The Oncologist®

Complementary and Alternative Therapies for Cancer

BARRIE R. CASSILETH, GARY DENG

Integrative Medicine Service, Memorial Sloan-Kettering Cancer Center, New York, New York, USA

Key Words. *Cancer · Alternative medicine · Complementary therapies · Herbs · Dietary supplements*

LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Describe the differences between complementary and alternative therapies.
2. List common complementary and alternative therapies used by cancer patients.
3. Know where to access reliable information.

CME Access and take the CME test online and receive one hour of AMA PRA category 1 credit at CME.TheOncologist.com

ABSTRACT

Many cancer patients use therapies promoted as literal alternatives to conventional medical care. Such "alternative" modalities are unproven or were studied and found worthless. These can be harmful. An even greater proportion of cancer patients uses "complementary" therapies along with mainstream cancer treatment. Most are helpful adjunctive approaches that control symptoms and enhance quality of life. This review describes alternative as well as complementary therapies commonly used today by cancer patients. Herbal remedies also are discussed. Evidence regarding the efficacy and safety of complementary/alternative medicine (CAM) is reviewed, and implications for oncologists are discussed. To encourage open communication of CAM use by patients, oncologists should be knowledgeable about the most popular remedies and know where to find reliable information for themselves and for their patients.
The Oncologist *2004;9:80-89*

INTRODUCTION

Definitions

Terms applied to therapies not commonly included in mainstream medicine have repeatedly changed over time, evolving from a very negative "quackery" through "unorthodox," "unconventional," "questionable," "unproven," and "alternative." Current, but still evolving, terminology favors "complementary" and "alternative" medicine, or the acronym of both: CAM. The shifting language is exemplified by the creation over a decade ago of the National Institutes of Health (NIH) Office of Alternative Medicine, which, in 1999, was renamed the National Center for Complementary and Alternative Medicine (NCCAM).

We have long promoted what we see as a necessary distinction between complementary and alternative therapies, despite the acronymic convenience, and the viability of a newer term, integrative oncology. Complementary therapies are used as adjuncts to mainstream cancer care. They are supportive measures that control symptoms, enhance well-being, and contribute to overall patient care. Alternative therapies typically are promoted for use instead of mainstream treatment. This is especially problematic in oncology, when delayed treatment can diminish the possibility of

Correspondence: Barrie R. Cassileth, Ph.D., Integrative Medicine Service, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, H13, New York, New York 10021, USA. Telephone: 212-639-8629; Fax: 212-794-5851; e-mail: Cassileth@mskcc.org
Received July 11, 2003; accepted for publication October 28, 2003. ©AlphaMed Press 1083-7159/2004/$12.00/0

remission and cure. Moreover, interventions sold as literal alternatives to chemotherapy, surgery, and radiation therapy tend to be biologically active, potentially harmful, and extremely costly. Over time, some complementary therapies are proven safe and effective. These become integrated into mainstream care, producing integrative oncology, a synthesis of the best of mainstream cancer treatment and rational, data-based, adjunctive complementary therapies. Such integration is evolving. The very term applied to the program at the Memorial Sloan-Kettering Cancer Center (Integrative Medicine Service) and similar titles applied to related programs in North America, the United Kingdom, and Europe, suggest that complementary therapies are being brought into mainstream medicine, including cancer care. Integration varies from country to country, as does the quality of therapies offered.

CAM Users

The use of CAM for cancer is widespread. By various accounts, from less than 10% to more than 60% of cancer patients have used CAM [1-5]. The Datamonitor 2002 Survey indicated that 80% of cancer patients used an alternative or complementary modality [6].

Virtually all studies conducted to date of cancer patients and of the general public internationally show that those who seek CAM therapies tend to be better educated, of higher socioeconomic status, female, and younger than those who do not. Typically, they are more health conscious and utilize more mainstream medical services than do people who do not use CAM. There is some indication of growth in CAM use by cancer patients in recent years [7]. It is likely that this reflects expanded numbers of over-the-counter remedies as well as their ready availability. A recent study found the three most commonly used therapies to be spiritual healing or prayer (13.7%), herbal medicine (9.6%), and chiropractic therapies (7.6%) [8]. Although, in some cases, use of CAM was seen as a marker of greater psychosocial distress and poorer quality of life [9, 10], patients say they use CAM to improve physiologic and psychosocial well-being, because they value the closer relationships possible with CAM practitioners, and because they want more control and greater responsibility for self-care [11].

CAM Practitioners

Major categories of CAM practitioners outside of mainstream medicine include chiropractors, naturopaths, and acupuncturists. Acupuncturists often practice a broader range of traditional Chinese medicine involving herbal remedies [12-14]. The professions of massage therapy, music therapy, and mind-body therapies also have skilled practitioners [15].

Chiropractors, naturopathic doctors, and acupuncturists must complete several years of training and pass standardized national examinations in order to practice in the states that license these practitioners [16-18]. Many states allow physicians to practice acupuncture with little or no training, although states increasingly require national accreditation and an associated specified length of training [18]. An organization representing only acupuncturists with a medical doctor (M.D.) or doctor of osteopathy (D.O.) license was founded in 1987. This organization, the American Academy of Medical Acupuncture, has grown to more than 1,600 members. The National Certification Commission for Acupuncture and Oriental Medicine (NCCAOM), based in Washington, DC, has certified more than 13,000 practitioners since its inception [19].

At the institutional level, numerous hospitals and medical centers have developed research and programs in CAM. Cancer programs as well as many comprehensive cancer centers have or are creating programs of varying complexity. A 1999 survey of 26 National Cancer Institute (NCI)-designated centers showed that 88% had a CAM practitioner and 54% offered CAM programs, the most common being support groups, guided imagery, and nutritional counseling [20].

Economic Impact

The economic impact of CAM is enormous. It was estimated that visits to CAM practitioners increased from 427 million in 1990 to 629 million in 1997, exceeding visits to all U.S. primary care physicians [5]. These 1997 data back a conservative estimate of total U.S. out-of-pocket CAM expenditure of $27.0 billion, with $12.2 billion spent on CAM professional services.

The profound influence of 1994 legislation allowing herbal medicines and other “food supplements” to be sold over the counter without U.S. Food and Drug Administration (FDA) review is evident in the increased use of herbal remedies from 3% in 1991 to over 20% in 1999 [21]. It is estimated that sales of dietary supplements have more than doubled since the passage of the 1994 law. Sale of the five major categories of dietary supplements reached $15 billion in 2000 [22]. A lobbying effort is under way to provide more government protection concerning the safety and efficacy of these readily available products, many of which are contaminated or dangerous (see later sections of this chapter). The food supplement industry continues to oppose these efforts.

Information about CAM is readily available on the internet. The keywords “alternative cancer medicine” searched for on Google.com produced close to 900,000 hits. It is difficult, if not impossible, for most readers to distinguish between reputable sources of information and promotions of unproven alternatives pushed by vested interests.

Reflecting public interest in CAM and the need for vigorous research in this area, appropriations to the NCCAM rose from $2 million in 1992 to $50 million in 1999 and to $114 million for fiscal year 2003. Other governmental agencies, including the NCI, as well as private foundations, also support CAM research.

THERAPIES

CAM therapies may be categorized in a variety of ways. NCCAM currently classifies CAM therapies into five categories: alternative medical systems, mind-body interventions, biologically based therapies, manipulative and body-based methods, and energy therapies. Currently popular therapies within each of these categories are discussed below. Many of these approaches are unproven methods promoted as alternatives to mainstream cancer treatment. Helpful complementary or adjunctive therapies are discussed in a following section.

Traditional Medical Systems

These complete systems of theory and practice were developed by ancient cultures and remain essentially intact. Prominent examples include traditional Chinese medicine (TCM), India's ayurvedic medicine, homeopathy, and naturopathic medicine [23]. A common feature across alternative medical systems is an emphasis on working with internal natural forces to achieve a harmonic state of mind and body. Although this concept has great appeal to many members of the general public, the underlying assumptions concerning human physiology and disease are outmoded and inconsistent with current scientific understanding.

Traditional Chinese Medicine

TCM views people as ecosystems in miniature. Any imbalance between opposing forces, such as yin-yang, heat-cold, dampness-dryness, or disruption in the circulation of *Chi* or *Qi*, meaning life energy or vital force, produces illness. Maintaining the balance and the flow of "life elements," therefore, is essential to the maintenance or restoration of health.

Diagnostic techniques include examination of complexion and tongue coating, detection of distinctive scents in bodily materials, and palpation of the radial pulse for its speed and tactile characteristics. This information is matched to specific patterns of signs and symptoms to provide a TCM diagnosis (e.g., dampness of spleen). Treatment is then geared to correcting imbalances or disruptions, primarily with herbal formulas or acupuncture.

Hundreds of botanical, animal, and mineral preparations were categorized in traditional Chinese pharmacopoeias starting millennia ago. Approximately 140 biologically active compounds have been isolated from medicinal plants [24]. Among anticancer agents, camptothecin, paclitaxel, vincristine, and indirubin are developed from *Camptotheca acuminata, Taxus chinensis, Catharanthus roseus,* and *Baphicacanthus cusia,* respectively, although the original plants were not used traditionally to treat cancer.

Ayurveda

The term ayurveda comes from the Sanskrit words *ayur* (life) and *veda* (knowledge). Ayurveda's ancient healing techniques are based on the classification of people into one of three predominant body types. There are specific remedies for disease, and regimens to promote health, for each body type. This medical system has a strong mind-body component, stressing the need to keep consciousness in balance. It uses techniques such as yoga and meditation to do so. Ayurveda also emphasizes regular detoxification and cleansing through all bodily orifices.

Homeopathy

Homeopathy, or homeopathic medicine, originated in 18th century Germany before the advent of modern medicine. It was based on the concept of *similia principle* or "like cures like," and the concept of "potentiation," or serial dilution and vigorous shaking of a substance to extract its vital essence. The body's own healing process is believed to be stimulated by these highly diluted substances derived from plants, minerals, or animals.

Homeopathic remedies are available over the counter without prescriptions. If a claim were to state that a homeopathic remedy could treat a serious disease, such as cancer, by U.S. law, it could be sold by prescription only [25]. However, efficacy is unlikely due to the extreme dilution of active ingredients in homeopathy, which eventuates in less than one molecule of the original substance, meaning that there is nothing in the solution [26]. Systematic reviews and meta-analyses of homeopathy clinical trials show no definitive proof that homeopathic remedies are effective for any medical condition [27-29].

Naturopathy

Naturopathy, or naturopathic medicine, is an alternative medical system that relies exclusively on "natural" healing approaches (such as herbs, nutrition, and movement or manipulation of the body). It is based on the belief that the body will repair itself and recover from illness spontaneously once a healthy internal environment is achieved. Many remedies in naturopathy, for example, mistletoe, saw palmetto, red clover, wheat grass, and flax seed oil, overlap with those in other categories of CAM; they are reviewed in their respective sections.

Questionable Alternative Therapies

Diet and Vitamin Cancer "Cures"

Advocates of dietary cancer treatments typically extend mainstream assumptions about the protective effects of fruits, vegetables, fiber, and avoidance of excessive dietary fat in reducing cancer risk to the idea that foods or vitamins can cure cancer. Current examples include the no-dairy diet, the macrobiotic diet, fruit and vegetable cures, and metabolic therapies, offered in Tijuana, Mexico clinics. One of the best known sites for this questionable practice is the Gerson Clinic, where liver damage is counteracted with a low-salt, high-potassium diet, coffee enemas, and a gallon of fruit and vegetable juice daily [30]. Its use of oral crude liver extract was associated with repeated cases of bacterial contamination [31], although the Gerson.org website (as of 10-01-03) includes "injectable crude liver extract" among its "medications." Other clinics and practitioners provide their own versions of metabolic therapy, each applying an individualized diet plus vitamins, minerals, enzymes, and detoxification regimens, which typically involve multiple "colonic cleansing" procedures.

Modern variations on the older approach to internal cleansing are drinkable cleansing formulas, said to detoxify and rejuvenate the body. These products tend to function as major laxatives, potentially dangerous when taken over days or weeks or on a regular basis as recommended by promoters, especially for cancer patients. Neither the presence of toxins nor the benefit of eliminating them has been documented.

The macrobiotic diet was developed in the 1930s by *George Ohsawa*, a Japanese philosopher who sought to integrate traditional oriental medicine, Christian teachings, and aspects of Western medicine [32, 33]. This is essentially a vegetarian diet, with emphasis on whole grains, legumes, fresh vegetables, and the occasional intake of fish. The main macrobiotics web site is extremely persuasive and attractive, which probably contributes to an apparent resurgence of interest in this dietary fad (http://www.kushi institute.org). The selection of foods is so limited that people on this diet may develop significant nutritional deficiencies. Although healthful nutrition is important for patients and has value in cancer prevention, neither this nor any other diet alone has been shown to cure cancer.

Some patients and alternative practitioners believe that large dosages of vitamins or intravenous infusions of high-dose vitamin C can cure disease. In 1968, Nobel Laureate *Linus Pauling* coined the term "orthomolecular" to describe the treatment of disease with large quantities of nutrients. His claims that massive doses of vitamin C could cure cancer were not confirmed by clinical trials [34, 35], but megavitamin and orthomolecular therapy, the latter adding minerals and other nutrients, remain popular. Perhaps the simplicity of this approach and the fact that patients can prescribe and obtain their own over-the-counter therapy contribute to its appeal. However, megavitamin or orthomolecular therapy has not been proven to be an effective cancer treatment.

Energy Therapies

Energy therapies are based on the theory that there are energy fields around the human body. It is believed that by changing the purported energy field by manual manipulations, such as *Qigong* or therapeutic touch, or the application of electromagnetic fields, disease can be eliminated. The existence of such energy fields has not been scientifically proven.

Therapeutic touch (TT), despite its name, involves no direct contact. Instead, healers move their hands a few inches above a patient's body and sweep away "blockages" to the patient's energy field. Although a study published in the *Journal of the American Medical Association* showed that experienced TT practitioners were unable to detect the investigator's "energy field" [36] and despite mainstream scientists' unwillingness to accept its fundamental premises, TT is taught in North American nursing schools and widely practiced by nurses in the U.S. and other countries [37].

TT healers in many areas of the U.S. claim the ability to cure people of cancer. Although their ministrations may cause only minor difficulties when patients also receive mainstream care, many patients are firmly convinced of these healers' abilities and decline even to have tumors removed surgically [38].

Bioelectromagnetic field therapies involve the use of pulsed, alternating or direct current and magnetic fields to treat medical conditions. Clinical trials have been conducted to test magnetic field therapies in managing pain [39, 40], tremor [41], epilepsy [42], and migraine headaches [43]. No data support their role in any illness.

Biologic Treatments

Because this group of alternative treatments is invasive and biologically active, it is highly controversial. One such therapy is antineoplastons, developed by *Stanislaw Burzynski* in his clinic in Houston, Texas [44]. A joint research effort by the NIH Office of Alternative Medicine and the NCI failed to accrue sufficient numbers of patients, and none of the six patients assessable for response showed tumor regression [45]. Further research at the Burzynski Institute was permitted under an Investigational New Drug permit [46]. The group's preliminary report from a single-arm phase II study of 12 patients showed a 50% response rate [46]. Researchers at the NCI and elsewhere continue to investigate phenylacetate, a metabolite of the amino acid

phenylalanine, which makes up 80% of antineoplastons [47, 48].

Immuno-augmentation therapy (IAT), subcutaneous injections of sera derived from the blood of healthy donors, was developed by the late *Lawrence Burton* and offered in his clinic in the Bahamas. *Burton* claimed that IAT was particularly effective in treating mesothelioma [49]. Documentation of IAT's efficacy remains anecdotal. The clinic has continued to operate following *Burton's* death, but its popularity seems to have waned [50].

Advocates of shark cartilage as a cancer therapy base their therapy on its putative antiangiogenic properties [51]. A phase I/II trial of shark cartilage found no clinical benefit [52]. Neovastat, another cartilage extract, was associated with a survival benefit in renal cell carcinoma in higher versus lower doses [53]. However, that trial was not randomized. Two large NIH-sponsored phase III trials were recently initiated [54].

Many additional unproven methods, such as Laetrile [55, 56], bioresonance therapy, oxygen and ozone therapies, insulin potentiation therapy, and many more [26], are promoted as literal alternatives to mainstream cancer treatment. Their popularities wax and wane over time.

Dietary Supplements and Herbal Remedies

Cancer patients use over-the-counter dietary supplements in addition to or instead of other cancer treatments. Preliminary data from the Women's Healthy Eating and Living study showed that up to 80% of non-stage IV breast cancer patients took dietary supplements such as vitamins, antioxidants, and herbs [57, 58]. An important trend is the increased use of herbal products instead of other supplements in recent years [58]. Systematic, evidence-based information on popular dietary supplements used by cancer patients and herb-drug interactions in oncology is available to consumers and health care professionals [26, 59].

The general public tends not to be aware that herbs are dilute natural drugs that contain scores of different chemicals, most of which have not been documented [60]. Their effects are not always predictable [61]. Neither the FDA nor any other agency examines herbal remedies for safety and effectiveness. Few products have been formally tested for side effects or quality control. Patients undergoing active treatment should be told to stop using herbal remedies, because some herbs cause problematic interactions with chemotherapeutic agents, sensitization of the skin to radiation therapy, dangerous blood pressure swings, and other unwanted interactions with anesthetics during surgery [62].

Herbs such as feverfew, garlic, ginger, and ginkgo have anticoagulant effects and should be avoided by patients on coumadin, heparin, aspirin, and related agents. Concerns have been raised recently even about dietary antioxidants, which may interact with radiation therapy or chemotherapeutic agents [63]. The risk of herb-drug interactions appears to be greatest for patients with kidney or liver problems [64, 65].

Essiac, one of the most popular herbal alternative cancer medicines in North America, was developed initially by a Native healer from southwestern Canada. It was popularized in the 1920s by a Canadian nurse, and comprises four herbs: burdock, turkey rhubarb, sorrel, and slippery elm. Evidence of anticancer activity has been limited to anecdotal reports [66]. No clinical studies support the use of essiac (also sold as flor-essence).

Iscador, a derivative of mistletoe, is a popular cancer remedy in Europe, where it is said to have been in continuous use as a folk treatment since the time of the Druids. Iscador is available in many mainstream European cancer clinics. European governments have funded studies of the effectiveness of iscador against cancer. The results are mixed, with all studies suffering some methodological shortcomings [67]. None of the methodologically stronger trials showed efficacy in survival, according to another systematic review [68].

Several mushroom-derived compounds are approved for use as cancer treatments in Japan. Trials on polysaccharide Kureha (PSK), an extract of the mushroom *Coriolus versicolor*, showed superior survival with PSK compared with controls in both gastrectomy [69, 70] and esophagectomy patients [71]. Two randomized trials of PSK given after curative resection for colorectal cancer showed that both disease-free and overall survival rates were significantly higher in the PSK group [72, 73]. Results were less encouraging in breast cancer [74, 75] and leukemia [76]. The proposed mechanism was immune modulation. Interestingly, an association between response to PSK treatment and HLA type was reported [77].

A combination of eight herbs, all but two from TCM, PC-SPES (PC for prostate cancer; *spes* is the Latin word for hope) reduced prostate-specific antigen levels in men with advanced prostate cancer regardless of whether their disease was androgen dependent [78-81]. Improvements in quality of life also have been reported [82]. Estrogenic side effects occurred with PC-SPES, and its mechanism of action, although uncertain, may relate to its phytoestrogenic effects. PC-SPES was suspended from the market in early 2002 when undisclosed contamination with anxiolytic and antithrombotic agents was uncovered [83].

Helpful Complementary Therapies

Mind-body interventions aim to utilize the reciprocal relationship between body and mind to help patients relax, reduce stress, and relieve symptoms associated with cancer and cancer treatments. Hypnosis and relaxation techniques

are often used by conventional practitioners, such as clinical psychologists. Several randomized trials have shown effects of hypnosis on both procedural and malignant pain [84, 85] and on anxiety, depression, and mood in newly diagnosed cancer patients [86-88]. Trials also have generally found hypnosis and relaxation training to be beneficial against chemotherapy-induced nausea in adults [89, 90], although some studies found no differences between groups [91].

Music therapy is provided by professional musicians who are also trained music therapists. Typically they hold graduate degrees in music therapy and are trained to deal with the psychosocial as well as clinical issues faced by patients and family members. Music therapy is particularly effective in the palliative care setting, with randomized trials indicating benefit for reducing anxiety [92-96], depression [97-99], and pain [100, 101].

The benefits of massage therapy are documented, especially for seriously ill and palliative care patients. Several randomized trials suggest that massage reduces anxiety, at least in the short-term, in groups as varied as adolescent psychiatric patients [102] and elderly people in care homes [103]. In a high-quality, if underpowered, trial, 35 patients were randomized to receive either up to nine 20-minute massages during inpatient stays or standard care (control). Massage was superior to the control treatment in reducing anxiety, nausea, and fatigue and improving general well-being [104]. In the largest study to date, 87 hospitalized cancer patients were randomized to receive either foot massage or a control treatment. Pain and anxiety scores were lower with massage, with differences between groups achieving both statistical and clinical significance [105].

Acupuncture is the stimulation of certain points along "meridians" on the body by needle (acupuncture), pressure (acupressure), or heat (moxibustion). Modern versions include electrical pulses (electro-acupuncture) or laser (laser acupuncture) to provide extra stimulation [106]. Stimulation is thought to regulate the flow of *Qi*. The biological basis of *Qi* or of meridian channels has not been found, but modern research suggests that the effect of acupuncture may be mediated by the release of neurotransmitters [107-109]. Data from clinical trials support the use of acupuncture for emesis [110-112] and pain [113-118]. The NIH issued a concensus statement in 1997 supporting the efficacy of acupuncture for adult postoperative and chemotherapy-associated nausea and vomiting, and for postoperative dental pain [119].

Implications for Oncologists

Many cancer patients use complementary and alternative therapies [9, 120-123]. Patients appear increasingly willing to discuss the use of these remedies, especially when asked by their oncologists. In order to encourage open communication of CAM use by their patients, oncologists should be knowledgeable about the most commonly used remedies, or at least be able to direct patients to reliable sources of information. A few helpful web sites are listed in the reference section [26, 124-129].

Patients should be advised to avoid questionable alternative therapies in a receptive, evidence-based atmosphere. Many unproven alternatives are promoted in a very appealing and convincing fashion. Brushing the topic aside categorically without open discussion may not dissuade patients' use.

On the other hand, complementary therapies that help manage pain, nausea, fatigue, anxiety, and other symptoms should be integrated into the patient's overall care. In some cases, patients feel that problems they perceive as important fail to receive sufficient attention. Complementary therapies improve patients' qualities of life, patient satisfaction, and the physician-patient relationship.

References

1 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.

2 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.

3 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. NZ Med J 2003;116:U296.

4 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;92:1606-1609.

5 Eisenberg DM, Davis RB, Ettner SL et al. Trends in alternative medicine use in the United States, 1990-1997: results of a follow-up national survey. JAMA 1998;280:1569-1575.

6 Complementary and alternative medicines in cancer therapy. Publication BFHC0462. http://www.datamonitor.com/all/reports/product_summary.asp?pid=BFHC0462, accessed 12/19/2003.

7 Ernst E, Cassileth BR. The prevalence of complementary/alternative medicine in cancer: a systematic review. Cancer 1998;83:777-782.

8 Ni H, Simile C, Hardy AM. Utilization of complementary and alternative medicine by United States adults: results from the 1999 national health interview survey. Med Care 2002;40:353-358.

9 Burstein HJ, Gelber S, Guadagnoli E et al. Use of alternative medicine by women with early-stage breast cancer. N Engl J Med 1999;340:1733-1739.

10 Ganz PA, Desmond KA, Leedham B et al. Quality of life in long-term, disease-free survivors of breast cancer: a follow-up study. J Natl Cancer Inst 2002;94:39-49.

11 Vickers AJ, Cassileth BR. Unconventional therapies for cancer and cancer-related symptoms. Lancet Oncol 2001;2:226-232.

12 Cooper RA, Henderson T, Dietrich CL. Roles of nonphysician clinicians as autonomous providers of patient care. JAMA 1998;280:795-802.

13 Cherkin DC, Deyo RA, Sherman KJ et al. Characteristics of visits to licensed acupuncturists, chiropractors, massage therapists, and naturopathic physicians. J Am Board Fam Pract 2002;15:463-472.

14 Smith MJ, Logan AC. Naturopathy. Med Clin North Am 2002;86:173-184.

15 Eisenberg DM, Cohen MH, Hrbek A et al. Credentialing complementary and alternative medical providers. Ann Intern Med 2002;137:965-973.

16 American Chiropractic Association. Chiropractic: state of the art. Arlington, VA: American Chiropractic Association, 1994.

17 Baer HA. The sociopolitical status of U.S. naturopathy at the dawn of the 21st century. Med Anthropol Q 2001;15:329-346.

18 Leake R, Broderick JE. Current licensure for acupuncture in the United States. Altern Ther Health Med 1999;5:94-96.

19 National Certification Commission for Acupuncture and Oriental Medicine. About us. http://www.nccaom.org/aboutus.htm, accessed 09/29/03.

20 National Cancer Institute. Complementary and alternative medicine resources at NCI-designated cancer centers. Survey results. http://cpen.nci.nih.gov/planning_resources/cam_survey_results.htm, accessed 09/29/03.

21 Druss BG, Rosenheck RA. Association between use of unconventional therapies and conventional medical services. JAMA 1999;282:651-656.

22 Institute of Medicine. Exploring complementary and alternative medicine. In: The Richard and Hinda Rosenthal Lectures 2001. Washington, DC: The National Academies Press, 2003:26.

23 Cassileth BR. The Alternative Medicine Handbook: The Complete Reference Guide to Alternative and Complementary Therapies. New York: W. W. Norton & Company, Inc., 1998:16-52.

24 Zhang JT. New drugs derived from medicinal plants. Therapie 2002;57:137-150.

25 U.S. Food and Drug Administration. Homeopathy: real medicine or empty promises. http://www.fda.gov/fdac/features/096_home.html, accessed 09/29/03.

26 Memorial Sloan-Kettering Cancer Center. Information resource: About herbs, botanicals and other products. http://www.mskcc.org/abuotherbs, accessed 09/29/03.

27 Ernst E. A systematic review of systematic reviews of homeopathy. Br J Clin Pharmacol 2002;54:577-582.

28 Cucherat M, Haugh MC, Gooch M et al. Evidence of clinical efficacy of homeopathy. A meta-analysis of clinical trials. HMRAG. Homeopathic Medicines Research Advisory Group. Eur J Clin Pharmacol 2000;56:27-33.

29 Linde K, Clausius N, Ramirez G et al. Are the clinical effects of homeopathy placebo effects? A meta-analysis of placebo-controlled trials. Lancet 1997;350:834-843.

30 Green S. A critique of the rationale for cancer treatment with coffee enemas and diet. JAMA 1992;268:3224-3227.

31 Hildenbrand GL, Hildenbrand LC, Bradford K et al. Five-year survival rates of melanoma patients treated by diet therapy after the manner of Gerson: a retrospective review. Altern Ther Health Med 1995;1:29-37.

32 Macrobiotic diets for the treatment of cancer. CA Cancer J Clin 1989;39:248-251.

33 Kushi LH, Cunningham JE, Hebert JR et al. The macrobiotic diet in cancer. J Nutr 2001;131(suppl 11):3056S-3064S.

34 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;312:137-141.

35 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;301:687-690.

36 Rosa L, Rosa E, Sarner L et al. A close look at therapeutic touch. JAMA 1998;279:1005-1010.

37 O'Mathuna DP. Evidence-based practice and reviews of therapeutic touch. J Nurs Scholarsh 2000;32:279-285.

38 Cassileth BR, Vlassov VV, Chapman CC. Health care, medical practice, and medical ethics in Russia today. JAMA 1995;273:1569-1573.

39 Brown CS, Ling FW, Wan JY et al. Efficacy of static magnetic field therapy in chronic pelvic pain: a double-blind pilot study. Am J Obstet Gynecol 2002;187:1581-1587.

40 Segal NA, Toda Y, Huston J et al. Two configurations of static magnetic fields for treating rheumatoid arthritis of the knee: a double-blind clinical trial. Arch Phys Med Rehabil 2001;82:1453-1460.

41 Gironell A, Kulisevsky J, Lorenzo J et al. Transcranial magnetic stimulation of the cerebellum in essential tremor: a controlled study. Arch Neurol 2002;59:413-417.

42 Weinstein S. The anticonvulsant effect of electrical fields. Curr Neurol Neurosci Rep 2001;1:155-161.

43 Pelka RB, Jaenicke C, Gruenwald J. Impulse magnetic-field therapy for migraine and other headaches: a double-blind, placebo-controlled study. Adv Ther 2001;18:101-109.

44 Burzynski SR, Kubove E. Initial clinical study with antineoplaston A2 injections in cancer patients with five years' follow-up. Drugs Exp Clin Res 1987;13(suppl 1):1-11.

45 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;74:137-145.

46 Burzynski SR, Lewy RI, Weaver RA et al. Phase II study of antineoplaston A10 and AS2-1 in patients with recurrent diffuse intrinsic brain stem glioma: a preliminary report. Drugs R D 2003;4:91-101.

47 Harrison LE, Wojciechowicz DC, Brennan MF et al. Phenylacetate inhibits isoprenoid biosynthesis and suppresses growth of human pancreatic carcinoma. Surgery 1998;124:541-550.

48 Tsuda H, Sata M, Kumabe T et al. Quick response of advanced cancer to chemoradiation therapy with antineoplastons. Oncol Rep 1998;5:597-600.

49 Moss R. Cancer Therapy: The Burton Goldberg Group, Alternative Medicine. Puyallup, Washington: Future Medicine Publishing, Inc., 1993:577.

50 Questionable methods of cancer management. Immuno-augmentative therapy (IAT). CA Cancer J Clin 1991;41:357-364.

51 Dupont E, Falardeau P, Mousa SA et al. Antiangiogenic and antimetastatic properties of Neovastat (AE-941), an orally active extract derived from cartilage tissue. Clin Exp Metastasis 2002;19:145-153.

52 Miller DR, Anderson GT, Stark JJ et al. Phase I/II trial of the safety and efficacy of shark cartilage in the treatment of advanced cancer. J Clin Oncol 1998;16:3649-3655.

53 Batist G, Patenaude F, Champagne P et al. Neovastat (AE-941) in refractory renal cell carcinoma patients: report of a phase II trial with two dose levels. Ann Oncol 2002;13:1259-1263.

54 Falardeau P, Champagne P, Poyet P et al. Neovastat, a naturally occurring multifunctional antiangiogenic drug, in phase III clinical trials. Semin Oncol 2001;28:620-625.

55 Unproven methods of cancer management. Laetrile. CA Cancer J Clin 1991;41:187-192.

56 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;306:201-206.

57 Pierce JP, Faerber S, Wright FA et al. A randomized trial of the effect of a plant-based dietary pattern on additional breast cancer events and survival: the Women's Healthy Eating and Living (WHEL) Study. Control Clin Trials 2002;23:728-756.

58 Rock CL. Antioxidant supplement use in cancer survivors and the general population. In: Free Radicals: The Pros and Cons of Antioxidants. NIH: Bethesda, MD 2003.

59 Cassileth BR, Lucarelli CD. Herb-Drug Interactions in Oncology. Hamilton, Canada: B. C. Decker, 2003:1-467.

60 Slifman NR, Obermeyer WR, Aloi BK et al. Contamination of botanical dietary supplements by Digitalis lanata. N Engl J Med 1998;339:806-811.

61 Drew AK, Myers SP. Safety issues in herbal medicine: implications for the health professions. Med J Aust 1997;166:538-541.

62 Cheng B, Hung CT, Chiu W. Herbal medicine and anaesthesia. Hong Kong Med J 2002;8:123-130.

63 Labriola D, Livingston R. Possible interactions between dietary antioxidants and chemotherapy. Oncology (Huntingt) 1999;13:1003-1008; discussion 1008, 1011-1002.

64 Izzo AA, Ernst E. Interactions between herbal medicines and prescribed drugs: a systematic review. Drugs 2001;61:2163-2175.

65 Fugh-Berman A. Herb-drug interactions. Lancet 2000;355:134-138.

66 Tamayo C, Richardson MA, Diamond S et al. The chemistry and biological activity of herbs used in Flor-Essence herbal tonic and Essiac. Phytother Res 2000;14:1-14.

67 Kienle GS, Berrino F, Bussing A et al. Mistletoe in cancer—a systematic review on controlled clinical trials. Eur J Med Res 2003;8:109-119.

68 Ernst E, Schmidt K, Steuer-Vogt MK. Mistletoe for cancer? A systematic review of randomised clinical trials. Int J Cancer 2003;107:262-267.

69 Niimoto M, Hattori T, Tamada R et al. Postoperative adjuvant immunochemotherapy with mitomycin C, futraful and PSK for gastric cancer. An analysis of data on 579 patients followed for five years. Jpn J Surg 1988;18:681-686.

70 Nakazato H, Koike A, Saji S et al. Efficacy of immunochemotherapy as adjuvant treatment after curative resection of gastric cancer. Study Group of Immunochemotherapy with PSK for Gastric Cancer. Lancet 1994;343:1122-1126.

71 Ogoshi K, Satou H, Isono K et al. Immunotherapy for esophageal cancer. A randomized trial in combination with radiotherapy and radiochemotherapy. Cooperative Study Group for Esophageal Cancer in Japan. Am J Clin Oncol 1995;18:216-222.

72 Torisu M, Hayashi Y, Ishimitsu T et al. Significant prolongation of disease-free period gained by oral polysaccharide K (PSK) administration after curative surgical operation of colorectal cancer. Cancer Immunol Immunother 1990;31:261-268.

73 Mitomi T, Tsuchiya S, Iijima N et al. Randomized, controlled study on adjuvant immunochemotherapy with PSK in curatively resected colorectal cancer. The Cooperative Study Group of Surgical Adjuvant Immunochemotherapy for Cancer of Colon and Rectum (Kanagawa). Dis Colon Rectum 1992;35:123-130.

74 Toi M, Hattori T, Akagi M et al. Randomized adjuvant trial to evaluate the addition of tamoxifen and PSK to chemotherapy in patients with primary breast cancer. 5-Year results from the Nishi-Nippon Group of the Adjuvant Chemoendocrine Therapy for Breast Cancer Organization. Cancer 1992;70:2475-2483.

75 Morimoto T, Ogawa M, Orita K et al. Postoperative adjuvant randomised trial comparing chemoendocrine therapy, chemotherapy and immunotherapy for patients with stage II breast cancer: 5-year results from the Nishinihon Cooperative Study Group of Adjuvant Chemoendocrine Therapy for Breast Cancer (ACETBC) of Japan. Eur J Cancer 1996;32A:235-242.

76 Iino Y, Yokoe T, Maemura M et al. Immunochemotherapies versus chemotherapy as adjuvant treatment after curative resection of operable breast cancer. Anticancer Res 1995;15:2907-2911.

77 Yokoe T, Iino Y, Takei H et al. HLA antigen as predictive index for the outcome of breast cancer patients with adjuvant immunochemotherapy with PSK. Anticancer Res 1997;17:2815-2818.

78 Small EJ, Frohlich MW, Bok R et al. Prospective trial of the herbal supplement PC-SPES in patients with progressive prostate cancer. J Clin Oncol 2000;18:3595-3603.

79 de la Taille A, Buttyan R, Hayek O et al. Herbal therapy PC-SPES: in vitro effects and evaluation of its efficacy in 69 patients with prostate cancer. J Urol 2000;164:1229-1234.

80 Oh WK, George DJ, Hackmann K et al. Activity of the herbal combination, PC-SPES, in the treatment of patients with androgen-independent prostate cancer. Urology 2001;57:122-126.

81 de la Taille A, Hayek OR, Buttyan R et al. Effects of a phytotherapeutic agent, PC-SPES, on prostate cancer: a preliminary investigation on human cell lines and patients. BJU Int 1999;84:845-850.

82 Pfeifer BL, Pirani JF, Hamann SR et al. PC-SPES, a dietary supplement for the treatment of hormone-refractory prostate cancer. BJU Int 2000;85:481-485.

83 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;94:1275-1281.

84 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;276:313-318.

85 Sellick SM, Zaza C. Critical review of 5 nonpharmacologic strategies for managing cancer pain. Cancer Prev Control 1998;2:7-14.

86 Bindemann S, Soukop M, Kaye SB. Randomised controlled study of relaxation training. Eur J Cancer 1991;27:170-174.

87 Bridge LR, Benson P, Pietroni PC et al. Relaxation and imagery in the treatment of breast cancer. BMJ 1988;297:1169-1172.

88 Walker LG, Walker MB, Ogston K et al. Psychological, clinical and pathological effects of relaxation training and guided imagery during primary chemotherapy. Br J Cancer 1999;80:262-268.

89 Vasterling J, Jenkins RA, Tope DM et al. Cognitive distraction and relaxation training for the control of side effects due to cancer chemotherapy. J Behav Med 1993;16:65-80.

90 Morrow GR, Morrell C. Behavioral treatment for the anticipatory nausea and vomiting induced by cancer chemotherapy. N Engl J Med 1982;307:1476-1480.

91 Arakawa S. Use of relaxation to reduce side effects of chemotherapy in Japanese patients. Cancer Nurs 1995;18:60-66.

92 Smith M, Casey L, Johnson D et al. Music as a therapeutic intervention for anxiety in patients receiving radiation therapy. Oncol Nurs Forum 2001;28:855-862.

93 Wang SM, Kulkarni L, Dolev J et al. Music and preoperative anxiety: a randomized, controlled study. Anesth Analg 2002;94:1489-1494.

94 Kaempf G, Amodei ME. The effect of music on anxiety. A research study. AORN J 1989;50:112-118.

95 Kwekkeboom KL. Music versus distraction for procedural pain and anxiety in patients with cancer. Oncol Nurs Forum 2003;30:433-440.

96 Haun M, Mainous RO, Looney SW. Effect of music on anxiety of women awaiting breast biopsy. Behav Med 2001;27:127-132.

97 Hanser SB, Thompson LW. Effects of a music therapy strategy on depressed older adults. J Gerontol 1994;49:P265-P269.

98 Burns DS. The effect of the bonny method of guided imagery and music on the mood and life quality of cancer patients. J Music Ther 2001;38:51-65.

99 Waldon EG. The effects of group music therapy on mood states and cohesiveness in adult oncology patients. J Music Ther 2001;38:212-238.

100 Zimmerman L, Pozehl B, Duncan K et al. Effects of music in patients who had chronic cancer pain. West J Nurs Res 1989;11:298-309.

101 Beck SL. The therapeutic use of music for cancer-related pain. Oncol Nurs Forum 1991;18:1327-1337.

102 Field T, Morrow C, Valdeon C et al. Massage reduces anxiety in child and adolescent psychiatric patients. J Am Acad Child Adolesc Psychiatry 1992;31:125-131.

103 Fraser J, Kerr JR. Psychophysiological effects of back massage on elderly institutionalized patients. J Adv Nurs 1993;18:238-245.

104 Ahles TA, Tope DM, Pinkson B et al. Massage therapy for patients undergoing autologous bone marrow transplantation. J Pain Symptom Manage 1999;18:157-163.

105 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;23:237-243.

106 Kaptchuk TJ. Acupuncture: theory, efficacy, and practice. Ann Intern Med 2002;136:374-383.

107 Han JS. Acupuncture: neuropeptide release produced by electrical stimulation of different frequencies. Trends Neurosci 2003;26:17-22.

108 Shen J. Research on the neurophysiological mechanisms of acupuncture: review of selected studies and methodological issues. J Altern Complement Med 2001;7(suppl 1):S121-S127.

109 Foster JM, Sweeney BP. The mechanisms of acupuncture analgesia. Br J Hosp Med 1987;38:308-312.

110 Shen J, Wenger N, Glaspy J et al. Electroacupuncture for control of myeloablative chemotherapy-induced emesis: a randomized controlled trial. JAMA 2000;284:2755-2761.

111 Lee A, Done ML. The use of nonpharmacologic techniques to prevent postoperative nausea and vomiting: a meta-analysis. Anesth Analg 1999;88:1362-1369.

112 Vickers AJ. Can acupuncture have specific effects on health? A systematic review of acupuncture antiemesis trials. J R Soc Med 1996;89:303-311.

113 Alimi D, Rubino C, Leandri EP et al. Analgesic effects of auricular acupuncture for cancer pain. J Pain Symptom Manage 2000;19:81-82.

114 Ernst E, Pittler MH. The effectiveness of acupuncture in treating acute dental pain: a systematic review. Br Dent J 1998;184:443-447.

115 Melchart D, Linde K, Fischer P et al. Acupuncture for idiopathic headache. Cochrane Database Syst Rev 2001;1:CD001218.

116 Filshie J, Redman D. Acupuncture and malignant pain problems. Eur J Surg Oncol 1985;11:389-394.

117 Leng G. A year of acupuncture in palliative care. Palliat Med 1999;13:163-164.

118 Dillon M, Lucas C. Auricular stud acupuncture in palliative care patients. Palliat Med 1999;13:253-254.

119 Acupuncture. NIH Consens Statement 1997;15:1-34.

120 Cassileth BR, Schraub S, Robinson E et al. Alternative medicine use worldwide: the International Union Against Cancer survey. Cancer 2001;91:1390-1393.

121 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;18:2505-2514.

122 Bernstein BJ, Grasso T. Prevalence of complementary and alternative medicine use in cancer patients. Oncology (Huntingt) 2001;15:1267-1272; discussion 1272-1278, 1283.

123 Cassileth BR. Complementary therapies: overview and state of the art. Cancer Nurs 1999;22:85-90.

124 National Institutes of Health, National Center for Complementary and Alternative Medicine. http://nccam.nih.gov, accessed 09/29/03.

125 National Cancer Institute, Office of Cancer Complementary and Alternative Medicine. http://www3.cancer.gov/occam, accessed 09/29/03.

126 American Cancer Society. Making treatment decisions: complementary and alternative therapies. http://www.cancer.org/docroot/ETO/ETO_5.asp?sitearea=ETO, accessed 09/29/03.

127 National Cancer Institute. Complementary and alternative medicine. http://www.cancer.gov/cancerinfo/treatment/cam, accessed 09/29/03.

128 Barrett S. Quackwatch: your guide to health fraud, quackery, and intelligent decisions. http://www.quackwatch.org, accessed 09/29/03.

129 The University of Texas, M.D. Anderson Cancer Center. Complementary/integrative medicine. http://www.mdanderson.org/departments/cimer, accessed 09/29/03.