Advising Patients Who Seek Complementary and Alternative Medical Therapies for Cancer

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Many patients with cancer use complementary and alternative medical (CAM) therapies. Physicians need authoritative information on CAM therapies to responsibly advise patients who seek these interventions. This article summarizes current evidence on the efficacy and safety of selected CAM therapies that are commonly used by patients with cancer. The following major categories of interventions are covered: dietary modification and supplementation, herbal products and other biological agents, acupuncture, massage, exercise, and psychological and mind–body therapies. Two categories of evidence on efficacy are considered: possible effects on disease progression and survival and possible palliative effects. In evaluating evidence on safety, two types of risk are considered: the risk for direct adverse effects and the risk for interactions with conventional treatments. For each therapy, the current balance of evidence on efficacy and safety points to whether the therapy may be reasonably recommended, accepted (for example, dietary fat reduction in well-nourished patients with breast or prostate cancer), or discouraged (for example, high-dose vitamin A supplementation). This strategy allows the development of an approach for providing responsible, evidence-based, patient-centered advice to persons with cancer who seek CAM therapies.

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In this article, we summarize the current scientific medical literature on complementary and alternative medical (CAM) therapies commonly used by persons with cancer. We focus on evidence about disease progression and palliation rather than cancer prevention. For this paper, we define CAM therapies as interventions not generally available in hospital-based oncology practices in the United States, with the understanding that some of these therapies are gaining acceptance in the conventional realm and may eventually fail to meet our current definition (1). We examine dietary modification (fat reduction and radical dietary regimens); supplementation with antioxidant vitamins, soy, herbs, and other "natural products"; acupuncture; massage; exercise; and psychological and mind–body interventions. Although patients with cancer often use spiritual approaches, these approaches are beyond the scope of this paper. For supplements, we present major categories of adverse effects and interactions with conventional treatments. Finally, we propose a strategy to engage patients who seek advice about CAM therapies.

Methods

We collected references from the following sources: databases (searched without restriction to particular years), including MEDLINE, CANCERLIT, AMED, EMBASE, and PsycINFO; Web sites, including the Longwood Herbal Task Force (www.mcp.edu/herbal/), the Center for Alternative Medicine Research in Cancer at the University of Texas–Houston Health Science Center (www.sph.uth.tmc.edu:8052/utcam/therapy.htm; updated information currently available at www.mdanderson.org/cimer), and the National Cancer Institute (www.cancer.gov/cancerinfo/treatment/cam); Medscape's Hematology-Oncology MedPulse (electronic newsletter; subscription available at www.medscape.com); Media Watch (electronic mailing list on cancer news; subscription available through lpchef@earthlink.net); bibliographies prepared by experts; recommendations of colleagues; and citations of papers identified from the preceding sources.

In evaluating efficacy of a therapy, we gave results of randomized, controlled trials (RCTs) the highest priority. We evaluated results of uncontrolled trials or observational data only if no RCTs had been completed, and we did not consider evidence from these sources to be conclusive. In evaluating safety of a therapy, we considered both preclinical and clinical data, although we most heavily weighted clinical reports of life-threatening or permanently disabling adverse events.

One of the authors is an employee of the National Center for Complementary and Alternative Medicine (NCCAM) at the National Institutes of Health; therefore, NCCAM approval of the article was required at the time of submission for publication. With this exception, the funding agencies had no role in the collection, analysis, and interpretation of the data or the decision to submit this article for publication.

Criteria for Advice on CAM Therapies

In **Table 1**, we propose criteria for placing individual therapies along a continuum that ranges from "recommend" to "accept" to "discourage" (2). These criteria allow physicians to use existing data to provide evidence-based advice to patients. We apply these criteria to the therapies evaluated in this paper.

Evidence on Efficacy and Safety of CAM Therapies

Tables 2 and **3** briefly summarize the therapies reviewed.

Table 1. **Criteria Used To Determine Whether a Complementary and Alternative Medical Therapy May Reasonably Be Recommended, Accepted, or Discouraged by Physicians***

Requirements	Recommend	Accept; May Consider Recommending	Accept	Discourage
Basic	Evidence supports both efficacy and safety	Evidence supports both efficacy and safety	Evidence on efficacy is inconclusive but evidence supports safety	Evidence indicates either inefficacy or serious risk
Efficacy	≥3 RCTs have evaluated the therapy ≥75% of trials support efficacy or a meta-analysis of trials supports efficacy For ≥3 of the trials that support efficacy: Trial has >50 patients *and* Trial is of adequate quality† Evidence supporting efficacy must come from >1 research team	≥1 RCT has evaluated the therapy >50% of trials support efficacy Evidence supporting efficacy fails to meet the criteria for therapies that may be recommended	Existing evidence is inadequate to conclude whether the therapy is effective or ineffective Data on efficacy fail to meet the criteria for considering recommendation Data on efficacy fail to meet the criteria for discouragement	≥2 RCTs have evaluated the therapy ≥67% of trials suggest that the therapy is ineffective For ≥2 of the trials that suggest lack of efficacy: Trial has >50 patients *and* Trial is of adequate quality†
Safety‡	Any documented adverse events associated with the therapy are minor (not life-threatening or permanently disabling) *and* Based on current information, no obvious theoretical potential for major (life-threatening or permanently disabling) adverse events exists	Any documented adverse events associated with the therapy are minor (not life-threatening or permanently disabling) *and* Based on current information, no obvious theoretical potential for major (life-threatening or permanently disabling) adverse events exists	Any documented adverse events associated with the therapy are minor (not life-threatening or permanently disabling) *and* Based on current information, no obvious theoretical potential for major (life-threatening or permanently disabling) adverse events exists	There is reliable documentation of a major (life-threatening or permanently disabling) adverse event occurring in association with the therapy *or* Based on current information, a theoretical potential for major adverse events exists

* RCT = randomized, controlled trial.
† Study quality was assessed for two types of therapies: those supported by RCTs of adequate number and size to qualify for recommendation and those with inefficacy suggested by RCTs of adequate number and size to qualify for discouragement. Quality was assessed by using the Jadad scale, a validated instrument that assigns scores for randomization, blinding, and reporting of withdrawals (3). Studies were rated by 2 authors; discrepancies were resolved by discussion. If double-blinding of a given therapy was both practical and ethical, an aggregate score of 3 points (of a maximum of 5) was considered adequate. If double-blinding was impractical or unethical, a score of 2 points (of a maximum of 3 for unblinded studies) was considered adequate.
‡ In some instances, a given therapy appears to pose a greater risk for a particular group of patients (e.g., patients undergoing radiation or chemotherapy or patients at increased risk for bleeding); the therapy should therefore be avoided by that group. In such cases, the conclusion that it is generally reasonable to recommend or accept a therapy will be qualified by a list of specific contraindications.

Dietary Modification and Supplementation

Dietary Fat Reduction

Dietary fat reduction has received attention in the treatment of both breast and prostate cancer. With regard to breast cancer, reduction of fat intake has been shown to reduce estrogen levels in both premenopausal and postmenopausal women (4). Survival of postmenopausal patients with resected breast cancer is greater in Japan, where diets are low in fat, than in the United States (5). However, differences between American and Japanese diets go beyond fat content; in particular, soy consumption is higher in Japan. The Nurses' Health Study (a cohort study) did not find evidence of a strong adverse effect of high postdiagnostic fat intake on survival (6). The Women's Intervention Nutrition Study (WINS), an ongoing RCT testing the hypothesis that postdiagnostic reduction of fat intake (to 15% of total calories) will increase survival, should provide more definitive information (**Appendix Table 1,** available at www.annals.org) (5). Currently, evidence is inadequate to recommend dietary fat reduction in women with breast cancer. However, it is reasonable to accept fat reduction in well-nourished patients who elect to try this approach.

Epidemiologic studies suggest that factors in the American diet may promote the progression of latent prostate cancer to the clinical stage. Autopsy studies show that latent prostate cancer occurs at equal rates in men of Asian countries and the United States, whereas clinical prostate cancer is much more common in the United States. Within a generation, Japanese and Chinese men who immigrate to the United States develop a risk for clinical cancer that approaches the U.S. average (7). The hypothesis that fat is at least one contributing dietary factor is supported by several observational studies that suggest a positive association between intake of saturated or animal fat and the progression of prostate cancer (8–11). In summary, observational data suggest that reduction of saturated or animal fat might slow progression of prostate cancer, but data from randomized dietary intervention trials are needed to support specific dietary advice. As with breast cancer, it is currently reasonable for physicians to accept dietary fat reduction in well-nourished men with prostate cancer.

Radical Dietary Regimens

Space does not permit evaluation of all radical dietary regimens used by patients with cancer. Our discussion of macrobiotics, a regimen that has yielded well-publicized testimonials of cancer remission (12, 13), is intended to

demonstrate an evaluative approach that can be applied in consideration of other regimens.

Macrobiotic diets are mainly vegetarian, consisting primarily of whole grains (14, 15). Macrobiotic diets are low in fat, and some are high in phytoestrogens (including isoflavonoids, which are derived primarily from soy) (16). Scientific evidence on the potential benefits of macrobiotic diets for patients with cancer is limited to two retrospective studies with serious methodologic flaws (17). No RCTs of macrobiotics have been conducted.

Potential risks are associated with macrobiotics. The macrobiotic philosophy may lead patients to delay or dis-

Table 2. **Complementary and Alternative Medical Therapies Intended To Affect Disease Progression and Patient Survival***

CAM Therapy	Efficacy—Level of Evidence†	Efficacy—Direction of Evidence‡	Level of Risk§ (in the Absence of Specific Contra-indications)	Contra-indications‖	Reasonable Advice¶ (in the Absence of Specific Contra-indications)	References
Reduction of fat intake for breast cancer	II–2	→	1	N	Accept and monitor	6
Reduction of fat intake for prostate cancer	II–2	→	1	N	Accept and monitor	8–11
Macrobiotic diet	III	→	2	E, N	Accept and monitor	16, 17, 19
Vitamin A	I (2 RCTs, *n* = 307 and *n* = 29 133)**	→	6	A, T	Discourage and monitor	25, 27, 29–32
Vitamin C	I (2 RCTs, *n* = 100 and *n* = 150)	↓	2	A, B	Discourage and monitor	33–38
Vitamin E for latent prostate cancer	I (1 RCT, *n* = 29 133)	↑ (logical extension of study results)††	1	A, B	Accept (may consider recommending) and monitor	27, 37, 40
Vitamin E for cancer other than latent prostate cancer	III	→	1	A, B	Accept and monitor	37, 40, 173
Soy for breast cancer	III	→	4	A, B, E	Discourage and monitor	41–44, 61, 67–71
Soy for prostate cancer	III	→	1	A, B	Accept and monitor	7, 41, 42, 71
PC-SPES	I (1 RCT, *n* = 90; only preliminary report available)	→	6	C	PC–SPES currently unavailable	73, 76–81, 91–93
Shark cartilage	III	→	3	H, An	Accept and monitor	94–97, 99–102
Mind–body therapies	I (10 RCTs, *n* = 63–271; 1 quasi-randomized trial, *n* = 94)	→	2		Accept and monitor	133, 137, 142, 150–159

* PC-SPES = prostate cancer and "hope" (in Latin); RCT = randomized, controlled trial.

† Level of evidence: Taken from criteria of U.S. Preventive Services Task Force (195). I = evidence obtained from at least one properly designed RCT; II–1 = evidence obtained from well-designed controlled trials without randomization; II–2 = evidence obtained from well-designed cohort or case–control analytic studies, preferably from more than one center or research group; II–3 = evidence obtained from multiple time series with or without the intervention; III = opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

‡ Direction of evidence: ↑ = current evidence suggests therapy is effective; ↓ = current evidence suggests therapy is not effective; → = current evidence is inconclusive. ↗ = current evidence is mixed, but most studies suggest therapy is effective; ↘ = current evidence is mixed, but most studies suggest therapy is not effective.

§ Level of risk: Level 4 or higher indicates that it is prudent to discourage a therapy. 6 = documentation of major (life-threatening or permanently disabling) adverse event that occurred in association with therapy in multiple instances with causal relationship established; 5 = documentation of major adverse event that occurred in association with therapy; 4 = theoretical possibility of major adverse event occurring as a result of therapy (based on current understanding of mechanism of action or preclinical data) but no clinical cases documented to date; 3 = documentation of minor adverse event that occurred in association with therapy; 2 = theoretical possibility of minor adverse event occurring as a result of therapy but no clinical cases documented to date; and 1 = no adverse events documented and, theoretically, adverse events seem unlikely.

‖ Contraindications: A = antioxidant. Avoid concurrent use with radiation or chemotherapy (see text for current evidence supporting this contraindication). An = potential inhibitor of angiogenesis. Avoid in pregnancy, childhood, the perioperative period and in patients with vascular insufficiency (including coronary artery disease). B = potential risk for bleeding. Avoid in patients who are receiving anticoagulant therapy or who are thrombocytopenic (for oral agents, also avoid during perioperative period). C = no data on use in combination with radiation or cytotoxic chemotherapy. Until more evidence is gathered, it is prudent to avoid concurrent use. E = phytoestrogen. Avoid in women with breast cancer, especially those with estrogen receptor–positive tumors. In particular, patients taking tamoxifen should be warned of potential interaction. Also avoid in women with endometrial cancer. (See discussion in text of soy supplementation, which presents the current evidence supporting this contraindication.) H = high calcium content. Avoid in patients with history of hypercalcemia. N = restrictive diet. Avoid in patients with poor nutritional status. T = teratogen. Avoid in patients who may be pregnant.

¶ Criteria for final advice: See Table 1.

** See text for full discussion of these RCTs and data from other trials that raise questions about the findings of these two studies.

†† In this study (27), persons taking vitamin E had a significantly decreased incidence of clinical prostate cancer, but the effect on the incidence of latent prostate cancer was not significant. These findings suggest that vitamin E supplementation may prevent progression of latent prostate cancer to clinical prostate cancer.

Table 3. **Complementary and Alternative Medical Therapies Intended for Palliation of Symptoms Associated with Cancer or Side Effects of Conventional Treatment***

CAM Therapy and Problem	Efficacy—Level of Evidence†	Efficacy—Direction of Evidence‡	Level of Risk§ (in the Absence of Specific Contra-indications)	Contra-indications‖	Reasonable Advice¶ (in the Absence of Specific Contra-indications)	References
Acupuncture for chemotherapy-related nausea and vomiting	I (6 RCTs, *n* = 10–104)	↑	3	B	Accept (may consider recommending) and monitor	103–109, 119–121
Acupuncture for chronic pain (related to underlying disease or conventional treatment)	III	→	3**	B	Accept and monitor	103, 111–121
Massage for anxiety	I (2 RCTs, *n* = 7 and *n* = 34)	↑	3	B†† (see text for other cautions)	Accept (may consider recommending) and monitor	122, 123, 129, 130, 196, 197
Massage for pain (related to underlying disease or conventional treatment)	I (3 RCTs, *n* = 34–103)	→	3	B†† (see text for other cautions)	Accept and monitor	122, 124, 125, 129, 130, 196, 197
Massage for nausea (related to autologous bone marrow transplantation)	I (1 RCT, *n* = 34)	↑	3	B†† (see text for other cautions)	Accept (may consider recommending) and monitor	122, 129, 130, 196, 197
Massage (manual lymph drainage) for lymphedema	I (1 RCT, *n* = 28; 1 quasi-randomized trial, *n* = 40)	↑	2	See text for cautions	Accept (may consider recommending) and monitor	126, 127
Exercise to improve physical function and psychological and physical symptoms in patients receiving conventional therapy	I (3 RCTs, *n* = 62–123; 2 quasi-randomized trials, *n* = 50 and *n* = 62)	↑ ‡‡	2	See Appendix Table 6§§ for cautions	Accept (may consider recommending) and monitor	198–202

* RCT = randomized, controlled trial.
† Level of evidence: Taken from criteria of U.S. Preventive Services Task Force (195). I = evidence obtained from at least one properly designed randomized, controlled trial; II–1 = evidence obtained from well-designed controlled trials without randomization; II–2 = evidence obtained from well-designed cohort or case–control analytic studies, preferably from more than one center or research group; II–3 = evidence obtained from multiple time series with or without the intervention; and III = opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.
‡ Direction of evidence: ↑ = current evidence suggests therapy is effective; ↓ = current evidence suggests therapy is not effective; → = current evidence is inconclusive; ↗ = current evidence is mixed, but most studies suggest therapy is effective; ↘ = current evidence is mixed, but most studies suggest therapy is not effective.
§ Level of risk: Level 4 or higher indicates that it is prudent to discourage a therapy. 6 = documentation of major (life-threatening or permanently disabling) adverse event that occurred in association with therapy in multiple instances with causal relationship established; 5 = documentation of major adverse event that occurred in association with therapy; 4 = theoretical possibility of major adverse event occurring as a result of therapy (based on current understanding of mechanism of action or preclinical data) but no clinical cases documented to date; 3 = documentation of minor adverse event that occurred in association with therapy; 2 = theoretical possibility of minor adverse event occurring as a result of therapy but no clinical cases documented to date; and 1 = no adverse events documented and theoretically, adverse events seem unlikely.
‖ Contraindications: A = antioxidant. Avoid concurrent use with radiation or chemotherapy (see text for current evidence supporting this contraindication). An = potential inhibitor of angiogenesis. Avoid in pregnancy, childhood, the perioperative period and in patients with vascular insufficiency (including coronary artery disease). B = potential risk for bleeding. Avoid in patients who are receiving anticoagulant therapy or who are thrombocytopenic (for oral agents, also avoid during perioperative period). C = no data on use in combination with radiation or cytotoxic chemotherapy. Until more evidence is gathered, it is prudent to avoid concurrent use. E = phytoestrogen. Avoid in women with breast cancer, especially those with estrogen receptor–positive tumors. In particular, patients taking tamoxifen should be warned of potential interaction. Also avoid in women with endometrial cancer. (See discussion in text of soy supplementation, which presents the current evidence supporting this contraindication.) H = high calcium content. Avoid in patients with history of hypercalcemia. N = restrictive diet. Avoid in patients with poor nutritional status. T = teratogen. Avoid in patients who may be pregnant.
¶ Criteria for final advice: See Table 1.
** Although there have been case reports of more serious adverse events (such as pneumothorax), such incidents are very unlikely when accepted techniques are used by a competent practitioner.
†† This contraindication applies to deep tissue or forceful massage; gentle massage (including manual lymph drainage, a specialized form of massage used for lymphedema) may be used with caution in patients at increased risk for bleeding.
‡‡ All trials reported benefits for at least one of the following outcomes: physical function, psychological distress, and physical symptoms.
§§ Available at www.annals.org.

continue conventional therapy (14, 18). Limited data suggest that macrobiotic diets may alter the metabolism of some drugs (19). Although it seems that a carefully formulated macrobiotic diet can provide adequate nutrition (20, 21), it seems prudent to avoid highly restrictive diets in poorly nourished patients (22). Because some macrobiotic diets have a high phytoestrogen content, it seems prudent to discourage their use by women with breast cancer (especially those who have estrogen receptor–positive tumors or who are taking tamoxifen) or endometrial cancer (see discussion of soy).

For well-nourished patients who do not have breast or endometrial cancer, it seems reasonable to accept macrobiotics as an adjunct to conventional treatment. Physicians should closely monitor patients who are following macrobiotic diets for signs of malnutrition or altered metabolism of conventional medications.

Antioxidant Vitamin Supplementation

The antioxidant vitamins include vitamin A (comprising both retinol and its carotenoid precursors), vitamin C, and vitamin E (23, 24). Because oxidative damage to cells might increase the risk for cancer, it is plausible that antioxidants could help in the primary prevention of cancer;

however, their potential role in the progression of cancer is less clear. Aside from their antioxidant activity, these vitamins might possibly affect cancer progression through such mechanisms as inducing cellular differentiation or enhancing immune function (23, 25, 26).

The combination of antioxidants with radiation therapy or chemotherapy causes special concern. We discuss this topic later in the paper.

Vitamin A: Specific retinoids (retinol analogues) are used as differentiation agents in the conventional medical treatment of certain cancers; the most notable example is all-*trans* retinoic acid, which is commonly used to induce remission in acute promyelocytic leukemia. However, little evidence exists on the possible effects of nonprescription vitamin A supplements on cancer progression. One RCT suggested that vitamin A might actually promote progression of latent prostate cancer to the clinical stage (with vitamin A, the incidence of clinical tumors increased, whereas the incidence of latent tumors did not) (27). Two other RCTs failed to find any effect of vitamin A on the overall incidence of prostate cancer; however, these studies did not distinguish between latent and clinical cancer (28, 29). In an RCT of vitamin A as adjuvant therapy in patients with stage I non–small-cell lung cancer after curative resection, vitamin A failed to show benefits in terms of tumor recurrence or overall survival, although it seemed to prevent the development of second primary tumors related to tobacco consumption (30). Two much larger RCTs have suggested that vitamin A may actually increase the incidence of lung cancer in high-risk populations (29, 31, 32).

The toxic syndrome known as *hypervitaminosis A* results from intake of very large doses of vitamin A in the form of retinol (this syndrome is not seen with intake of large doses of carotenoids) (25). Two of the trials described earlier (30, 32) administered retinol. Although no signs of hypervitaminosis A were reported in the trial that administered approximately eight times the recommended daily allowance (RDA) (32), typical manifestations of hypervitaminosis A (including hepatotoxicity) were noted in the trial that administered approximately 100 times the RDA (24, 30).

The limited available data suggest little benefit of high-dose vitamin A supplementation and some potential harm. Therefore, at present, it seems prudent to discourage vitamin A supplementation in excess of the RDA.

Vitamin C: Data on vitamin C and cancer progression are limited. Two RCTs ($n = 100$ and $n = 150$), both of adequate quality, failed to show any benefit of high-dose vitamin C in patients with advanced cancer (**Table 1**) (**Appendix Table 2,** available at www.annals.org) (33, 34). Concerning safety, several studies have found that vitamin C has anticoagulant effects (35–38). On the basis of the apparent lack of efficacy of vitamin C, it seems reasonable for physicians to discourage patient use of high-dose vitamin C to treat cancer. For patients who are thrombocytopenic, are taking medications with anticoagulant effects, or are undergoing surgery, the risk for bleeding is an additional reason to avoid high-dose vitamin C.

Vitamin E: One RCT suggests that vitamin E supplementation (at a dose of approximately three times the RDA) may prevent progression of latent prostate cancer to clinical cancer (27, 39); however, data are lacking on vitamin E and the progression of clinical cancer. With regard to safety, vitamin E has been shown to diminish platelet function (37, 40). Although it seems generally reasonable for physicians to accept patients' use of vitamin E to treat prostate cancer, patients who are thrombocytopenic, are taking medications with anticoagulant effects, or are undergoing surgery should avoid high-dose vitamin E.

Soy Supplementation

Soy may contribute to the suggested protective effects of the Japanese diet on breast cancer survival and progression of latent prostate cancer to the clinical stage (5, 7, 41, 42). Soy products are the major dietary source of isoflavonoid phytoestrogens (41, 42). Isoflavonoids could affect cancer progression through several possible mechanisms.

The weak estrogenic effects of isoflavonoids are of particular interest in relation to breast and prostate cancer. Several studies have focused on mechanisms by which isoflavonoids might limit activity of endogenous sex hormones. Isoflavonoids compete with estradiol for binding sites (as does the antiestrogen tamoxifen) (43). However, in vitro data suggest that, at physiologically relevant concentrations, it is possible for isoflavonoids to enhance rather than inhibit the proliferative effects of estradiol on estrogen-dependent breast cancer cells (44). Isoflavonoids inhibit enzymes involved in estrogen and androgen synthesis (45, 46), and, by stimulating production of sex hormone–binding globulin, could reduce activity of both estradiol and testosterone (47). However, it is not clear that clinically significant effects on sex hormone synthesis or levels of sex hormone–binding globulin would occur at physiologically relevant concentrations (43, 45–48). Several RCTs have studied the hormonal effects of increasing isoflavonoid intake in women; most have not demonstrated significant decreases in estrogen levels or increases in sex hormone–binding globulin (49–56). In men, isoflavonoids might reduce testosterone levels by acting on the hypothalamus and pituitary gland (as does the synthetic estrogen diethylstilbestrol [DES]), although RCTs to date do not support such an effect (57, 58).

Potential antitumor effects of the isoflavonoid genistein go beyond interactions with sex hormones—inhibition of tyrosine kinases (59) and topoisomerase II (60), suppression of in vitro cell proliferation (41, 43, 47, 60–63), and inhibition of angiogenesis in vitro (64, 65). However, these effects require concentrations that may exceed levels attainable in vivo with oral administration (43, 48). Studies of oral genistein supplementation in animal models of hormone-independent cancer have produced mixed results (63, 66).

In breast cancer, the net effects of isoflavonoids will be determined by the balance of three factors: pro-estrogenic effects, potential inhibition of the effects of endogenous estrogens, and possible antitumor effects unrelated to estrogenic activity. No clinical data are currently available on the effects of soy supplementation on breast cancer progression, but evidence suggests that harmful pro-estrogenic effects may occur in some patients (43, 44, 61, 67–70). Dietary soy can stimulate the growth of estrogen-dependent tumors in mice, and two small studies suggest that soy supplementation may cause estrogenic stimulation of the breasts in premenopausal women (67–69).

At present, it seems prudent to discourage soy supplementation in women with breast cancer (especially those with estrogen receptor–positive tumors) or endometrial cancer. Because data obtained from an animal study indicate that genistein can negate the inhibitory effect of tamoxifen on breast cancer growth, women taking tamoxifen should especially avoid soy supplements (70).

No published clinical studies evaluate the effects of soy supplements on prostate cancer progression. However, unlike with breast cancer, the pro-estrogenic activity of isoflavonoids might possibly have benefits in prostate cancer. A federally funded RCT is currently testing isoflavonoids as an adjunct to androgen ablation therapy (**Appendix Table 3**, available at www.annals.org). Currently, it seems reasonable to accept the use of soy supplements by patients with prostate cancer who elect to try them.

Because isoflavonoids have antioxidant activity, the combination of soy supplements with radiation therapy or chemotherapy causes special concern (42). Isoflavonoids may inhibit platelet aggregation in nonhuman primates (71); thus, it seems prudent for patients who are thrombocytopenic, are taking medications with anticoagulant effects, or are undergoing surgery to avoid soy supplements.

Herbal Products and Other Biological Agents: Selected Examples

Given the numerous herbal products and other biological agents used by patients with cancer, discussion of all such supplements is beyond the scope of this paper. Instead, we focus on PC-SPES and shark cartilage as examples of supplements that are purported to slow disease progression. Our discussion of these examples demonstrates an evaluative approach that can be applied to other supplements.

PC-SPES

PC-SPES ("PC" refers to prostate cancer; "spes" means "hope" in Latin) (BotanicLab, Brea, California) is purported to slow the progression of prostate cancer and to increase quality of life. It is an oral supplement composed of extracts of eight herbs (**Appendix Table 4**, available at www.annals.org). Estrogenic properties have been reported for licorice and *Panax* species (72), which are among the herbal components of PC-SPES, and specific phytoestrogens have been identified in the product (73–75). The synthetic estrogen DES has also been detected in some samples of PC-SPES (see discussion of contamination). Several studies of PC-SPES have demonstrated estrogenic effects in vitro (73, 76), in mice (76), and in humans (76–81). Nevertheless, in vitro activity of PC-SPES cannot be explained solely by estrogenic effects. In vitro sensitivity of tumor cell lines to PC-SPES cannot be predicted by the presence or absence of sex hormone receptors (82), and PC-SPES shows transcriptional effects in androgen-sensitive prostate cancer cells that are distinct from those of DES or estradiol (83).

In vitro studies document that PC-SPES inhibits growth of various cancer cell lines, including both androgen-sensitive and androgen-insensitive prostate cancer cells (73, 82–88). Preclinical data support potential antitumor activity of specific phytochemicals found in PC-SPES (73, 74, 89, 90). However, studies in mice that examined the effects of PC-SPES on the growth of androgen-insensitive human prostate carcinoma cells have produced mixed results (80, 87).

Five open-label studies suggest that PC-SPES can decrease levels of prostate-specific antigen (PSA) (76–78, 80, 81), stabilize or improve metastatic disease (81), reduce pain (78), and increase quality of life (78). These studies reported PSA decreases of more than 50% in most patients (76–78, 80, 81), even in men refractory to conventional hormone-ablative therapy (77, 78, 80, 81). Preliminary results from a small RCT ($n = 90$) of PC-SPES in hormone-refractory patients showed PC-SPES to be more effective than DES in reducing PSA (although significance was borderline) (91). The effect of PC–SPES on survival has not yet been investigated.

Many of the reported adverse effects of PC-SPES may result from its estrogenic properties—thrombotic events (noted in approximately 3% of patients) (76–78, 80, 81, 91, 92), breast tenderness or enlargement (76–81), sexual dysfunction (76, 79, 81), hot flashes (77, 80, 81), edema (77, 79), decreased body hair (79), and hypertriglyceridemia (81). In contrast with many reports of thrombotic events (76, 78, 80, 81, 91, 92), a case report of profound bleeding diathesis suggests an anticoagulant effect of PC-SPES (93). In another case report, PC-SPES use was associated with increased international normalized ratio in a patient taking warfarin (92). Other reported adverse effects include gastrointestinal symptoms (77, 78, 81), leg cramps (77, 81), fatigue (77, 81), and allergic reactions (81). No data on potential interactions between PC-SPES and radiation therapy or cytotoxic chemotherapy are available.

Recent analyses have revealed contamination of PC-SPES with conventional medications (DES, warfarin, and indomethacin) (73, 91, 93). Two studies found variable amounts of DES in most PC-SPES samples tested (73, 91), although two other studies failed to find evidence of DES contamination in analyzed samples (76, 83). Because DES has shown clinical efficacy against prostate cancer, the discovery of DES contamination raises the question of whether observed clinical results can be attributed to PC-SPES herbal components (73). One study found that an-

tineoplastic potency in vitro correlated with DES content of PC-SPES samples (73). However, in the RCT described earlier (91), the effects of PC-SPES seemed to go beyond those attributable to DES. Although patients in the PC-SPES group of the study received only 0.01% to 3.1% of the DES dose administered to patients in the DES group, PC-SPES seemed to be more effective than DES (91). Investigation of the above-mentioned case of profound bleeding diathesis suggested warfarin contamination of PC-SPES; the presence of warfarin was subsequently verified in some PC-SPES samples (naturally occurring phytocoumarins are likely to be present in PC-SPES as well) (73, 93). A third drug, indomethacin, has also been detected in PC-SPES (73). In addition to variable contamination with conventional medications, considerable intersample variation has been found in the levels of potentially active phytochemicals (73). In February 2002, the Food and Drug Administration (FDA) warned patients to stop taking PC-SPES. The sole manufacturer issued a recall and subsequently went out of business. PC-SPES is currently unavailable.

Preliminary evidence supporting efficacy of PC-SPES is provocative. However, its use has been associated with major adverse events, and analysis indicates both contamination with conventional medications and variation in levels of potentially active natural compounds. Advice on the use of PC-SPES must await reintroduction of a product that is proven to be free of conventional medications and well-standardized for phytochemical components, particularly phytoestrogens and phytocoumarins. The case of PC-SPES highlights the lack of adequate quality control in the herbal industry today.

Shark Cartilage

Current evidence indicates that cartilage contains proteins that inhibit angiogenesis. Although angiogenesis inhibitors could prove useful in cancer treatment, commercial shark cartilage products are intended for oral or rectal administration, making it unlikely that antiangiogenic proteins would enter the circulation intact. **Appendix Table 5** (available at www.annals.org) summarizes data on potential mechanisms of action of cartilage products.

Current clinical evidence does not support the efficacy of oral shark cartilage in cancer treatment. In a trial of 60 patients with various advanced cancers (59 patients refractory to conventional treatment and 1 patient who declined conventional treatment), disease progression was similar to historical controls, and quality of life did not improve overall (94). Preliminary results from three other small uncontrolled trials of patients with advanced cancers refractory to conventional therapy also failed to support efficacy (95, 96). One study of 22 patients with refractory renal-cell carcinoma compared outcomes for two different doses of shark cartilage. Median survival was significantly increased in the higher-dose group; however, group assignment was not randomized, and there was no control group of patients not taking shark cartilage. The results are, therefore, difficult to interpret (97). All studies described here were restricted to advanced cases in which conventional treatment had failed; shark cartilage might possibly be more effective at earlier stages of disease (98). Three RCTs of shark cartilage are under way (**Appendix Tables 1** and **3**).

In general, oral shark cartilage seems to be well tolerated. The most common adverse effects are gastrointestinal (94–97, 99). One study noted possible allergic reactions (99). A typical daily dose (70 g) of shark cartilage contains approximately 14 g of calcium, and recurrent hypercalcemia has been reported in two patients with a history of previous episodes (95, 100). Concerns have also been raised about potential adverse effects of angiogenesis inhibition in certain situations, such as surgery, vascular insufficiency (including coronary artery disease), pregnancy, and childhood (101, 102). No interactions with conventional radiation therapy or chemotherapy have been reported.

Despite the popularity of shark cartilage, there is currently insufficient evidence to support its efficacy in cancer treatment. However, adverse effects generally seem to be minor. Until the ongoing clinical trials provide further evidence, it seems reasonable for physicians to accept the use of shark cartilage in the absence of specific contraindications. It seems prudent to discourage the use of shark cartilage in patients with a history of hypercalcemia and in situations where angiogenesis inhibition might be harmful.

Acupuncture

A National Institutes of Health (NIH) Consensus Conference concluded that clear evidence supports efficacy of acupuncture in the control of chemotherapy-related nausea and vomiting (103). Six RCTs (five with placebo controls; only two with >50 patients) suggest that stimulation at P6 (a specific point proximal to the wrist), either alone or in conjunction with stimulation at ST36 (another point on the lower leg), serves as an effective adjunct to standard antiemetic medication (104–109). These findings are consistent with a larger body of data supporting the efficacy of various methods of P6 stimulation in the control of postoperative nausea and vomiting (110).

Another potential role of acupuncture in patients with cancer is the palliation of chronic pain. Several case reports and series suggest that acupuncture may provide relief when conventional measures fail to control chronic pain resulting from underlying disease or conventional treatments (surgery or radiation) (111–118). However, RCTs are needed to confirm the value of acupuncture in the management of chronic cancer-related pain.

The NIH Consensus Conference concluded that the overall frequency of acupuncture-related adverse events is extremely low (103), and prospective studies have indicated that even minor adverse events are rare (119). Treatment of nausea can be limited to a single specific point proximal to the wrist (in some cases combined with a second point on the leg). Unlike treatment of nausea, treatment of pain may require needle insertion at a wide variety

of points, some of which overlie organs and nerves. Although case reports have described serious adverse events (such as pneumothorax), such incidents are very unlikely when a competent practitioner uses accepted techniques (119–121). However, it seems prudent to avoid insertion of acupuncture needles in patients who are thrombocytopenic or who are receiving anticoagulant therapy.

In summary, RCTs to date, although limited in size, suggest that it is certainly reasonable to accept the use of acupuncture in conjunction with standard antiemetics to control chemotherapy-related nausea and vomiting and that recommendation for this purpose might be considered. Fewer data are available on the use of acupuncture in palliation of chronic cancer-related pain, but it seems reasonable to accept this approach if patients elect to try it.

Massage

Few studies have evaluated massage in patients with cancer. Two small RCTs indicate that massage may reduce anxiety (122, 123). For relief of cancer-related pain, data are inconclusive; only one of three RCTs (ranging in size from 34 to 103 patients) found significant benefits for massage (122, 124, 125). However, these trials provided standardized massages; none attempted to direct treatment toward areas where individual patients experienced pain. Finally, one small RCT found that massage reduced nausea in patients undergoing autologous bone marrow transplantation (122).

Manual lymph drainage is a specialized form of massage used in patients with lymphedema. Two small trials (one randomized and one quasi-randomized) found manual lymph drainage to be an effective adjunct to compression bandaging or sleeves in patients with arm lymphedema after surgery for breast cancer (126, 127).

Currently, no evidence indicates that massage promotes tumor metastasis. However, it seems prudent to avoid massage directly over known tumors or even predictable metastasis sites without known disease (128). Particular caution should be exercised in patients with bony metastases, who may be prone to fracture.

Several other considerations are relevant for certain patients. Care must be taken to avoid further injury to tissues damaged by surgery or radiation therapy (128). Caution must be used in patients who are prone to bleeding (those who are thrombocytopenic or are receiving anticoagulant therapy). These patients may develop hematomas from pressures that would normally have no adverse effects (129). Deep abdominal massage has been associated with internal bleeding, even in the absence of coagulation abnormalities (130), and should be avoided in hypocoagulable patients. Hypercoagulability may also lead to problems because strong pressure over a thrombus can cause embolization (131); massage should be avoided over known thrombi (128). Finally, massage should be avoided over stents or other prosthetic devices because displacement can occur (132).

If the described precautions are observed, available evidence suggests that it is reasonable for physicians to accept the use of massage for relief of anxiety and as adjunct therapy for lymphedema and that physicians might consider recommending massage for these purposes. Although evidence on the benefits of massage for relief of cancer-related pain remains inconclusive, it seems reasonable to accept this approach if patients elect to try it.

Exercise

Although conventional medicine recognizes various health-related benefits of exercise, exercise regimens have not yet become standard adjuncts to conventional cancer therapy. **Appendix Tables 6** and 7 (available at www.annals.org) summarize trials assessing potential benefits of exercise in patients undergoing conventional treatment.

Psychological and Mind–Body Therapies

Examples of psychological and mind–body therapies include various forms of individual and group therapy, relaxation, imagery, hypnosis, and meditation. Several RCTs suggest that such interventions may alleviate emotional distress in patients with cancer (133–145). There is also some evidence that psychological and mind–body approaches may alleviate certain physical symptoms of disease and side effects of conventional treatment. For example, several RCTs support the efficacy of these approaches for alleviating cancer-related pain (142, 146–149). Because palliative applications of psychological and mind–body interventions have gained a certain level of acceptance in the conventional realm, use of these interventions for palliative purposes will not be discussed further.

A more controversial question is whether psychological and mind–body interventions enhance survival. Proposed mechanisms through which these interventions might increase survival in patients with cancer include improvement in immune function and beneficial behavioral change (**Appendix Table 8**, available at www.annals.org). Trials completed to date have yielded mixed results. Four studies (three randomized [150–152] and one quasi-randomized [153]) found significant survival benefits for such interventions, and an additional RCT showed a borderline significant increase in survival (154, 155). However, five other RCTs failed to find survival benefits (133, 142, 156–158), and an RCT evaluating response to chemotherapy rather than actual survival also failed to find benefits (137, 159). Most of the studies in both groups—trials that support survival benefits and trials that do not—have potential problems that may affect interpretation of results. Considering the limitations of the studies to date and their inconsistent results, conclusions on survival benefits of psychological and mind–body interventions remain premature.

For now, it seems reasonable to accept the use of psychological and mind–body interventions by patients who believe these techniques can extend survival. However, unrealistic expectations should not be encouraged. Physicians

may guide patients toward realistic expectations for these interventions by explaining that, although survival benefits are uncertain, there are other potential benefits in terms of emotional state and physical symptoms.

CAM Supplements in Cancer: Major Categories of Adverse Effects and Interactions with Conventional Treatments

Anticoagulant Effects

Appendix Table 9 (available at www.annals.org) lists commonly used supplements with potential anticoagulant effects. Such supplements should be avoided by patients who are thrombocytopenic, are taking medications with anticoagulant effects, or are in the perioperative period.

Phytoestrogenic Effects

Current data on soy suggest that it is prudent to discourage phytoestrogen supplementation in women with breast cancer (especially those who have estrogen receptor–positive tumors or who are taking tamoxifen) or endometrial cancer. In addition to soy supplements, several phytoestrogenic herbal products are commercially available. Some versions of Essiac (an herbal mixture commonly used by patients with cancer) contain the phytoestrogenic ingredient red clover (160–162). Furthermore, some herbs used in the broader population contain phytoestrogens. Evidence indicates that phytoestrogens are present in some preparations of ginseng, which is among the most popular herbs on the market today. Preclinical studies of various ginseng extracts have produced conflicting data about estrogenicity and about the effects of these extracts on the growth of breast cancer cells (163–165). However, case reports indicate that clinically significant estrogenic effects have occurred with commercially available products (165, 166). Finally, as noted earlier, some versions of the macrobiotic diet are high in phytoestrogens (16).

Alteration of Levels of Conventional Drugs

Supplements may alter blood levels of conventional medications through effects on metabolism. The popular herb St. John's wort, an inducer of the cytochrome P450 enzyme system and drug-transporting P-glycoprotein, reduces levels of various drugs (for example, cyclosporine and indinavir) (167–169). A recent RCT found that concomitant administration of St. John's wort significantly reduces levels of the active metabolite of the chemotherapeutic agent irinotecan (169). It seems prudent to avoid combining St. John's wort with chemotherapeutic agents or other drugs for which failure to achieve therapeutic levels could lead to serious consequences. Future research will likely identify numerous supplements that increase or decrease drug levels. Dietary changes (for example, consuming grapefruit juice) may also alter drug levels (170). As noted, limited data suggest that macrobiotic diets may affect metabolism of some drugs (19).

Interaction of Antioxidants with Radiation and Chemotherapy

Free radicals and reactive oxygen species mediate antitumor activity as well as adverse effects of some conventional agents. Antioxidants may limit adverse effects but could also theoretically diminish antitumor efficacy (171–173). Our discussion focuses on evidence regarding alterations in efficacy of conventional treatments by concurrent administration of antioxidants, and it is restricted to antioxidants that have not been approved for use with conventional treatments.

Because the generation of free radicals is central to the cytotoxic effects of radiation, the theoretical risk that antioxidants might diminish efficacy of radiation therapy is particularly high (171, 174). In addition, certain chemotherapeutic agents may rely on free radicals and reactive oxygen species as mediators of cytotoxicity (**Appendix Table 10**, available at www.annals.org); these agents must also be considered at high risk for potential inhibition by antioxidants (172). Studies that have tested the combination of nonprescription antioxidants with these "high-risk" conventional therapies have yielded mixed results. Most RCTs have not demonstrated significant differences in efficacy with concurrent antioxidant administration. One RCT combined radiation therapy with chemotherapy (175), one RCT used radiation therapy as the sole conventional therapy (173, 176), and five RCTs used chemotherapy regimens incorporating "high-risk" agents (177–181). However, some studies have reported either potentiation or inhibition of "high-risk" conventional therapies by antioxidants. In three RCTs, the antioxidant melatonin seemed to enhance the efficacy of radiation therapy (182) as well as some regimens incorporating "high-risk" chemotherapeutic agents (183, 184). Conversely, one RCT suggested inhibition of "high-risk" chemotherapeutic agents by an antioxidant (vitamin B_6) (185). Although no RCTs have yet shown inhibition of radiation efficacy by antioxidants, inhibition has been noted in two animal studies (186, 187). Of particular note, animal data suggest that a single antioxidant may cause either potentiation or inhibition, depending on dosage and timing of administration relative to irradiation (186, 188).

Certain chemotherapeutic agents do not seem to depend on free radicals and reactive oxygen species for therapeutic efficacy (**Appendix Table 10,** available at www.annals.org). These agents might be considered theoretically at low risk for potential inhibition by antioxidants (172). However, unexpected interactions may nonetheless result in either potentiation or inhibition of these "low-risk" agents. For example, the effects of 5-fluorouracil were enhanced by vitamin E in one animal study (189) and inhibited by β-carotene in another (190).

Three factors may complicate attempts to predict interactions between antioxidants and conventional therapies. First, individual antioxidants have unique properties in addition to their general antioxidant activity. Such prop-

erties could result in either potentiation or inhibition of conventional treatments. Elsewhere in this paper, we discuss individual effects of several antioxidants (the antioxidant vitamins and the isoflavonoids in soy protein). A second point is that uptake of certain antioxidants may vary among cell types (191, 192). However, no formula is available for determining which antioxidants are likely to be taken up by various types of malignant cells. Finally, our understanding of the cytotoxic mechanisms of chemotherapeutic agents is incomplete. Even if a specific agent is known to generate free radicals, it is not always clear that these radicals play an essential role in antitumor activity (193).

In summary, the limited data to date suggest that concurrent administration of antioxidants may result in either potentiation or inhibition of radiation therapy and chemotherapy. The outcome of any given pairing of an antioxidant with a conventional regimen is difficult to predict from theoretical models. Future studies will probably identify specific antioxidants that may be used in certain cancers to reduce toxicity of particular conventional agents without diminishing efficacy. Two antioxidants, dexrazoxane and amifostine, have already been approved to limit toxicity of specified regimens in certain patient populations (194). However, at this time, it is clear that antioxidants can reduce efficacy of conventional treatments in some cases, and it seems prudent to discourage concurrent use of nonprescription antioxidants with radiation therapy or chemotherapy until more evidence becomes available.

Current Trials of CAM Therapies in Patients with Cancer

Appendix Table 3 (available at www.annals.org) presents federally funded RCTs, and **Appendix Table 1** lists RCTs with nonfederal sponsors.

Discussing CAM Therapies with Patients Who Have Cancer

When a patient with cancer seeks CAM therapy, the physician has an obligation to provide evidence-based advice in a manner that shows respect for the patient's beliefs and choices. Although the discussion will vary according to individual patient concerns, we believe that the following strategy will serve as a useful guide.

The physician may begin by explaining that CAM therapies offer no "magic bullets" and that current evidence supporting CAM is stronger for alleviation of cancer-related symptoms than for slowing of disease progression. The physician might then summarize the CAM therapies he or she believes it would be reasonable to accept as part of the patient's care (**Tables 2** to **4**).

Several general cautions may be presented before discussing specific CAM therapies it seems prudent to avoid. The physician should discourage any intervention that delays conventional treatments of proven efficacy, treatment by unlicensed professionals, and the injection of substances not approved by the FDA. The patient should be informed that "natural" does not necessarily mean "safe" and that current labeling regulations do not ensure that what is found in the bottle corresponds to what is on the label (203). The physician should explain that because current evidence is inadequate to predict which supplements may increase or diminish the effects of radiation therapy or chemotherapy, it seems prudent to avoid combining these interventions until more information becomes available. Aside from these general cautions, there are many specific CAM therapies it seems prudent to avoid in certain situations and others that it seems prudent to avoid in all patients. The therapies we have reviewed that fall into these categories are summarized in **Table 5** (also see **Tables 2** and **3**).

When a patient decides to use a therapy, close follow-up by the physician is essential, regardless of the physician's advice about that therapy. The physician

Table 4. **Complementary and Alternative Medical Therapies That May Reasonably Be Accepted and, in Some Cases, Considered for Recommendation***

Certain dietary regimens (see text for information on dietary fat reduction in patients with breast or prostate cancer and on macrobiotic diets)
Vitamin E supplementation
Soy supplementation in prostate cancer
Certain herbal products and biological agents (see text for information on shark cartilage)
Acupuncture for chemotherapy-related nausea and vomiting or for pain
Massage for anxiety or pain
Moderate exercise
Psychological and mind–body therapies (e.g., support groups, relaxation training, imagery)

* See Tables 2 and 3 in addition to the text for contraindications to the use of particular therapies in specific groups of patients.

Table 5. **Specific Complementary and Alternative Medical Therapies To Discourage and Avoid**

Therapy	Situation in Which It Is Prudent To Avoid Therapy
Highly restrictive dietary regimens	Poor nutritional status
Antioxidants	Concurrent radiation or chemotherapy
Supplements with anticoagulant effects	Thrombocytopenia, anticoagulant therapy, surgery
Phytoestrogens	Breast cancer (especially in the case of estrogen receptor–positive tumors or tamoxifen therapy), endometrial cancer
Acupuncture	Thrombocytopenia, anticoagulant therapy
Deep-tissue or forceful massage	Thrombocytopenia, anticoagulant therapy
St. John's wort	Concurrent chemotherapy or use of other drugs for which failure to achieve therapeutic levels could lead to serious consequences
High-dose vitamin A	Prudent for all patients to avoid
High-dose vitamin C	Prudent for all patients to avoid

should remain alert for signs of adverse effects or interactions with conventional treatments. When a CAM (or conventional) therapy is started, use of a symptom diary may help determine whether the therapy is beneficial for the individual patient (204).

CONCLUSION

Several CAM therapies offer potential benefits for patients with cancer. Others, however, seem to be ineffective, and many present risks for direct adverse effects or interactions with conventional treatments. Therefore, it is important for physicians to communicate openly with patients about CAM use. Current evidence, although limited, suggests that physicians may reasonably accept some CAM therapies as adjuncts to conventional care and discourage others. As more data are gathered, the evidence-based recommendation of some CAM therapies and the evidence-based rejection of others will become more definitive.

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Appendix Table 1. **Non–Federally Funded Ongoing Phase II and III Randomized, Controlled Trials of Complementary and Alternative Medical Therapies for Cancer***

Therapy	Type of Cancer and Entry Criteria	Phase of Trial and Number of Patients	Comparison	Outcomes	Site and Sponsor
Dietary intervention (WINS): low fat (15% of total calories) with individual and group counseling plus adjuvant therapy (accrual closed)	Breast cancer stage I–IIIa (postmenopausal); postsurgery, patient receiving adjuvant therapy (endocrine therapy or chemotherapy)	III, $n = 2500$	USDA and USDHHS dietary guidelines plus adjuvant therapy	Overall and disease-free survival	Multicenter (American Health Foundation, Valhalla, NY)
Shark cartilage extract	Metastatic renal cancer (refractory to immunotherapy)	III, $n = 280$	Placebo	Survival, time to progression, tumor response, duration of response, quality of life, safety	Multicenter (Aeterna, Quebec City, Quebec, Canada)
Wobe–Mugos E enzyme plus standard treatment (in June 2002, trial discontinued because of accrual difficulties related to changes in standard treatment options)	Multiple myeloma stage II or III (chemotherapy naive); patient receiving standard treatment (melphalan and prednisone)	III, $n = 250$	Placebo plus standard treatment	Survival, tumor response, metastasis, reduction of side effects from standard treatment, quality of life	Multicenter (Mucos Pharma GmbH, Geretsried, Germany)
Stress reduction with Transcendental Meditation (20 min twice daily) plus standard care	Breast cancer stage II–IV	III, $n = 166$	Basic literature on breast cancer plus standard care	Survival, quality of life	St. Joseph Hospital, Chicago (Retirement Research Foundation, Chicago, IL)
Lifestyle (diet, exercise, stress management)	Prostate cancer (PSA level, ≥ 4 to ≤ 10; Gleason score, ≤ 7); no conventional therapy	III, $n = 120$	Watchful waiting	Disease progression, PSA	UCSF (UCSF and CaP CURE, Santa Monica, CA)
PC-SPES herbal mixture (in early 2002, trial closed because PC-SPES contamination discovered)	Prostate cancer (hormone-refractory)	II (crossover), $n = 108$	Estrogen (DES)	Disease progression, sex hormone levels, SHBG, tumor estrogen receptor concentration, toxicity, mechanism of action	UCSF (UCSF)
Chinese herbal mixture (21 herbs) plus adjuvant chemotherapy	Breast cancer (advanced, metastatic); patient receiving adjuvant chemotherapy (doxorubicin and cyclophosphamide)	II, $n = 60$	Placebo plus adjuvant chemotherapy	Immune measures, side effects of adjuvant chemotherapy	UCSF (State of California BCRP)

* Includes all studies that could be identified by the authors as of May 2001. Because information on privately funded research is not always widely distributed in the public domain, it is likely that this list is incomplete. Phase II trials assess efficacy and safety in smaller samples; phase III trials confirm efficacy, monitor side effects, and compare outcomes with commonly used treatments in larger samples. BCRP = Breast Cancer Research Program; DES = diethylstilbestrol; PC-SPES = prostate cancer and "hope" (in Latin); PSA = prostate-specific antigen; SHBG = sex hormone–binding globulin; UCSF = University of California, San Francisco; USDA = U.S. Department of Agriculture; USDHHS = U.S. Department of Health and Human Services; WINS = Women's Intervention Nutrition Study.

Appendix Table 2. **Quality Assessment (Using Jadad Scale) of Randomized, Controlled Trials of Vitamin C in Patients with Cancer (3)**

Trial, Year (Reference)	Patients, *n*	Described as Randomized? (0, +1)*	Described as Double-Blind? (0, +1)*	Description of Withdrawals? (0, +1)†	Randomization Method Described and Appropriate? (0, +1, −1)‡	Double-Blinding Method Described and Appropriate? (0, +1, −1)‡	Aggregate Score (Sum of 5 Individual Scores)§
Creagan et al., 1979 (33)	150	+1	+1	+1	0	+1	4
Moertel et al., 1985 (34)	100	+1	+1	+1	0	+1	4

* A study receives a score of +1 for "yes" or 0 for "no."
† A study receives a score of +1 only if the number of withdrawals and the reasons for withdrawal are given for each group.
‡ A study receives a score of 0 if no description is given, +1 if the method is described and appropriate, and −1 if the method is described but inappropriate.
§ Double-blinding in these randomized, controlled trials is both practical and ethical. Therefore, an aggregate score of 3 points (of a maximum score of 5) will be required for quality to be considered adequate (see Table 1).

Appendix Table 3. **Federally Funded Ongoing Phase II and III Randomized, Controlled Trials of Complementary and Alternative Medical Therapies for Cancer***

Therapy	Type of Cancer and Entry Criteria	Phase of Trial and Number of Patients	Comparison	Outcomes	Site (Funding Agency)
Dietary intervention (low fat, high fiber, fruits, vegetables) (accrual closed)	Breast cancer stage I–IIIa (no concurrent chemotherapy or endocrine therapy)	III, $n = 3000$	USDA and NCI dietary guidelines	Event-free survival; impact of diet, carotenoid level, and estrogen level changes on secondary cancers	UCSD (NCI)
Dietary intervention (low fat, high fiber, soy, fruits, vegetables, green tea, vitamin E) with nutrition counseling	Prostate cancer (minimal 30% increase in PSA levels after surgery or radiation therapy)	III, $n = 154$	NCI dietary guidelines, nutrition counseling	PSA, serum cholesterol level, obesity, hypertension, PSA-related anxiety, adherence	Memorial Sloan-Kettering Cancer Center (NCI)
Gonzalez regimen	Pancreatic cancer stage II–IV	III (not randomized)†, $n = 72–90$	Gemcitabine	Survival, quality of life	Columbia University (NCCAM and NCI)
Shark cartilage plus chemotherapy and radiation therapy	Non–small-cell lung cancer stage IIIa–b, unresectable, newly diagnosed (induction chemotherapy and radiation therapy planned)	III, $n = 756$	Placebo plus chemotherapy and radiation therapy	Survival (overall, progression-free, metastasis-free), tolerability	M.D. Anderson Cancer Center and Community Clinical Oncology Program (NCCAM and NCI)
Shark cartilage powder plus standard care	Advanced breast cancer or colon cancer	III, $n = 600$	Placebo plus standard care	Survival, quality of life, toxicity	Mayo Clinic and North Central Cancer Treatment Group (NCCAM and NCI)
Soy isoflavones (200 mg/d) with nutrition workshops (NCI dietary guidelines)	Prostate cancer (patient receiving androgen ablation therapy)	II (crossover), $n = 60$	Placebo with nutrition workshops (NCI dietary guidelines)	PSA, SHBG, endogenous sex hormones, isoflavone levels, surrogate markers of osteoporosis, quality of life	Stanford University (NCCAM)
PC-SPES herbal mixture (as of August 2002, trial suspended pending resolution of PC-SPES contamination issues)	Prostate cancer (hormone-refractory)	II, $n = 99$	1. Estrogen 2. Placebo	Disease progression; neuroendocrine, immunologic, and antioxidant measures; sexual function; quality of life; safety	Johns Hopkins University (NCCAM)
Acustimulation wrist band (TENS) for 5 consecutive days plus antiemetic (serotonin receptor antagonist)	Mixed; patient receiving chemotherapy	II, $n = 700$	1. Acupressure wrist band (5 consecutive days) plus antiemetic 2. Antiemetic alone	Chemotherapy-induced nausea and vomiting, quality of life	Multicenter (NCI and University of Rochester Cancer Center Community Clinical Oncology Program)
Acupressure plus antiemetics	Breast cancer (newly diagnosed); patient receiving chemotherapy (doxorubicin-containing regimen; patients enter study after demonstrating nausea during first cycle)	II, $n = 237$	1. Placebo acupressure plus antiemetics 2. Antiemetics alone	Chemotherapy-induced nausea, anxiety, quality of life, functional status	UCSF (NCI)
Acupuncture after conventional treatment	Breast cancer (early stage)	II, $n = 81$	1. Control needling 2. Usual care	Hormone levels, hot flashes after treatment, sleep, joint pain, headaches, cognitive function, mood, nervousness, quality of life	Duquesne University (NCI)

Continued on following page

Appendix Table 3—**Continued**

Therapy	Type of Cancer and Entry Criteria	Phase of Trial and Number of Patients	Comparison	Outcomes	Site (Funding Agency)
Massage (six 50-min weekly sessions)	Breast, ovarian, colorectal, or prostate cancer (patient starting 21- or 28-day course of chemotherapy)	II, $n = 60$	1. Sham massage 2. Chemotherapy alone	Chemotherapy-related fatigue; psychological outcomes; quality of life; validation of sham therapy; impact of the therapist's sex and patient sociocultural background on outcomes	UCSF (NCCAM)
Education–support group therapy (eight 90-min weekly sessions) plus standard care	Breast cancer (newly diagnosed)	II (some patients select group, others randomly assigned), $n = 136$	Standard care alone	Survival and recurrence, lymphocyte proliferation, physical and emotional well-being, self-transcendence	University of Texas (NCCAM and National Institute of Nursing Research)
Supportive expressive group therapy (twelve 90-min weekly sessions) plus standard care	Prostate cancer stage I or II	II, $n = 480$	Educational materials plus standard care	Psychological health, quality of life, feasibility	University of Rochester (NCI)
Hypnosis plus standard care	Breast cancer (before lumpectomy)	II, $n = 140$	Standard care alone	Postoperative recovery, nausea, pain	Mt. Sinai (NCI)
Distant healing plus radiation therapy	Glioblastoma (rapidly progressing, patient starting radiation therapy)	II, $n = 150$	Placebo plus radiation therapy	Survival, functional status	California Pacific Medical Center (NCCAM)
Prayer	Breast cancer (African-American women after surgery and radiation therapy)	II, $n = 80$	Wait-listed control	Neuroendocrine stress markers, immune measures, perceived stress, psychosocial functioning, quality of life	Johns Hopkins University (NCCAM)
Hyperbaric oxygen (pre- and postsurgery)	Head and neck cancer	II, $n = 54$	Surgery alone	Postsurgical complication rates, hypoxia and vascularization in surgical zones, quality of life	University of Pennsylvania (NCCAM)

* Includes all studies that could be identified by the authors as of May 2001. Information about these trials can be accessed at two National Institutes of Health Web sites: www.clinicaltrials.gov and www.cancer.gov/search/clinical_trials. Trials in which the primary focus is cancer prevention are not included in this list. Phase II trials assess efficacy and safety in smaller samples; phase III trials confirm efficacy, monitor side effects, and compare outcomes with commonly used treatments in larger samples. NCCAM = National Center for Complementary and Alternative Medicine; NCI = National Cancer Institute; PC-SPES = prostate cancer and "hope" (in Latin); PSA = prostate-specific antigen; SHBG = sex hormone–binding globulin; TENS = transcutaneous electrical nerve stimulation; UCSD = University of California, San Diego; UCSF = University of California, San Francisco; USDA = U.S. Department of Agriculture.
† Gonzalez regimen trial: Initial plans to require randomized assignment were changed to facilitate accrual.

Appendix Table 4. **Herbal Components of PC-SPES (72,76,78,79,84,93,205)***

Herbs†	Common Names	Additional Information
Isatis indigotica	Da qing ye	
Glycyrrhiza glabra	Licorice	Estrogenic properties reported
Panax pseudoginseng	San qi	Estrogenic properties reported for *Panax* species
Ganoderma lucidum	Ling zhi	A root fungus
Scutellaria baicalensis	Huang qin; Chinese skullcap	Contains phytocoumarins
Chrysanthemum morifolium	Chrysanthemum	
Rabdosia rubescens		
Serenoa repens	Saw palmetto	Shown to be effective in the management of benign prostatic hyperplasia

* PC-SPES was produced by BotanicLab, Brea, California (BotanicLab is not currently in business). PC-SPES = prostate cancer and "hope" (in Latin).
† Herbs are listed in the order in which they appear on the product label. The relative amounts of each herbal extract are not reported.

Appendix Table 5. **Cartilage Products for Patients with Cancer: Plausible Mechanisms and Implications for Route of Administration**

Many studies have explored potential mechanisms by which cartilage products (shark, bovine, rabbit, and human) might exert anticancer activity. Most researchers have not found significant inhibition of tumor cell growth in vitro (206–214). However, numerous studies suggest that cartilage extracts could exert indirect anticancer effects by inhibiting angiogenesis (in vitro [206, 208, 210, 213–219], in animals [206, 207, 209, 210, 213–215, 218, 220–225], and in humans [226]) or tumor cell invasion (in vitro [211, 212]). Cartilage-derived products can inhibit several processes essential for angiogenesis: endothelial cell proliferation (206, 208, 210, 213–218), endothelial cell migration (206, 213, 215), and collagenase activity (206, 211, 212, 215, 224, 227–230). Collagenase inhibition could also potentially prevent local invasion or distant metastasis of tumors (231, 232). Several studies of cartilage have identified proteins or glycoproteins with antiangiogenic or anticollagenase activity (206, 210, 213, 215–218, 227, 228). Three of these studies tested the identified compounds in animal models of cancer; antitumor effects were observed in all cases (206, 213, 218). Several other studies have reported antitumor activity of less highly purified cartilage-derived products (207, 209, 210, 214, 221, 222, 230, 233).

Patients with cancer typically use shark cartilage preparations that are administered orally or rectally. Because the potentially active compounds identified to date are proteins or glycoproteins, it seems unlikely that they would enter the circulation intact; however, certain proteins have been detected in the blood after oral administration (234). Three studies (two in animal, one in humans) have reported antiangiogenic effects after oral ingestion of shark cartilage (214, 220, 226). Peer-reviewed animal studies of the antitumor effects of orally administered shark cartilage preparations have produced mixed results (206, 214, 230, 233, 235). Of particular note, one study reported significant antitumor effects when the preparation was injected but not when it was given orally (206). As discussed in the text, trials in humans of oral shark cartilage have to date failed to support efficacy in cancer treatment.

Appendix Table 6. **Exercise in Patients with Cancer**

No data are available on the possible effects of exercise on cancer progression. Studies to date have focused on the potential palliative effects of exercise. The physical symptoms and psychological distress experienced by patients may lead to physical inactivity. This inactivity can cause deconditioning, which compounds the disability resulting from cancer and its treatment (199, 202). Five controlled trials (3 randomized [198, 200, 202] and 2 quasi-randomized [199, 201], ranging in size from 50 to 123 patients) have studied the effects of moderate exercise in patients receiving conventional treatments. Three of these trials included women with early-stage breast cancer who were receiving adjuvant therapy (radiation, chemotherapy, or hormonal therapy) after surgery (198, 199, 202); the other two trials studied patients who were receiving high-dose chemotherapy and stem-cell transplantation (200, 201). All five trials found benefits of exercise, and none reported adverse effects.

Four of these trials assessed various measures of physical function; all found that the performance of patients who exercised was superior to that of controls (198, 199, 200, 202). Of three trials assessing psychological distress, two found benefits for exercise (199, 201, 202). Some trials also examined the effects of exercise on physical symptoms. One trial of patients with breast cancer evaluated insomnia; benefits were found for exercise (199). Of two breast cancer trials assessing effects of exercise on fatigue, only one reported benefits (199, 202). One trial of patients receiving stem-cell transplantation evaluated treatment-related side effects; results suggested that exercise might limit neutropenia, thrombocytopenia, diarrhea, and pain (200).

Although the number (three) and size (n = 62 to 123) of randomized, controlled trials supporting benefits of exercise meet our criteria for recommendation, only two randomized, controlled trials (200, 202) meet our criteria for adequate quality (see Table 1 and Appendix Table 7). Until more evidence is gathered, it is reasonable for physicians to accept moderate exercise as an adjunct to conventional cancer treatment, and recommendation of exercise may be considered in accordance with each physician's clinical judgment about individual patients. However, caution must be used by patients who are prone to bruising (as a result of thrombocytopenia or anticoagulation) or fractures (as a result of bony metastases), and exercise should be avoided when patients are febrile or dehydrated or have abnormal electrolyte levels (200, 201, 236).

Appendix Table 7. **Quality Assessment (Using Jadad Scale) of Randomized and Quasi-Randomized Trials of Exercise in Patients with Cancer (3)**

Trial, Year (Reference)	Patients, *n*	Described as Randomized? (0, +1)*	Described as Double-Blind? (0, +1)*	Description of Withdrawals? (0, +1)†	Randomization Method Described and Appropriate? (0, +1, −1)‡	Double-Blinding Method Described and Appropriate? (0, +1, −1)‡	Aggregate Score (Sum of 5 Individual Scores)§
Segal et al., 2001 (202)	123	+1	0	0	+1	0	2
Dimeo et al., 1999 (201)	62	0	0	+1	0	0	1
Dimeo et al., 1997 (200)	70	+1	0	+1	0	0	2
Mock et al., 1997 (199)	50	+1	0	0	−1	0	0
MacVicar et al., 1989 (198)	62	+1	0	0	0	0	1

* A study receives a score of +1 for "yes" or 0 for "no."
† A study receives a score of +1 only if the number of withdrawals and the reasons for withdrawal are given for each group.
‡ A study receives a score of 0 if no description is given, +1 if the method is described and appropriate, and −1 if the method is described but inappropriate.
§ A double-blinded trial would require development of a sham exercise intervention. Such an intervention would consist of a series of physical movements that are unlikely to provide direct benefits with regard to muscular strength or cardiovascular fitness. However, it might be questioned whether it is ethical to blindly assign patients with cancer to a regimen that is designed not to provide direct physical benefits but requires investment of substantial amounts of time and effort over a period of weeks to months. Therefore, an aggregate score of 2 points (of a maximum score of 3 for unblinded studies) will be judged as adequate quality (see Table 1).

Appendix Table 8. **Psychological and Mind–Body Interventions: Potential Mechanisms for Increased Cancer Survival**

Much speculation has been devoted to the mechanisms through which psychological and mind–body interventions could potentially improve cancer survival. In three small randomized, controlled trials, patients receiving such interventions showed changes in various immunological measures relative to controls (237–239). However, it is not known whether the observed changes have clinical significance for cancer progression (240–243). Only two of these randomized, controlled trials assessed both immunologic changes and disease progression, and neither demonstrated a direct correlation between these variables (137, 151, 159, 237, 239, 244).

Another mechanism through which psychological and mind–body interventions might conceivably enhance survival is beneficial behavioral change. Decreased physical and psychological distress could result in improved compliance with conventional treatment, higher levels of physical activity, and improved nutritional intake (150, 151, 242, 245, 246). However, discussion of potential mechanisms must remain speculative as long as evidence for survival benefits remains inconclusive.

Appendix Table 9. **Supplements Shown To Have Anticoagulant Effects***

Supplements	Anticoagulant Effects†	Case Reports of Adverse Events Possibly Related to Anticoagulant Effects	Case Reports of Altered INR in Patients Taking Warfarin
Supplements commonly used to treat cancer			
Vitamin C	Inhibition of platelet aggregation (35–37), increased fibrinolytic activity (38)	None	None
Vitamin E	Inhibition of platelet aggregation (37, 40)	ATBC trial: 50% higher mortality from hemorrhagic stroke in patients receiving vitamin E; however, not reported to be statistically significant (31)	1 case report: PT increased (247)
Soy isoflavones	Inhibition of platelet aggregation reported in nonhuman primate study (71) but not found in single human trial to date (248)	None	None
PC-SPES	Warfarin contamination found in some samples (73); component herb contains phytocoumarins (93) (however, see footnote on procoagulant effects)‡	1 case report (93) (however, as noted in footnote on procoagulant effects, there have been multiple reports of thrombotic events)‡	1 case report: INR increased (92)
Herbs commonly used in the broader population			
Garlic	Inhibition of platelet aggregation (249–254), inhibition of platelet adhesion to fibrinogen (254), decreased fibrin formation (255), increased fibrinolytic activity (255, 256)	3 case reports (257–259)	1 report (included two cases): INR increased (260)
Ginger	Inhibition of platelet aggregation (261, 262)	None	None
Ginkgo	Inhibition of platelet aggregation (263)	6 case reports (264–269)	None
Panax ginseng (Asian ginseng)	Inhibition of platelet aggregation (270), prolongation of APTT (270), prolongation of TT (270) (these results were reported in a single animal study; no human trials have been conducted to date)	None	1 case report: INR decreased (271) (see footnote on procoagulant effects)‡

* APTT = activated partial thromboplastin time; ATBC = Alpha-Tocopherol, Beta Carotene Cancer Prevention Study; INR = international normalized ratio; PC-SPES = prostate cancer and "hope" (in Latin); PT = prothrombin time; TT = thrombin time.
† All reported effects were measured after oral administration in humans, unless otherwise specified.
‡ Procoagulant effects: Some supplements may have procoagulant effects. Despite warfarin contamination of some samples of PC-SPES, there have been multiple reports of thrombotic events associated with PC-SPES use. An increased risk for such events is consistent with the estrogenic nature of PC-SPES (see discussion in text). Some supplements may reduce the effectiveness of warfarin. Coenzyme Q10, an antioxidant that is popular in patients with cancer, is chemically related to vitamin K_2, and decreases in INR have been reported in patients taking warfarin who use this supplement (272, 273). Use of St. John's wort has also been associated with decreased INR in patients taking warfarin (274). As noted above, one case report suggests that *Panax ginseng* (Asian ginseng) may decrease the effectiveness of warfarin (271), even though other data suggest that this herb may have an anticoagulant effect when taken alone (270).

Appendix Table 10. **Chemotherapeutic Agents: Reliance on Free Radicals and Reactive Oxygen Species as Mediators of Cytotoxicity (172,173,275,276)**

Agents That May Rely on Free Radicals and Reactive Oxygen Species*	Agents That Do Not Seem To Rely on Free Radicals and Reactive Oxygen Species
Anthracyclines	Antimetabolites
Bleomycin	Vinca alkaloids
Dactinomycin	Hormonal agents
Epipodophyllotoxins	Taxanes
Platinum compounds	Biological response modifiers
Alkylating agents	

*These agents have a higher theoretical risk for inhibition by antioxidants.