>

The SIO and its *Medline*-indexed journal (*Journal of the Society of Integrative Oncology*), founded by leading oncologists and oncology professionals from major cancer centers and organizations, promote quality research and appropriate application of useful, adjunctive complementary modalities

(<http://www.IntegrativeOnc.org>). The SIO assembled a panel of experts in oncology and integrative medicine to evaluate the current level of evidence regarding complementary therapies in the care of cancer patients. To help health care professionals make evidence-based treatment decisions in integrative oncology, the panel made specific recommendations based on the strength of the evidence and the risks/benefits ratio. These practice guidelines, developed by the authors and endorsed by the Executive Committee of the SIO, address principles for clinical encounters, followed by individual classes of treatment modalities.

There is an essential difference between “complementary” and “alternative” therapies. “Alternative” therapies are typically promoted as a substitute for mainstream care. By definition, alternative therapies have not been scientifically proven, often have no scientific foundation, and have sometimes even been disproved. However, complementary medicine makes use of unconventional treatment modalities and approaches that are nonsurgical and nonpharmaceutical but that have known efficacy. When combined with mainstream care, these modalities can enhance effectiveness and reduce adverse symptoms. The use of complementary and alternative therapies by cancer patients is common, and given that complementary therapies can be helpful in symptom control, but the substitution of therapies with no evidence of safety and/or efficacy can delay or impede treatment, we strongly recommend that medical professionals routinely inquire as to the use of such therapies during the initial evaluation of cancer patients.

The extensive use of complementary and alternative therapies can also challenge and frustrate both health care professionals and patients, leading to a gap in communication that negatively affects the patient-provider relationship. This communication gap may also arise from the patient's perception that health care professionals are indifferent to or object to the use of unconventional therapies, a perception that can lead to a loss of trust within the therapeutic bond. Health care professionals, who remain open to inquiries and aware of subtle, nonverbal messages from patients, can create an environment where patients feel free to openly discuss all choices in their care. Evidence suggests that patients supported in this manner are less likely to pursue potentially dangerous alternative therapies and are more likely to adhere to conventional, evidence-based treatment programs. We strongly recommend that qualified professionals provide guidance in an open, evidence-based, and patient-centric manner with those who use or are interested in pursuing complementary or alternative medicine so that they can approach these therapies appropriately. Patients should

be informed of the conventional treatment approach, the nature of specific alternative therapies, the realistic expectations, and the potential risks and benefits.

### **Mind-Body Modalities**

In these practice guidelines, mind-body modalities are recommended for incorporation as part of a multidisciplinary approach for reducing anxiety, mood disturbance, and chronic pain and for improving quality of life (QoL) in cancer patients. Evidence shows the benefit of support groups, supportive/expressive therapy, cognitive-behavioral therapy, and cognitive-behavioral stress management.

### **Massage Therapy**

We recommend considering massage therapy as part of a multimodality treatment approach in patients experiencing anxiety or pain.

### **Physical Activity**

Regular physical activity and exercise improve QoL, physical functioning, and emotional well-being and relieve fatigue. Health-related benefits include cardiovascular fitness, muscular strength, body composition, and physical functioning. We recommend referral to a qualified exercise specialist for guidelines on physical activity to promote basic health.

### **Energy Therapies**

When considering therapies based purely on the putative manipulation of bioenergy fields, patients should be informed that the mechanism of action is not fully understood and that the benefits vary from individual to individual and take the financial implications into consideration. They may reduce stress and have a modest effect on pain relief but have no antitumor effects.

### **Acupuncture**

The scientific rationale for acupuncture is better understood today, including interactions with muscle fascia and peripheral and central neurologic pathways. Acupuncture is strongly recommended as a complementary therapy when pain is poorly controlled, when side effects from other modalities are clinically significant, when chemotherapy-induced nausea and vomiting (CINV) are poorly controlled, or when reducing the amount of pain medicine becomes a clinical goal. Acupuncture may also have a role in reducing xerostomia. The value of acupuncture in treating nicotine addiction, dyspnea, fatigue, chemotherapy-induced neuropathy,

or hot flashes has not been established, but it can be tried if symptoms are severe and mainstream treatments are ineffective or adverse effects of mainstream therapies cannot be tolerated. Acupuncture is safe when performed by qualified practitioners. Caution should be exercised in patients with bleeding tendency.

### Diet

Despite the role that diet plays in cancer prevention, individual dietary supplementation has not been shown to prevent cancer or cancer recurrence. It is recommended that patients get the necessary dietary components in whole foods. Patients should be queried about the use of dietary supplements, in particular herbal products, prior to starting cancer treatment to assess possible side effects and potential interaction with other drugs. It is recommended that cancer patients and cancer survivors, especially older patients who are at risk for nutritional inadequacies, be referred to trained professionals for guidance on nutritional supplementation to promote optimum nutritional status, manage tumor- and treatment-related symptoms, meet increased nutritional needs, and correct any nutritional deficits during treatment.

### Dietary Supplements

Guidance should also be provided regarding the safe use of dietary supplements, recognized nutritional guidelines, clinical evaluation of the risk/benefit ratio based on available evidence, and close monitoring of adverse effects.

Despite the long history of many complementary therapies, only a few have been evaluated with scientific research tools. A gap exists between the current level of scientific evidence and what we need to know to provide evidence-based advice, but rigorous scientific research is ongoing. A demonstrably favorable risk/benefit profile is essential for the use of complementary therapies, as it is for any form of medicine. The advantages of a rigid, evidence-based approach based on reductionism, however, do not translate easily into the holistic approach required for complex health issues. A rational, balanced, patient-centered approach using all available data is strongly recommended to address patients' concerns.

### Methods

*Medline* manuscripts and textbook chapters were searched using the key words *cancer*, *oncology*, *complementary therapies*, *CAM*, *alternative therapies*, and *integrative medicine* and the specific treatment modalities. Data have been

summarized and recommendations developed on the basis of the criteria listed in Table 1.

### Introduction

Integrative oncology emphasizes awareness of and sensitivity to the mental, emotional, and spiritual needs of a patient, combining the best of evidence-based, complementary therapies and mainstream care in a multidisciplinary approach to evaluate and treat the whole person.<sup>3,4</sup> The SIO proposes these guidelines for a variety of approaches that function as adjuncts to conventional cancer therapies of surgery, chemotherapy, molecular therapeutics, and radiotherapy to facilitate health.<sup>2</sup>

It should be noted that there is a major distinction between "complementary" and "alternative" therapies. Complementary therapies, adjuncts to mainstream therapies, comprise supportive measures that help control symptoms, enhance well-being, and contribute to overall patient care.<sup>5</sup> Over time, some complementary therapies have been proven safe and effective. These can then be integrated into the mainstream as part of a program of integrative medicine and, in fact, the standard of care. Alternative therapies, on the other hand, are scientifically unproven fraudulent therapeutic options, offered as substitutes for mainstream care. This is especially problematic in oncology, when delayed treatment diminishes the possibility of remission and cure.<sup>6</sup>

The following SIO guidelines summarize the data relevant to clinical problems encountered by cancer patients and offer practical recommendations based on the strength of evidence.

### Recommendations and Discussion

According to the National Institutes of Health's National Center for Complementary and Alternative Medicine complementary and alternative medicine (CAM) practices can be loosely grouped into five categories (see Table 2). Therapies in these categories vary. Some components may be helpful, but others have not been proven to be efficacious.

SIO recommendations are organized according to the clinical encounter and interventions and graded as 1A, 1B, 1C, 2A, 2B, or 2C based on the strength of evidence (see Table 1). Within each modality, recommendations supported by a strong level of evidence (grades A and B) are discussed first, followed by a review of selected topics in which only grade C recommendations can be made. Selectivity in grade C is often required because of the nascent research in this particular area; for some relevant therapies, there is not sufficient evidence to make meaningful recommendations. The grading system is adapted from those of the American College of Chest Physicians.<sup>7</sup>

**Table 1.** Grading Recommendations

<i>Grade</i>	<i>Recommendations</i>	<i>Benefit vs Risk and Burdens</i>	<i>Strength of Supporting Evidence</i>	<i>Implications</i>
1A	Strong recommendation, high-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	RCTs without important limitations or overwhelming evidence from observational studies	Strong recommendation; can apply to most patients in most circumstances without reservation
1B	Strong recommendation, moderate-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	
1C	Strong recommendation, low- or very low-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	Observational studies or case series	Strong recommendation may change when higher-quality evidence is available
2A	Weak recommendation, high-quality evidence	Benefits closely balanced with risks and burden	RCTs without important limitations or overwhelming evidence from observational studies	Weak recommendation; best action may differ depending on circumstances or patients' or societal values
2B	Weak recommendation, moderate-quality evidence	Benefits closely balanced with risks and burden	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	
2C	Weak recommendation, low- or very low-quality evidence	Uncertainty in estimates of benefits, risks, and burden; may be closely balanced	Observational studies or case series	Very weak recommendations; other alternatives may be equally reasonable

RCTs = randomized controlled trials.

**Organization of Recommendations**

Recommendations are organized as follows:

- The clinical encounter (approaches to integrative oncology counseling)
- Mind-body modalities (mind-body medicine, music therapy)
- Touch therapies (massage)

- Fitness (physical activity)
- Energy therapies
- Acupuncture
- Diet and nutritional supplements (nutrition, antioxidants, botanicals)

Cancer care is multifaceted and patient centered, combining a complex package of interventions that cannot be considered

**Table 2.** Characteristics of Complementary Therapies

<i>Therapeutic Approaches</i>	<i>Characteristics</i>
Biologically based practices	Herbal remedies, vitamins, other dietary supplements
Mind-body techniques	Meditation, guided imagery, expressive arts (music therapy, art therapy, dance therapy)
Manipulative and body-based practices	Massage, reflexology, exercise
Energy therapies	Magnetic field therapy, Reiki, Healing Touch, qi gong
Ancient medical systems	Traditional Chinese medicine, ayurvedic medicine, acupuncture

in isolation. There is an increasing emphasis on cancer care that moves beyond a primary focus on cancer diagnosis and treatment. A new research framework is needed to address these complexities and to address the comprehensive multimodal treatments necessary to improve management that includes both function and the multifaceted aspects of QoL. Such a framework includes both qualitative research (eg, in-depth interviews, focus groups) and quantitative designs (observational and interventional research including randomized controlled trials [RCTs]).<sup>8</sup> It is important to note that important aspects of care may not be completely captured in the recommendations made from empirical evidence based on RCTs.

### 1. Complementary and Alternative Therapies

*Recommendation 1: Inquire about the use of complementary and alternative therapies as a routine part of initial evaluations of cancer patients. Grade of recommendation: 1C*

#### *Rationale and Evidence*

The most comprehensive and reliable findings on Americans' use of CAM come from the National Center for Health Statistics (NCHS) National Health Interview Survey. The NCHS is an agency of the Centers for Disease Control and Prevention.<sup>9</sup> Of 31,044 adults surveyed, 75% used some form of CAM. Exclusion of prayer reduces the figure to 50%.

Studies reveal CAM use from 10 to > 60% in cancer patients, depending on the definitions applied.<sup>10–15</sup> The Data Monitor 2002 Survey indicated that 80% of cancer patients used CAM, mainly as complementary therapy. There is some indication of a growth in CAM use by cancer patients in recent years.<sup>16</sup> When compared with other cancer diagnoses, the prevalence of CAM use was highest in lung cancer patients (53%) according to a nationwide survey in Japan.<sup>17</sup> European surveys report different data.<sup>18</sup> Consistent across all surveys, however, is the finding that CAM users are younger, more educated, and more affluent, representing a health-conscious segment of the population that is eager and able to play an active role in self-care. A more recent survey found that up to 40% of cancer patients in the United States use CAM during the survivorship period following acute cancer therapies.<sup>19</sup>

Even though people with cancer typically use complementary therapies along with conventional treatment, studies reveal that 38 to 60% of patients with cancer are taking complementary medicines without informing their health care team.<sup>14,15</sup> There are a variety of reasons why open communication about complementary therapies is not taking

place in medical clinics. The most common reason patients give is that it never comes up in the discussion; that is, no one asks them, and they do not think it is important. Or patients may believe that the topic will be received with indifference or dismissed without discussion, and health care professionals may not know how to respond to questions or may avoid initiating a time-consuming discussion.<sup>14,15</sup> However, it is critical that health care professionals ask patients about their use of complementary therapies and be open and receptive when patients disclose their use. Not asking can put the patient at risk from adverse interactions and could exclude them from effective therapies.<sup>20</sup>

*Recommendation 2: All patients with cancer should receive guidance about the advantages and limitations of complementary therapies in an open, evidence-based, and patient-centered manner by a qualified professional. Patients should be fully informed of the treatment approach, the nature of the specific therapies, potential risks/benefits, and realistic expectations. Grade of recommendation: 1C*

#### *Rationale and Evidence*

Surveys show that most cancer patients rely on friends, family members, the media, and the Internet rather than health care professionals for CAM information.<sup>17,18</sup> Information obtained from these nonprofessional sources is often inaccurate. A majority of patients use botanicals or other supplements with the expectation that they suppress the growth of cancer.<sup>17,18</sup> They may not realize that much of this research is still in the preclinical stage, that information is based on in vitro or animal studies, and that there is little evidence to date showing that any CAM therapies can suppress or cure cancer in the clinical setting. Many supplements are often produced with minimal if any quality control, making their content uncertain.<sup>21</sup> Some may interact with prescription medications, including chemotherapy, possibly decreasing efficacy or increasing toxicity.<sup>22,23</sup> Some patients use dietary supplements indiscriminately for possible benefits in cancer prevention and cancer treatment. However, some supplements could do more harm than good; for example, supplementation of  $\beta$ -carotene may actually increase the risk of lung cancer in current smokers and recent quitters.<sup>24,25</sup> Ironically, therapies that are backed by supportive evidence for symptom control and favorable risk/benefit ratios, such as acupuncture and mind-body techniques, are used less frequently than botanicals.<sup>17,18</sup>

Most patients who use unconventional therapies do so to complement rather than to replace mainstream treatment. However, because of desperation or fear, or because of inadequate support and communication, patients may seek alternative therapies. Research studies conclude that patients who abandon conventional biomedical treatments do so for many reasons, including the following<sup>26–30</sup> :

- *Anger and fear.* Patients may be angry at the health care system or their physician. Others fear the clinical health care environment, adverse side effects, or the blunt presentation of prognosis. Some patients may not be able to cope because of underlying depression.
- *Lack of control.* Some patients feel a loss of control in the conventional health care system, whereas a primary alternative approach can give them a sense of empowerment. On the other hand, open decision making may be overwhelming, and some patients give themselves over to the alternative practitioner.
- *Belief in a cure.* The alternative approach may provide a more positive belief system for cure. A negative prognostic approach by a conventional practitioner could persuade a patient to seek an alternative therapy that is unjustly branded as delivering a cure.
- *Social associations.* A peer group of social support can be persuasive in encouraging alternative therapies, based on misinformation but the urge to be helpful.
- *Mysticism.* The unfamiliar nature of some therapies offers patients hope for unexpected benefits.

Open communication will help patients make informed treatment decisions. With the Internet, patients have access to an enormous amount of health care information. Although the Internet has enabled self-empowerment, the validity of information is not regulated. Many alternative therapies are touted as “cures” for cancer and deliver

misleading pseudoscientific information with a heavy commercial bias.<sup>31</sup> A survey of Web sites on CAM for cancer rated the quality of information from an evidence-based perspective.<sup>32</sup> The most popular Web sites offer information of extremely variable quality, many endorsing unproven therapies, some of which have the potential for harm. Some sites discourage conventional therapies such as surgery, chemotherapy, and radiotherapy, which they refer to as “cutting, poisoning, and burning.” Patients should be directed to credible sites (Table 3).

To ensure the safety and effectiveness of cancer management, it is important for health care professionals to know whether their patients are using CAM and if so, why. Professionals have ethical and legal obligations to their patients, including the obligation to respect patient autonomy. This latter obligation extends to the use of CAM and needs to be addressed early in the patient-provider relationship. As a lack of education in this field and a lack of time during patient consultations are barriers to discussing CAM with patients, health care professionals should be aware of the resources available to facilitate such discussions. Discussing CAM with patients is the professional’s responsibility as it will facilitate evidence-based, patient-centered cancer care.<sup>33,34</sup>

Two further barriers that hinder open communication on CAM use are a perceived lack of familiarity with CAM modalities and a dismissive attitude among many mainstream health care professionals. Medical degree courses rarely include a review of common CAM therapies, and many physicians who provide cancer care are unable to discuss these approaches in an informed, open, patient-centered fashion. Increasing numbers of educational resources, including review articles, books,<sup>35–37</sup> continuing medical education courses, and reliable Web sites, are available to interested physicians, nurses, and other practitioners (see Table 3).

**Table 3.** Recommended Web Sites for Evidence-Based CAM Resources and Legal Issues

Organization/Web Site	Address/URL
National Cancer Institute’s Office of Cancer Complementary and Alternative Medicine	<a href="http://www.cancer.gov/cam/health_pdq.html">http://www.cancer.gov/cam/health_pdq.html</a>
Memorial Sloan-Kettering Cancer Center	<a href="http://www.mskcc.org/mskcc/html/44.cfm">http://www.mskcc.org/mskcc/html/44.cfm</a>
University of Texas M. D. Anderson Cancer Center Complementary/Integrative Medicine Education Resources	<a href="http://www.mdanderson.org/CIMER">http://www.mdanderson.org/CIMER</a>
The Cochrane Review Organization	<a href="http://www.cochrane.org/index2.htm">http://www.cochrane.org/index2.htm</a>
Natural Standard	<a href="http://www.naturalstandard.com/">http://www.naturalstandard.com/</a>
Natural Medicines Comprehensive Database	<a href="http://www.naturaldatabase.com/">http://www.naturaldatabase.com/</a>
American Botanical Council	<a href="http://www.herbalgram.org">http://www.herbalgram.org</a>

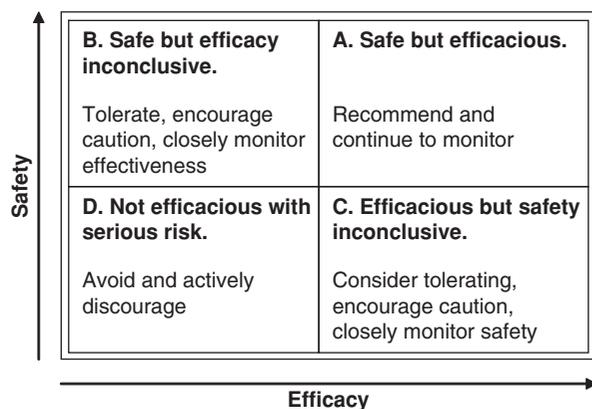
CAM = complementary and alternative medicine.

Today, most major cancer centers have established integrative medicine programs to study and combine helpful complementary therapies with mainstream oncology care.<sup>35</sup> They also teach cancer patients to avoid therapies that lack safety or efficacy data, to avoid potentially harmful therapies, and to be aware of the possibility of herb–drug interactions. The health professionals in these programs are valuable resources for busy oncologists who lack the time or knowledge for in-depth discussions with patients about CAM. Some states license CAM providers (eg, acupuncturists, naturopathic doctors, massage therapists), but it is also essential that they participate in recognized institutional courses that reflect their role in managing cancer patients.

One strategy for safely guiding patients in CAM decision making is to examine the safety and efficacy evidence to be found in the results of RCTs and epidemiologic reports, case reports, historical reports (in terms of safety), and reviews of studies. It can be helpful to consider a grid with safety along one axis and efficacy along the other (Figure 1).

These recommendations are meant as a guide, with the understanding that health care professionals will vary in their opinions as to what constitutes enough evidence on efficacy, balanced with the information on safety. When evidence for safety and efficacy is strong, it obviously makes sense to accept or recommend the therapy. On the other hand, when the evidence for safety and efficacy is weak, it is sensible to discourage the patient from using that therapy.

At the same time, the evidence of safety and efficacy for many complementary therapies is mixed or limited. The stronger the evidence that a therapy may be dangerous or ineffective, the more likely it is that harm will result.



**Figure 1.** Clinical decision making based on risk versus efficacy. Adapted from Cohen MH and Eisenberg DM.<sup>38</sup>

Conversely, the stronger the evidence for safety or efficacy, the stronger the argument that the therapy should be considered within the standard of care.<sup>13,34,38</sup> Thus, when a patient mentions complementary therapy, the first step for a physician is to determine the level of risk by examining the safety evidence and whether that therapy is complementary or conventional. The second step is to estimate the efficacy of that therapy. Both of these steps require an efficient search for evidence-based resources. Accordingly, busy clinicians can take advantage of reviews by recognized experts and organizations. Patients must also be reminded of the financial implications of any intervention.

Physicians may need to shift perspectives to understand a patient's point of view and be sensitive to the need for autonomy and empowerment.<sup>34</sup> Simply asking about CAM use and being willing to respectfully listen to the answer without prejudice and judgment can start an open, trustful dialogue. Today's informed patients value those on the health care team who respect them as participants in their own choices.<sup>39,40</sup>

The physician or other health care provider is an informed intermediary, an expert guide, and a consultant. It is appropriate for the patient and the physician to decide together on therapeutic management options at each stage of cancer care, from prevention to acute active care (radiation, chemotherapy, surgery), to post-acute care (survivorship issues, follow-up visits, and prevention of recurrence), to end-of-life palliative care. The purpose of the patient-physician discussion is not to prove or disprove the efficacy of CAM treatments but to answer the questions that arise when faced with uncertain information about therapies and to consider all the risks and benefits.

To help cancer patients become informed and autonomous, health care professionals should consider following these steps<sup>41</sup>:

1. Identify the patient's beliefs, fears, hopes, expectations, and experience with complementary and integrative medicine.
2. Learn what conventional treatments have been tried and what the patient is interested in, has not found useful, or has rejected because of safety, QoL, cost, or other issues.
3. Acknowledge the patient's spiritual and religious values and beliefs, including views about QoL and end-of-life issues, and seek to understand how these affect health care choices.
4. Discover what levels of support the patient receives from family, community, faith, and friends.<sup>34</sup>

## 2. Mind-Body Techniques (Mind-Body Medicine, Music Therapy)

*Recommendation 3: Mind-body modalities are recommended as part of a multidisciplinary approach to reduce anxiety, mood disturbance, chronic pain, and improve QoL. Grade of recommendation: 1B*

### *Rationale and Evidence*

The belief that what we think and feel can influence our health and healing dates back thousands of years.<sup>42</sup> The importance of the role of the mind, emotions, and behaviors in health and well-being is central to traditional Chinese, Tibetan, and ayurvedic medicine, as well as other medical traditions of the world. Many cancer patients believe that stress plays a role in the etiology and progression of their disease. Although the role of stress in cancer remains controversial, there is substantial evidence showing the negative health consequences of sustained stress on health and well-being through profound psychological, behavioral, and physiologic effects.<sup>43,44</sup> There is also evidence to suggest that chronic stress plays a role in disease progression<sup>45</sup> and that it may contribute to overall mortality.<sup>46,47</sup> The relationship between stress-related physiologic changes and changes in the tumor microenvironment has not been widely studied. However, these changes could be significant enough to affect not only the immediate health of the patient but also the course of the disease and thus the future health of the patient.<sup>44</sup> Decreasing distress and maintaining the functional integrity of the immune system and other physiologic systems are therefore important in helping patients adjust to cancer treatment, recovery, treatment complications, and possibly metastatic growth. Although stress research is relatively new, it has been demonstrated that psychological factors can result in behavioral and regulatory system changes that, in turn, may affect future health.<sup>43,44</sup> This has helped legitimize what is called the mind-body connection and mind-body medicine research and has led to an increased interest in these therapies in the management of stress.<sup>48</sup>

The mind-body connection is an important aspect of integrative oncology, as emphasized in the recent Institute of Medicine (IOM) report “Cancer Care for the Whole Patient.”<sup>49</sup> This comprehensive report states that “cancer care today often provides state-of-the-science biomedical treatment, but fails to address the psychological and social (psychosocial) problems associated with the illness. These problems—including anxiety, depression or other emotional problems—cause additional suffering, weaken adherence to prescribed treatments, and threaten patients’ return

to health.” Extensive research has documented that mind-body interventions address many of the issues mentioned in this IOM report.

Some techniques in mind-body modalities, including meditation, hypnosis, relaxation techniques, cognitive-behavioral therapy, biofeedback, and guided imagery, are quickly becoming part of mainstream care. A survey found that 19% of American adults used at least one mind-body therapy in a 1-year period.<sup>50</sup> A 2002 US nationwide survey showed that 12% of respondents used deep-breathing relaxation techniques and 8% practiced meditation.<sup>9</sup> A meta-analysis of 116 studies found that mind-body therapies reduced anxiety, depression, and mood disturbance in cancer patients and assisted them in their coping skills.<sup>51</sup> Mind-body techniques also may help reduce chronic low back pain, joint pain, headache, and procedural pain.<sup>52</sup> In a 2002 systematic review of psychological therapies for patients with cancer, Newell and colleagues examined the benefits of different psychological strategies, recommended interventions involving self-practice and hypnosis for managing conditioned nausea and vomiting, and suggested research to examine the benefits of relaxation training and guided imagery.<sup>53</sup> Moreover, they also recommended that further research should examine the benefits of relaxation and guided imagery for managing general nausea, anxiety, QoL, and overall physical symptoms. More recently, Ernst and colleagues examined the change in the evidence for mind-body therapies in various medical conditions between 2000 and 2005 and found evidence supporting the use of relaxation techniques for anxiety, hypertension, insomnia, and nausea caused by chemotherapy.<sup>54</sup>

The mind-body approach and its techniques can transform the meaning of cancer and mitigate the stress it invariably brings. As people with cancer use these techniques, they reduce both their psychological vulnerability to stress and its physiological consequences. Any of the techniques, such as relaxation, meditation, and imagery, as well as autogenic training hypnosis, self-expression, and exercise, provide specific psychological and physiologic benefits, that is, decreases in stress; improvements in sleep, mood, and pain; a decrease in stress hormones; and improvement in immunity. Each time patients feel the benefit of a technique they are using, they reinforce a sense of control over their own lives and counter feelings of hopelessness and helplessness.<sup>55</sup> Mind-body techniques must be practiced regularly to produce beneficial effects, so estimation of compliance needs to be a component when evaluating their use.<sup>56</sup>

**Meditation** focuses attention on increasing mental awareness and clarity of mind (concentrative meditation) or opens attention to whatever goes through the mind and to the flow of sensations experienced from moment to moment

(mindfulness meditation). The most extensively studied form of meditation in oncology is a multicomponent program called Mindfulness-Based Stress Reduction (MBSR), which includes mindfulness meditation, yoga stretching, and group dynamics.<sup>57,58</sup> In a randomized wait-list control study of 109 cancer patients, participation in a 7-week MBSR program was associated with significant improvement in mood disturbance and stress symptoms.<sup>59</sup> Importantly, the effect was maintained even 6 months after the program ended.<sup>60</sup> A single-arm study of breast and prostate cancer patients showed significant improvement in overall QoL, stress, and sleep quality, but symptom improvement was not significantly correlated with program attendance or minutes of home practice.<sup>61</sup> In this study, MBSR was associated with improved mood, aspects of QoL, cortisol levels, and inflammatory cytokines (interferon- $\gamma$ , tumor necrosis factor, and interleukin-4), and the improvements continued for 6 to 12 months after the training.<sup>62,63</sup> A more recent nonrandomized case-control study of MBSR in women with stage 0–II breast cancer who did not receive chemotherapy (83% were undergoing radiotherapy) found similar outcomes, with improved QoL, increased natural killer cell (NK) cytotoxicity, and decreased inflammatory cytokines and cortisol levels associated with the intervention.<sup>64</sup> The limitation of this research is that most of the studies were single-arm trials.<sup>56,57,61,65</sup>

**Yoga** combines physical movement, breath control, and meditation; it improved sleep quality in a trial of 39 lymphoma patients. Practicing a form of Tibetan yoga that incorporates controlled breathing and visualization significantly decreased sleep disturbance when compared with wait-list controls.<sup>66</sup> A recent RCT after chemotherapy in women with breast cancer found less decrease in social well-being among women in the yoga group than among a wait-list control group and favorable outcomes for overall QoL, social and emotional well-being, and spirituality for yoga participants, specifically those not receiving chemotherapy.<sup>67</sup> A trial conducted in India examined the effects of yoga versus a supportive therapy/coping-preparation intervention for women with breast cancer undergoing conventional treatment.<sup>68</sup> Women in the yoga group reported decreased frequency and intensity of nausea, including anticipatory nausea, following four cycles of chemotherapy and better QoL and mood (depression and anxiety) by the end of chemotherapy than women in the control group. In a separate series of analyses from the same study, the investigators reported less reduction in NK cell percentages from pre- to postsurgery and after chemotherapy in the yoga group than in the control group, and NK cell percentages were significantly higher in the yoga group than in the control group after chemotherapy.<sup>69</sup> A similar study from the same investigators examined the effects of

yoga in women with breast cancer undergoing radiotherapy and found significantly less anxiety, depression, perceived stress, and deoxyribonucleic acid (DNA) damage in the yoga group compared with the supportive counseling control group.<sup>70</sup>

**Tai chi** incorporates physical movement, breath control, and meditation. It has been associated with increased aerobic capacity, muscular strength and flexibility, and improved health-related QoL and self-esteem in women with breast cancer when compared with a psychosocial support therapy control group.<sup>71,72</sup>

**Hypnosis** is an artificially induced state of consciousness in which a person is made highly receptive to suggestions. A trancelike state (similar to deep daydreaming) can be achieved by first inducing relaxation and then directing attention to specific thoughts or objects. For best results, the patient and the therapist must have good rapport with a strong level of trust, the environment must be comfortable and free from distractions, and the patient must be willing to undergo the process and wish to be hypnotized. Research shows that hypnosis is beneficial in reducing pain, anxiety, phobias, nausea, and vomiting.

In one study, 20 excisional breast biopsy patients were randomly assigned to a hypnosis group or a control group (standard care).<sup>73</sup> Postsurgery pain and distress were reduced in the hypnosis group. In another study, children undergoing multiple painful procedures, such as bone marrow aspiration or lumbar puncture, were randomized to receive hypnosis, a package of cognitive-behavioral coping skills, or no intervention. Those who received either hypnosis or cognitive-behavioral therapy experienced greater pain relief than control patients. The effects were similar between hypnosis and cognitive-behavioral therapy. Both therapies reduced anxiety and distress, with hypnosis showing more effectiveness.<sup>74</sup> Hypnosis was studied in an RCT of 60 patients undergoing elective plastic surgery.<sup>75</sup> Peri- and postoperative anxiety and pain were significantly reduced in the hypnosis group compared with the control group that received only stress reduction training. Reduction in anxiety and pain was also achieved, along with a significant reduction in intraoperative requirements for sedatives and analgesics. Additional RCTs have shown that hypnotic techniques effectively reduce pain, anxiety, and other symptoms; reduce procedure time; stabilize vital signs; and reduce hospital costs. Adjunctive hypnotic treatments involve no additional cost and result in overall cost saving.<sup>76</sup>

In a study of 67 bone marrow transplant patients, subjects were randomized to one of four intervention groups: hypnosis training, cognitive-behavioral coping skills training, therapist contact control, or usual care.<sup>77</sup> Oral pain from

mucositis was reduced in the hypnosis group. A National Institutes of Health (NIH) Technology Assessment Panel found evidence that hypnosis alleviated cancer-related pain.<sup>78</sup> Hypnosis has effectively treated anticipatory nausea in pediatric<sup>79</sup> and adult cancer patients<sup>80</sup> and reduced post-operative nausea and vomiting.<sup>75</sup> In addition, additional research studies published in peer-reviewed journals have reported that hypnotic techniques used in people with cancer reduced severe pain by  $\geq 50\%$ , decreased nausea and vomiting in patients undergoing chemotherapy, decreased anxiety, enhanced QoL, and facilitated pain-free procedures.<sup>81–89</sup>

Selection of patients and the qualifications of the hypnotherapist contribute to safe hypnotherapy. The World Health Organization cautions that hypnosis should not be performed on anyone with psychosis or certain personality disorders. A small percentage of patients may experience dizziness, nausea, or headache, symptoms that usually result from being brought out of a trance by an inexperienced hypnotherapist.

**Relaxation techniques** were shown in RCTs to significantly ameliorate anxiety and distress. A randomized study of relaxation therapy versus alprazolam (Xanax) showed that both approaches significantly decreased anxiety and depression, although the effect of alprazolam was slightly quicker for anxiety and stronger for depressive symptoms.<sup>90</sup> Relaxation achieves the effect without side effects and at a lower cost. A randomized trial of 82 patients undergoing radiation therapy found significant reductions in tension, depression, anger, and fatigue for those who received relaxation imagery or training.<sup>91</sup>

A meta-analysis of 59 studies showed improved sleep induction and maintenance with psychological interventions.<sup>92</sup> Although pharmaceuticals may produce a more rapid response, some studies suggest that behavioral therapies maintain longer-term improvement in sleep quality. An NIH consensus panel concluded that behavioral techniques, particularly relaxation and biofeedback, produce improvements in some aspects of sleep, but improvement in sleep onset and time did not achieve clinical significance.<sup>78</sup>

Regular relaxation training has yielded impressive results in people with cancer: decreased levels of stress and increased immune system functioning, decreased pain, fewer side effects from chemotherapy, decreased anxiety, improved mood, and less emotional suppression. Generally, brief use of relaxation techniques has only short-term effects, whereas ongoing practice throughout and beyond the course of conventional treatment is likely to produce more lasting benefits.<sup>93–95</sup>

**Music therapy** employs music to produce psychological, physiologic, and social changes in individuals with developmental and learning disabilities, behavior and psychiatric

disorders, and other medical illnesses. The form that music therapy takes depends on the individual and the circumstances. A music therapist undergoes specialized, rigorous training in using music as a therapeutic tool. Because music therapy is geared to the patient's situation and experience with music, the therapy can vary from listening to music, actively creating music with instruments, talking about music, and lyric writing, among others.

The use of music in the oncology setting has become more common in recent years. Reviews of music therapy literature reveal extensive descriptive research but a limited number of RCTs.<sup>96–99</sup> Several quantitative studies have established the impact of music on pain reduction, anxiety, and nausea. Music therapy has also been successful in mitigating mood and side effects of treatment, and RCTs support similar findings. Evidence shows that listening to specially selected music reduces anxiety.<sup>100,101</sup> Music therapy has been shown to increase relaxation and comfort levels in bone marrow transplant patients. In terminally ill patients, music therapy reduced anxiety, as well as pain, tiredness, and drowsiness.<sup>102</sup> Patients undergoing radiation experienced less anxiety and treatment-related distress than controls.<sup>103</sup> In this study, the amount of music listening after a music therapy session was directly related to improved levels of distress. In another trial, 50 patients on chemotherapy demonstrated positive changes in anxiety, fear, relaxation, and diastolic blood pressure compared with controls.<sup>104</sup> However, another investigation with 60 chemotherapy patients did not detect significant differences between those who underwent music therapy versus those in standard care.<sup>105</sup> Attrition affected the statistical power of the study, and pre- to post-music therapy session data showed significant changes in psychological report and heart rate. One study found 50% cancer-related pain relief in patients listening to music as opposed to controls.<sup>106</sup> In another experiment with 80 terminal cancer patients, QoL increased as a result of music therapy sessions, whereas life quality decreased in the control group.<sup>107</sup> Furthermore, in another study, patients participating in music listening and active music improvisation sessions showed increased relaxation and energy levels, increased salivary immunoglobulin A, and lower cortisol levels relative to controls.<sup>108</sup> When combined with conventional cancer treatments, music therapy has been found to help patients maintain a better QoL; better communicate their fear, sadness, or other feelings; and better manage stress while alleviating physical pain and discomfort.<sup>109</sup>

Although some studies suggest that music therapy may be useful in an oncology setting, there are several limitations to this research. Many of the studies used small samples, and only a few employed a randomized, controlled design. Many interventions also had the participants listen to music from a

predetermined selection. It is not clear, therefore, what role, if any, a music therapist played in the process. Guided imagery was also frequently combined with the music, making it hard to determine which component was effective.

**Other forms of expressive arts therapies** have been incorporated into the oncology setting, including dance, art, journaling, and others. However, there are few data to support the utility of these interventions in improving QoL. Few risks are associated with the therapies, however, so if patients are interested in trying them, they could be supported.

*Recommendation 4: Support groups, supportive/expressive therapy, cognitive-behavioral therapy, and cognitive-behavioral stress management are recommended as part of a multidisciplinary approach to reduce anxiety, mood disturbance, chronic pain, and improve QoL. Grade of recommendation: 1A*

#### Rationale and Evidence

Extensive epidemiologic research has found evidence for the importance of social support in helping people adapt to life-threatening illness, resulting in better psychological functioning and physiologic and biologic outcomes.<sup>110</sup> The beneficial effects of social support and the negative effects of social isolation have been associated with mortality.<sup>111,112</sup> Studies of people diagnosed with cancer reveal that those with a higher degree of social involvement—more friends and relatives, greater participation in religious and other community groups—have a better QoL and, indeed, tend to live longer.<sup>55,113,114</sup>

There have been extensive studies examining the benefits of support groups for people with cancer. The initial work was mainly conducted in women with breast cancer, but subsequent studies have examined other populations. Irvin Yalom, one of the pioneers of group therapy, conducted a landmark study to examine the effects of group support on the QoL of women with metastatic breast cancer.<sup>115</sup> He and his colleagues found that women who were randomly assigned to participate in the weekly year-long support group did, in fact, have better QoL outcomes than the control group. Most importantly, Spiegel and colleagues conducted a 10-year survival analysis and found that women in the support group lived twice as long as women in the control group.<sup>116</sup>

Since this early research, the role of support groups in prolonging survival has been controversial, with only some studies supporting the initial findings, including a large study that specifically tried to replicate Spiegel and colleagues' findings and one by Spiegel himself.<sup>117–125</sup> What is not in dispute

is that support groups do improve QoL, coping skills, outlook on life, and a number of other factors. People with greater levels of distress, pain, or other symptoms and lower levels of social support tend to benefit more from this type of intervention.<sup>121,126,127</sup>

Structured programs such as cognitive-behavioral therapy or cognitive-behavioral stress management have also been found to improve many aspects of QoL, reduce stress hormones, and improve immune function.<sup>48,128–134</sup> More recently, Andersen and colleagues reported that psychologist-led group support that focused on strategies to reduce stress, improve mood, alter health behaviors, and maintain adherence to cancer treatment and care resulted in improvements in QoL, in aspects of immune function, and in life expectancy.<sup>135</sup>

### 3. Manipulative and Body-Based Practices

*Recommendation 5: For cancer patients experiencing anxiety or pain, massage therapy delivered by an oncology-trained massage therapist is recommended as part of multimodality treatment. Grade of recommendation: 1C*

*Recommendation 6: The application of deep or intense pressure is not recommended near cancer lesions or enlarged lymph nodes, radiation field sites, medical devices (such as indwelling intravenous catheters), or anatomic distortions such as postoperative changes or in patients with a bleeding tendency. Grade of recommendation: 2B*

#### Rationale and Evidence

The many types of body-based practices share in the manipulation or movement of parts of the body to achieve health benefits. Massage therapists apply pressure to muscle and connective tissue to reduce tension and pain, improve circulation, and encourage relaxation. Massage therapy includes variations in technique, such as Swedish massage, Thai massage, and shiatsu. Massage modalities most commonly used in oncology include Swedish massage, aromatherapy massage, reflexology, and acupressure. All involve manual manipulation of soft tissues of the body for the purpose of enhancing well-being. However, the methods of applying touch, degree of educational preparation, regulatory requirements, and underlying theoretical frameworks vary widely among these modalities. Other bodywork techniques, such as the Alexander Technique and Pilates, address posture and movement. One type of massage, known as manual lymph drainage, uses precise light rhythmic motions to reduce

edema. Several studies have evaluated this for patients with edema of the arm following mastectomy, and today it is generally accepted as part of a physical therapy standard of care in combination with compression bandaging.

Massage therapy helps relieve symptoms commonly experienced by cancer patients. It reduces anxiety and pain,<sup>136-140</sup> as well as fatigue and distress.<sup>136</sup> Evidence on reduction of nausea is promising but inconclusive.<sup>141,142</sup> Anxiety and pain were evaluated in a crossover study of 23 inpatients with breast or lung cancer receiving reflexology (stimulation of specific points in the feet [or hands] that affect distant anatomic organs or sites) or usual care.<sup>137</sup> Patients experienced significant decreases in anxiety, and in one of three pain measures, breast cancer patients experienced significant decreases in pain as well. In another study, 87 hospitalized cancer patients were randomized to receive foot massage or an appropriate control.<sup>88</sup> Pain and anxiety improved with massage, with group differences achieving statistical and clinical significance.<sup>88,138,143</sup> The use of aromatic oil seemed to enhance the effect of massage in early studies,<sup>139,144</sup> but significant enhancement was not seen in more recent RCTs.<sup>145-148</sup> Preliminary evidence suggests that massage and acupuncture in combination reduce pain and depressive mood in postoperative cancer patients when compared with usual care alone.<sup>141</sup> For noncancer subacute and chronic back pain, massage therapy was found to be effective in a systematic review of RCTs, and preliminary data suggest that it may help reduce the costs of care.<sup>149</sup> In the largest observational, uncontrolled study to date, 1,290 patients were treated.<sup>140</sup> Symptom scores were reduced by approximately 50%, even for patients reporting high baseline scores.

In one recent trial, massage did not reduce anxiety or depression,<sup>150</sup> whereas another trial found massage to be associated with significant benefit.<sup>140</sup> A more recent RCT of 380 patients with advanced cancer showed that both six (30-minute) massage sessions and simple-touch sessions over 2 weeks reduced pain and improved mood.<sup>151</sup> Massage was significantly superior for both immediate pain and mood but not for sustained pain, worst pain, QoL, symptom distress, or analgesic medication use.

Sometimes patients are exposed to aroma during a massage session for additional therapeutic benefit. In an RCT of 288 cancer patients, aromatherapy massage did not appear to confer benefit for anxiety and/or depression in the long term but was associated with clinically important benefits up to 2 weeks after the intervention.<sup>148</sup>

Massage therapy is generally safe when given by credentialed practitioners. Serious adverse events are rare and associated with exotic types of massage or untrained or inexperienced practitioners.<sup>152,153</sup> One recent case report

warned about the obvious dangers of vigorous massage to the legs with deep venous thrombosis.<sup>154</sup> In work with cancer patients, the application of deep or intense pressure should be avoided, especially near lesions or enlarged lymph nodes or other anatomic distortions such as postoperative changes or on or near medical devices to prevent dislodging the device or increasing discomfort and potential infection. Patients with bleeding tendencies should receive only gentle, light-touch massage. Geccedi described other common-sense adaptations to massage treatment for oncology patients receiving radiation, including the precaution of not massaging on or near the field of treatment to prevent increasing tenderness to irradiated skin and not using excessive rocking motions for patients with nausea.<sup>155</sup>

#### 4. Exercise and Physical Activity

*Recommendation 7: Regular physical activities can play many positive roles in cancer care. Patients should be referred to a qualified exercise specialist for guidelines on physical activity to promote basic health. Grade of recommendation: 1B (1A for breast cancer survivors post-therapy for QoL)*

##### *Rationale and Evidence*

Research on physical activity and exercise in cancer patients and survivors has increased dramatically in the past decade. Most researchers have focused on supportive care end points in breast cancer survivors, such as QoL, physical functioning, emotional well-being, and fatigue and included health-related end points such as cardiovascular fitness, muscular strength, body composition, and objective physical functioning. McNeely and colleagues conducted a systematic review and meta-analysis of 14 RCTs involving exercise interventions in 717 breast cancer survivors age 35 to 72 years.<sup>156</sup> Pooled data from these trials showed significant positive effects of exercise on QoL, cardiorespiratory fitness, and cardiovascular fitness. The pooled data also demonstrated a statistically significant impact on fatigue reduction, but only during the survivorship phase. Several recent large exercise trials have been reported since McNeely and colleagues' systematic review and provide further support for exercise as a supportive care intervention in breast cancer survivors.<sup>157, 158</sup> Evidence is also emerging for supportive care benefits from physical activity and exercise in prostate cancer patients and survivors.<sup>159,160</sup>

Recent large epidemiologic studies have provided evidence of an association between postdiagnosis physical activity levels and disease end points in breast and colon cancer survivors. Holmes and colleagues followed 2,987 breast cancer survivors from the Nurses Health Study for a median of

8 years between 1984 and 1998.<sup>161</sup> Physical activity was assessed by self-report every 2 years. After adjusting for other prognostic factors, analyses showed that women reporting 9 to 15 metabolic equivalent task (MET) hours of physical activity per week (equivalent to 3 to 5 hours of average-speed walking) had a 50% lower risk of breast cancer–specific mortality compared with women reporting < 3 MET hours per week (about 1 hour of walking). At the 10-year follow-up, women with > 9 MET hours/week had an absolute survival advantage of 6% (92% vs 86%) compared with women reporting < 9 MET hours/week. Similar risk reductions were observed for breast cancer recurrence and all-cause mortality. Subsequent research has supported these initial observations in breast and colorectal cancer patients.<sup>162–164</sup>

Based on the current evidence, the American Cancer Society has recommended regular exercise for cancer survivors.<sup>165</sup> As indicated here, the evidence is most compelling for breast cancer survivors. In general, exercise during adjuvant therapy will be a struggle for cancer patients, but it is usually feasible, and supportive care benefits can likely be realized. Cancer survivors should be encouraged to exercise to tolerance during adjuvant therapy, including reducing intensity and durations (eg, 10 minutes), if needed. Resistance training may be particularly helpful for cancer survivors during adjuvant therapy.

After treatments, the public health exercise guidelines can be recommended for most cancer survivors.<sup>166</sup> These guidelines propose two different exercise prescriptions for general health. The more traditional prescription is to perform at least 20 minutes of continuous vigorous-intensity exercise (ie,  $\geq 75\%$  of maximal heart rate) at least 3 days per week. An alternative prescription is to accumulate at least 30 minutes of moderate-intensity exercise (ie, 50–75% of maximal heart rate) in durations of at least 10 minutes on  $\geq 5$  days per week. Fitness and cancer care professionals should feel comfortable recommending exercise to cancer patients during and after treatments, based on the evidence for supportive care benefits.

## 5. Energy Therapies

*Recommendation 8: Therapies based on a philosophy of bioenergy fields are safe and may provide some benefit for reducing stress and enhancing QoL. There is limited evidence as to their efficacy for symptom management, including reducing pain and fatigue. Grade of recommendation: 1B for reducing anxiety; 1C for pain, fatigue, and other symptom management*

### *Rationale and Evidence*

Energy therapies are based on a theory that manipulation of a patient’s “bioenergy” has therapeutic value. These therapies exert their effects through light touch, mind-body interaction, or positive expectation. Some blinded, placebo-controlled trials of Therapeutic Touch and Healing Touch found benefit with this therapy even in the absence of touching patients.<sup>143,167</sup> Individuals who can benefit include those wishing to avoid physical touch.

Therapies that are intended to work exclusively with biofields, such as Reiki, Therapeutic Touch, Healing Touch, polarity therapy, and external qi gong, are known to be safe, but there is limited evidence for efficacy and, to date, insufficient scientific evidence for the mechanism of action. Light touch is often applied as part of these therapies, and polarity therapy includes both massage and touch. Although therapies such as yoga, tai chi, and qi gong work with so-called bioenergy, they may also exert strong effects through the physical connection of touch and mind-body effects.

The relationship with the energy therapist may alleviate stress, enhance relaxation, and enable a sense of protection or feeling safe. Some limited clinical trials show that these interventions can improve symptoms, QoL, and a sense of control and hope.<sup>168–170</sup> The most common effects are relaxation and calming.<sup>143,167</sup> A Cochrane systematic review concluded that touch therapies may have a modest effect in pain relief. More studies on Healing Touch and Reiki in relieving pain are needed.<sup>171</sup> Two energy therapies, Healing Touch and Therapeutic Touch, come out of a nursing background and provide certification to providers meeting specific educational and practice criteria.<sup>172</sup> However, other providers may be unlicensed and/or unregulated.

Bioelectromagnetically based therapies involve the unconventional use of electromagnetics, such as pulsed fields, magnetic fields, or alternating current or direct current fields. Most research in bioelectromagnetics is concerned with theoretical genotoxicity of environmental electromagnetic fields, such as whether exposure to power lines or cell phones increases the risk of cancer.<sup>173–175</sup> There have been no controlled trials showing that bioelectromagnetic therapies are effective for either cancer treatment or symptom control.<sup>176,177</sup>

Patients who seek such therapies should be informed that their benefits vary from individual to individual, the mechanism of action is not fully understood, and these therapies do not have antitumor effects.<sup>171</sup> Patients should also take financial implications into consideration.

## 6. Acupuncture

Acupuncture is a therapeutic modality originating from traditional Chinese medicine. It is theoretically based on regulation of the flow of “qi” (vital energy) by stimulation with needles, heat, or pressure on certain points on the body (acupressure). Acupuncture has been used traditionally for almost every ailment, but few such applications are supported by rigorous clinical studies. Recent scientific research suggests that its effects are likely mediated by the nervous system. Release of neurotransmitters and change of brain functional magnetic resonance imaging (fMRI) signals have been observed during acupuncture.<sup>178,179</sup> Nevertheless, evidence supports the use of acupuncture in treating some common symptoms experienced by cancer patients. Acupuncture also suppresses nausea and vomiting caused by pregnancy,<sup>180</sup> surgery,<sup>181</sup> and motion sickness.<sup>182,183</sup>

Acupuncture is a popular and proven treatment for many forms of pain, including adult postoperative pain, postoperative dental pain, and osteoarthritis of the knee.<sup>184,185</sup> At The Status and Future of Acupuncture Research: 10 Years Post-NIH Consensus Conference in Baltimore in 2007, researchers reported a breadth of acupuncture research and practice, from mechanism of action studies to medium and large definitive phase III trials.<sup>186</sup>

*Recommendation 9: Acupuncture is recommended as a complementary therapy when pain is poorly controlled, when nausea and vomiting associated with chemotherapy or surgical anesthesia are poorly controlled, or when the side effects from other modalities are clinically significant. Grade of recommendation: 1A*

### *Rationale and Evidence*

Acupuncture can relieve both acute (eg, postoperative dental pain) and chronic (eg, headache) pain, the most common and best studied indications for its use.<sup>185,187</sup> An NIH consensus statement in 1997 supported acupuncture for adult postoperative pain, CINV, and postoperative dental pain.<sup>185</sup> Insufficient evidence was available to support other claims of efficacy at that time, but since then, many publications have documented the utility of acupuncture as an adjunctive treatment for pain, emesis, and other symptoms.

Acupuncture appears to be effective against cancer-related pain. A randomized placebo-controlled trial tested auricular (outer ear) acupuncture for patients with pain despite stable medication. Ninety patients were randomized to have needles placed at correct acupuncture points (treatment

group) versus acupuncture or pressure at nonacupuncture points. The authors selected acupuncture points by measuring electrodermal signals. Pain intensity decreased by 36% at 2 months from baseline in the treatment group—a statistically significant difference compared with the two control groups, for whom little pain reduction was seen.<sup>188</sup> Skin penetration per se showed no significant analgesic effect. These results are especially important because most of the patients had neuropathic pain, which rarely responds to conventional treatment.

Recent clinical trials have also used auricular acupuncture alone or together with full-body acupuncture, and the results add further evidence to support the utility of acupuncture in treating chronic, cancer-related pain. A randomized trial evaluated auricular and full-body acupuncture treatment for aromatase inhibitor–induced arthralgia in breast cancer patients.<sup>189</sup> Twenty-one postmenopausal women with breast cancer were randomized to receive acupuncture twice weekly for 6 weeks followed by observation or vice versa. The worst pain scores, pain severity, and pain-related functional interference were all significantly reduced by acupuncture treatment.

In short, the benefits of acupuncture for cancer-related pain have been shown to clearly outweigh the risks. More trials and mechanistic research will likely continue to strengthen this recommendation.

Acupuncture and acupressure also help lessen CINV.<sup>185,190,191</sup> In one study, 104 breast cancer patients receiving highly emetogenic chemotherapy were randomized to receive electroacupuncture at the PC6 and ST36 acupuncture points, minimal needling at nonacupuncture points, or pharmacotherapy alone.<sup>192</sup> Electroacupuncture (application of electrical pulses to acupuncture needles) significantly reduced the number of episodes of total emesis from a median of 15 to 5 when compared with pharmacotherapy only. Most patients did not know the group to which they had been assigned. The effects of acupuncture do not appear to be entirely due to attention, clinician–patient interaction, or placebo.

The combination of acupuncture and serotonin receptor antagonists, the newest generation of antiemetics, showed mixed results. In a trial of patients with rheumatic disease, the combination decreased the severity of nausea and the number of vomiting episodes more than ondansetron alone in patients receiving methotrexate (an agent also used in chemotherapy).<sup>193</sup> However, a study of cancer patients receiving high-dose chemotherapy and autologous stem cell transplantation reported no significant benefit for ondansetron plus acupuncture versus ondansetron plus placebo acupuncture.<sup>194</sup>

A number of reviews continue to strongly recommend acupuncture for acute CINV, and positive clinical trials also support this claim.<sup>195,196</sup> The general consensus suggests that electroacupuncture is more effective than manual acupuncture, which is more effective than acupressure (without needles).<sup>196</sup> However, for delayed CINV, more studies on electroacupuncture, acupuncture, and acupressure are necessary.

Recently published clinical trials also showed that acupuncture is effective in the pediatric oncology setting. A study by Gottschling and colleagues demonstrated that children receiving highly emetogenic chemotherapy for solid tumors needed significantly less rescue antiemetic medication and experienced reduced episodes of vomiting following treatment with acupuncture.<sup>197</sup> Other new trials of acupressure also support the indication that acupressure at the location of the PC-6 acupuncture point may help reduce CINV, especially in refractory patients.<sup>198</sup>

When used for the prevention of postoperative nausea and vomiting, electroacupuncture or ondansetron was more effective than placebo, with a greater degree of patient satisfaction, but electroacupuncture seems to be more effective in controlling nausea compared with ondansetron.<sup>199</sup>

Acupressure wristbands that render continuous stimulation of the PC-6 point also have been tested for CINV. In an RCT of 739 patients, wearing acupressure wrist bands on the PC-6 acupoint on the day of chemotherapy significantly reduced nausea in those patients wearing wristbands compared with no-band controls.<sup>200</sup> No significant differences were found for delayed CINV.

*Recommendation 10: Acupuncture is recommended as a complementary therapy for radiation-induced xerostomia. Grade of recommendation: 1B*

#### *Rationale and Evidence*

Over the past decade, several published reports have shown that acupuncture can stimulate saliva flow in patients with radiation-induced xerostomia. These studies were conducted in different countries by different investigators using different acupuncture points, yet all showed similar positive results.<sup>201–208</sup> One study evaluating various symptoms in 123 cancer patients, 32% of whom suffered from xerostomia, reported a 30% improvement in symptoms with acupuncture treatment.<sup>201</sup> Another study demonstrated a long-term (> 3 years) increase in beneficial saliva production after acupuncture.<sup>209</sup>

Clinical trials published within the past 2 years continue to support this hypothesis. One recent mechanistic study used fMRI to measure central changes and salivary

production with application of the traditional acupuncture point large intestine-2 (LI-2).<sup>210</sup> This randomized, sham-controlled, blinded clinical trial demonstrated that manual acupuncture stimulation (unilateral) at LI-2 was associated with bilateral activation of the insula and adjacent operculum, changes not seen with the sham acupuncture point. Moreover, the true acupuncture induced greater saliva production than the sham acupuncture.<sup>210</sup>

*Recommendation 11: Acupuncture does not appear to be more effective than sham acupuncture for treatment of vasomotor symptoms (hot flashes) in postmenopausal women in general. In patients experiencing severe symptoms not amenable to pharmacologic treatment, however, a trial of acupuncture treatment can be considered. Grade of recommendation: 1B*

#### *Rationale and Evidence*

Hot flashes are common in breast cancer patients undergoing natural or treatment-induced menopause. Approximately two-thirds of breast cancer patients report hot flashes.<sup>211</sup> With an increasing number of breast cancer survivors on hormone therapy, reduction of hot flashes would have a significant impact on QoL. Estrogen replacement therapy, the traditional treatment of choice, is contraindicated, having been associated with increased risk of breast cancer, coronary artery disease, stroke, and other thromboembolic events.<sup>212,213</sup> It is also contraindicated in estrogen receptor-positive breast cancer patients. Other pharmacologic agents, including megestrol acetate,<sup>214</sup> clonidine,<sup>215,216</sup> and selective serotonin reuptake inhibitors (SSRIs),<sup>217–220</sup> can be helpful, but they are not effective in all patients, they may not be tolerated by others, and systematic review has concluded that they are not optimal choices for most women.<sup>221</sup> Several natural products, such as soy phytoestrogens,<sup>222–229</sup> red clover,<sup>230</sup> black cohosh,<sup>231–233</sup> and vitamin E,<sup>234</sup> have also been investigated but failed to produce clinically meaningful results.<sup>235</sup>

Several uncontrolled studies suggest that acupuncture may reduce hot flashes in postmenopausal women, breast cancer patients receiving tamoxifen treatment, or prostate cancer patients receiving androgen blockage therapy.<sup>236–238</sup> However, controlled studies of acupuncture have shown mixed results.<sup>239,240</sup>

A recent RCT compared twice-weekly acupuncture for 4 weeks versus sham acupuncture in 72 breast cancer patients.<sup>241</sup> Both interventions reduced hot flashes. True acupuncture was associated with 0.8 fewer hot flashes per day than sham acupuncture at 6 weeks, but the difference did not reach statistical significance. When participants in the sham acupuncture group crossed over to true acupuncture,

a further reduction in the frequency of hot flashes was seen. The reduction in hot flash frequency persisted for up to 6 months after completion of treatment.<sup>241</sup> Another randomized sham-controlled study was conducted in 103 women without cancer who were experiencing hot flashes. No significant difference in the percentage of residual hot flashes was observed between the two interventions.<sup>242</sup> In another RCT comparing true acupuncture, sham acupuncture, and usual care, there was a significant decrease in the mean frequency of hot flashes across all groups. The two acupuncture groups showed a significantly greater decrease than the usual-care group but did not differ from each other.<sup>243</sup> However, in a randomized, placebo-controlled study of 29 postmenopausal women with more severe symptoms (at least seven moderate to severe hot flashes per 24 hours), true acupuncture produced a significantly greater decrease in the severity but not the frequency of hot flashes when compared with sham acupuncture.<sup>244</sup> A small, randomized trial of acupuncture versus venlafaxine for women with breast cancer experiencing hot flashes caused by tamoxifen found acupuncture to be as effective as venlafaxine in controlling hot flashes and not associated with the negative side effects of venlafaxine, which includes nausea, dry mouth, headache, insomnia, dizziness, double vision, constipation, fatigue, anxiety, feeling “spaced out,” and/or body spasms at night.<sup>245</sup>

So far, the data do not show true acupuncture to be significantly more effective than sham acupuncture in reducing hot flashes. However, in patients experiencing more severe symptoms who are not candidates for other interventions, it can be argued that a trial course of acupuncture treatment should be considered.

*Recommendation 12: For patients who do not stop smoking despite use of other options or those suffering from symptoms such as cancer-related dyspnea, cancer-related fatigue, chemotherapy-induced neuropathy, or post-thoracotomy pain, a trial of acupuncture may be helpful, but more clinical studies of acupuncture are warranted. Grade of recommendation: 2C*

#### *Rationale and Evidence*

Smoking cessation has the largest impact on lung cancer prevention. Educational, behavioral, and medical interventions are the mainstay for smoking cessation. The study of acupuncture has produced mixed results. A meta-analysis of 22 studies concluded that acupuncture is no more effective than placebo in smoking cessation.<sup>246</sup> However, the same meta-analysis found that acupuncture did no worse than any other intervention.<sup>6</sup> A randomized trial of 141 subjects tested

auricular acupuncture, education, or the combination in achieving smoking cessation.<sup>247</sup> The authors found that both modalities, alone or in combination, significantly reduced smoking. The combination showed a significantly greater effect in subjects with a greater pack-year history.

Brain imaging studies show that smoking suppresses blood flow to the anterior cingulate cortex, hippocampus, and amygdala.<sup>248</sup> Curiously, these are the same areas suppressed by acupuncture.<sup>179</sup> Given the huge public health impact of smoking and the imperfect results of existing smoking cessation techniques, a trial of acupuncture along with supportive behavioral therapy and psychotherapy is acceptable for someone who has been unable to quit smoking. Further studies using refined techniques guided by recent advances in acupuncture research appear to be warranted.

Cancer patients with advanced disease may experience dyspnea as a result of parenchymal tumor burden, pleural effusion, or other causes. Oxygen and opioids comprise the mainstay of symptomatic treatment, although confusion and constipation are common side effects of these treatments. An uncontrolled study in cancer patients receiving palliative care showed a marked reduction in dyspnea after a session of acupuncture.<sup>249</sup> Subsequent randomized, sham-controlled trials did not show significant improvement in subjective sensation of dyspnea in advanced lung or breast cancer patients.<sup>250</sup> However, two recent trials in patients with chronic obstructive pulmonary disease found that acupuncture may relieve dyspnea assessed subjectively<sup>251</sup> and objectively.<sup>252</sup> The lack of conclusive evidence supporting the effectiveness of acupuncture is balanced by the favorable safety record and the lack of other viable treatment options. Patients should be fully informed so that they know the potential risks, have realistic expectations, and know the financial implications.

Fatigue following chemotherapy or radiotherapy, another major and common problem, has few reliable treatments in patients without a correctable cause, such as anemia.<sup>253</sup> In an uncontrolled trial of fatigue after chemotherapy, acupuncture reduced fatigue by 31% after 6 weeks of treatment. Among those with severe fatigue at baseline, 79% had nonsevere fatigue scores at follow-up,<sup>254</sup> whereas fatigue was reduced only in 24% of patients receiving usual care at another center.<sup>255</sup>

Although acupuncture is commonly used to treat neuropathy, most previous research was done in human immunodeficiency virus (HIV)-related neuropathy or diabetic neuropathy. An RCT of 239 patients with HIV-related peripheral neuropathy compared a standardized acupuncture regimen with a control-point regimen. A reduction in pain scores was observed in both groups, with no significant group differences.<sup>256</sup> Forty-six diabetic patients with chronic painful peripheral neuropathy were treated with

acupuncture in a single-arm study. Significant improvement in symptoms was reported by 77% of patients; this is a much higher response than is usually expected from placebo. There was no significant change in the peripheral neurologic examination scores.<sup>257</sup> No clinical trial of acupuncture for chemotherapy-induced neuropathy has been reported, although a recent small case series showed positive results.<sup>258</sup>

If patients experience discomfort as a result of neuropathy despite conventional treatment, it is not unreasonable to accept a patient's choice to try acupuncture for symptom reduction. The lack of conclusive evidence supporting its effectiveness is balanced by the favorable safety record and the lack of other viable treatment options. Patients should be fully informed so that they know the potential risks, have realistic expectations, and know the financial implications.

*Recommendation 13: Acupuncture should be performed only by qualified practitioners and used cautiously in patients with bleeding tendencies. Grade of recommendation: 1C*

#### *Rationale and Evidence*

Acupuncture needles are regulated as a medical device in the United States. They are filiform, sterile, single use, and very thin (28–40 gauge). Insertion of acupuncture needles causes minimal or no pain and less tissue injury than phlebotomy or parenteral injection. Acupuncture performed by experienced, well-trained practitioners is safe. Only 6 cases of potentially serious adverse events were reported in a recent study of 97,733 patients receiving acupuncture in Germany. They included exacerbation of depression, hypertensive crisis, vasovagal reaction, asthma attack, and pneumothorax (collapsed lung). The most common minor adverse events included local bleeding and needling pain, both in < 0.05% of patients.<sup>259</sup> It is prudent to avoid acupuncture at the site of tumor or metastasis, in limbs with lymphedema, in areas with considerable anatomic distortion from surgery, and in patients with severe thrombocytopenia, coagulopathy, or neutropenia. Cancer patients require certified practitioners who are experienced in treating patients with malignant diseases.

## 7. Diet

*Recommendation 14: Research in diet and cancer prevention is based mainly on studies of populations consuming dietary components in whole-food form, with secure food supplies and access to a variety of food and drinks. Therefore, nutritional adequacy should be met by selecting a wide variety of foods; dietary supplements are usually unnecessary. Grade of recommendation: 1B*

*Recommendation 15: It is recommended that patients be advised regarding proper nutrition to promote basic health. Grade of recommendation: 1B*

#### *Rationale and Evidence*

Many epidemiologic studies demonstrate an association between diet and cancer incidence. Other than smoking cessation and exercise, a healthy diet is perhaps the most important lifestyle change a person can make to help reduce the risk of cancer. A recent document from the combined work of the American Institute of Cancer Research and the World Cancer Research Fund presents evidence and recommendations on the role of food, nutrition, and physical activity in cancer prevention and survivorship. This expert report included thousands of studies and hundreds of experts worldwide. An independent panel of 21 world-renowned scientists assessed and evaluated the vast body of evidence and made the following recommendations in the report “Food, Nutrition, Physical Activity, and the Prevention of Cancer: Global Perspective”<sup>260,261</sup>:

1. Be as lean as possible without becoming underweight.
2. Be physically active for at least 30 minutes every day.
3. Avoid sugary drinks. Limit consumption of energy-dense foods (particularly processed foods high in added sugar, low in fiber, or high in fat).
4. Eat a variety of vegetables, fruits, whole grains, and legumes, such as beans.
5. Limit consumption of red meats (such as beef, pork, and lamb) and avoid processed meats.
6. If consumed at all, limit alcoholic drinks to two for men and one for women a day.
7. Limit consumption of salty foods and foods processed with salt (sodium).
8. Do not use supplements to protect against cancer.
9. It is best for mothers to breast-feed exclusively for up to 6 months and then feed babies other liquids and foods.
10. After treatment, cancer survivors should follow nutritional recommendations for cancer prevention.

## 8. Nutritional Supplements

A nutritional supplement (also called dietary supplement) is a product that contains vitamins, minerals, herbs or other botanicals, amino acids, enzymes, and/or other ingredients intended to supplement the diet. The US Food and Drug Administration (FDA) has established special labeling requirements requiring that dietary supplements meet the following conditions:

- It is a product (other than tobacco) intended to supplement the diet and contains one or more of the following: vitamins, minerals, herbs or other botanicals, amino acids, or any combination of the above ingredients.
- It is intended to be taken in tablet, capsule, powder, soft-gel, gelcap, or liquid form.
- It is not represented for use as a conventional food or as a sole item of a meal or the diet.
- It is labeled as a dietary supplement.

Dietary supplements are usually natural products with a record of historical use. By law, the manufacturers are not allowed to claim that their product will diagnose, cure, mitigate, treat, or prevent a disease. However, patients often take them with such expectations.

*Recommendation 16: Based on a current review of the literature, specific dietary supplements are not recommended for cancer prevention. Grade of recommendation: 1A*

#### *Rationale and Evidence*

Epidemiologic studies over the past three decades have demonstrated that the wide geographic variation in cancer incidence and mortality rate can be attributed to variations in diet and other lifestyle factors.<sup>262–267</sup> Based on this epidemiologic evidence, several specific dietary components used alone or in combination have been evaluated in preclinical studies that have corroborated this evidence, demonstrating an impact on the occurrence of cancer and disease progression. More recently, these nutrients have been tested in whole-food forms and as nutritional supplements in early phase I and II clinical trials examining their role in preventing and inhibiting the development of pre-invasive and invasive cancer and its progression. However, only a few RCTs have confirmed the observations of epidemiologic studies and demonstrated some reduction in cancer risk. These promising studies need confirmation in well-powered phase III clinical trials.<sup>268,269</sup> Other RCTs have resulted in null<sup>270–276</sup> or unexpected outcomes<sup>262,269,277</sup> with nutritional supplementation and in some cases even increasing the risk of cancer and other diseases.<sup>24,25,278–280</sup> Thus, based on the current review of the literature, specific dietary supplements are not recommended for cancer prevention. Nutritional adequacy should be met through the use of a wide variety of whole foods. However, certain populations may benefit from the use of dietary supplements.<sup>267</sup>

*Recommendation 17: Evaluation of patients' use of dietary supplements prior to the start of cancer treatment is recommended. Also recommended are referral of cancer patients to trained professionals for guidelines on diets, nutritional supplementation, promotion of optimum nutritional status, management of tumor- and treatment-related symptoms, satisfaction of increased nutritional needs, and correction of any nutritional deficits while on active treatment. Grade of recommendation: 1B*

*Recommendation 18: It is recommended that dietary supplements, including botanicals and megadoses of vitamins and minerals, be evaluated for possible side effects and potential interaction with other drugs. Those that are likely to interact adversely with other drugs, including chemotherapeutic agents, should not be used concurrently with immunotherapy, chemotherapy, or radiation or prior to surgery. Grade of recommendation: 1B*

#### *Rationale and Evidence*

Malnutrition is defined as the state of altered nutritional status associated with increased risk of adverse clinical events such as complications or death. The etiology of malnutrition in cancer may be tumor- or treatment-related (surgery, chemotherapy, radiation, and immunotherapy) or a result of inadequate intake or absorption, increased metabolic requirements imposed by disease, excessive loss of nutrients and drug–nutrient antagonisms, relative intake of other nutrients, and increased demands. Malnutrition adversely affects QoL, limits or interrupts serial treatment, and may be life threatening if left untreated. This is the most common comorbidity in a cancer patient, with 30 to 87% of cancer patients diagnosed with malnutrition and 30 to 60% with protein-calorie malnutrition. Although it is logical to attempt to treat nutritional deficits during cancer treatment by nutritional supplementation to reduce the possibility of malnutrition, limitations in the utility and safety of supplementation have been identified.

The use of antioxidants for cytoprotection and the decline in antioxidant status as measured by total radical antioxidant parameters has been demonstrated, but the benefits and risks of dietary supplements during cancer treatment are still controversial.<sup>281–283</sup> Some argue that antioxidants scavenge the reactive oxygen species integral to the activity of certain chemotherapy drugs, thereby diminishing treatment efficacy. Others suggest that antioxidants may mitigate toxicity

and thus allow for uninterrupted treatment schedules and a reduced need for lowering chemotherapy doses.<sup>281,283</sup> In a systematic review of randomized trials reporting antioxidant-based mitigation of chemotherapy toxicity, Block and colleagues observed that 24 of the 33 studies reported decreased toxicities from concurrent use of antioxidants with chemotherapy.<sup>284</sup> Nine studies reported no difference in toxicities between the two groups. Only one study (vitamin A) reported a significant increase in toxicity in the antioxidant group. Five studies reported that the antioxidant group completed more full doses of chemotherapy or had fewer dose reductions than control groups. Statistical power and poor study quality were concerns with some studies.

In a systematic review of antioxidants and cancer therapy, Ladas and colleagues reviewed more than 100 citations, of which 52 met their criteria and 21 were intervention trials.<sup>285</sup> This review concluded that adequately powered trials among patients with a specific cancer diagnosis receiving a specific therapy are needed to make concrete recommendations regarding antioxidant nutritional supplements during cancer treatment. Similarly, in a meta-analysis of over 22 trials focused on breast cancer, Greenlee and colleagues summarized that the current evidence is insufficient to inform clinical and patient guidelines on the use of antioxidant supplements such as vitamin C, vitamin E, antioxidant combinations, and multivitamins and minerals during breast cancer treatment.<sup>286</sup> There is also insufficient evidence at present that selenium supplementation, a popular antioxidant used by cancer patients, alleviates the side effects of tumor-specific chemotherapy or radiotherapy treatments.<sup>287</sup> Also lacking is evidence that selenium improves the side effects of surgery, improves QoL in cancer patients, or reduces secondary lymphedema. Potential hazards of supplementing a trace mineral should be kept in mind. Systematic review of the evidence demonstrates that antioxidants do hold the potential for reducing dose-limiting toxicities, and large, well-designed RCTs of antioxidant supplementation concurrent with specific treatments and cancers are warranted.

Symptoms of acute radiation enteritis, dominated by diarrhea, occur in more than 70% of patients receiving pelvic irradiation, and supplements such as probiotics have been evaluated for this indication.<sup>288–291</sup> Prophylactic administration of probiotics reduced the incidence of acute radiation enteritis in a large placebo-controlled trial.<sup>288</sup> Bowel mucosal injury associated with 5-fluorouracil (5-FU) treatment might result in secondary lactose intolerance.<sup>290</sup> *Lactobacillus* GG supplementation is well tolerated and may reduce the frequency of severe diarrhea and abdominal discomfort related to 5-FU-based chemotherapy.<sup>290</sup> Other probiotic treatments have

been observed to ameliorate chemotherapy-induced diarrhea following chemotherapy with irinotecan.<sup>289</sup> Increasing knowledge on probiotics in cancer symptom management is exciting, but large-scale RCTs are needed to define which probiotics (single strains or a combination) are most effective in specific treatments related to cancer. Well-designed RCTs are required to further define the role of probiotics as preventive and therapeutic agents during cancer treatment.

Folate is a water-soluble vitamin that has been shown to be important for cells and tissues that rapidly divide.<sup>292</sup> Cancer cells divide rapidly, and drugs such as methotrexate that interfere with folate metabolism are used to treat cancer. As folic acid is an essential vitamin, there are several studies under way to determine if folic acid supplements can help control the side effects of methotrexate without decreasing its effectiveness in chemotherapy.<sup>293,294</sup> It is important for anyone receiving methotrexate to follow medical advice on the use of folic acid supplements.

Evidence from laboratory and clinical studies has demonstrated that eicosapentaenoic acid (EPA), an omega-3 fatty acid, has antitumor and anticachectic effects.<sup>295–298</sup> Studies in animal models have demonstrated that nuclear factor  $\kappa$ B (NF- $\kappa$ B) is upregulated in cancer cachexia, increasing proteolysis and inducing apoptosis in myotubes. Several recent laboratory studies have shown that EPA may attenuate protein degradation by preventing NF- $\kappa$ B accumulation in the nucleus.<sup>295</sup> Nutritional supplementation alone has been unable to reverse the process of muscle wasting because it arises from activation of the ubiquitin proteasome pathway, which is independent of nutritional intake. It is only logical then to hypothesize that agents such as EPA that can inhibit NF- $\kappa$ B might stimulate recovery of muscle mass in this patient population and offer promise for the development of a molecularly based approach to treat cancer cachexia. In a recent systematic review of the current literature, Colomer and colleagues suggested that administration of omega-3 fatty acid (EPA and docosahexaenoic acid [DHA]) in doses of at least 1.5 g/d for a prolonged period in patients with advanced cancer is associated with improved clinical, biologic, and QoL parameters.<sup>296</sup> In other randomized clinical trials, administration of omega-3 fatty acid (EPA and DHA) capsules or supplements with EPA has been associated with weight stabilization, gain in lean body mass, and improvement in QoL markers in patients losing weight as a result of advanced pancreatic and head and neck cancers.<sup>297–299</sup>

The concurrent use of nutritional supplements, especially high-dose antioxidants during cancer treatment, is not recommended without the guidance of the medical team. Lack

of effectiveness, safety data, potential drug–nutrient interaction, quality control, and adulteration of nutritional supplements are major issues that need to be considered.<sup>300</sup>

*Recommendation 19: For cancer patients who wish to use nutritional supplements, including botanicals for purported antitumor effects, it is recommended that they consult a trained professional. During the consultation, the professional should provide support, discuss realistic expectations, and explore potential benefits and risks. It is recommended that use of those agents occur only in the context of clinical trials, recognized nutritional guidelines, clinical evaluation of the risk/benefit ratio based on available evidence, and close monitoring of adverse effects. Grade of recommendation: 1C*

#### *Rationale and Evidence*

The use of biologically based complementary therapies, such as herbs and other dietary supplements, is popular among cancer patients.<sup>17,18,301</sup> Most users expect the supplements to help cancer treatment or reduce side effects, but such expectations are often unrealistic and unmet.<sup>18</sup> The purported benefits of supplements are usually supported by preclinical studies. Although some have been evaluated in clinical trials, small numbers of participants, design problems, and mixed outcomes produce limited conclusions. The concurrent use of supplements, especially high-dose antioxidants or complex botanical agents, during chemotherapy or radiation therapy can be problematic because of drug–supplement interaction.<sup>302,303</sup> Because of their chemical structure, some botanicals may have adverse effects in perioperative use. Their antiplatelet activity may increase bleeding tendency; they may produce gastrointestinal distress, hepatotoxicity, and nephrotoxicity; and they can have a synergistic effect when combined with opioid analgesics or central nervous system depressant drugs.<sup>304</sup> Quality control and adulteration of dietary supplements are additional issues that need to be considered.<sup>300</sup>

Cancer patients, especially those with advanced disease and poor prognosis, want to explore all treatment options, including the use of botanicals or other natural products, in the hope that those agents may produce therapeutic effects, often based on antitumor effects observed in preclinical studies. Botanicals and other natural products are a valuable resource for the development of therapeutic agents when they are carefully studied for safety and efficacy. About one-quarter of all prescription drugs contain active ingredients derived from plants, including several chemotherapeutic agents (paclitaxel [Taxol], docetaxel [Taxotere]), camptothecins (irinotecan

[Camptosar], topotecan [Hycamtin]), and vinca alkaloids (vincristine [Oncovin], vinblastine [Velban], vinorelbine [Navelbine]). They are sold as dietary supplements; however, they are rarely produced at the same high standards. Some herbs cause significant side effects. Detrimental herb–drug interactions may occur. Finally, product inconsistency and contamination have been reported.<sup>300,305</sup>

Most claims made by producers of herbal supplements are based on historical experience or laboratory studies unconfirmed by clinical trials. Many herbs show direct antitumor activity in vitro or in animal experiments,<sup>306,307</sup> but translating preclinical to clinical use often fails because the active components, often unknown, are insufficiently potent or metabolized before reaching their target. The composition of herbs is complex, typically containing hundreds of constituents. Moreover, some herbal remedies function through the synergistic effects of their multiple constituents, hindering identification of active ingredients.

Herbs and other botanical products that enhance immune function are especially popular among cancer patients and may prove useful in cancer treatment or prevention. Some show immunomodulatory effects in preclinical studies, assisting tumor rejection or resistance to pathogens.<sup>308–310</sup> However, echinacea, the most popular immune-boosting herb in the United States that is used commonly to treat colds, showed disappointing results in RCTs.<sup>311–314</sup> These and other botanical research results have been controversial as questions have been raised about dose and species used (eg, *Echinacea purpurea* versus *Echinacea angustifolia*).<sup>315</sup>

Because botanicals contain biologically active constituents, they carry health risks if not used properly. The botanical kava kava, for example, proved more effective than placebo in treating anxiety, stress, and insomnia<sup>316,317</sup> and was considered a viable alternative to benzodiazepines because of its benefits and the absence of potential dependency and addiction. However, some case reports associate this herbal remedy with severe hepatotoxicity, resulting in liver failure and death in a small number of patients.<sup>318</sup>

Historically, herbal medicine has been practiced by those with at least some knowledge of their side effects. Today, however, many herbal and other botanical products are readily available to US consumers under the Dietary Supplement Health and Education Act of 1994, which regulates them only as food supplements and requires no previous studies of safety and efficacy. A few herbal products have been removed from the market by the US FDA because of adverse events. A recent example is ephedra as its sympathomimetic activity has been associated with cardiovascular complication, including death.

Herbs may attenuate or lessen the effect of a drug either by direct action on its target or by altering its pharmacokinetics.<sup>23,319</sup> Herbs such as feverfew, garlic, ginger, and ginkgo have anticoagulant effects and should be avoided by patients on warfarin, heparin, aspirin, and related agents. Patients on tamoxifen or aromatase inhibitors should not use red clover, dong quai, and licorice because of their phytoestrogen components. St. John's wort was a popular product for depression, at least equivalent in efficacy to tricyclic antidepressants and SSRIs in mild to moderate depression and with a side-effect profile superior to both.<sup>320,321</sup> St. John's wort induces cytochrome P-450 CYP3A4. Reduced plasma levels of SN38, an active metabolite of irinotecan, have been reported following simultaneous use.<sup>322</sup> Such metabolic interactions preclude St. John's wort for patients on medications metabolized by CYP3A4.<sup>323</sup>

Although not an herb, grapefruit juice was shown to significantly increase the plasma level of many prescription drugs. Further study found that grapefruit furanocoumarin derivatives inhibit intestinal CYP3A4, which consequently increases the bioavailability of drugs that are substrate to first-pass metabolism by this enzyme.<sup>324,325</sup>

*Recommendation 20: As with nutritional supplementation during treatment, survivors should be evaluated for supplement use and referred to a trained professional for evaluation to meet specific nutritional needs and to correct nutritional deficits as indicated. For older cancer survivors, nutritional supplementation may reduce nutrient inadequacies, although survivors who use supplements are usually the least likely to need them. Grade of recommendation: 2B*

#### Rationale and Evidence

A majority of cancer survivors (40–74%) reported taking supplements, the most predominant being multivitamins, calcium and vitamin D, and antioxidants.<sup>19,326</sup> In a systematic summary of 32 studies published between 1999 and 2006 assessing vitamin and mineral supplement use among US adult cancer patients and survivors, it was observed that supplement use is widespread among cancer patients and long-term survivors. In studies combining different cancer sites, 64 to 81% of survivors reported using any vitamin or mineral supplements and 26 to 77% reported using any multivitamins.<sup>326</sup>

Based on observational findings regarding the use of minerals and vitamins for cancer prevention, large doses of vitamins, minerals, and other dietary supplements are not recommended in the survivor population.<sup>25,165,278</sup> However, specific populations may benefit from taking dietary supplements. During and after cancer treatment, there is a probable

benefit in taking a standard multivitamin and mineral supplement that contains approximately 100% of the Dietary Reference Intake because of tumor- and treatment-related symptoms that may compromise nutritional intake or use.<sup>327,328</sup> Research among children with cancer demonstrated that diets were inadequate in vitamins C and E and total carotenoids. In this same study, diets with sufficient vitamin E were associated with lower risk for infection, and diets adequate in vitamin C were associated with fewer delays in treatment related to low blood counts.<sup>329</sup> As with nutritional supplementation during treatment, survivors must be evaluated for supplement use and referred to an appropriately trained professional for evaluation of appropriateness to meet specific nutritional needs and correction of any nutritional deficits (ie, bone loss requiring calcium and/or vitamin D supplementation), as indicated. In fact, increasing evidence suggests that vitamin D<sub>3</sub> and calcium supplementation may have a variety of health benefits for cancer risk reduction and other common medical conditions experienced by the elderly. For older cancer survivors, nutritional supplements may reduce nutrient inadequacies, although survivors who use supplements are the least likely to need them.<sup>165,330</sup>

#### Indications for Future Research

Despite the long history of most complementary therapies, rigorous scientific research is a recent phenomenon. This research is limited by a lack of sufficient funding, a lack of qualified investigators, and methodological and ethical issues unique to studying complementary therapies. Therefore, gaps in research are the norm rather than the exception in this field. Many complementary therapies were derived from traditional medical systems and were used historically to treat almost every ailment. Only a few of these modalities have been evaluated with scientific research tools. More comprehensive evidence-based recommendations will become feasible when the research expands as anticipated. Once a sufficient evidence base is available for individual interventions, research into the potential synergy of whole systems can be considered.

We view the following as high-priority areas for research: (1) complementary therapies in the management of symptoms or disease processes for which current treatment options are not satisfactory; (2) mechanisms of action based on contemporary biomedical science; (3) definitive database of drug-supplement interactions; and (4) new cancer therapies derived from botanicals, supplements, and other natural products for cancer treatment or for synergistic effect when combined with conventional medicine. Given that some nutritional patterns have been associated with cancer

prevention, the potential role of nutrients in the prevention of recurrence, metastasis, and/or second primary tumors warrants further research.

Cancer care is multifactorial and patient centered. It constitutes a complex package of interventions, including supportive and self-care, that cannot be evaluated in isolation. There is an increasing recognition of the need to move beyond a limited focus on diagnosis and treatment. A new research framework is required to address the complexities of cancer care, one that will incorporate comprehensive simultaneous approaches that enhance well-being. Such a framework would include both qualitative research methods (eg, in-depth interviews, focus groups) and quantitative designs (observational research and, when appropriate, intervention research).<sup>8</sup>

## Conclusions

Integrative oncology is an approach that fosters the physical, mental, and spiritual well-being of cancer patients by integrating evidence-based, adjunctive complementary therapies and mainstream care, using a multidisciplinary approach. The “unofficial” use of complementary and alternative therapies is common among cancer patients. These therapies are diverse in their origin, theory, practice, safety, and efficacy. Some therapies have been helpful in reducing symptoms. These complementary therapies (used as adjuncts to mainstream treatment) are being increasingly integrated into regular oncologic care, as in the practice of integrative oncology. Dietary supplements, herbs, and other botanicals can be problematic because of their potential adverse effects or interactions with chemotherapy, radiotherapy, or surgery but may be beneficial when patients are not undergoing these treatments. However, therapies promoted as “alternatives” to take the place of mainstream cancer treatment endanger patients, who then forego effective treatments. It is important for everyone involved to help patients assess complementary and alternative therapies appropriately to receive benefit while avoiding harm. A patient-centered approach should be used to address concerns and needs, including a risk/benefit discussion and incorporation of reliable sources of information as tools. After examining the levels of evidence and the risks and benefits from reliable sources, specific advice should be provided.

## Summary of Recommendations

### The Clinical Encounter

Advantages: good clinical practice  
Limitations: none

*Recommendation 1: Inquire about the use of complementary and alternative therapies as a routine part of initial evaluations of cancer patients. Grade of recommendation: 1C*

*Recommendation 2: All patients with cancer should receive guidance about the advantages and limitations of complementary therapies in an open, evidence-based, and patient-centered manner by a qualified professional. Patients should be fully informed of the treatment approach, the nature of the specific therapies, potential risks/benefits, and realistic expectations. Grade of recommendation: 1C*

### Mind-Body Medicine

Advantages: safe, good evidence  
Limitations: time consuming

*Recommendation 3: Mind-body modalities are recommended as part of a multidisciplinary approach to reduce anxiety, mood disturbance, and chronic pain and improve QoL. Grade of recommendation: 1B*

*Recommendation 4: Support groups, supportive/expressive therapy, cognitive-behavioral therapy, and cognitive-behavioral stress management are recommended as part of a multidisciplinary approach to reduce anxiety, mood disturbance, chronic pain, and improve QoL. Grade of recommendation: 1A*

### Touch Therapies

Advantages: safe, skills readily available  
Limitations: none

*Recommendation 5: For cancer patients experiencing anxiety or pain, massage therapy delivered by an oncology-trained massage therapist is recommended as part of multimodality treatment. Grade of recommendation: 1C*

*Recommendation 6: The application of deep or intense pressure is not recommended near cancer lesions or enlarged lymph nodes, radiation field sites, medical devices (such as indwelling intravenous catheters), or anatomic distortions such as postoperative changes or in patients with a bleeding tendency. Grade of recommendation: 2B*

### Physical Activity

Advantages: good evidence, safe

Limitations: none

*Recommendation 7: Regular physical activities can play many positive roles in cancer care. Patients should be referred to a qualified exercise specialist for guidelines on physical activity to promote basic health. Grade of recommendation: 1B (1A for breast cancer survivors post-therapy for QoL)*

### Energy Therapies

Advantages: safe

Limitations: no good evidence

*Recommendation 8: Therapies based on a philosophy of bioenergy fields are safe and may provide some benefit for reducing stress and enhancing QoL. There is limited evidence as to their efficacy for symptom management, including reducing pain and fatigue. Grade of recommendation: 1B for reducing anxiety; 1C for pain, fatigue, and other symptom management*

### Acupuncture

Advantages: good evidence

Limitations: skills not always readily available

*Recommendation 9: Acupuncture is recommended as a complementary therapy when pain is poorly controlled, when nausea and vomiting associated with chemotherapy or surgical anesthesia are poorly controlled, or when the side effects from other modalities are clinically significant. Grade of recommendation: 1A*

*Recommendation 10: Acupuncture is recommended as a complementary therapy for radiation-induced xerostomia. Grade of recommendation: 1B*

*Recommendation 11: Acupuncture does not appear to be more effective than sham acupuncture for treatment of vasomotor symptoms (hot flashes) in postmenopausal women in general. In patients experiencing severe symptoms not amenable to pharmacologic treatment, however, a trial of acupuncture treatment can be considered. Grade of recommendation: 1B*

*Recommendation 12: For patients who do not stop smoking despite use of other options or those suffering from symptoms such as cancer-related dyspnea, cancer-related fatigue, chemotherapy-induced neuropathy, or post-thoracotomy pain, a trial of acupuncture may be helpful, but more clinical studies of acupuncture are warranted. Grade of recommendation: 2C*

*Recommendation 13: Acupuncture should be performed only by qualified practitioners and used cautiously in patients with bleeding tendencies. Grade of recommendation: 1C*

### Diet and Nutritional Supplements

Advantages: interest the most patients

Limitations: potential adverse effects

*Recommendation 14: Research in diet and cancer prevention is based mainly on studies of populations consuming dietary components in whole-food form, with secure food supplies and access to a variety of food and drinks. Therefore, nutritional adequacy should be met by selecting a wide variety of foods; dietary supplements are usually unnecessary. Grade of recommendation: 1B*

*Recommendation 15: It is recommended that patients be advised regarding proper nutrition to promote basic health. Grade of recommendation: 1B*

*Recommendation 16: Based on a current review of the literature, specific dietary supplements are not recommended for cancer prevention. Grade of recommendation: 1A*

*Recommendation 17: Evaluation of patients' use of dietary supplements prior to the start of cancer treatment is recommended. Also recommended are referral of cancer patients to trained professionals for guidelines on diets, nutritional supplementation, promotion of optimum nutritional status, management of tumor- and treatment-related symptoms, satisfaction of increased nutritional needs, and correction of any nutritional deficits while on active treatment. Grade of recommendation: 1B*

*Recommendation 18: It is recommended that dietary supplements, including botanicals and megadoses of vitamins and minerals, be evaluated for possible side effects and potential interaction with other drugs. Those that are likely to interact adversely with other drugs, including chemotherapeutic agents, should not be used concurrently with immunotherapy, chemotherapy, or radiation or prior to surgery. Grade of recommendation: 1B*

*Recommendation 19: For cancer patients who wish to use nutritional supplements, including botanicals for purported antitumor effects, it is recommended that they consult a trained professional. During the consultation, the professional should provide support, discuss realistic expectations, and explore potential benefits and risks. It is recommended that use of those agents occur only in the context of clinical trials, recognized nutritional guidelines, clinical evaluation of the risk/benefit ratio based on available evidence, and close monitoring of adverse effects. Grade of recommendation: 1C*

*Recommendation 20: As with nutritional supplementation during treatment, survivors should be evaluated for supplement use and referred to a trained professional for evaluation to meet specific nutritional needs and to correct nutritional deficits as indicated. For older cancer survivors, nutritional supplementation may reduce nutrient inadequacies, although survivors who use supplements are usually the least likely to need them. Grade of recommendation: 2B*

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## References

1. Kligler B, Maizes V, Schachter S, et al. Core competencies in integrative medicine for medical school curricula: a proposal. *Acad Med* 2004;79:521–31.
2. Sagar SM. The integrative oncology supplement—a paradigm for both patient care and communication. *Curr Oncol* 2008;15:166–7.
3. Cassileth B, Deng G, Vickers A, Yeung KS. *PDQ integrative oncology*. Hamilton (ON): BC Decker; 2005.
4. Remen RN. Practicing a medicine of the whole person: an opportunity for healing. *Hematol Oncol Clin North Am* 2008;22:767–73, x.
5. Deng G, Cassileth BR, Yeung KS. Complementary therapies for cancer-related symptoms. *J Support Oncol* 2004;2:419–26; discussion 427–19.
6. Cassileth BR, Deng G. Complementary and alternative therapies for cancer. *Oncologist* 2004;9:80–9.
7. Guyatt G, Gutterman D, Baumann MH, et al. Grading strength of recommendations and quality of evidence in clinical guidelines: report from an American College of Chest Physicians task force. *Chest* 2006;129: 174–81.
8. Verhoef MJ, Leis A. From studying patient treatment to studying patient care: arriving at methodologic crossroads. *Hematol Oncol Clin North Am* 2008;22:671–82, viii–ix.
9. Barnes PM, Powell-Griner E, McFann K, Nahin RL. Complementary and alternative medicine use among adults: United States, 2002. *Adv Data* 2004;(343):1–19.
10. Adams J, Sibbritt DW, Easthope G, Young AF. The profile of women who consult alternative health practitioners in Australia. *Med J Aust* 2003;179:297–300.
11. Chrystal K, Allan S, Forgeson G, Isaacs R. The use of complementary/alternative medicine by cancer patients in a New Zealand regional cancer treatment centre. *N Z Med J* 2003;116:U296.
12. Lee MM, Chang JS, Jacobs B, Wrensch MR. Complementary and alternative medicine use among men with prostate cancer in 4 ethnic populations. *Am J Public Health* 2002;92:1606–9.
13. Weiger WA, Smith M, Boon H, et al. Advising patients who seek complementary and alternative medical therapies for cancer. *Ann Intern Med* 2002; 137:889–903.
14. Navo MA, Phan J, Vaughan C, et al. An assessment of the utilization of complementary and alternative medication in women with gynecologic or breast malignancies. *J Clin Oncol* 2004;22:671–7.
15. Richardson MA, Sanders T, Palmer JL, et al. Complementary/alternative medicine use in a comprehensive cancer center and the implications for oncology. *J Clin Oncol* 2000;18:2505–14.
16. Ernst E, Cassileth BR. The prevalence of complementary/alternative medicine in cancer: a systematic review. *Cancer* 1998;83:777–82.
17. Hyodo I, Amano N, Eguchi K, et al. Nationwide survey on complementary and alternative medicine in cancer patients in Japan. *J Clin Oncol* 2005;23:2645–54.
18. Molassiotis A, Fernadez-Ortega P, Pud D, et al. Use of complementary and alternative medicine in cancer patients: a European survey. *Ann Oncol* 2005;16:655–63.
19. Gansler T, Kaw C, Crammer C, Smith T. A population-based study of prevalence of complementary methods

- use by cancer survivors: a report from the American Cancer Society's studies of cancer survivors. *Cancer* 2008;113:1048–57.
20. Ernst E. Complementary medicine: its hidden risks. *Diabetes Care* 2001;24:1486–8.
  21. Sovak M, Seligson AL, Konas M, et al. Herbal composition PC-SPES for management of prostate cancer: identification of active principles. *J Natl Cancer Inst* 2002;94:1275–81.
  22. Beijnen JH, Schellens JH. Drug interactions in oncology. *Lancet Oncol* 2004;5:489–96.
  23. Sparreboom A, Cox MC, Acharya MR, Figg WD. Herbal remedies in the United States: potential adverse interactions with anticancer agents. *J Clin Oncol* 2004;22:2489–503.
  24. Albanes D, Heinonen OP, Taylor PR, et al. Alpha-tocopherol and beta-carotene supplements and lung cancer incidence in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study: effects of base-line characteristics and study compliance. *J Natl Cancer Inst* 1996;88:1560–70.
  25. The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. The Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group. *N Engl J Med* 1994; 330:1029–35.
  26. White MA, Verhoef MJ. Decision-making control: why men decline treatment for prostate cancer. *Integr Cancer Ther* 2003;2:217–24.
  27. Shumay DM, Maskarinec G, Kakai H, Gotay CC. Why some cancer patients choose complementary and alternative medicine instead of conventional treatment. *J Fam Pract* 2001;50:1067.
  28. Montbriand MJ. Abandoning biomedicine for alternate therapies: oncology patients' stories. *Cancer Nurs* 1998;21:36–45.
  29. Verhoef MJ, Balneaves LG, Boon HS, Vroegindewey A. Reasons for and characteristics associated with complementary and alternative medicine use among adult cancer patients: a systematic review. *Integr Cancer Ther* 2005;4:274–86.
  30. Druss BG, Rosenheck RA. Association between use of unconventional therapies and conventional medical services. *JAMA* 1999;282:651–6.
  31. Schmidt K. CAM and the desperate call for cancer cures and alleviation what can websites offer cancer patients? *Complement Ther Med* 2002;10:179–80.
  32. Schmidt K, Ernst E. Assessing websites on complementary and alternative medicine for cancer. *Ann Oncol* 2004;15:733–42.
  33. Verhoef MJ, Boon HS, Page SA. Talking to cancer patients about complementary therapies: is it the physician's responsibility? *Curr Oncol* 2008;15 Suppl 2:s88–93.
  34. Frenkel M, Ben-Arye E, Baldwin CD, Sierpina V. Approach to communicating with patients about the use of nutritional supplements in cancer care. *South Med J* 2005;98:289–94.
  35. Cohen L, Markman M, editors. *Integrative oncology: incorporating complementary medicine into conventional cancer care*. Totowa (NJ): Humana Press; 2008.
  36. Abrams D, Weil A, editors. *Integrative oncology*. New York: Oxford University Press; 2009.
  37. Mumber MP, editor. *Integrative oncology: principles and practice*. London: Informa HealthCare; 2005.
  38. Cohen MH, Eisenberg DM. Potential physician malpractice liability associated with complementary and integrative medical therapies. *Ann Intern Med* 2002;136:596–603.
  39. O'Connor AM. Using decision aids to help patients navigate the "grey zone" of medical decision-making. *CMAJ* 2007;176:1597–8.
  40. O'Connor AM, Wennberg JE, Legare F, et al. Toward the 'tipping point': decision aids and informed patient choice. *Health Aff (Millwood)* 2007;26:716–25.
  41. Frenkel M. Clinical consultation, a personal perspective: components of a successful integrative medicine clinical consultation. *J Soc Integr Oncol* 2008; 6:129–33.
  42. Shankar K, Liao LP. Traditional systems of medicine. *Phys Med Rehabil Clin N Am* 2004;15:725–47, v.
  43. Antoni MH, Lutgendorf SK, Cole SW, et al. The influence of bio-behavioural factors on tumour biology: pathways and mechanisms. *Nat Rev Cancer* 2006; 6:240–8.
  44. Glaser R, Kiecolt-Glaser JK. Stress-induced immune dysfunction: implications for health. *Nat Rev Immunol* 2005;5:243–51.
  45. Thaker PH, Han LY, Kamat AA, et al. Chronic stress promotes tumor growth and angiogenesis in a mouse model of ovarian carcinoma. *Nat Med* 2006;12:939–44.
  46. Chida Y, Hamer M, Wardle J, Steptoe A. Do stress-related psychosocial factors contribute to cancer incidence and survival? *Nat Clin Pract Oncol* 2008;5:466–75.
  47. Steel JL, Geller DA, Gamblin TC, et al. Depression, immunity, and survival in patients with hepatobiliary carcinoma. *J Clin Oncol* 2007;25:2397–405.
  48. 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;22:3570–80.

49. Adler NE, Page AEK, editors. *Cancer Care for the Whole Patients: Meeting Psychosocial Health Needs*. Washington (DC): National Academies Press; 2008.
50. Wolsko PM, Eisenberg DM, Davis RB, Phillips RS. Use of mind-body medical therapies. *J Gen Intern Med* 2004;19:43–50.
51. Devine EC, Westlake SK. The effects of psychoeducational care provided to adults with cancer: meta-analysis of 116 studies. *Oncol Nurs Forum* 1995;22:1369–81.
52. Astin JA. Mind-body therapies for the management of pain. *Clin J Pain* 2004;20:27–32.
53. Newell SA, Sanson-Fisher RW, Savolainen NJ. Systematic review of psychological therapies for cancer patients: overview and recommendations for future research. *J Natl Cancer Inst* 2002;94:558–84.
54. Ernst E, Pittler MH, Wider B, Boddy K. Mind-body therapies: are the trial data getting stronger? *Altern Ther Health Med* 2007;13:62–4.
55. Gordon JS. Mind-body medicine and cancer. *Hematol Oncol Clin North Am* 2008;22:683–708, ix.
56. Shapiro SL, Bootzin RR, Figueredo AJ, et al. 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.
57. Ott MJ, Norris RL, Bauer-Wu SM. Mindfulness meditation for oncology patients: a discussion and critical review. *Integr Cancer Ther* 2006;5:98–108.
58. Smith JE, Richardson J, Hoffman C, Pilkington K. Mindfulness-based stress reduction as supportive therapy in cancer care: systematic review. *J Adv Nurs* 2005;52:315–27.
59. 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;62:613–22.
60. Carlson LE, Ursuliak Z, Goodey E, et al. 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;9:112–23.
61. Carlson LE, Specia M, Patel KD, Goodey E. Mindfulness-based stress reduction in relation to quality of life, mood, symptoms of stress, and immune parameters in breast and prostate cancer outpatients. *Psychosom Med* 2003;65:571–81.
62. Carlson LE, Specia M, Faris P, Patel KD. One year pre-post intervention follow-up of psychological, immune, endocrine and blood pressure outcomes of mindfulness-based stress reduction (MBSR) in breast and prostate cancer outpatients. *Brain Behav Immun* 2007;21:1038–49.
63. Carlson LE, Specia M, Patel KD, Goodey E. Mindfulness-based stress reduction in relation to quality of life, mood, symptoms of stress and levels of cortisol, dehydroepiandrosterone sulfate (DHEAS) and melatonin in breast and prostate cancer outpatients. *Psychoneuroendocrinology* 2004;29:448–74.
64. Witek-Janusek L, Albuquerque K, Chroniak KR, et al. Effect of mindfulness based stress reduction on immune function, quality of life and coping in women newly diagnosed with early stage breast cancer. *Brain Behav Immun* 2008;22:969–81.
65. Carlson LE, Garland SN. Impact of mindfulness-based stress reduction (MBSR) on sleep, mood, stress and fatigue symptoms in cancer outpatients. *Int J Behav Med* 2005;12:278–85.
66. Cohen L, Warneke C, Fouladi RT, et al. Psychological adjustment and sleep quality in a randomized trial of the effects of a Tibetan yoga intervention in patients with lymphoma. *Cancer* 2004;100:2253–60.
67. 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;25:4387–95.
68. Raghavendra RM, Nagarathna R, Nagendra HR, et al. Effects of an integrated yoga programme on chemotherapy-induced nausea and emesis in breast cancer patients. *Eur J Cancer Care (Engl)* 2007;16:462–74.
69. Rao RM, Telles S, Nagendra HR, et al. Effects of yoga on natural killer cell counts in early breast cancer patients undergoing conventional treatment. *Med Sci Monit* 2008;14(2):LE3–4.
70. Banerjee B, Vadiraj HS, 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;6:242–50.
71. Mustian KM, Katula JA, Zhao H. A pilot study to assess the influence of tai chi chuan on functional capacity among breast cancer survivors. *J Support Oncol* 2006;4:139–45.
72. Mustian KM, Katula JA, Gill DL, et al. Tai Chi Chuan, health-related quality of life and self-esteem: a randomized trial with breast cancer survivors. *Support Care Cancer* 2004;12:871–6.
73. 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.
74. Lioffi C, Hatira P. Clinical hypnosis versus cognitive behavioral training for pain management with pediatric cancer patients undergoing bone marrow aspirations. *Int J Clin Exp Hypn* 1999;47:104–16.
75. Faymonville ME, Mambourg PH, Joris J, et al. Psychological approaches during conscious sedation. Hypnosis versus stress reducing strategies: a prospective randomized study. *Pain* 1997;73:361–7.
76. Flory N, Lang E. Practical hypnotic interventions during invasive cancer diagnosis and treatment. *Hematol Oncol Clin North Am* 2008;22:709–25, ix.
77. Syrjala KL, Cummings C, Donaldson GW. Hypnosis or cognitive behavioral training for the reduction of pain and nausea during cancer treatment: a controlled clinical trial. *Pain* 1992;48:137–46.
78. Integration of behavioral and relaxation approaches into the treatment of chronic pain and insomnia. NIH Technology Assessment Panel on Integration of Behavioral and Relaxation Approaches into the Treatment of Chronic Pain and Insomnia. *JAMA* 1996;276:313–8.
79. Zeltzer LK, Dolgin MJ, LeBaron S, LeBaron C. A randomized, controlled study of behavioral intervention for chemotherapy distress in children with cancer. *Pediatrics* 1991;88:34–42.
80. Morrow GR, Morrell C. Behavioral treatment for the anticipatory nausea and vomiting induced by cancer chemotherapy. *N Engl J Med* 1982;307:1476–80.
81. Marcus J, Elkins G, Mott F. A model of hypnotic intervention for palliative care. *Adv Mind Body Med* 2003;19:24–7.
82. Spiegel D, Moore R. Imagery and hypnosis in the treatment of cancer patients. *Oncology (Williston Park)* 1997;11:1179–89; discussion 1189–95.
83. Spiegel D. The use of hypnosis in controlling cancer pain. *CA Cancer J Clin* 1985;35:221–31.
84. Richardson J, Smith JE, McCall G, et al. Hypnosis for nausea and vomiting in cancer chemotherapy: a systematic review of the research evidence. *Eur J Cancer Care (Engl)* 2007;16:402–12.
85. Rheingans JI. A systematic review of nonpharmacologic adjunctive therapies for symptom management in children with cancer. *J Pediatr Oncol Nurs* 2007;24:81–94.
86. Feldman CS, Salzberg HC. The role of imagery in the hypnotic treatment of adverse reactions to cancer therapy. *J S C Med Assoc* 1990;86:303–6.
87. 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;99:1304–12.
88. Taylor EE, Ingleton C. Hypnotherapy and cognitive-behaviour therapy in cancer care: the patients' view. *Eur J Cancer Care (Engl)* 2003;12:137–42.
89. Marchioro G, Azzarello G, Viviani F, et al. Hypnosis in the treatment of anticipatory nausea and vomiting in patients receiving cancer chemotherapy. *Oncology* 2000;59:100–4.
90. Holland JC, Morrow GR, Schmale A, et al. A randomized clinical trial of alprazolam versus progressive muscle relaxation in cancer patients with anxiety and depressive symptoms. *J Clin Oncol* 1991;9:1004–11.
91. Decker TW, Cline-Elsen J, Gallagher M. Relaxation therapy as an adjunct in radiation oncology. *J Clin Psychol* 1992;48:388–93.
92. Morin CM, Culbert JP, Schwartz SM. Nonpharmacological interventions for insomnia: a meta-analysis of treatment efficacy. *Am J Psychiatry* 1994; 151:1172–80.
93. Krischer MM, Xu P, Meade CD, Jacobsen PB. Self-administered stress management training in patients undergoing radiotherapy. *J Clin Oncol* 2007;25:4657–62.
94. Campos de Carvalho E, Martins FT, dos Santos CB. A pilot study of a relaxation technique for management of nausea and vomiting in patients receiving cancer chemotherapy. *Cancer Nurs* 2007;30:163–7.
95. Anderson KO, Cohen MZ, Mendoza TR, et al. Brief cognitive-behavioral audiotape interventions for cancer-related pain: immediate but not long-term effectiveness. *Cancer* 2006;107:207–14.
96. Hanser SB. Music therapy research in adult oncology. *J Soc Integr Oncol* 2006;4:62–6.
97. Hilliard RE. Music therapy in pediatric oncology: a review of the literature. *J Soc Integr Oncol* 2006;4:75–9.
98. Hilliard RE. Music therapy in hospice and palliative care: a review of the empirical data. *Evid Based Complement Alternat Med* 2005;2:173–8.
99. Rykov M, Salmon D. Bibliography for music therapy in palliative care, 1963–1997. *Am J Hosp Palliat Care* 1998;15:174–80.

100. Frank JM. The effects of music therapy and guided visual imagery on chemotherapy induced nausea and vomiting. *Oncol Nurs Forum* 1985;12:47–52.
101. Sabo CE, Michael SR. The influence of personal message with music on anxiety and side effects associated with chemotherapy. *Cancer Nurs* 1996;19:283–9.
102. Horne-Thompson A, Grocke D. The effect of music therapy on anxiety in patients who are terminally ill. *J Palliat Med* 2008;11:582–90.
103. Clark M, Isaacks-Downton G, Wells N, et al. Use of preferred music to reduce emotional distress and symptom activity during radiation therapy. *J Music Ther* 2006;43:247–65.
104. Ferrer AJ. The effect of live music on decreasing anxiety in patients undergoing chemotherapy treatment. *J Music Ther* 2007;44:242–55.
105. Hanser SB, Bauer-Wu SM, 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;5:14–23.
106. Beck SL. The therapeutic use of music for cancer-related pain. *Oncol Nurs Forum* 1991;18:1327–37.
107. Hilliard RE. The effects of music therapy on the quality and length of life of people diagnosed with terminal cancer. *J Music Ther* 2003;40:113–37.
108. Burns SJ, Harbuz MS, Hucklebridge F, Bunt L. A pilot study into the therapeutic effects of music therapy at a cancer help center. *Altern Ther Health Med* 2001;7:48–56.
109. Richardson MM, Babiak-Vazquez AE, Frenkel MA. Music therapy in a comprehensive cancer center. *J Soc Integr Oncol* 2008;6:76–81.
110. Reblin M, Uchino BN. Social and emotional support and its implication for health. *Curr Opin Psychiatry* 2008;21:201–5.
111. House JS, Landis KR, Umberson D. Social relationships and health. *Science* 1988;241:540–5.
112. Berkman LF, Syme SL. Social networks, host resistance, and mortality: a nine-year follow-up study of Alameda County residents. *Am J Epidemiol* 1979;109:186–204.
113. Kroenke CH, Kubzansky LD, Schernhammer ES, et al. Social networks, social support, and survival after breast cancer diagnosis. *J Clin Oncol* 2006;24:1105–11.
114. Maunsell E, Brisson J, Deschenes L. Social support and survival among women with breast cancer. *Cancer* 1995;76:631–7.
115. Spiegel D, Bloom JR, Yalom I. Group support for patients with metastatic cancer. A randomized outcome study. *Arch Gen Psychiatry* 1981;38:527–33.
116. Spiegel D, Bloom JR, Kraemer HC, Gotthel E. Effect of psychosocial treatment on survival of patients with metastatic breast cancer. *Lancet* 1989;2(8668):888–91.
117. Fawzy FI, Fawzy NW, Hyun CS, et al. Malignant melanoma. Effects of an early structured psychiatric intervention, coping, and affective state on recurrence and survival 6 years later. *Arch Gen Psychiatry* 1993;50:681–9.
118. Fawzy FI, Cousins N, Fawzy NW, et al. A structured psychiatric intervention for cancer patients. I. Changes over time in methods of coping and affective disturbance. *Arch Gen Psychiatry* 1990;47:720–5.
119. Fawzy FI, Kemeny ME, Fawzy NW, et al. A structured psychiatric intervention for cancer patients. II. Changes over time in immunological measures. *Arch Gen Psychiatry* 1990;47:729–35.
120. Cunningham AJ, Watson K. How psychological therapy may prolong survival in cancer patients: new evidence and a simple theory. *Integr Cancer Ther* 2004;3:214–29.
121. Goodwin PJ, Leszcz M, Ennis M, et al. The effect of group psychosocial support on survival in metastatic breast cancer. *N Engl J Med* 2001;345:1719–26.
122. Richardson JL, Shelton DR, Krailo M, Levine AM. The effect of compliance with treatment on survival among patients with hematologic malignancies. *J Clin Oncol* 1990;8:356–64.
123. Spiegel D, Butler LD, Giese-Davis J, et al. Effects of supportive-expressive group therapy on survival of patients with metastatic breast cancer: a randomized prospective trial. *Cancer* 2007;110:1130–8.
124. Cunningham AJ, Phillips C, Lockwood GA, et al. Association of involvement in psychological self-regulation with longer survival in patients with metastatic cancer: an exploratory study. *Adv Mind Body Med* 2000;16:276–87.
125. Cunningham AJ, Edmonds CV, Phillips C, et al. A prospective, longitudinal study of the relationship of psychological work to duration of survival in patients with metastatic cancer. *Psychooncology* 2000;9:323–39.
126. Helgeson VS, Cohen S, Schulz R, Yasko J. Group support interventions for women with breast cancer: who benefits from what? *Health Psychol* 2000;19:107–14.
127. Helgeson VS, Cohen S, Schulz R, Yasko J. Education and peer discussion group interventions and adjustment to breast cancer. *Arch Gen Psychiatry* 1999;56:340–7.
128. Savard J, Simard S, Ivers H, Morin CM. Randomized study on the efficacy of cognitive-behavioral therapy for

- insomnia secondary to breast cancer, part I: sleep and psychological effects. *J Clin Oncol* 2005;23:6083–96.
129. 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.
130. Cruess DG, Antoni MH, McGregor BA, et al. Cognitive-behavioral stress management reduces serum cortisol by enhancing benefit finding among women being treated for early stage breast cancer. *Psychosom Med* 2000;62:304–8.
131. 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;74:1143–52.
132. Savard J, Simard S, Ivers H, Morin CM. Randomized study on the efficacy of cognitive-behavioral therapy for insomnia secondary to breast cancer, part II: immunologic effects. *J Clin Oncol* 2005;23:6097–106.
133. Antoni MH, Wimberly SR, Lechner SC, et al. Reduction of cancer-specific thought intrusions and anxiety symptoms with a stress management intervention among women undergoing treatment for breast cancer. *Am J Psychiatry* 2006;163:1791–7.
134. Penedo FJ, Molton I, Dahn JR, et al. A randomized clinical trial of group-based cognitive-behavioral stress management in localized prostate cancer: development of stress management skills improves quality of life and benefit finding. *Ann Behav Med* 2006;31:261–70.
135. Andersen BL, Yang HC, Farrar WB, et al. Psychologic intervention improves survival for breast cancer patients: a randomized clinical trial. *Cancer* 2008;113:3450–8.
136. Ahles TA, Tope DM, Pinkson B, et al. Massage therapy for patients undergoing autologous bone marrow transplantation. *J Pain Symptom Manage* 1999;18:157–63.
137. 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.
138. Grealish L, Lomasney A, Whiteman B. Foot massage. A nursing intervention to modify the distressing symptoms of pain and nausea in patients hospitalized with cancer. *Cancer Nurs* 2000;23:237–43.
139. Wilkinson S, Aldridge J, Salmon I, et al. An evaluation of aromatherapy massage in palliative care. *Palliat Med* 1999;13:409–17.
140. Cassileth BR, Vickers AJ. Massage therapy for symptom control: outcome study at a major cancer center. *J Pain Symptom Manage* 2004;28:244–9.
141. Mehling WE, Jacobs B, Acree M, et al. Symptom management with massage and acupuncture in postoperative cancer patients: a randomized controlled trial. *J Pain Symptom Manage* 2007;33:258–66.
142. Billhult A, Bergbom I, Stener-Victorin E. Massage relieves nausea in women with breast cancer who are undergoing chemotherapy. *J Altern Complement Med* 2007;13:53–7.
143. Post-White J, Kinney ME, Savik K, et al. Therapeutic massage and healing touch improve symptoms in cancer. *Integr Cancer Ther* 2003;2:332–44.
144. Ballard CG, O'Brien JT, Reichelt K, Perry EK. Aromatherapy as a safe and effective treatment for the management of agitation in severe dementia: the results of a double-blind, placebo-controlled trial with Melissa. *J Clin Psychiatry* 2002;63:553–8.
145. Graham PH, Browne L, Cox H, Graham J. Inhalation aromatherapy during radiotherapy: results of a placebo-controlled double-blind randomized trial. *J Clin Oncol* 2003;21:2372–6.
146. Soden K, Vincent K, Craske S, et al. A randomized controlled trial of aromatherapy massage in a hospice setting. *Palliat Med* 2004;18:87–92.
147. Gedney JJ, Glover TL, Fillingim RB. Sensory and affective pain discrimination after inhalation of essential oils. *Psychosom Med* 2004;66:599–606.
148. 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;25:532–9.
149. Cherkin DC, Sherman KJ, Deyo RA, Shekelle PG. A review of the evidence for the effectiveness, safety, and cost of acupuncture, massage therapy, and spinal manipulation for back pain. *Ann Intern Med* 2003;138:898–906.
150. Billhult A, Lindholm C, Gunnarsson R, Stener-Victorin E. The effect of massage on cellular immunity, endocrine and psychological factors in women with breast cancer—a randomized controlled clinical trial. *Auton Neurosci* 2008;140:88–95.
151. 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;149:369–79.
152. Ernst E. The safety of massage therapy. *Rheumatology (Oxford)* 2003;42:1101–6.

153. Cambron JA, Dexheimer J, Coe P, Swenson R. Side-effects of massage therapy: a cross-sectional study of 100 clients. *J Altern Complement Med* 2007; 13:793–6.
154. Jabr FI. Massive pulmonary emboli after legs massage. *Am J Phys Med Rehabil* 2007;86:691.
155. Geccedi RA. Massage therapy for patients with cancer. *Clin J Oncol Nurs* 2002;6:52–4.
156. McNeely ML, Campbell KL, Rowe BH, et al. Effects of exercise on breast cancer patients and survivors: a systematic review and meta-analysis. *CMAJ* 2006;175:34–41.
157. Courneya KS, Segal RJ, Mackey JR, et al. Effects of aerobic and resistance exercise in breast cancer patients receiving adjuvant chemotherapy: a multi-center randomized controlled trial. *J Clin Oncol* 2007; 25:4396–404.
158. Mutrie N, Campbell AM, Whyte F, et al. Benefits of supervised group exercise programme for women being treated for early stage breast cancer: pragmatic randomised controlled trial. *BMJ* 2007;334:517.
159. Segal RJ, Reid RD, Courneya KS, et al. Randomized controlled trial of resistance or aerobic exercise in men receiving radiation therapy for prostate cancer. *J Clin Oncol* 2009;27:344–51.
160. Thorsen L, Courneya KS, Stevinson C, Fossa SD. A systematic review of physical activity in prostate cancer survivors: outcomes, prevalence, and determinants. *Support Care Cancer* 2008;16:987–97.
161. Holmes MD, Chen WY, Feskanich D, et al. Physical activity and survival after breast cancer diagnosis. *JAMA* 2005;293:2479–86.
162. Holick CN, Newcomb PA, Trentham-Dietz A, et al. Physical activity and survival after diagnosis of invasive breast cancer. *Cancer Epidemiol Biomarkers Prev* 2008;17:379–86.
163. Meyerhardt JA, Giovannucci EL, Holmes MD, et al. Physical activity and survival after colorectal cancer diagnosis. *J Clin Oncol* 2006;24:3527–34.
164. Meyerhardt JA, Heseltine D, Niedzwiecki D, et al. Impact of physical activity on cancer recurrence and survival in patients with stage III colon cancer: findings from CALGB 89803. *J Clin Oncol* 2006; 24:3535–41.
165. Doyle C, Kushi LH, Byers T, et al. Nutrition and physical activity during and after cancer treatment: an American Cancer Society guide for informed choices. *CA Cancer J Clin* 2006;56:323–53.
166. Haskell WL, Lee IM, Pate RR, et al. Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. *Med Sci Sports Exerc* 2007;39:1423–34.
167. Cook CA, Guerrerio JF, Slater VE. Healing touch and quality of life in women receiving radiation treatment for cancer: a randomized controlled trial. *Altern Ther Health Med* 2004;10:34–41.
168. Roscoe JA, Matteson SE, Mustian KM, et al. Treatment of radiotherapy-induced fatigue through a nonpharmacological approach. *Integr Cancer Ther* 2005;4:8–13.
169. Olson K, Hanson J, Michaud M. A phase II trial of Reiki for the management of pain in advanced cancer patients. *J Pain Symptom Manage* 2003;26:990–7.
170. Wilkinson DS, Knox PL, Chatman JE, et al. The clinical effectiveness of healing touch. *J Altern Complement Med* 2002;8:33–47.
171. So PS, Jiang Y, Qin Y. Touch therapies for pain relief in adults. *Cochrane Database Syst Rev* 2008;(4):CD006535.
172. Engebretson J, Wardell DW. Energy-based modalities. *Nurs Clin North Am* 2007;42:243–59, vi.
173. Meltz ML. Radiofrequency exposure and mammalian cell toxicity, genotoxicity, and transformation. *Bioelectromagnetics* 2003;Suppl 6:S196–213.
174. Elwood JM. Epidemiological studies of radio frequency exposures and human cancer. *Bioelectromagnetics* 2003;Suppl 6:S63–73.
175. Kheifets LI. Electric and magnetic field exposure and brain cancer: a review. *Bioelectromagnetics* 2001;Suppl 5:S120–31.
176. Finegold L, Flamm BL. Magnet therapy. *BMJ* 2006;332:4.
177. Carpenter JS, Wells N, Lambert B, et al. A pilot study of magnetic therapy for hot flashes after breast cancer. *Cancer Nurs* 2002;25:104–9.
178. Han JS. Acupuncture: neuropeptide release produced by electrical stimulation of different frequencies. *Trends Neurosci* 2003;26:17–22.
179. Wu MT, Hsieh JC, Xiong J, et al. Central nervous pathway for acupuncture stimulation: localization of processing with functional MR imaging of the brain—preliminary experience. *Radiology* 1999;212: 133–41.
180. Rosen T, de Veciana M, Miller HS, et al. A randomized controlled trial of nerve stimulation for relief of nausea and vomiting in pregnancy. *Obstet Gynecol* 2003;102:129–35.
181. Streitberger K, Diefenbacher M, Bauer A, et al. Acupuncture compared to placebo-acupuncture for

- postoperative nausea and vomiting prophylaxis: a randomised placebo-controlled patient and observer blind trial. *Anaesthesia* 2004;59:142–9.
182. Bertolucci LE, DiDario B. Efficacy of a portable acupuncture device in controlling seasickness. *Aviat Space Environ Med* 1995;66:1155–8.
183. Ming JL, Kuo BI, Lin JG, Lin LC. The efficacy of acupressure to prevent nausea and vomiting in postoperative patients. *J Adv Nurs* 2002;39:343–51.
184. Berman BM, Lao L, Langenberg P, et al. Effectiveness of acupuncture as adjunctive therapy in osteoarthritis of the knee: a randomized, controlled trial. *Ann Intern Med* 2004;141:901–10.
185. NIH Consensus Conference. Acupuncture. *JAMA* 1998;280:1518–24.
186. Schnyer R, Lao L, Hammerschlag R, et al. Society for Acupuncture Research: 2007 conference report: “The status and future of acupuncture research: 10 years post-NIH Consensus Conference.” *J Altern Complement Med* 2008;14:859–60.
187. Melchart D, Linde K, Fischer P, et al. Acupuncture for recurrent headaches: a systematic review of randomized controlled trials. *Cephalalgia* 1999;19:779–86; discussion 765.
188. Alimi D, Rubino C, Pichard-Leandri E, et al. Analgesic effect of auricular acupuncture for cancer pain: a randomized, blinded, controlled trial. *J Clin Oncol* 2003;21:4120–6.
189. 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;1:283–91.
190. Ezzo JM, Richardson MA, Vickers A, et al. Acupuncture-point stimulation for chemotherapy-induced nausea or vomiting. *Cochrane Database Syst Rev* 2006;(2):CD002285.
191. Lee A, Done ML. Stimulation of the wrist acupuncture point P6 for preventing postoperative nausea and vomiting. *Cochrane Database Syst Rev* 2004;(3):CD003281.
192. Shen J, Wenger N, Glaspy J, et al. Electroacupuncture for control of myeloablative chemotherapy-induced emesis: a randomized controlled trial. *JAMA* 2000;284:2755–61.
193. Josefson A, Kreuter M. Acupuncture to reduce nausea during chemotherapy treatment of rheumatic diseases. *Rheumatology (Oxford)* 2003;42:1149–54.
194. Streitberger K, Friedrich-Rust M, Bardenheuer H, et al. Effect of acupuncture compared with placebo-acupuncture at P6 as additional antiemetic prophylaxis in high-dose chemotherapy and autologous peripheral blood stem cell transplantation: a randomized controlled single-blind trial. *Clin Cancer Res* 2003;9:2538–44.
195. Ernst E. Acupuncture: what does the most reliable evidence tell us? *J Pain Symptom Manage* 2009;37:709–14.
196. Naeim A, Dy SM, Lorenz KA, et al. Evidence-based recommendations for cancer nausea and vomiting. *J Clin Oncol* 2008;26:3903–10.
197. 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;220:365–70.
198. Gardani G, Cerrone R, Biella C, et al. A progress study of 100 cancer patients treated by acupressure for chemotherapy-induced vomiting after failure with the pharmacological approach. *Minerva Med* 2007;98:665–8.
199. 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;99:1070–5.
200. Roscoe JA, Morrow GR, Hickok JT, et al. The efficacy of acupressure and acustimulation wrist bands for the relief of chemotherapy-induced nausea and vomiting. A University of Rochester Cancer Center Community Clinical Oncology Program multicenter study. *J Pain Symptom Manage* 2003;26:731–42.
201. Johnstone PA, Niemtow RC, Riffenburgh RH. Acupuncture for xerostomia: clinical update. *Cancer* 2002;94:1151–6.
202. Johnstone PA, Peng YP, May BC, et al. Acupuncture for pilocarpine-resistant xerostomia following radiotherapy for head and neck malignancies. *Int J Radiat Oncol Biol Phys* 2001;50:353–7.
203. Johnstone PA, Polston GR, Niemtow RC, Martin PJ. Integration of acupuncture into the oncology clinic. *Palliat Med* 2002;16:235–9.
204. Dawidson I, Angmar-Mansson B, Blom M, et al. Sensory stimulation (acupuncture) increases the release of calcitonin gene-related peptide in the saliva of xerostomia sufferers. *Neuropeptides* 1999;33:244–50.
205. Rydholm M, Strang P. Acupuncture for patients in hospital-based home care suffering from xerostomia. *J Palliat Care* 1999;15:20–3.
206. Dawidson I, Angmar-Mansson B, Blom M, et al. Sensory stimulation (acupuncture) increases the release of vasoactive intestinal polypeptide in the

- saliva of xerostomia sufferers. *Neuropeptides* 1998; 32: 543–8.
207. Andersen SW, Machin D. Acupuncture treatment of patients with radiation-induced xerostomia. *Oral Oncol* 1997;33:146–7.
  208. Blom M, Dawidson I, Fernberg JO, et al. Acupuncture treatment of patients with radiation-induced xerostomia. *Eur J Cancer B Oral Oncol* 1996;32B:182–90.
  209. Blom M, Lundeborg T. Long-term follow-up of patients treated with acupuncture for xerostomia and the influence of additional treatment. *Oral Dis* 2000;6:15–24.
  210. Deng G, Hou BL, Holodny AI, Cassileth BR. Functional magnetic resonance imaging (fMRI) changes and saliva production associated with acupuncture at LI-2 acupuncture point: a randomized controlled study. *BMC Complement Altern Med* 2008;8:37.
  211. Carpenter JS, Andrykowski MA, Cordova M, et al. Hot flashes in postmenopausal women treated for breast carcinoma: prevalence, severity, correlates, management, and relation to quality of life. *Cancer* 1998;82:1682–91.
  212. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002;288:321–33.
  213. Anderson GL, Limacher M, Assaf AR, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA* 2004; 291:1701–12.
  214. Loprinzi CL, Michalak JC, Quella SK, et al. Megestrol acetate for the prevention of hot flashes. *N Engl J Med* 1994;331:347–52.
  215. Goldberg RM, Loprinzi CL, O'Fallon JR, et al. Transdermal clonidine for ameliorating tamoxifen-induced hot flashes. *J Clin Oncol* 1994;12:155–8.
  216. Pandya KJ, Raubertas RF, Flynn PJ, et al. Oral clonidine in postmenopausal patients with breast cancer experiencing tamoxifen-induced hot flashes: a University of Rochester Cancer Center Community Clinical Oncology Program study. *Ann Intern Med* 2000;132:788–93.
  217. Loprinzi CL, Pisansky TM, Fonseca R, et al. Pilot evaluation of venlafaxine hydrochloride for the therapy of hot flashes in cancer survivors. *J Clin Oncol* 1998;16:2377–81.
  218. Yanklowitz BA. Giant cell tumor of tendon sheath: a literature review and case report. *J Am Podiatry Assoc* 1978;68:706–11.
  219. Lee EH, Remmler O, Fernando MA, et al. Robenidone-resistant *Eimeria* spp other than *Eimeria maxima*. *Vet Rec* 1976;99:466–7.
  220. Bichet DG, Arthus MF, Lonergan M. Is testing with dDAVP useful in detecting carriers of the nephrogenic diabetes insipidus gene? *Nephron* 1991;58:372–3.
  221. Nelson HD, Vesco KK, Haney E, et al. Nonhormonal therapies for menopausal hot flashes: systematic review and meta-analysis. *JAMA* 2006;295:2057–71.
  222. Albertazzi P, Steel SA, Bottazzi M. Effect of pure genistein on bone markers and hot flashes. *Climacteric* 2005;8:371–9.
  223. Lewis JE, Nickell LA, Thompson LU, et al. A randomized controlled trial of the effect of dietary soy and flaxseed muffins on quality of life and hot flashes during menopause. *Menopause* 2006;13:631–42.
  224. Verhoeven MO, van der Mooren MJ, van de Weijer PH, et al. Effect of a combination of isoflavones and *Actaea racemosa* Linnaeus on climacteric symptoms in healthy symptomatic perimenopausal women: a 12-week randomized, placebo-controlled, double-blind study. *Menopause* 2005;12:412–20.
  225. MacGregor CA, Canney PA, Patterson G, et al. 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;41:708–14.
  226. Secreto G, Chiechi LM, Amadori A, et al. Soy isoflavones and melatonin for the relief of climacteric symptoms: a multicenter, double-blind, randomized study. *Maturitas* 2004;47:11–20.
  227. Burke GL, Legault C, Anthony M, et al. Soy protein and isoflavone effects on vasomotor symptoms in peri- and postmenopausal women: the Soy Estrogen Alternative Study. *Menopause* 2003;10:147–53.
  228. 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;18:1068–74.
  229. Van Patten CL, Olivetto 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;20:1449–55.
  230. Tice JA, Ettinger B, Ensrud K, et al. Phytoestrogen supplements for the treatment of hot flashes: the Isoflavone Clover Extract (ICE) Study: a randomized controlled trial. *JAMA* 2003;290:207–14.
  231. Pockaj BA, Gallagher JG, Loprinzi CL, et al. Phase III double-blind, randomized, placebo-controlled

- crossover trial of black cohosh in the management of hot flashes: NCCTG Trial N01CC1. *J Clin Oncol* 2006;24:2836–41.
232. 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;19:2739–45.
233. Newton KM, Reed SD, LaCroix AZ, et al. Treatment of vasomotor symptoms of menopause with black cohosh, multibotanicals, soy, hormone therapy, or placebo: a randomized trial. *Ann Intern Med* 2006;145:869–79.
234. 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.
235. Kronenberg F, Fugh-Berman A. Complementary and alternative medicine for menopausal symptoms: a review of randomized, controlled trials. *Ann Intern Med* 2002;137:805–13.
236. Harding C, Harris A, Chadwick D. Auricular acupuncture: a novel treatment for vasomotor symptoms associated with luteinizing-hormone releasing hormone agonist treatment for prostate cancer. *BJU Int* 2009;103:186–90.
237. Dong H, Ludicke F, Comte I, et al. An exploratory pilot study of acupuncture on the quality of life and reproductive hormone secretion in menopausal women. *J Altern Complement Med* 2001;7:651–8.
238. Porzio G, Trapasso T, Martelli S, et al. Acupuncture in the treatment of menopause-related symptoms in women taking tamoxifen. *Tumori* 2002;88:128–30.
239. Carpenter JS, Neal JG. Other complementary and alternative medicine modalities: acupuncture, magnets, reflexology, and homeopathy. *Am J Med* 2005;118 Suppl 12B:109–17.
240. Lee MS, Shin BC, Ernst E. Acupuncture for treating menopausal hot flushes: a systematic review. *Climacteric* 2009;12:16–25.
241. 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;25:5584–90.
242. Vincent A, Barton DL, Mandrekar JN, et al. Acupuncture for hot flashes: a randomized, sham-controlled clinical study. *Menopause* 2007;14:45–52.
243. Avis NE, Legault C, Coeytaux RR, et al. A randomized, controlled pilot study of acupuncture treatment for menopausal hot flashes. *Menopause* 2008;15:1070–8.
244. Nir Y, Huang MI, Schnyer R, et al. Acupuncture for postmenopausal hot flashes. *Maturitas* 2007;56:383–95.
245. Walker EM, Rodriguez AI, Kohn B, et al. Acupuncture for the treatment of vasomotor symptoms in breast cancer patients receiving hormone suppression treatment [abstract]. *Int J Radiat Oncol Biol Phys* 2008;72:S103.
246. White AR, Rampes H, Campbell JL. Acupuncture and related interventions for smoking cessation. *Cochrane Database Syst Rev* 2006;(1):CD000009.
247. Bier ID, Wilson J, Studt P, Shakleton M. Auricular acupuncture, education, and smoking cessation: a randomized, sham-controlled trial. *Am J Public Health* 2002;92:1642–7.
248. Domino EF, Ni L, Xu Y, et al. Regional cerebral blood flow and plasma nicotine after smoking tobacco cigarettes. *Prog Neuropsychopharmacol Biol Psychiatry* 2004;28:319–27.
249. Filshie J, Penn K, Ashley S, Davis CL. Acupuncture for the relief of cancer-related breathlessness. *Palliat Med* 1996;10:145–50.
250. Vickers AJ, Feinstein MB, Deng GE, Cassileth BR. Acupuncture for dyspnea in advanced cancer: a randomized, placebo-controlled pilot trial [ISRCTN89462491]. *BMC Palliat Care* 2005;4:5.
251. Suzuki M, Namura K, Ohno Y, et al. The effect of acupuncture in the treatment of chronic obstructive pulmonary disease. *J Altern Complement Med* 2008;14:1097–105.
252. Lau KS, Jones AY. A single session of Acu-TENS increases FEV1 and reduces dyspnoea in patients with chronic obstructive pulmonary disease: a randomised, placebo-controlled trial. *Aust J Physiother* 2008;54:179–84.
253. Mock V, Atkinson A, Barsevick A, et al. NCCN practice guidelines for cancer-related fatigue. *Oncology (Huntingt)* 2000;14(11A):151–61.
254. Vickers AJ, Straus DJ, Fearon B, Cassileth BR. Acupuncture for postchemotherapy fatigue: a phase II study. *J Clin Oncol* 2004;22:1731–5.
255. Escalante CP, Grover T, Johnson BA, et al. A fatigue clinic in a comprehensive cancer center: design and experiences. *Cancer* 2001;92(6 Suppl):1708–13.
256. Shlay JC, Chaloner K, Max MB, et al. Acupuncture and amitriptyline for pain due to HIV-related peripheral neuropathy: a randomized controlled trial. *Terry Beinr Community Programs for Clinical Research on AIDS. JAMA* 1998;280:1590–5.
257. Abuaisa BB, Costanzi JB, Boulton AJ. Acupuncture for the treatment of chronic painful peripheral diabetic neuropathy: a long-term study. *Diabetes Res Clin Pract* 1998;39:115–21.
258. Wong R, Sagar S. Acupuncture treatment for chemotherapy-induced peripheral neuropathy—a case series. *Acupunct Med* 2006;24:87–91.

259. Melchart D, Weidenhammer W, Streng A, et al. Prospective investigation of adverse effects of acupuncture in 97 733 patients. *Arch Intern Med* 2004;164:104–5.
260. World Cancer Research Fund/American Institute for Cancer Research. Food, nutrition, physical activity, and the prevention of cancer: a global perspective. Washington (DC): American Institute for Cancer Research; 2007.
261. Wiseman M. The second World Cancer Research Fund/American Institute for Cancer Research expert report. Food, nutrition, physical activity, and the prevention of cancer: a global perspective. *Proc Nutr Soc* 2008;67:253–6.
262. Clark LC, Combs GF Jr, Turnbull BW, et al. Effects of selenium supplementation for cancer prevention in patients with carcinoma of the skin. A randomized controlled trial. Nutritional Prevention of Cancer Study Group. *JAMA* 1996;276:1957–63.
263. Peto R, Doll R, Buckley JD, Sporn MB. Can dietary beta-carotene materially reduce human cancer rates? *Nature* 1981;290:201–8.
264. Sporn MB. Combination chemoprevention of cancer. *Nature* 1980;287:107–8.
265. Martinez ME, Marshall JR, Giovannucci E. Diet and cancer prevention: the roles of observation and experimentation. *Nat Rev Cancer* 2008;8:694–703.
266. Albanes D. Vitamin supplements and cancer prevention: where do randomized controlled trials stand? *J Natl Cancer Inst* 2009;101:2–4.
267. McMichael AJ. Food, nutrition, physical activity and cancer prevention. Authoritative report from World Cancer Research Fund provides global update. *Public Health Nutr* 2008;11:762–3.
268. Baron JA, Beach M, Mandel JS, et al. Calcium supplements for the prevention of colorectal adenomas. Calcium Polyp Prevention Study Group. *N Engl J Med* 1999;340:101–7.
269. Blot WJ, Li JY, Taylor PR, et al. Nutrition intervention trials in Linxian, China: supplementation with specific vitamin/mineral combinations, cancer incidence, and disease-specific mortality in the general population. *J Natl Cancer Inst* 1993;85:1483–92.
270. Lin J, Cook NR, Albert C, et al. Vitamins C and E and beta carotene supplementation and cancer risk: a randomized controlled trial. *J Natl Cancer Inst* 2009;101:14–23.
271. Wactawski-Wende J, Kotchen JM, Anderson GL, et al. Calcium plus vitamin D supplementation and the risk of colorectal cancer. *N Engl J Med* 2006;354:684–96.
272. Lee IM, Cook NR, Gaziano JM, et al. Vitamin E in the primary prevention of cardiovascular disease and cancer: the Women's Health Study: a randomized controlled trial. *JAMA* 2005;294:56–65.
273. Hercberg S, Galan P, Preziosi P, et al. The SU.VI.MAX Study: a randomized, placebo-controlled trial of the health effects of antioxidant vitamins and minerals. *Arch Intern Med* 2004;164:2335–42.
274. Schatzkin A, Lanza E, Corle D, et al. Lack of effect of a low-fat, high-fiber diet on the recurrence of colorectal adenomas. Polyp Prevention Trial Study Group. *N Engl J Med* 2000;342:1149–55.
275. Hennekens CH, Buring JE, Manson JE, et al. Lack of effect of long-term supplementation with beta carotene on the incidence of malignant neoplasms and cardiovascular disease. *N Engl J Med* 1996;334:1145–9.
276. Prentice RL, Thomson CA, Caan B, et al. Low-fat dietary pattern and cancer incidence in the Women's Health Initiative Dietary Modification Randomized Controlled Trial. *J Natl Cancer Inst* 2007;99:1534–43.
277. Lippman SM, Klein EA, Goodman PJ, et al. Effect of selenium and vitamin E on risk of prostate cancer and other cancers: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). *JAMA* 2009;301:39–51.
278. Omenn GS, Goodman GE, Thornquist MD, et al. Effects of a combination of beta carotene and vitamin A on lung cancer and cardiovascular disease. *N Engl J Med* 1996;334:1150–5.
279. Cole BF, Baron JA, Sandler RS, et al. Folic acid for the prevention of colorectal adenomas: a randomized clinical trial. *JAMA* 2007;297:2351–9.
280. Omenn GS, Goodman GE, Thornquist MD, et al. Risk factors for lung cancer and for intervention effects in CARET, the Beta-Carotene and Retinol Efficacy Trial. *J Natl Cancer Inst* 1996;88:1550–9.
281. Block K, Koch A, Mead M, et al. Re: Should supplemental antioxidant administration be avoided during chemotherapy and radiation therapy? *J Natl Cancer Inst* 2009;101:124–5; author reply 125–6.
282. Brambilla D, Mancuso C, Scuderi MR, et al. The role of antioxidant supplement in immune system, neoplastic, and neurodegenerative disorders: a point of view for an assessment of the risk/benefit profile. *Nutr J* 2008;7:29.
283. Lawenda BD, Kelly KM, Ladas EJ, et al. Should supplemental antioxidant administration be avoided during chemotherapy and radiation therapy? *J Natl Cancer Inst* 2008;100:773–83.

284. Block KI, Koch AC, Mead MN, et al. Impact of antioxidant supplementation on chemotherapeutic toxicity: a systematic review of the evidence from randomized controlled trials. *Int J Cancer* 2008;123:1227–39.
285. Ladas EJ, Jacobson JS, Kennedy DD, et al. Antioxidants and cancer therapy: a systematic review. *J Clin Oncol* 2004;22:517–28.
286. Greenlee H, Hershman DL, Jacobson JS. Use of antioxidant supplements during breast cancer treatment: a comprehensive review. *Breast Cancer Res Treat* 2009;115(3):437–52.
287. Dennert G, Horneber M. Selenium for alleviating the side effects of chemotherapy, radiotherapy and surgery in cancer patients. *Cochrane Database Syst Rev* 2006;(3):CD005037.
288. Zimmerer T, Bocker U, Wenz F, Singer MV. Medical prevention and treatment of acute and chronic radiation induced enteritis—is there any proven therapy? A short review. *Z Gastroenterol* 2008;46:441–8.
289. Bowen JM, Stringer AM, Gibson RJ, et al. VSL#3 probiotic treatment reduces chemotherapy-induced diarrhea and weight loss. *Cancer Biol Ther* 2007;6:1449–54.
290. Osterlund P, Ruotsalainen T, Peuhkuri K, et al. Lactose intolerance associated with adjuvant 5-fluorouracil-based chemotherapy for colorectal cancer. *Clin Gastroenterol Hepatol* 2004;2:696–703.
291. St Jean AT, Zhang M, Forbes NS. Bacterial therapies: completing the cancer treatment toolbox. *Curr Opin Biotechnol* 2008;19:511–7.
292. Kamen B. Folate and antifolate pharmacology. *Semin Oncol* 1997;24(5 Suppl 18):S18–30–9.
293. Branda RF, Nigels E, Lafayette AR, Hacker M. Nutritional folate status influences the efficacy and toxicity of chemotherapy in rats. *Blood* 1998;92:2471–6.
294. Shiroky JB. The use of folates concomitantly with low-dose pulse methotrexate. *Rheum Dis Clin North Am* 1997;23:969–80.
295. Tisdale MJ. Catabolic mediators of cancer cachexia. *Curr Opin Support Palliat Care*. 2008;2(4):256–61.
296. Colomer R, Moreno-Nogueira JM, Garcia-Luna PP, et al. N-3 fatty acids, cancer and cachexia: a systematic review of the literature. *Br J Nutr* 2007;97:823–31.
297. Dewey A, Baughan C, Dean T, et al. Eicosapentaenoic acid (EPA, an omega-3 fatty acid from fish oils) for the treatment of cancer cachexia. *Cochrane Database Syst Rev* 2007;(1):CD004597.
298. de Luis DA, Izaola O, Aller R, et al. A randomized clinical trial with two omega 3 fatty acid enhanced oral supplements in head and neck cancer ambulatory patients. *Eur Rev Med Pharmacol Sci* 2008;12:177–81.
299. Fearon KC, Von Meyenfeldt MF, Moses AG, et al. Effect of a protein and energy dense N-3 fatty acid enriched oral supplement on loss of weight and lean tissue in cancer cachexia: a randomised double blind trial. *Gut* 2003;52:1479–86.
300. Ko RJ. A U.S. perspective on the adverse reactions from traditional Chinese medicines. *J Chin Med Assoc* 2004;67:109–16.
301. Kumar NB, Hopkins K, Allen K, et al. Use of complementary/integrative nutritional therapies during cancer treatment: implications in clinical practice. *Cancer Control* 2002;9:236–43.
302. Labriola D, Livingston R. Possible interactions between dietary antioxidants and chemotherapy. *Oncology (Williston Park)* 1999;13:1003–8; discussion 1008, 1011–2.
303. Seifried HE, McDonald SS, Anderson DE, et al. The antioxidant conundrum in cancer. *Cancer Res* 2003;63:4295–8.
304. Kumar NB, Allen K, Bell H. Perioperative herbal supplement use in cancer patients: potential implications and recommendations for presurgical screening. *Cancer Control* 2005;12:149–57.
305. Cassileth B, Lucarelli C. *Herb-drug interactions in oncology*. Hamilton (ON): BC Decker; 2003.
306. Cohen I, Tagliaferri M, Tripathy D. Traditional Chinese medicine in the treatment of breast cancer. *Semin Oncol* 2002;29:563–74.
307. Vickers A. Botanical medicines for the treatment of cancer: rationale, overview of current data, and methodological considerations for phase I and II trials. *Cancer Invest* 2002;20:1069–79.
308. Kodama N, Harada N, Nanba H. A polysaccharide, extract from *Grifola frondosa*, induces Th-1 dominant responses in carcinoma-bearing BALB/c mice. *Jpn J Pharmacol* 2002;90:357–60.
309. Ooi VE, Liu F. Immunomodulation and anti-cancer activity of polysaccharide-protein complexes. *Curr Med Chem* 2000;7:715–29.
310. Wasser SP, Weis AL. Therapeutic effects of substances occurring in higher Basidiomycetes mushrooms: a modern perspective. *Crit Rev Immunol* 1999;19:65–96.
311. Taylor JA, Weber W, Standish L, et al. Efficacy and safety of echinacea in treating upper respiratory tract infections in children: a randomized controlled trial. *JAMA* 2003;290:2824–30.

312. Yale SH, Liu K. *Echinacea purpurea* therapy for the treatment of the common cold: a randomized, double-blind, placebo-controlled clinical trial. *Arch Intern Med* 2004;164:1237–41.
313. Barrett BP, Brown RL, Locken K, et al. Treatment of the common cold with unrefined echinacea. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 2002;137:939–46.
314. Turner RB, Bauer R, Woelkart K, et al. An evaluation of *Echinacea angustifolia* in experimental rhinovirus infections. *N Engl J Med* 2005;353:341–8.
315. Blumenthal M, Farnsworth NR. Echinacea angustifolia in rhinovirus infections. *N Engl J Med* 2005;353:1971–72; author reply 1971–72.
316. Geier FP, Konstantinowicz T. Kava treatment in patients with anxiety. *Phytother Res* 2004;18:297–300.
317. Lehl S. Clinical efficacy of kava extract WS 1490 in sleep disturbances associated with anxiety disorders. Results of a multicenter, randomized, placebo-controlled, double-blind clinical trial. *J Affect Disord* 2004;78:101–10.
318. Centers for Disease Control and Prevention. Hepatic toxicity possibly associated with kava-containing products—United States, Germany, and Switzerland, 1999–2002. *JAMA* 2003;289:36–7.
319. Gurley BJ, Gardner SF, Hubbard MA, et al. In vivo assessment of botanical supplementation on human cytochrome P450 phenotypes: *Citrus aurantium*, *Echinacea purpurea*, milk thistle, and saw palmetto. *Clin Pharmacol Ther* 2004;76:428–40.
320. Linde K, Mulrow CD. St John's wort for depression. *Cochrane Database Syst Rev* 2000;(2):CD000448.
321. Schrader E. Equivalence of St John's wort extract (Ze 117) and fluoxetine: a randomized, controlled study in mild-moderate depression. *Int Clin Psychopharmacol* 2000;15:61–8.
322. Mathijssen RH, Verweij J, de Bruijn P, et al. Effects of St. John's wort on irinotecan metabolism. *J Natl Cancer Inst* 2002;94:1247–9.
323. Markowitz JS, Donovan JL, DeVane CL, et al. Effect of St John's wort on drug metabolism by induction of cytochrome P450 3A4 enzyme. *JAMA* 2003;290:1500–4.
324. Kane GC, Lipsky JJ. Drug-grapefruit juice interactions. *Mayo Clin Proc* 2000;75:933–42.
325. Bailey DG, Dresser GK. Interactions between grapefruit juice and cardiovascular drugs. *Am J Cardiovasc Drugs* 2004;4:281–97.
326. Velicer CM, Ulrich CM. Vitamin and mineral supplement use among US adults after cancer diagnosis: a systematic review. *J Clin Oncol* 2008;26:665–73.
327. Fletcher RH, Fairfield KM. Vitamins for chronic disease prevention in adults: clinical applications. *JAMA* 2002;287:3127–9.
328. Willett WC, Stampfer MJ. Clinical practice. What vitamins should I be taking, doctor? *N Engl J Med* 2001;345:1819–24.
329. Kennedy DD, Tucker KL, Ladas ED, et al. Low antioxidant vitamin intakes are associated with increases in adverse effects of chemotherapy in children with acute lymphoblastic leukemia. *Am J Clin Nutr* 2004;79:1029–36.
330. Miller P, Demark-Wahnefried W, Snyder DC, et al. Dietary supplement use among elderly, long-term cancer survivors. *J Cancer Surviv* 2008;2:138–48.