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Key words: cancer, oncology, complementary therapies, CAM, integrative medicine

The Society for Integrative Oncology (SIO) is an international organization established to encourage scientific evaluation, dissemination of evidence-based information, and appropriate clinical integration of complementary therapies (<<http://www.Integrativeonc.org>>).

Practice Guidelines were developed by the authors listed below and by the Executive Committee of the Society for Integrative Oncology, which approved this document. Guidelines are a work in progress; they will be updated as needed and are available on the SIO Web site as well: <www.IntegrativeOnc.org>.

Contents

Executive Summary and Methods
 Key Words and Abbreviations

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DOI 10.2310/7200.2007.002

Introduction
 Recommendations and Discussion
 Summary of Recommendations
 References

Executive Summary

The use of complementary therapies is common among cancer patients. “Alternative therapies” draw a far smaller percentage of patients but remain a serious issue. The difference between “complementary” and “alternative” therapies is important and essential to recognize. “Alternative” therapies are typically promoted as viable options for use in lieu of mainstream care. By definition, alternative therapies have not been scientifically proven to work and have sometimes been disproved. They are sometimes invasive, biologically active, and costly. Complementary medicine, however, makes use of nonconventional treatment modalities, some of which have known efficacy, but they are used in combination with mainstream care.

The Society for Integrative Oncology (SIO) and its Medline-listed journal (*Journal of the Society of Integrative Oncology*), formed by leading oncologists and oncology

professionals from major cancer centers and organizations, deliberately uses terminology meant to distinguish itself from inappropriate therapies and “alternatives,” as well as to display quality research and appropriate application of useful, adjunctive complementary modalities (<www.IntegrativeOnc.org>). This chapter includes minimal discussion of unproven approaches and recommends that readers obtain additional information about therapies not included here at <www.mskcc.org/aboutherbs>, <www.mdanderson.org/cimer>, <www.quackwatch.org>, <www.cancer.gov/cam/>, or <<http://nccam.nih.gov/>>.

This chapter addresses complementary therapies, which are therapies used as adjuncts to mainstream care. Complementary therapies are typically not used to treat cancer but are used primarily to treat the symptoms associated with cancer and mainstream treatments. In some circumstances, they may increase the efficacy of mainstream treatments. This also includes the study of botanicals, vitamins, and other supplements. The examination of natural products is not new and has proven a fruitful approach to new drug discovery. Extensive ongoing research around the world is examining natural products for their role in cancer prevention and treatment. However, until there is evidence for the safety and efficacy of the substance, they should not be used as alternatives to mainstream care. Clinical trials of some herbs and other botanicals aside, most complementary therapies are not specific to a particular cancer diagnosis. Instead, they are used typically to treat symptoms shared by patients across many cancer diagnoses. This is generally appropriate as symptoms tend to stem less from the primary diagnosis than from involvement of a particular organ or toxicities associated with treatment, which evoke similar symptoms in patients across cancer diagnoses.

Health care professionals should be able to provide evidence-based, patient-centered advice to guide patients to receive benefit while avoiding harm. A panel of experts in oncology and integrative medicine was assembled to evaluate the current level of evidence regarding complementary therapies relevant to the care of cancer patients. Specific recommendations are made based on the strength of evidence and the risks/benefit ratio.

Because the use of complementary and alternative therapies by cancer patients is common, a strong recommendation is made to inquire about the use of these therapies as a routine part of all initial evaluations of cancer patients. Complementary therapies can be helpful in symptom control, whereas the use of therapies for which there is no evidence for safety and efficacy used instead of mainstream care can delay or impair treatment.

It is strongly recommended that qualified professionals provide guidance in an open, evidence-based, and patient-centered manner to those patients who use or who are interested in complementary or alternative medicine so that they can approach these therapies appropriately. Patients should be fully informed of the potential risks/benefits, to have realistic expectations, and to know the financial implications of all treatment modalities. This is especially true for treatments that are deemed safe for which there are not as much data on efficacy.

Mind-body modalities are strongly recommended to be incorporated into a multidisciplinary approach in reducing anxiety, mood disturbance, and chronic pain and improving quality of life in cancer patients. A strong recommendation is made to consider massage therapy as part of a multimodality treatment approach in patients experiencing anxiety or pain. Application of deep or intense pressure during massage therapy should be avoided near cancer lesions or anatomic distortions such as postoperative changes, as well as in patients with a bleeding tendency (weak recommendation). Therapies based purely on the putative manipulation of bioenergy fields should be used with caution, and patients should be informed that there is no currently plausible scientific mechanism for the benefits of such therapies. Patients should not use these therapies in place of mainstream care and should be fully informed of the potential risks/benefits, to have realistic expectations, and to know the financial implications.

Acupuncture is strongly recommended as a complementary therapy for pain control when pain is poorly controlled, when side effects from other modalities are clinically significant, or when reducing the amount of pain medicine becomes a clinical goal. Acupuncture is also strongly recommended as a complementary therapy when nausea and vomiting associated with chemotherapy are poorly controlled or when side effects from other modalities are clinically significant. Electrostimulation wristbands have been shown to be useful for controlling nausea on the day of chemotherapy but should not, at this time, be used long-term to reduce delayed chemotherapy-induced nausea and vomiting.

The value of acupuncture in treating nicotine addiction, dyspnea, or fatigue is not conclusive; however, it can be tried if mainstream treatments have been ineffective. Trials of acupuncture for chemotherapy-induced neuropathy and xerostomia showed positive results. Acupuncture for post-thoracotomy pain is under study. Given some reports of potential benefit and extensive data on safety, a trial of acupuncture is acceptable as a complementary therapy that can address patients' concerns and

needs. Acupuncture is safe when performed by qualified practitioners. Caution should be exercised in patients with bleeding tendency.

Taking dietary supplements can be beneficial in some circumstances and harmful in others. Supplementation of vitamin B₁₂ and folic acid is required in patients receiving pemetrexed treatment. However, megadoses may disturb the balance of related B vitamins and cause exacerbation or addition of some problems. A strong recommendation is made for dietary supplements used by patients, in particular herbal products, to be evaluated for side effects and potential interaction with other drugs. Until there are more definitive data, those that are likely to interact with chemotherapeutic agents should not be used during chemotherapy and those with other drug interactions need to be avoided depending on the patient's other medications and comorbidities.

It is strongly recommended that patients be advised to avoid using treatments for which there is no scientific information on safety and efficacy in lieu of mainstream care. Such practice can lead to significant harm to cancer patients because it delays effective treatment and causes unpredictable adverse effects. All cancer care professionals need to be aware of all therapies being recommended and used by patients. Ideally, care among all modalities used should be communicated and coordinated.

Despite the long history of many complementary therapies, only a few have been evaluated with modern scientific research tools in a handful of indications. A large gap exists between our current level of scientific evidence and what we need to provide evidence-based advice. More rigorous scientific research is being conducted to enrich our knowledge base. A rational, balanced, patient-centered approach using available data is strongly recommended to address patients' concerns.

Methods

Medline manuscripts and textbook chapters were searched using the following key words: cancer, oncology, com-

plementary therapies, CAM, alternative therapies, and integrative medicine. Data were summarized and recommendations developed on the basis of the criteria listed in Table 2.

Abbreviations

ATBC = alpha-tocopherol, beta-carotene
CAM = complementary and alternative medicine
CARET = Beta-Carotene and Retinol Efficacy Trial
CNS = central nervous system
DSHEA = Dietary Supplement Health and Education Act
GI = gastrointestinal
HIV = human immunodeficiency virus
MRI = magnetic resonance imaging
NCCAM = National Center for Complementary and Alternative Medicine
NCHS = National Center for Health Statistics
NHIS = National Health Interview Survey
NIH = National Institutes of Health
SSRI = selective serotonin reuptake inhibitor
WHEL = Women's Healthy Eating and Lifestyle Study
WHI = Women's Health Initiative
WINS = Women's Intervention Nutrition Study

Introduction

A distinction between "complementary" and "alternative" therapies is required. *Complementary therapies*, used as adjuncts to mainstream care, are supportive measures that help control symptoms, enhance well-being, and contribute to overall patient care.¹ *Alternative therapies* are scientifically unproven and are used instead of mainstream treatment or offered as viable therapeutic options instead of mainstream care. This is especially problematic in oncology, when delayed treatment can diminish the possibility of remission and cure.² Over time, some complementary therapies are proven safe and effective.

Table 1. Categories and Examples of Complementary and Alternative Therapies

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, qigong
Ancient medical systems	Traditional Chinese medicine, ayurvedic medicine, acupuncture

Table 2. Grading of Recommendations

<i>Grade of Recommendation</i>	<i>Benefit versus Risk and Burdens</i>	<i>Methodologic Strength of Supporting Evidence</i>	<i>Implications</i>
Strong recommendation, high-quality evidence 1A	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
Strong recommendation, moderate-quality evidence 1B	Benefits clearly outweigh risk and burdens, or vice versa	RCTs with important limitations (inconsistent results, methodologic flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	
Strong recommendation, low- or very low-quality evidence 1C	Benefits clearly outweigh risk and burdens, or vice versa	Observational studies or case series	Strong recommendation but may change when higher-quality evidence becomes available
Weak recommendation, high-quality evidence 2A	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
Weak recommendation, moderate-quality evidence 2B	Benefits closely balanced with risks and burden	RCTs with important limitations (inconsistent results, methodologic flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	
Weak recommendation, low- or very low-quality evidence 2C	Uncertainty in the estimates of benefits, risks, and burden; benefits, risk, and burden may be closely balanced	Observational studies or case series	Very weak recommendations; other alternatives may be equally reasonable

RCT = randomized controlled trial.

These become integrated into mainstream care. Both alternative and complementary medicine focus on treatment modalities. Integrative oncology is not about specific mainstream or nonconventional treatment modalities but is an approach to treating patients. It is an approach that addresses patients' concerns using a rational risk/benefit evaluation. It is the ability to integrate the best of complementary and mainstream care using a multidisciplinary approach, combining the best of mainstream cancer care and rational, data-based, adjunctive complementary therapies.³

Most complementary and alternative medicine (CAM) practices can be loosely grouped into five categories according to the National Institutes of Health (NIH) National Center for Complementary and Alternative Medicine (NCCAM; Table 1). The therapies in these categories are quite mixed: some helpful, others known not to work, and some for which there is limited evidence. There is also considerable overlap. For example, traditional Chinese medicine uses biologically active botanicals and acupuncture.

Yoga has mind-body and manipulative components and theory from ayurvedic medicine. Some interventions, such as tai chi and yoga, are often included in two categories (mind-body and energy therapies).

Most complementary therapies are not specific to a particular cancer diagnosis. Instead, they are used typically to treat symptoms shared by patients across many cancer diagnoses. This is generally appropriate as symptoms tend to stem less from the primary diagnosis than from involvement of a particular organ or toxicities associated with treatment, which evoke similar symptoms in patients across cancer diagnoses. For example, bone metastases cause pain regardless of whether the primary lesion is from the breast or prostate; chemotherapy-induced nausea and vomiting are associated more closely with the emetogenic potency of the drug used than with the underlying cancer diagnosis.

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

Recommendations and Discussion

The recommendations are organized according to modalities (see Table 1). Within each modality, recommendations supported by a strong level of evidence (Grade A and B – state criteria) are discussed first. Review of selected topics where only Grade C recommendations can be made follows. Selectivity in Grade C is often required because of the nascent nature of research in this area; for some relevant therapies, there is not sufficient evidence on which to base meaningful recommendations.

1. Use of Complementary and Alternative Therapies

Recommendation 1: All patients with cancer should be asked specifically about their use of complementary and alternative therapies. Grade of recommendation: 1C

Rationale and Evidence

The most comprehensive and reliable findings on Americans' use of CAM in general come from the National Center for Health Statistics (NCHS) 2002 National Health Interview Survey (NHIS). NCHS is an agency of the Centers for Disease Control and Prevention.⁴ Of 31,044 adults surveyed, 75% used some form of CAM. When prayer specifically for health reasons is excluded, the percentage is 50%.

By various accounts, 10 to over 60% of cancer patients have used CAM, depending primarily on the definitions applied.^{5–10} The Datamonitor 2002 Survey indicated that 80% of cancer patients used an alternative or complementary modality.¹¹ There is some indication of a growth in CAM use by cancer patients in recent years.¹² When compared with other cancer diagnoses, the prevalence of CAM use was the highest in lung cancer patients (53%) according to a nationwide survey in Japan.¹³ European surveys found different data.¹⁴ Consistent across all surveys, however, is that CAM users are younger, more educated, and more affluent, representing a more health-conscious segment of the population who are eager and able to play an active role in their own care.

Even though people with cancer typically use complementary medicines along with conventional treatment, 38 to 60% of patients with cancer are taking complementary medicines without informing any member of their health care team.^{9,10} There are a variety of reasons why open communication about complementary treatments is not taking place in medical clinics. The most common reason patients give is that it just never came up in the

discussion, that is, no one asked them, and they did not think it was important. Patients may fear that the topic will be received with indifference or dismissed without discussion, and health care professionals may fear not knowing how to respond to questions or fear initiating a time-consuming discussion.^{9,10} Regardless, it is critical that health care professionals ask patients about their use of complementary medicines and be open and receptive when patients disclose their use.

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. Grade of recommendation: 1C

Rationale and Evidence

Surveys show that most cancer patients rely on friends and family members, the media, and the Internet, rather than health care professionals, for CAM information.^{13,14} Information obtained from such nonprofessional sources is often inaccurate. A majority of patients used botanicals or other supplements expecting them to suppress the growth or even cure cancer,^{13,14} not realizing that much of the research is still in the preclinical stage and the information is based on in vitro or animal studies. There has been little evidence to date showing that any CAM therapies can suppress or cure disease in clinical settings. Many supplements are often produced with minimal, if any, quality control, making their actual content uncertain.¹⁵ Some may interact with many prescription medications, including chemotherapy, possibly decreasing efficacy or increasing toxicity.^{16,17} Some patients use dietary supplements indiscriminately for possible benefits in cancer prevention and cancer treatment. However, some supplements may 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.^{18,19} Ironically, therapies backed by supportive evidence for symptom control and favorable risk/benefit ratios, such as acupuncture and mind-body techniques, were used less frequently than were botanicals.^{13,14}

Two further barriers that hinder open communication on CAM use are the perceived lack of familiarity with CAM modalities and a dismissive attitude among many mainstream health care professionals. Medical degree courses rarely include review of common CAM therapies, and many physicians who provide cancer patient care are unable to discuss these approaches in an open, patient-centered

fashion. Increasing numbers of educational resources, including review articles, books, continuing medical education courses, and reliable Web sites, are available to interested physicians, nurses, and other practitioners. (Table 3).

Major cancer centers in North America and elsewhere have established integrative medicine programs to study and combine helpful complementary therapies with mainstream oncology care, while educating cancer patients to avoid therapies lacking data on safety or efficacy, on potentially harmful therapies, and on herb–drug interactions. The health professionals in these programs are valuable resources for busy oncologists who lack time or knowledge for in-depth discussion with patients about CAM. Some states license CAM providers and naturopathic doctors trained in herb–drug and nutraceutical interactions as well as the safe way to administer CAM therapies. Licensed naturopathic physicians now may be board certified in naturopathic oncology.

One strategy for safely guiding patients in shared decision-making is to examine the evidence of safety and efficacy available for any given therapy. Evidence-based information about CAM can come from randomized controlled trials and epidemiologic reports, case reports, historical reports (in terms of safety), and reviews of such studies. It can be helpful to consider a grid, with safety along one axis and efficacy along the other (Figure 1).²⁰

When the evidence of safety and efficacy is strong, it makes clinical sense to recommend the therapy. On the other hand, when the evidence of safety and efficacy is weak, it makes clinical sense to avoid and discourage the patient from using that therapy. This, of course, is meant as a guide, and health care professionals will vary in their opinions as to what constitutes enough evidence on efficacy, balanced with the information on safety.

The challenge is that 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 patient harm will result. Conversely, the stronger the evidence of safety or efficacy, the stronger the argument is that the therapy is, or at least should be, considered within the standard of care and less likely to injure the patient.^{8,20,21} Thus, when a patient mentions a therapy, the first step for the physician is to determine the level of risk by examining the evidence for safety, whether that therapy is considered complementary or conventional. The second step is to estimate the efficacy of that therapy. Both of these steps, however, require efficient searching for and acquisition of evidence-based resources. Accordingly, busy clinicians need to take advantage of previously conducted reviews by recognized experts and organizations. More importantly, if the evidence of safety is good and there is less information on efficacy, which is often the case, patients should be fully informed of the potential risks and benefits. In this case, they need to have realistic expectations and they should take into consideration the financial implications and that there is little information to suggest that the therapy will help them. Having provided evidence-based information on the risks and benefits is a patient-centered approach that is informed by evidence.

2. Mind-Body Techniques

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

Rationale and Evidence

Mind-body modalities, including meditation, hypnosis, relaxation techniques, cognitive-behavioral therapy, bio-

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

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

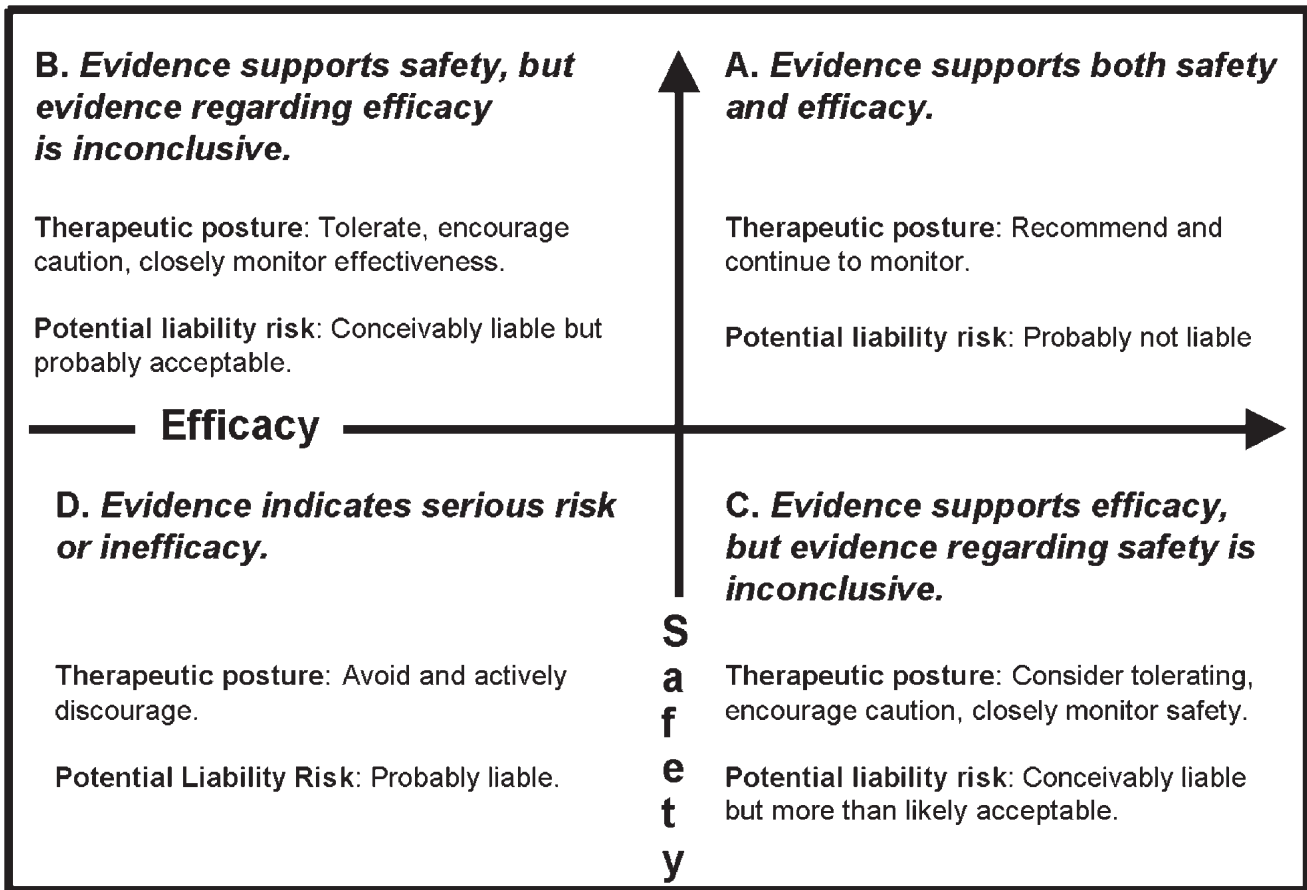


Figure 1. The spectrum of clinical risk. Adapted with publisher's permission from figure on page 597 of article, "Potential Physician Malpractice Liability Associated with Complementary and Integrative Medical Therapies" by Michael H. Cohen JD and David M. Eisenberg, MD in *Annals of Internal Medicine*, 2002;136(8):596–603.

feedback, and guided imagery, are increasingly becoming part of mainstream care over the years. A survey found that 19% of American adults used at least one mind-body therapy in a 1-year period.²² The 2002 US nationwide survey showed that 12% of the respondents used deep breathing relaxation techniques and 8% used meditation.⁴ A meta-analysis of 116 studies found that mind-body therapies could reduce anxiety, depression, and mood disturbance in cancer patients and assist their coping skills.²³ Mind-body techniques also may help reduce chronic low back pain, joint pain, headache, and procedural pain.²⁴ A 2002 systematic review of psychological therapies for patients with cancer examined the benefits of different psychological strategies for different outcomes. In particular, they recommended interventions

involving self-practice and hypnosis for managing conditioned nausea and vomiting and suggested that further research is warranted to examine the benefits of relaxation training and guided imagery. Moreover, they recommend that further research be done to examine the benefits of relaxation and guided imagery for managing general nausea, anxiety, quality of life, and overall physical symptoms.²⁵

Mind-body techniques must be practiced to produce beneficial effects, so estimated compliance needs to be a component when evaluating the use of mind-body techniques with patients.²⁶

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).

In a randomized wait-list control study of 109 cancer patients, participation in a 7-week mindfulness-based stress reduction program was associated with significant improvement in mood disturbance and symptoms of stress.²⁷ A single-arm study of breast and prostate cancer patients showed significant improvement in overall quality of life, stress, and sleep quality, but symptom improvement was not significantly correlated with program attendance or minutes of home practice.²⁸ Mindfulness-based stress reduction techniques must be practiced to produce beneficial effects.²⁶

Yoga, which combines physical movement, breath control, and meditation, improved sleep quality in a trial of 39 lymphoma patients. Practicing a form of yoga that incorporates controlled breathing and visualization significantly decreased sleep disturbance when compared with wait-list controls.²⁹

Tai chi, which combines physical movement, breath control, and meditation, was associated with increased aerobic capacity, muscular strength, and flexibility and improved health-related quality of life and self-esteem in women with breast cancer when compared with a psychosocial support therapy control group.^{30,31}

Hypnosis is an artificially induced state of consciousness in which a person is 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 a good rapport with a level of trust; the environment must be comfortable and free from distractions; and the patient must be willing to undergo the process and must desire to be hypnotized. Research shows that hypnosis is beneficial in reducing pain, anxiety, phobias, and nausea and vomiting.

In one study, 20 excisional breast biopsy patients were randomly assigned to a hypnosis or control group (standard care). Postsurgery pain and distress were reduced in the hypnosis group.³² 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 more pain relief than control patients. The effects were similar between hypnosis and cognitive-behavioral therapy. Both therapies also reduce anxiety and distress, with hypnosis showing greater effectiveness.³³ Hypnosis was studied in a randomized controlled trial of 60 patients undergoing elective

plastic surgery. Peri- and postoperative anxiety and pain were significantly reduced in the hypnosis group when compared with the control group, who just received stress reduction training. Reduction in anxiety and pain was achieved, along with significant reduction in intraoperative requirements for sedatives and analgesics.³⁴

In a study of 67 bone marrow transplant patients, subjects were randomized to one of the four intervention groups: hypnosis training, cognitive-behavioral coping skills training, therapist contact control, or usual care. Oral pain from mucositis was reduced in the hypnosis group.³⁵ An NIH Technology Assessment Panel found strong evidence for hypnosis in alleviating cancer-related pain.³⁶ Hypnosis effectively treats anticipatory nausea in pediatric³⁷ and adult cancer patients³⁸ and reduces postoperative nausea and vomiting.³⁴

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

Relaxation techniques were shown in randomized controlled trials to ameliorate anxiety and distress significantly. A randomized study of relaxation therapy versus alprazolam (Xanax Pfizer, New York, NY) showed that both approaches significantly decreased anxiety and depression, although the effect of alprazolam was slightly quicker for anxiety and stronger for depressive symptoms.³⁹ Relaxation achieves the effect without side effects and at a lower cost. A randomized trial of 82 radiation therapy patients found significant reductions in tension, depression, anger, and fatigue for those who received relaxation training or imagery.⁴⁰

A meta-analysis of 59 studies showed improved sleep induction and maintenance with psychological interventions.⁴¹ Although pharmaceuticals may produce a rapid response, some studies suggest that behavioral therapies help maintain longer-term improvement in sleep quality. The NIH consensus panel concluded that behavioral techniques, particularly relaxation and biofeedback, produce improvements in some aspects of sleep, but the magnitude of improvement in sleep onset and time may not achieve clinical significance.³⁶

Music therapy employs the use of music to effect psychological, physiologic, and social changes in individuals who have problems, including developmental and learning disabilities, behavior and psychiatric disorders, as well as

other medical illnesses. The form music therapy takes varies depending on the individual and his or her circumstances. A music therapist is a qualified practitioner who has undergone rigorous training specializing in using music as a therapeutic tool. They are trained to assess each patient with regard to his or her problem and experience with music. The therapist then decides what mode of therapy would benefit the patient based on music therapy principles and techniques. Because the therapy is individual to the patient's situation and experience with music, the modality of therapy can vary. Therapies can range from listening to music, actively creating music with instruments, talking about music, and lyric writing, among others.

The use of music in the oncologic setting has become more common in recent years. It has been used frequently to reduce pain, anxiety, and nausea. Music therapy has also been successfully used to affect mood and the side effects of treatment. Evidence has shown that listening to music selected to relax the patient reduces anxiety.^{42,43} Music therapy increased relaxation and comfort levels in bone marrow transplant patients.⁴⁴ Furthermore, in another study, patients participating in music listening and active music improvisation sessions showed increased relaxation and energy levels and increased salivary immunoglobulin A and lower cortisol levels relative to controls.⁴⁵

Although there are only a few studies suggesting that music therapy may be useful in an oncology setting, there are several limitations to this research. Most of the studies have used small samples, and only a few used 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, an actual music therapist plays in the process. Guided imagery was also frequently combined with the music, and, therefore, it is hard to determine which component is effective.

Other forms of expressive arts have been used in the oncology setting, including dance therapy, art therapy, journaling, and many others. However, there are few data to support the utility of these interventions at improving aspects of quality of life. As there are few risks associated with these therapies, if patients are interested in trying them, this can, of course, be supported.

3. Manipulative and Body-Based Practices

Recommendation 4: 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 5: The application of deep or intense pressure is not recommended near cancer lesions or enlarged lymph nodes or anatomic distortions, such as postoperative changes, as well as in patients with a bleeding tendency. Grade of recommendation: 2B

Rationale and Evidence

The many types of body-based practices have in common 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 has variations in techniques, such as Swedish massage, Thai massage, and shiatsu. Other bodywork techniques, such as the Alexander technique and Pilates, address posture and movement. One type of manipulative therapy 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 it is generally accepted as part of 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^{46–49} as well as fatigue and distress.⁴⁶ 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. Patients experienced significant decreases in anxiety, and in one of three pain measures, breast cancer patients experienced significant decreases in pain as well.⁴⁷ In the largest study to date, 87 hospitalized cancer patients were randomized to receive foot massage or control. Pain and anxiety scores fell with massage, with differences between groups achieving statistical and clinical significance.^{48,50,51} The use of aromatic oil seemed to enhance the effect of massage in early studies,^{49,52} but significant enhancement was not seen in more recent randomized controlled trials.^{53–55} For noncancer subacute and chronic back pain, massage therapy was found effective in a systematic review of randomized controlled trials, and preliminary data suggest that it may help reduce the costs of care.⁵⁶

Massage therapy is generally safe when practiced by credentialed practitioners. Serious adverse events are rare and associated with exotic types of massage or untrained or inexperienced practitioners.⁵⁷ 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. Patients with bleeding tendencies should receive only gentle, light-touch massage.

4. Energy Therapies

Recommendation 6: Therapies based on manipulation of putative bioenergy fields are safe but cannot be encouraged due to limited evidence on efficacy. Grade of recommendation: 1C

Rationale and Evidence

Energy therapies are based on the theory that manipulation of “energy fields” around a patient has therapeutic value. Two types of “energy fields” are involved: biofield and electromagnetic field.

Biofield therapies are intended to affect energy fields that purportedly surround and penetrate the human body. Because no convincing scientific evidence has yet emerged to prove or disprove the existence of such fields, some of the therapies, although originally developed from the theory of bioenergy fields, may exert their effects on patients through light touch or mind-body interaction. However, there have been some blinded, placebo-controlled trials of therapeutic touch that found some benefit to the therapy in the absence of touching the patients.^{51,58} Although therapies such as yoga, tai chi, and qigong are intended to work with bodily “energetic fields,” they are likely to exert strong effects through a mind-body connection.

Therapies that are intended to work exclusively with biofields, such as reiki, therapeutic touch, healing touch, and external qigong, are known to be safe, but there is limited evidence for efficacy, and, to date, there is no scientific evidence for the mechanism of action. However, these therapies may improve aspects of quality of life, provide a sense of control, and provide hope. Patients who seek out such therapies need to have realistic expectations; they should take into consideration the financial implications; they should be informed that there is little information to suggest that the therapy will help them; and they need to be informed that the benefits may likely be due to the placebo effect. They should never use such therapies in place of mainstream care.

Bioelectromagnetic-based therapies involve the unconventional use of electromagnetic fields, such as pulsed fields, magnetic fields, or alternating-current or direct-current fields. Most research in bioelectromagnetics focuses on genotoxicity of environmental electromagnetic

fields, such as whether exposure to power lines or cell phones increases the risk of cancer.^{59–61} There have been no reports of controlled trials showing the bioelectromagnetic therapies to be effective in cancer treatment or symptom control.

5. Acupuncture

Acupuncture is a modality originated from traditional Chinese medicine. The theory is that one can regulate the flow of “qi” (vital energy) by the stimulation of certain points on the body with needles, heat, or pressure. Recent scientific research suggests that the effects of acupuncture are likely mediated by the nervous system, but this has not been definitively established. Release of neurotransmitters and change in brain-functional magnetic resonance imaging (MRI) signals are observed during acupuncture.^{62,63} Acupuncture was used traditionally for almost every ailment, but few such applications are supported by rigorous clinical studies. However, evidence supports the use of acupuncture in treating some common symptoms experienced by cancer patients and others.

Recommendation 7: Acupuncture is recommended as a complementary therapy when pain is poorly controlled. Grade of recommendation: 1A

Rationale and Evidence

Pain is the most common and the best studied indication for acupuncture. Acupuncture relieves both acute (eg, postoperative dental pain) and chronic (eg, headache) pain.^{64,65} An NIH consensus statement in 1997 supported acupuncture for adult postoperative pain, chemotherapy-related nausea and vomiting, and postoperative dental pain.⁶⁴ Insufficient evidence was available to support other claims of efficacy at that time, but in the ensuing years, many publications have documented the utility of acupuncture as an adjunct treatment for pain, emesis, and other symptoms.

A recent randomized controlled trial of 570 patients with osteoarthritis of the knee found that a 26-week course of acupuncture significantly improved pain and dysfunction when compared with a sham-acupuncture control. In this study, all patients received other usual care for osteoarthritis. At 8 weeks, both pain and function improved, but the difference between groups was significant only for function.⁶⁶ A companion article reported the results of a randomized controlled trial of acupuncture for chronic mechanical neck pain. Acupuncture was found

to reduce neck pain and produce a statistically, but not clinically, significant effect compared with placebo.⁶⁷ For short-term relief of chronic low back pain, acupuncture is significantly more effective than sham treatment according to a meta-analysis. Data on acute low back pain are inconclusive.⁶⁸

Acupuncture appears to be effective against cancer-related pain. A randomized placebo-controlled trial tested auricular acupuncture for patients with pain despite stable medication. A total of 90 patients were randomized to have needles placed at correct acupuncture points (treatment group) versus acupuncture or pressure at nonacupuncture points. 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.⁶⁹ Skin penetration per se showed no significant analgesic effect. The authors selected acupuncture points by measuring electrodermal signals. These results are especially important because most of the patients had neuropathic pain, which is often refractory to conventional treatment.

Brain imaging technology is now being used to examine the specific nervous pathways involved in acupuncture. In functional MRI studies, true acupuncture induces brain activation in the hypothalamus and nucleus accumbens and deactivates areas of the anterior cingulate cortex, amygdala, and hippocampus. Such changes are not observed in control stimulations, which affect only sensory cortex change. Deactivation of the amygdala and hippocampus has been observed also with electroacupuncture. These data suggest that acupuncture modulates the affective-cognitive aspect of pain perception.⁶³ Correlations between signal intensities and analgesic effects also have been reported.⁷⁰

Recommendation 8: Acupuncture is recommended as a complementary therapy for radiation-induced xerostomia. Grade of recommendation: 1B

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.⁷¹⁻⁷⁹ In one study evaluating the relief of various symptoms in 123 cancer patients, 32% of whom suffered from xerostomia, a 30% improvement in symptoms after acupuncture treatment was demonstrated.⁷³ Another study demonstrated a long-term

(> 3 years) increase in saliva production after acupuncture.⁷⁴

Recommendation 9: Acupuncture is recommended as a complementary therapy when nausea and vomiting associated with chemotherapy or surgical anesthesia are poorly controlled or when side effects from other modalities, such as muscle spasm or dysfunction following head and neck surgery, are clinically significant. Grade of recommendation: 1B

Rationale and Evidence

Acupuncture and acupressure help lessen chemotherapy-induced nausea and vomiting.⁸⁰ 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. Electroacupuncture 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.⁸¹ 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).⁸² 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.⁸³ Acupuncture also suppresses nausea and vomiting caused by pregnancy,⁸⁴ surgery,⁸⁵ and motion sickness.^{86,87}

When used for the prevention of postoperative nausea and vomiting, electroacupoint stimulation or ondansetron was more effective than placebo, with a greater degree of patient satisfaction, but electroacupoint stimulation seems to be more effective in controlling nausea compared with ondansetron.⁸⁸ Stimulation at P6 also has analgesic effects.

Recommendation 10: Electrostimulation wristbands may be recommended on the day of chemotherapy but are not recommended for managing delayed chemotherapy-induced nausea and vomiting. Grade of recommendation: 1B

Acupressure wristbands that render continuous stimulation of the PC6 point also have been tested for chemotherapy-related nausea and vomiting. In a randomized controlled trial of 739 patients, nausea on the day of chemotherapy was reduced significantly in patients wearing wristbands compared with no-band controls. No significant differences were found for delayed nausea or vomiting.⁸⁹ Unlike acupressure wristbands, the expected efficacy of electrostimulation wristbands was not significantly related to any component of nausea or to antiemetic use. It was postulated that the electrical stimulus generated by the electrostimulation band could act as a conditioned stimulus (akin to a reminder) of the nausea that patients are trying to control and thereby actually accentuate the development of nausea in some individuals.⁸⁹

Recommendation 11: When cancer patients do not stop smoking despite use of other options, a trial of acupuncture is recommended to assist in smoking cessation. Grade of recommendation: 2C

Rationale and Evidence

Smoking cessation has the largest impact in preventing lung cancer. Educational, behavioral, and medical interventions are the mainstay for smoking cessation. The effect of acupuncture has been studied, with mixed results. A meta-analysis of 22 studies concluded that acupuncture is no more effective than placebo in smoking cessation. However, the same meta-analysis found that acupuncture did no worse than any other intervention.⁹⁰ A more recent randomized trial of 141 subjects tested auricular acupuncture, education, or the combination in achieving smoking cessation. 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.⁹¹

Brain imaging studies show that smoking suppresses blood flow to the anterior cingulate cortex, hippocampus, and amygdala.⁹² Curiously, these are the same areas suppressed by acupuncture.⁶³ Given the huge public health impact of smoking and the imperfect results of existing smoking cessation techniques, it is acceptable, although not encouraged, for someone who has been unable to quit smoking to try acupuncture. Further studies using refined acupuncture techniques guided by recent advances in acupuncture research appear to be warranted.

Recommendation 12: For patients suffering from symptoms such as dyspnea, fatigue, chemotherapy-induced neuropathy, or post-thoracotomy pain, a trial of acupuncture is recommended. Grade of recommendation: 2C

Rationale and Evidence

Cancer patients with advanced disease may experience dyspnea due to parenchymal tumor burden, pleural effusion, or other causes. Oxygen and opioids remain the mainstay of symptomatic treatment, although confusion and constipation are common side effects. An uncontrolled study in cancer patients receiving palliative care showed marked reduction in dyspnea scores after a session of acupuncture.⁹³ However, a subsequent randomized, sham-controlled trial did not show significant improvement in subjective sensation of dyspnea in advanced lung or breast cancer patients.⁹⁴

Fatigue following chemotherapy or irradiation, another major and common problem, has few reliable treatments in patients without a correctable cause, such as anemia.⁹⁵ In an uncontrolled trial of fatigue after chemotherapy, acupuncture reduced fatigue 31% after 6 weeks of treatment. Among those with severe fatigue at baseline, 79% had nonsevere fatigue scores at follow-up,⁹⁶ whereas fatigue was reduced only in 24% of patients receiving usual care in another center.⁹⁷

Although acupuncture is commonly used to treat neuropathy, most previous research was done in human immunodeficiency virus (HIV)-related neuropathy or diabetic neuropathy. Patients with HIV-related peripheral neuropathy were treated with a standardized acupuncture regimen or control-point regimen in a randomized controlled trial of 239 patients. A reduction in pain scores was observed in both groups, and no significant difference between the groups was seen.⁹⁸ 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, a percentage higher than the usual response to placebo observed in pain trials. There was no significant change in the peripheral neurologic examination scores.⁹⁹ No clinical trial of acupuncture for chemotherapy-induced neuropathy has been reported, although a recent small case series showed positive results.¹⁰⁰ A randomized clinical trial to evaluate acupuncture in the treatment of post-thoracotomy neuropathic pain is under way.

If the above symptoms become a significant clinical problem in a particular patient 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 to the favorable safety record of acupuncture and the lack of other viable treatment options. Patients should be fully informed of the potential risks to have realistic expectations and to know the financial implications.

Recommendation 13: For patients with bleeding tendencies, it is recommended that acupuncture be performed by qualified practitioners and used cautiously. 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 to 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. The most common minor adverse events included local bleeding and needling pain, both in fewer than 0.05% of patients.¹⁰¹ It is prudent to avoid acupuncture at the site of tumor or metastasis and in limbs with lymphedema, areas with considerable anatomic distortion due to surgery, and patients with thrombocytopenia, coagulopathy, or neutropenia. Cancer patients require certified practitioners who are experienced in treating patients with malignant diseases.

6. Diet and Dietary Supplements Including Herbal Products

Many epidemiology studies demonstrate an association of diet and cancer incidence. Other than smoking cessation, a healthy diet is perhaps the most important lifestyle change a person can make to help prevent cancer, as well as cardiovascular disease, diabetes, etc. On the other hand, special dietary regimens have had very few trials among patients after diagnosis. One of two studies among patients with breast cancer reported increased risk of recurrence with more servings of butter, margarine, lard, and beer,¹⁰² and the other study reported reduced risk of death with more protein, vegetables, fiber, and omega-3 fatty acids.¹⁰³

A review of dietary patterns and supplements for a variety of cancers concluded that the impact of most nutritional interventions could not be reliably estimated because of the limited number of trials and because many of the trials were of low quality.¹⁰⁴ Larger studies with better designs are currently in process.

In spite of the lack of evidence from clinical studies after diagnosis, some dietary regimens have been promoted for cancer treatment, such as the macrobiotic diet or alkaline diet.

The use of biologically based complementary and alternative therapies, such as herbs and other dietary supplements, is very popular among cancer patients.^{13,14,105} Most users expect the supplements to help cancer treatment or reduce side effects, but such expectations are often unrealistic and unmet.¹⁴ The purported benefits of the supplements are usually supported by preclinical studies. Although some have been evaluated in clinical trials, small numbers of participants, design problems, and mixed outcomes have limited conclusions. The concurrent use of supplements, especially high-dose antioxidants or complex botanical agents, during chemotherapy or radiation therapy can be problematic due to drug-supplement interaction.^{106,107} Some botanicals, based on their chemical structure, may have adverse effects in perioperative use. Their antiplatelet activity may adversely interact with corticosteroids and central nervous system depressant drugs; they may produce gastrointestinal effects, hepatotoxicity, and nephrotoxicity; and they can produce additive effects when used concomitantly with opioid analgesics.¹⁰⁸ Quality control and adulteration of dietary supplements are additional major issues that need to be considered.¹⁰⁹

Recommendation 14: It is recommended that dietary supplements, including both herbal product and megadoses of vitamins and minerals, be evaluated for side effects and potential interaction with other drugs. Those that are likely to interact with other drugs, including chemotherapeutic agents, should not be used concurrently with chemotherapy or radiation or prior to surgery. Grade of recommendation: 1B

Recommendation 15: It is recommended that patients be referred to registered dietitians for guidelines on usual diets to promote basic health. Grade of recommendation: 1B

Recommendation 16: In cancer patients who either fail or decline antitumor therapies, it is recommended that use of botanical agents occur only in the context of clinical trials, recognized nutritional guidelines, or clinical evaluation of the

risk/benefit ratio based upon available evidence. Referral to a qualified expert in CAM modality, such as an Doctor of Naturopathy (ND) who is board certified in naturopathic oncology, may be considered. Grade of recommendation: 1C

Rationale and Evidence

Dietary supplements include vitamins, minerals, herbs or other botanicals, amino acids, and other substances intended to supplement the diet. They 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.

Botanicals and other natural products are a valuable source for the development of therapeutic agents when they are carefully studied for safety and efficacy. About one-quarter of 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). Sold as dietary supplements, however, they are rarely produced to the same high standards. Some herbs cause significant side effects. Detrimental herb–drug interactions may occur. Finally, product inconsistency and contamination have been reported.^{109,110}

Most claims made by producers of herbal supplements are based on historical experience, unconfirmed by clinical trials. Many herbs show direct antitumor activity in *in vitro* or animal experiments,^{111,112} but translating preclinical to clinical use often fails because the active constituents, 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 components.

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.^{113–115} However, the most popular immune-boosting herb in the United States used commonly to treat colds—echinacea—showed disappointing results in randomized controlled trials.^{116–119} These and other botanical research results have been controversial as questions were

raised about the dosage and species used (eg, *Echinacea purpurea* versus *Echinacea angustifolia*).¹²⁰

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,^{121,122} and it was considered a viable alternative to benzodiazepines because of its benefits and the absence of dependency and addiction. However, some case reports associate this herbal remedy with severe hepatotoxicity, resulting in liver failure and death for vulnerable populations.¹²³

Herbal medicine was practiced historically by those with at least some knowledge of the side effects of herbs. Today, however, many herbal and other botanical products are readily available to US consumers under the Dietary Supplement Health and Education Act of 1994 (DSHEA), which regulates them only as food supplements and requires no prior studies of safety and efficacy. A few herbal products have been removed from the market by the Food and Drug Administration due to adverse events. A recent example is agents that contain 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.^{17,124} Herbs such as feverfew, garlic, ginger, and ginkgo have anticoagulant effects and should be avoided by patients on Coumadin, 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 tricyclics and selective serotonin reuptake inhibitors in mild to moderate depression and with a side-effect profile superior to both.^{125,126} It was found, however, that 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.¹²⁷ Such metabolic interactions preclude St. John's wort for patients on medications metabolized by CYP3A4.¹²⁸

Although not an herb, grapefruit juice was found 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.^{129,130} Interestingly, such an interaction initially was discovered by accident in an ethanol–calcium channel blocker

interaction study in which grapefruit juice was used as the vehicle for the alcohol.¹³¹ Details of herb–drug interaction can be found at several sources.^{110,132}

Recommendation 17: It is recommended that patients be advised to avoid therapies promoted as “alternatives” to mainstream care. Grade of recommendation: 1A

Rationale and Evidence

Some alternative therapies thought to improve survival have largely been demonstrated to be ineffective in clinical trials, but some of those trials were underpowered to detect a difference, and detecting differences in the context of multiple dietary types and supplements is complex.¹³³ Randomized controlled trials have shown no benefit or, in some cases, shorter survival, for high-dose vitamin C (10+g),^{134,135} shark cartilage,¹³⁶ hydrazine sulfate,^{137–140} and mistletoe extracts.^{141–144} However, some recent reports show some clinical benefit in the use of mistletoe.^{145,146} Further research is warranted.

Cohort or phase II studies have shown no benefit to DiBella therapy,^{147,148} antineoplastons,¹⁴⁹ Livingston-Wheeler therapy,¹⁵⁰ Laetrile,¹⁵¹ and pau d’arco.¹⁵² In a population-based study, patients using alternative therapy have been shown to have shorter survival, after adjustment for known prognostic factors, than those avoiding such therapies.¹⁵³

Gaps in Research

In spite of the long history of most complementary modalities, rigorous scientific research on these therapies is a recent phenomenon. The research is further limited by lack of sufficient funding, lack of qualified investigators, and methodologic 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 a complete traditional medical system and were used historically to treat almost every ailment. Only a few modalities have been evaluated with modern scientific research tools. More comprehensive evidence-based recommendations will become feasible when the research basis expands as anticipated.

We view the following as high-priority areas of research: (1) effectiveness of complementary therapies in the management of symptoms or disease processes for which our current treatment options are not satisfactory; (2) mechanisms of action explained by contemporary

biomedical science; (3) a definitive database of drug–supplement interactions; and (4) development of new cancer therapies derived from botanicals, supplements, and other natural products for cancer treatment or their synergistic effect with conventional medicine. Since some nutritional patterns have been associated with prevention of cancer, their potential role in the prevention of recurrence, metastasis, and/or second primaries warrants further research.

Conclusions

The use of complementary and alternative therapies is common among cancer patients. These therapies are very diverse in their origin, theory, practice, safety, and efficacy. Some of the therapies have been shown in studies to be helpful in reducing symptoms experienced by cancer patients. These complementary therapies (used as adjuncts to mainstream cancer treatment) are increasingly integrated into regular oncologic care, as in the practice of integrative oncology. Dietary supplements, herbs, and other botanicals can be problematic due to their adverse effects or interactions with chemotherapy, radiotherapy, or surgery but may be beneficial when patients are not undergoing these treatments. Then there are those therapies promoted as “alternative” to mainstream cancer treatment. Patients who use these “alternative” therapies are at risk of missing the window of opportunity for effective treatment. It is important for all involved in the care of cancer patients to help patients distinguish between the two and to approach complementary and alternative therapies appropriately in order to receive benefit while avoiding harm. A patient-centered approach using a risk/benefit discussion and incorporating reliable sources of information as useful tools should be used to address patients’ concerns and needs. Specific advice should be provided after considering the level of evidence and the risk/benefits ratio. Health care professionals should know where to find reliable sources of information.

Summary of Recommendations

Recommendation 1: All patients with cancer should be asked specifically about their use of complementary and alternative therapies. 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. Grade of recommendation: 1C

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

Recommendation 4: 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 5: The application of deep or intense pressure is not recommended near cancer lesions or enlarged lymph nodes or anatomic distortions, such as postoperative changes, as well as in patients with a bleeding tendency. Grade of recommendation: 2C

Recommendation 6: Therapies based on manipulation of putative bioenergy fields are safe but cannot be encouraged due to limited evidence on efficacy. Quality of evidence: 1C

Recommendation 7: Acupuncture is recommended as a complementary therapy when pain is poorly controlled or when side effects, such as neuropathy or xerostomia from other modalities, are clinically significant. Grade of recommendation: 1A

Recommendation 8: Acupuncture is recommended as a complementary therapy for radiation-induced xerostomia. Grade of recommendation: 1B

Recommendation 9: Acupuncture is recommended as a complementary therapy when nausea and vomiting associated with chemotherapy are poorly controlled or when side effects from other modalities, such as muscle spasm or dysfunction following head and neck surgery, are clinically significant. Grade of recommendation: 1B

Recommendation 10: Electrostimulation wristbands are not recommended for managing delayed chemotherapy-induced nausea and vomiting but may be recommended on the day of chemotherapy. Grade of recommendation: 1B

Recommendation 11: When cancer patients do not stop smoking despite use of other options, a trial of acupuncture is recommended to assist in smoking cessation. Grade of recommendation: 2C

Recommendation 12: For patients suffering from symptoms such as dyspnea, fatigue, chemotherapy-induced neuropathy, or post-thoracotomy pain, a trial of acupuncture is recommended. Grade of recommendation: 2C

Recommendation 13: For patients with bleeding tendencies, it is recommended that acupuncture be performed by qualified practitioners and used cautiously. Grade of recommendation: 1C

Recommendation 14: It is recommended that dietary supplements, in particular herbal products, be evaluated for side effects and potential interaction with other drugs. Those that are likely to interact with other drugs, including chemotherapeutic agents, should not be used concurrently with chemotherapy or radiation or prior to surgery. Grade of recommendation: 1B

Recommendation 15: It is recommended that patients be referred to registered dietitians for guidelines on usual diets to promote basic health. Grade of recommendation: 1B

Recommendation 16: In cancer patients who either fail or decline antitumor therapies, it is recommended that use of botanical agents occur only in the context of clinical trials. Grade of recommendation: 1C

Recommendation 17: It is recommended that patients be advised to avoid therapies promoted as “alternatives” to mainstream care. Grade of recommendation: 1A

References

- Deng G, Cassileth BR, Yeung KS. Complementary therapies for cancer-related symptoms. *J Support Oncol* 2004;2:419–26, discussion 427–9.
- Cassileth BR, Deng G. Complementary and alternative therapies for cancer. *Oncologist* 2004;9:80–9.
- Cassileth B, Deng G, Vickers A, et al. PDQ integrative oncology. Hamilton (ON): BC Decker; 2005.
- Barnes PM, Powell-Griner E, McFann K, et al. Complementary and alternative medicine use among adults: United States, 2002. *Adv Data* 2004;1–19.
- Adams J, Sibbritt DW, Easthope G, et al. The profile of women who consult alternative health practitioners in Australia. *Med J Aust* 2003;179:297–300.
- Chrystal K, Allan S, Forgeson G, et al. The use of complementary/alternative medicine by cancer patients in a New Zealand regional cancer treatment centre. *N Z Med J* 2003;116:U296.
- Lee MM, Chang JS, Jacobs B, et al. Complementary and alternative medicine use among men with prostate cancer in 4 ethnic populations. *Am J Public Health* 2002;92:1606–9.
- 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.
- Navo MA, Phan J, Vaughan C, et al. An assessment of the utilization of complementary alternative medication in women with gynecologic or breast malignancies. *J Clin Oncol* 2004;22:671–7.
- 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.
- Exploring complementary and alternative medicine. In: Medicine Io, editor. *The Richard and Hinda Rosenthal Lectures* 2001. Washington (DC): The National Academies Press; 2003.

12. Ernst E, Cassileth BR. The prevalence of complementary/alternative medicine in cancer: a systematic review. *Cancer* 1998;83:777–82.
13. 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.
14. Molassiotis A, Fernandez-Ortega P, Pud D, et al. Use of complementary and alternative medicine in cancer patients: a European survey. *Ann Oncol* 2005;16:655–63.
15. 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.
16. Beijnen JH, Schellens JH. Drug interactions in oncology. *Lancet Oncol* 2004;5:489–96.
17. Sparreboom A, Cox MC, Acharya MR, et al. Herbal remedies in the United States: potential adverse interactions with anticancer agents. *J Clin Oncol* 2004;22:2489–503.
18. 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.
19. 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.
20. Cohen MH, Eisenberg DM. Potential physician malpractice liability associated with complementary and integrative medical therapies. *Ann Intern Med* 2002;136:596–603.
21. Frenkel M, Ben-Arye E, Baldwin CD, et al. Approach to communicating with patients about the use of nutritional supplements in cancer care. *South Med J* 2005;98:289–94.
22. Wolsko PM, Eisenberg DM, Davis RB, et al. Use of mind-body medical therapies. *J Gen Intern Med* 2004;19:43–50.
23. 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.
24. Astin JA. Mind-body therapies for the management of pain. *Clin J Pain* 2004;20:27–32.
25. 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.
26. 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.
27. Specia M, Carlson LE, Goodey E, et al. 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.
28. Carlson LE, Specia M, Patel KD, et al. 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.
29. 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.
30. 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.
31. 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.
32. Montgomery GH, Weltz CR, Seltz M, et al. Brief presurgery hypnosis reduces distress and pain in excisional breast biopsy patients. *Int J Clin Exp Hypn* 2002;50:17–32.
33. 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.
34. 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.
35. 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.
36. 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.
37. Zeltzer LK, Dolgin MJ, LeBaron S, et al. A randomized, controlled study of behavioral intervention for chemotherapy distress in children with cancer. *Pediatrics* 1991;88:34–42.
38. Morrow GR, Morrell C. Behavioral treatment for the anticipatory nausea and vomiting induced by cancer chemotherapy. *N Engl J Med* 1982;307:1476–80.
39. 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.
40. Decker TW, Cline-Elsen J, Gallagher M. Relaxation therapy as an adjunct in radiation oncology. *J Clin Psychol* 1992;48:388–93.
41. Morin CM, Culbert JP, Schwartz SM. Nonpharmacological interventions for insomnia: a meta-analysis of treatment efficacy. *Am J Psychiatry* 1994;151:1172–80.
42. Frank JM. The effects of music therapy and guided visual imagery on chemotherapy induced nausea and vomiting. *Oncol Nurs Forum* 1985;12:47–52.
43. 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.
44. Boldt S. The effects of music therapy on motivation, psychological well-being, physical comfort, and exercise endurance of bone marrow transplant patients. *J Music Ther* 1996;33:164–88.
45. Burns SJ, Harbuz MS, Hucklebridge F, et al. A pilot study into the therapeutic effects of music therapy at a cancer help center. *Altern Ther Health Med* 2001;7:48–56.
46. 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.

47. 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.
48. 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.
49. Wilkinson S, Aldridge J, Salmon I, et al. An evaluation of aromatherapy massage in palliative care. *Palliat Med* 1999;13:409–17.
50. Taylor AG, Galper DI, Taylor P, et al. Effects of adjunctive Swedish massage and vibration therapy on short-term post-operative outcomes: a randomized, controlled trial. *J Altern Complement Med* 2003;9:77–89.
51. 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.
52. Ballard CG, O'Brien JT, Reichelt K, et al. 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.
53. Graham PH, Browne L, Cox H, et al. Inhalation aromatherapy during radiotherapy: results of a placebo-controlled double-blind randomized trial. *J Clin Oncol* 2003;21:2372–6.
54. 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.
55. Gedney JJ, Glover TL, Fillingim RB. Sensory and affective pain discrimination after inhalation of essential oils. *Psychosom Med* 2004;66:599–606.
56. Cherkin DC, Sherman KJ, Deyo RA, et al. 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.
57. Ernst E. The safety of massage therapy. *Rheumatology (Oxford)* 2003;42:1101–6.
58. Cook CA, Guerrero 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.
59. Meltz ML. Radiofrequency exposure and mammalian cell toxicity, genotoxicity, and transformation. *Bioelectromagnetics Suppl* 2003;6:S196–213.
60. Elwood JM. Epidemiological studies of radio frequency exposures and human cancer. *Bioelectromagnetics Suppl* 2003;6:S63–73.
61. Kheifets LI. Electric and magnetic field exposure and brain cancer: a review. *Bioelectromagnetics Suppl* 2001;5:S120–31.
62. Han JS. Acupuncture: neuropeptide release produced by electrical stimulation of different frequencies. *Trends Neurosci* 2003;26:17–22.
63. 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.
64. NIH Consensus Conference. Acupuncture. *JAMA* 1998;280:1518–24.
65. 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.
66. 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.
67. White P, Lewith G, Prescott P, et al. Acupuncture versus placebo for the treatment of chronic mechanical neck pain: a randomized, controlled trial. *Ann Intern Med* 2004;141:911–9.
68. Manheimer E, White A, Berman B, et al. Meta-analysis: acupuncture for low back pain. *Ann Intern Med* 2005;142:651–63.
69. 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.
70. Zhang WT, Jin Z, Cui GH, et al. Relations between brain network activation and analgesic effect induced by low vs. high frequency electrical acupoint stimulation in different subjects: a functional magnetic resonance imaging study. *Brain Res* 2003;982:168–78.
71. Johnstone PA, Niemtow RC, Riffenburgh RH. Acupuncture for xerostomia: clinical update. *Cancer* 2002;94:1151–6.
72. 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.
73. Johnstone PA, Polston GR, Niemtow RC, et al. Integration of acupuncture into the oncology clinic. *Palliat Med* 2002;16:235–9.
74. Blom M, Lundeberg T. Long-term follow-up of patients treated with acupuncture for xerostomia and the influence of additional treatment. *Oral Dis* 2000;6:15–24.
75. Rydholm M, Strang P. Acupuncture for patients in hospital-based home care suffering from xerostomia. *J Palliat Care* 1999;15:20–3.
76. 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.
77. 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.
78. Andersen SW, Machin D. Acupuncture treatment of patients with radiation-induced xerostomia. *Oral Oncol* 1997;33:146–7.
79. 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.
80. Lee A, Done ML. Stimulation of the wrist acupuncture point P6 for preventing postoperative nausea and vomiting. *Cochrane Database Syst Rev* 2004;CD003281.
81. 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.
82. Josefson A, Kreuter M. Acupuncture to reduce nausea during chemotherapy treatment of rheumatic diseases. *Rheumatology (Oxford)* 2003;42:1149–54.
83. 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.
84. 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.

85. 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.
86. Bertolucci LE, DiDario B. Efficacy of a portable acustimulation device in controlling seasickness. *Aviat Space Environ Med* 1995; 66:1155–8.
87. Ming JL, Kuo BI, Lin JG, et al. The efficacy of acupressure to prevent nausea and vomiting in post-operative patients. *J Adv Nurs* 2002;39:343–51.
88. Gan TJ, Jiao KR, Zenn M, et al. 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.
89. 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 Oncology Program multicenter study. *J Pain Symptom Manage* 2003;26:731–42.
90. White AR, Rampes H, Ernst E. Acupuncture for smoking cessation. *Cochrane Database Syst Rev* 2002;CD000009.
91. Bier ID, Wilson J, Studt P, et al. Auricular acupuncture education, and smoking cessation: a randomized, sham-controlled trial. *Am J Public Health* 2002;92:1642–7.
92. 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.
93. Filshie J, Penn K, Ashley S, et al. Acupuncture for the relief of cancer-related breathlessness. *Palliat Med* 1996;10:145–50.
94. Vickers AJ, Feinstein MB, Deng GE, et al. Acupuncture for dyspnea in advanced cancer: a randomized, placebo-controlled pilot trial [ISRCTN89462491]. *BMC Palliat Care* 2005;4:5.
95. Mock V, Atkinson A, Barsevick A, et al. NCCN practice guidelines for cancer-related fatigue. *Oncology (Huntingt)* 2000;14:151–61.
96. Vickers AJ, Straus DJ, Fearon B, et al. Acupuncture for postchemotherapy fatigue: a phase II study. *J Clin Oncol* 2004; 22:1731–5.
97. Escalante CP, Grover T, Johnson BA, et al. A fatigue clinic in a comprehensive cancer center: design and experiences. *Cancer* 2001;92:1708–13.
98. Shlay JC, Chaloner K, Max MB, et al. Acupuncture and amitriptyline for pain due to HIV-related peripheral neuropathy: a randomized controlled trial. Terry Beirn Community Programs for Clinical Research on AIDS. *JAMA* 1998;280:1590–5.
99. Abuaisha 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.
100. Wong R, Sagar S. Acupuncture treatment for chemotherapy-induced peripheral neuropathy—a case series. *Acupunct Med* 2006;24:87–91.
101. 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.
102. Hebert JR, Hurley TG, Ma Y. The effect of dietary exposures on recurrence and mortality in early stage breast cancer. *Breast Cancer Res Treat* 1998;51:17–28.
103. Holmes MD, Stampfer MJ, Colditz GA, et al. Dietary factors and the survival of women with breast carcinoma. *Cancer* 1999;86: 826–35.
104. Davies AA, Davey Smith G, Harbord R, et al. Nutritional interventions and outcome in patients with cancer or preinvasive lesions: systematic review. *J Natl Cancer Inst* 2006;98:961–73.
105. 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.
106. Labriola D, Livingston R. Possible interactions between dietary antioxidants and chemotherapy. *Oncology (Williston Park)* 1999; 13:1003–8; discussion 1008, 1011–2.
107. Seifried HE, McDonald SS, Anderson DE, et al. The antioxidant conundrum in cancer. *Cancer Res* 2003;63:4295–8.
108. 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.
109. Ko RJ. A U.S. perspective on the adverse reactions from traditional Chinese medicines. *J Chin Med Assoc* 2004;67:109–16.
110. Cassileth B, Lucarelli C. Herb-drug interactions in oncology. Hamilton (ON): BC Decker; 2003.
111. Cohen I, Tagliaferri M, Tripathy D. Traditional Chinese medicine in the treatment of breast cancer. *Semin Oncol* 2002;29:563–74.
112. 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.
113. 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.
114. Ooi VE, Liu F. Immunomodulation and anti-cancer activity of polysaccharide-protein complexes. *Curr Med Chem* 2000;7:715–29.
115. Wasser SP, Weis AL. Therapeutic effects of substances occurring in higher Basidiomycetes mushrooms: a modern perspective. *Crit Rev Immunol* 1999;19:65–96.
116. 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.
117. 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.
118. 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.
119. 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.
120. Blumenthal M, Farnsworth NR. *Echinacea angustifolia* in rhinovirus infections. *N Engl J Med* 2005;353:1971–2; author reply 1971–2.
121. Geier FP, Konstantinowicz T. Kava treatment in patients with anxiety. *Phytother Res* 2004;18:297–300.
122. 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.
123. 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.

124. 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.
125. Linde K, Mulrow CD. St John's wort for depression. *Cochrane Database Syst Rev* 2000;CD000448.
126. 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.
127. 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.
128. 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.
129. Kane GC, Lipsky JJ. Drug-grapefruit juice interactions. *Mayo Clin Proc* 2000;75:933–42.
130. Bailey DG, Dresser GK. Interactions between grapefruit juice and cardiovascular drugs. *Am J Cardiovasc Drugs* 2004;4:281–97.
131. Bailey DG, Spence JD, Edgar B, et al. Ethanol enhances the hemodynamic effects of felodipine. *Clin Invest Med* 1989;12:357–62.
132. Memorial Sloan-Kettering Cancer Center, Available at: <http://www.mskcc.org/about/herbs> (accessed March 16, 2007).
133. Vickers A. Alternative cancer cures: “unproven” or “disproven”? *CA Cancer J Clin* 2004;54:110–8.
134. Creagan ET, Moertel CG, O'Fallon JR, et al. Failure of high-dose vitamin C (ascorbic acid) therapy to benefit patients with advanced cancer. A controlled trial. *N Engl J Med* 1979;301:687–90.
135. Moertel CG, Fleming TR, Creagan ET, et al. High-dose vitamin C versus placebo in the treatment of patients with advanced cancer who have had no prior chemotherapy. A randomized double-blind comparison. *N Engl J Med* 1985;312:137–41.
136. Loprinzi CL, Levitt R, Barton DL, et al. Evaluation of shark cartilage in patients with advanced cancer: a North Central Cancer Treatment Group trial. *Cancer* 2005;104:176–82.
137. Kosty MP, Fleishman SB, Herndon JE II, et al. Cisplatin, vinblastine, and hydrazine sulfate in advanced, non-small-cell lung cancer: a randomized placebo-controlled, double-blind phase III study of the Cancer and Leukemia Group B. *J Clin Oncol* 1994;12:1113–20.
138. Kosty MP, Herndon JE, II, Green MR, et al. Placebo-controlled randomized study of hydrazine sulfate in lung cancer. *J Clin Oncol* 1995;13:1529–30.
139. Loprinzi CL, Goldberg RM, Su JQ, et al. Placebo-controlled trial of hydrazine sulfate in patients with newly diagnosed non-small-cell lung cancer. *J Clin Oncol* 1994;12:1126–9.
140. Loprinzi CL, Kuross SA, O'Fallon JR, et al. Randomized placebo-controlled evaluation of hydrazine sulfate in patients with advanced colorectal cancer. *J Clin Oncol* 1994;12:1121–5.
141. Goebell PJ, Otto T, Suhr J, et al. Evaluation of an unconventional treatment modality with mistletoe lectin to prevent recurrence of superficial bladder cancer: a randomized phase II trial. *J Urol* 2002;168:72–5.
142. Kleeberg UR, Suci S, Brocker EB, et al. Final results of the EORTC 18871/DKG 80-1 randomised phase III trial. rIFN-alpha2b versus rIFN-gamma versus ISCADOR M versus observation after surgery in melanoma patients with either high-risk primary (thickness >3 mm) or regional lymph node metastasis. *Eur J Cancer* 2004;40:390–402.
143. Lenartz D, Dott U, Menzel J, et al. Survival of glioma patients after complementary treatment with galactoside-specific lectin from mistletoe. *Anticancer Res* 2000;20:2073–6.
144. Steuer-Vogt MK, Bonkowsky V, Ambrosch P, et al. The effect of an adjuvant mistletoe treatment programme in resected head and neck cancer patients: a randomised controlled clinical trial. *Eur J Cancer* 2001;37:23–31.
145. Bar-Sela G, Goldberg H, Beck D, et al. Reducing malignant ascites accumulation by repeated intraperitoneal administrations of a *Viscum album* extract. *Anticancer Res* 2006;26:709–13.
146. Grossarth-Maticek R, Kiene H, Baumgartner SM, et al. Use of *Iscaador*, an extract of European mistletoe (*Viscum album*), in cancer treatment: prospective nonrandomized and randomized matched-pair studies nested within a cohort study. *Altern Ther Health Med* 2001;7:57–66, 68–72, 74–6 passim.
147. Evaluation of an unconventional cancer treatment (the Di Bella multitherapy): results of phase II trials in Italy. Italian Study Group for the Di Bella Multitherapy Trials. *BMJ* 1999;318:224–8.
148. Buiatti E, Arniani S, Verdecchia A, et al. Results from a historical survey of the survival of cancer patients given Di Bella multitherapy. *Cancer* 1999;86:2143–9.
149. Buckner JC, Malkin MG, Reed E, et al. Phase II study of antineoplastons A10 (NSC 648539) and AS2-1 (NSC 620261) in patients with recurrent glioma. *Mayo Clin Proc* 1999;74:137–45.
150. Cassileth BR, Lusk EJ, Guerry D, et al. Survival and quality of life among patients receiving unproven as compared with conventional cancer therapy. *N Engl J Med* 1991;324:1180–5.
151. Moertel CG, Fleming TR, Rubin J, et al. A clinical trial of amygdalin (Laetrile) in the treatment of human cancer. *N Engl J Med* 1982;306:201–6.
152. Block JB, Serpick AA, Miller W, et al. Early clinical studies with lapachol (NSC-11905). *Cancer Chemother Rep* 1974;2 4:27–8.
153. Risberg T, Vickers A, Bremnes RM, et al. Does use of alternative medicine predict survival from cancer? *Eur J Cancer* 2003;39:372–7.