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Dietary Supplement Use in Cancer Care: Help or Harm

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The majority of cancer patients are using dietary supplements (DS) during all phases of cancer treatment, yet few topics are more controversial in integrative oncology. Despite increasing use by cancer patients, most conventional oncologists recommend complete avoidance of all supplements throughout most phases of cancer care [1]. This stance by oncologists limits disclosure of use of dietary supplements by patients and may, therefore, increase patients' risk. Furthermore, a closer look at the literature in this area does not support a blanket interdiction. Evidence of harm remains largely theoretic, while evidence of benefit in some cases may warrant active recommendation. This article looks at the evidence that exists both for and against use of dietary supplements during cancer care, to aid the practitioner in advising and managing care of patients using a wide variety of natural health products. Recommendations to maximize benefit and minimize harm while using DS are made.

Recent surveys confirm a high prevalence of complementary and alternative medicine (CAM) use, in some cases over 90% [2]. Even where general CAM use is low (23%), as in a recent survey of head and neck cancer patients, a large portion of CAM use involves herbs (47%) or herbal teas (23%) or vitamin-mineral preparations (12%) [3], products which conventional oncologists find particularly bothersome. CAM use increases after diagnosis [4], up almost eight times for herbs in one study [3], and remains high through out the spectrum of cancer care. High-risk women attending a genetic testing program were found to be using CAM at rates (53%) comparable to those reported in active treatment and use continued for at least one year, especially in breast cancer gene (BRCA)-1 positive patients [5,6]. Hospitalized cancer patients also have high rates of DS use (73% in previous 30 days) [7], and so do participants in National Institutes of Health (NIH) sponsored trials (63%) [8]. Use of biologically based CAM, defined as herbs, vitamins, and other dietary supplements, is still significant (34%), even in phase I trials of patients with advanced disease [9]. High rates of use of CAM (68%), with a large percentage using dietary

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supplements (80%), have also been reported in patients during radiation therapy [10]. Use of CAM modalities often continues long after completion of conventional oncology care [11].

Nondisclosure of CAM or DS use to medical providers is common throughout the spectrum of cancer care [10]. The majority (53%) of patients using dietary supplements during recent chemotherapy did not seek advice or guidance from a medical provider [7]. Disclosure, even if done, may be incomplete. In a recent survey, patients undergoing active, conventional therapy did disclose CAM use 57% of the time, but they were likely not to disclose all of the modalities they were using [2]. However, in situations where DS is part of routine medical care, such as head and neck cancer patients at an outpatient Veteran's Affairs clinic, disclosure is more common (62% disclosure of use). Patients are likely to hear about DS use from their physician (38%) and may even receive the supplement from the medical system directly (25%) [12]. Thus, involvement of the medical team in DS use facilitates full disclosure to the medical profession, which is crucial for optimal patient care.

Physicians' attitudes and knowledge about CAM therapies also influenced patient's likelihood of disclosure of use. Patients have cited expectations of a negative response or active opposition from their physicians as a reason to withhold disclosure [13], and this runs counter to their expectation for nonjudgment and support from their physician [14]. Many physicians do hold largely negative attitudes toward use of DS during cancer treatment [15], especially if CAM is perceived to be harmful or to be used as the sole treatment [16]. However, assessing harm maybe problematic, as many physicians have self-identified themselves as having little information about CAM cancer treatments [16] and their patients concur with this assessment [14].

In general, physicians do not share the same perception of benefit or possible benefit that their patients expect from CAM use [17]. They, like their patients, believe that CAM modalities can decrease side effects, but do not expect CAM to boost immunity or improve quality of life [17]. Strengthening the immune system is a common reason cited by patients, but not physicians, for DS use [18,19], as is a desire to decrease medication complications or relieve other symptoms, such as anxiety or depression [8,18]. While desire for a cure is less often stated as a reason, prevention of recurrence is a common reason for breast cancer patients to use CAM [19].

Furthermore, patients' and physicians' opinions diverge on what kind of evidence to use as a guide to CAM therapy. Patients place less emphasis on scientific evidence and rely on a much broader range of information, such as family, friends, and Internet sources [20]. Most oncologists place a much larger emphasis on scientific evidence [13], as they perceive complementary alternatives to be scientifically unproven [16]. However, when provided with online information, it has been shown that both patients and physicians have difficulty distinguishing high quality from low quality or biased information [21]. Therefore, in order for clinicians to be able to have a complete discussion with patients, they must first be aware of the existing clinical evidence.

RISKS OF ALTERNATIVE CANCER CARE

To fulfill the first caveat of clinical medicine, first do no harm, it is important to examine what evidence exists for risk associated with dietary supplement usage. Refusal of curative conventional treatment is often cited as a risk of CAM therapy by the conventional medical establishment [22]. Limited evidence does exist to support this concern. When alternative therapies were used as first-line treatment in a group of 33 women with breast cancer, early death and higher rates of recurrence were reported [23]. Furthermore, when tested in rigorous clinical trials, all “natural cancer cures” examined so far, such as shark cartilage [24,25], either have shown no benefit or, in the case of others such as laetrile [26], were found to be both ineffective and toxic. Fortunately, even for patients with advanced disease, most (88%) receive CAM care concurrently with conventional treatment [27] and it is the minority (8% in one study) who choose solely alternative cancer care [28]. Concurrent use of CAM with conventional care has generally shown no change in survival time [29]; however, some exceptions of both increased and decreased survival will be discussed below.

Risk from use of contaminated or adulterated dietary supplements has been suggested. When this occurs in products commonly used by cancer patients, patients can be exposed to unexpected ingredients that may themselves be toxic or may interfere with the action of pharmaceutical medications. In at least one case, substitution of one Chinese herb for another (*Stephania* for *Aristolochia*) caused acute nephrotoxicity and later development of genitourinary cancer [30]. Perhaps the most notorious example of a contaminated dietary supplement used by cancer patients is the herbal formula PC-SPEs, which was found to contain warfarin, DES, and other substances [31,32]. These failures in quality control of botanical products have prompted concern in the public as well as the medical community. New dietary supplement manufacturing rules recently released by Food and Drug Administration are designed to address issues of dietary supplement quality [33].

In addition, relatively few herbs have toxic constituents that are not recommended for general use [34]. One serious but infrequent side effect of concern to oncologists is liver toxicity, especially given the inherently toxic nature of chemotherapeutic agents. Hepatotoxicity has been reported for some common herbs, such as chaparral (*Larrea tridentate*), comfrey (*Symphytum officinale*), and kava (*Piper methysticum*) [35]. However, not all herbs with reports of hepatotoxicity have equally compelling evidence. For example, black cohosh (*Actea racemosa*), often used to treat menopausal symptoms—including those in women with or at high risk for breast cancer—has been alleged in a number of case reports to cause liver damage by at least two separate mechanisms, and has been subject to regulation by a number of international regulatory agencies [36]. However, in contrast, an expert conference that convened at the NIH in 2004 reviewed all of the available data and concluded that there was no demonstrated mechanism of action of hepatic injury for black cohosh, as well as insufficient evidence of toxicity, to warrant stopping or modifying clinical trials currently using black cohosh [37].

Herb-drug interactions, the form of adverse effect most often mentioned by oncologists, has been the subject of a number of reviews [38–42]. Despite these reviews and the concerns they raise, only two articles were identified that specifically tried to assess the degree of risk encountered by use of dietary supplements, including herbs, during cancer care [41,43]. Of the 76 chemotherapy patients surveyed to identify potentially negative chemotherapy-herb or vitamin interactions, only three of the patients were using herbs (St. John's wort or *Hypericum perforatum* and garlic or *Allium sativum*) that might have affected the metabolism of their chemotherapy. In 318 chemotherapy patients who were also using herbal remedies [43], 11% took supplements in higher than recommended doses and potential interactions were identified in 12% of the patients ($n = 20$). Most of the warnings were given to lymphoma patients taking echinacea on the basis on potential adverse effects of immune stimulation. In neither study were confirmed interactions observed.

Concern for interactions is based on the ability of herbal products to affect the cytochrome P450 enzyme system that is crucial in the metabolism of a number of chemotherapeutic agents. Potential for interaction has also been raised with adenosine triphosphate binding-cassette transporters, such as P-glycoprotein, multidrug resistance associated protein-1, and breast cancer resistance protein [38]. Although herbal remedies have been shown to both up- and down-regulate the activity of a variety of P450 isozymes in screening tests, relatively few human clinical trials exist to validate these results [44]. One review by Sparreboom and colleagues [38] attempted to assess the likelihood of interaction of a number of common herbal agents with chemotherapy based on a wide variety of preclinical, animal, and human data. The investigators concluded that interactions with saw palmetto (*Serenoa repens*), cranberry (*Vaccinium macrocarpon*), black cohosh, milk thistle (*Silybum marianum*), and bilberry (*Vaccinium myrtillus*) were not expected, while specific cautions were made for garlic, ginkgo (*Ginkgo biloba*), soy (*Glycine max*), ginseng (*Panax ginseng*), valerian (*Valeriana officinalis*), and kava, largely on the basis of preclinical data.

Despite the high level of concern expressed in these cited reviews, only a handful of human pharmacokinetic studies were identified in the literature that directly assessed the effect of any herb on a chemotherapeutic agent. Ten breast cancer subjects took 600 mg of a proprietary garlic extract containing 3,600 mcg of allicin twice a day for days 5 to 17 of their chemotherapy cycle [45]. Docetaxel pharmacokinetics assessed before and after the administration of garlic showed no change in peak concentration, area under the curve (AUC), or half-life. Milk thistle (*Silybum marianum*) was tested in six cancer subjects taking irinotecan [46]. Four days before their second dose of irinotecan, subjects were given 200 mg of a commercially available milk thistle extract, standardized to 80% silymarin, three times a day. No significant effect on irinotecan clearance was noted despite a slight but borderline statistically significant decrease in the AUC. Serum concentrations of silybin, one of the constituents of milk thistle, were felt to be too low to be of concern for drug interactions.

Most of the reviews cited above agree that the herb with the strongest risk of clinically significant interactions is St. John's wort. Three human studies of the effect of St. John's wort on imatinib confirm the need for caution. Ten subjects, given 400 mg of imatinib before and after a treatment with 300 mg of St. John's wort three times a day [47] showed significant alterations in the pharmacokinetics of imatinib (32% reduction in AUC and a 29% reduction in maximal concentration). In a second study, 12 healthy subjects who were given 300 mg of a standardized proprietary St. John's wort product three times a day also had a significant increase in imatinib clearance (43%), as well as a 30% reduction in AUC [48]. Significant reductions were also noted in half-life and maximum concentrations. More worrisome was a small study of five cancer subjects taking irinotecan concurrently with 900 mg per day of St. John's wort extract. Plasma levels of SN-38, the active metabolite of irinotecan, were statistically significantly reduced (42%, $P = .033$) and, more significantly, myelosuppression was less during cotreatment as well [49]. However, in none of the studies was the composition of the St. John's wort extract described or independently confirmed by the investigators. In the case of St. John's wort this is particularly important, as most of the induction of the CYP450 enzymes is felt to be because of hyperforin, one constituent of St. John's wort extracts [50].

Interference with coagulation by herbs or other dietary supplements is of particular concern for oncology patients as they undergo surgery or other invasive procedures [51]. The investigators of this recent review postulate that antiplatelet actions, as well as interference with warfarin, could put cancer patients at risk. However, when commercially available extracts of ginkgo, garlic, *Panax ginseng*, St. John's wort, and saw palmetto were given to 10 healthy volunteers for 2 weeks, no effect on platelet activity was demonstrated [52]. Likewise, evidence of interaction of warfarin with herbs is based largely on case reports of variable (mostly poor) quality, which is not confirmed by pharmacologic studies [53].

Herbal therapies with estrogenic, androgenic, or progesterone-like activity are a theoretic concern for patients with hormone-sensitive cancers, particularly breast, ovarian, endometrial, or prostate cancers [54]. However, the majority of the literature on hormonal effects of herbs focuses on the estrogen activity of herbs commonly used for treating menopause. In preclinical trials, soy isoflavones and red clover extracts have been shown to have estrogenic activity of uncertain clinical significance for estrogen receptor-positive breast cancer patients [55]. Black cohosh, although mistakenly referred to as a phytoestrogen, does not appear to have estrogenic activity as tested in a variety of *in vitro*, animal, and human studies [56–58]. Neither does it appear to increase breast density [59]. The only formal safety study of a proprietary black cohosh extract (Klimadynon) was done in normal menopausal women [58]. Four hundred women were given 20 mg of herbal drug for 12 months under close observation. No increased uterine hypertrophy or hepatotoxicity was noted during the trial. Breast density in the subset of women who had mammograms before and after the trial was lower, suggesting no toxic effect on breast tissue. Activity via

serotonergic neurons in the hypothalamus is thought to account for the clinical effect of black cohosh on vasomotor symptoms [60]. Therefore, the conservative recommendation to avoid consumption of high amounts of herbs with in vitro estrogenic activity does not apply to the use of black cohosh extract (BCE).

In summary, exposure has occurred from adulterated DS, such as PC-SPES, but few cases are noted. Evidence of hepatotoxicity of BCEs was not sufficient to warrant the interruption of ongoing clinical trials, nor is black cohosh a phytoestrogen. Despite widespread theoretic concern about herb-drug interactions, clinically significant interactions were only proved with St. John's wort. Observations from in vitro screening and animal studies need to be tested in human beings to confirm the presence or absence of clinically relevant interactions.

Evidence of interference with platelet function or warfarin activity was contradictory or absent for most herbs tested.

Antioxidants

Although antioxidant-rich foods are commonly associated with reduced risks of a variety of cancers, use of antioxidants, either singly or in formulas, as preventative agents for cancer has not been supported by large randomized trials [61]. In fact, at times antioxidant supplementation has been associated with harm when used preventatively [62]. Thus, use in conjunction with conventional therapy has remained a controversial area. Conventional practitioners usually have general prohibitions against use during chemotherapy or radiation [1]. However, a number of authorities have highlighted large amounts of preclinical and limited amounts of human clinical data in favor of use of at least some antioxidants [63–67]. Discussion of a limited selection of some of the key human clinical trials in this area will highlight key points in this debate.

Conventional clinicians cite fear of decreasing the effectiveness of conventional therapy as their major concern with the use of antioxidants during chemotherapy or radiation [1]. Some evidence exists for this concern. During a large randomized, double blind, placebo controlled trial of 540 patients with head and neck cancer undergoing radiation [68], subjects were given either placebo or a combination of antioxidants (400-IU alpha-tocopherol, 30-mg beta-carotene) daily throughout radiation therapy and for 3 years afterwards. Although acute side effects of radiation were significantly less in the antioxidant group, quality of life was not improved significantly, and the rate of local recurrence was higher in the supplemented group (odds ratio or OR 1.37; confidence interval or CI 0.93–2.02). Long-term follow-up of these subjects showed that at a median follow-up of 6.5 years, all-cause mortality was significantly higher in the treated group (hazard ratio or HR 1.38; CI 1.03–1.85) [69]. A historical cohort control study of 90 women who had taken large doses of beta-carotene, vitamin C, niacin, selenium, coenzyme Q10, and zinc during their conventional therapy were compared with matched controls [70]. Overall survival was the same for the two groups, but a trend toward reduction in disease-free survival was noted ($P = .08$). However, other studies

did not confirm harm for patients undergoing chemotherapy. Although combination antioxidant therapy (6,100-mg ascorbic acid, 1,050-mg dl-alpha tocopherol, and 60-mg beta-carotene per day) did not improve the response rate of 136 advanced non-small cell lung cancer patients, neither did it diminish response rate or increase toxicity [71].

The greatest proponents of vitamin C use, Linus Pauling and his collaborators, suggested benefit from high-dose (10 gm) vitamin C in terminal patients who had exhausted all conventional options [72]. A cohort of 100 “untreatable” cancer patients who took 10 gm of vitamin C showed a greater mean survival of 300 days and a greater number of survivors after 1 year (24% versus 0.4%) than in a historical control group of 1,000 patients. Two subsequent randomized, controlled trials by other investigators failed to confirm benefit, though no significant toxicity was noted [73,74]. However, new reports of positive cases have lead researchers to open an NIH trial investigating further use of high-dose vitamin C [75,76].

Antioxidant use has also had reported benefit during active cancer treatment. Lower antioxidant intakes in a group of children with acute lymphocytic leukemia were associated with increases in adverse events during chemotherapy [77]. A decreased rate of chemotherapy-related nephro- and ototoxicity was only seen in the patients—supplemented with vitamins C, E, and selenium—who achieved the highest serum levels [78]. Experts have also cited preclinical and some limited human data to support the use of coenzyme Q10 to reduce the toxicity of anthrocyclin-based chemotherapy [79]. Benefit derived from antioxidant treatment for specific side effects of treatment are discussed in subsequent sections.

In summary, use of antioxidants during chemotherapy and radiation remains controversial. Most concerns are theoretic, although limited evidence for harm exists, mainly for vitamin E with head and neck patients. Experts cite large amounts of pre-clinical data and limited human data to support use of antioxidants, such as vitamin C, coenzyme Q10, and vitamin E for reduction of chemotherapy-related toxicity and possible tumor response in the case of vitamin C.

POTENTIAL BENEFITS OF DIETARY SUPPLEMENTS

A variety of natural products have shown benefit for cancer patients, either globally for overall quality of life, or for relief of specific symptoms associated with cancer treatment. To a lesser degree, especially with immunomodulatory agents, modification of tumor response, increases in disease-free interval, or prolonged survival have been seen. Certain substances will not be discussed in any detail, despite the fact that patients commonly use them. Compounds, such as the lectins from mistletoe (*Viscum album*) or a proprietary Japanese polysaccharide extract from shitake (*Lentinus edodes*) are usually delivered intravenously or parenterally, and therefore are not dietary supplements according to regulatory standards in the United States. Whole cannabis, extracts, and to a lesser degree isolated compounds from cannabis, have been noted to

ameliorate a variety of symptoms in cancer patients, including pain, nausea, anorexia, and cachexia [80]. However useful many clinicians find the herbal form of this medicine, the legal ambiguity and challenges with standardization of dosage make use of this substance beyond the scope of this review.

Immune Modulation

Medicinal mushrooms and mushroom-derived polysaccharide preparations have been extensively studied as immune modulators and adjuvant agents in cancer treatment using in vitro and animal models with some human clinical trials as well [81–84]. In addition to improving quality of life or modifying tumor response, medicinal mushroom preparations have been shown to have beneficial effects on immune response, mainly in patients with solid, as opposed to hematologic, malignancies. One of the best studied preparations is a proprietary, protein-bound polysaccharide extract (PSK) of the medicinal mushroom, *Trametes versicolor*, also called *Coriolus versicolor*. PSK in a dose of 3 grams per day, was shown to decrease the serum level of the immunosuppressive acidic protein in a randomized trial of 207 stage II and III colorectal cancer patients, all of whom had conventional therapy [85,86]. After 5 years of follow-up, the treated patient group also had a greater percentage of 5-year disease free survival ($P = .038$) and a decreased relative risk of regional metastases (relative risk or RR 3.595; CI 1.518–8.518). These results are confirmed by a meta-analysis of three trials (reported in 10 articles) involving 1,094 subjects with colorectal cancer [87]. Those who took PSK showed a significant improvement in overall survival (RR 0.71; CI 0.55–0.90; $P = .006$) and disease-free survival (RR 0.72; CI 0.58–0.90; $P = .003$) [87]. Benefit of PSK was also demonstrated in a meta-analysis of 8,009 gastric cancer patients from eight randomized, controlled trials with an increased survival (HR 0.88; CI 0.79–0.98; $P = .0180$) [88]. Specific clinical trials additionally cited an increase in disease-free survival rate for gastric cancer patients taking PSK with minimal toxicity [89]. A different extract of *Trametes versicolor* (Yunzhi) in combination with *Salvia miltiorrhiza* (Danshen) decreased the decline in absolute T-lymphocyte counts and preserved populations of T-helper and suppressor cells in a group of nasopharyngeal cancer patients receiving radiotherapy [90]. Immunologic parameters were also better in a group of 82 breast cancer patients after taking the Yunzhi/Danshen combination with an increase in T4 helper cells, an improvement in the CD4+/CD8+ ratio and an increase in B-lymphocytes [91].

A polysaccharide extract (active hexose correlated compound or AHCC) of a proprietary hybrid mushroom identified as *Basidiomycotina* has been tested in several human trials. Eleven advanced cancer patients (breast, ovarian, prostate, and multiple myeloma) were given 3 g per day of AHCC in an uncontrolled trial [92]. They showed a 2.5 times increase in natural killer cell (NK) activity, and 6 of 11 subjects were reported to have a tumor response. When either AHCC ($n = 34$) or placebo ($n = 10$) was given to advanced liver cancer patients, statistically significant increases in lymphocyte percentage ($P = .026$), albumin levels ($P = .000$), general physical health status ($P = .037$), and

maintenance of activities of daily living ($P = .04$) were reported [93]. A highly statistically significant increase in survival was noted as well when compared with the control group ($P = .000$). A large cohort of 269 hepatocellular cancer subjects, after presumptively curative resection, was assigned prospectively after surgery to receive either 3-g of AHCC daily or control [94]. The treated group had a significantly longer disease-free interval (HR 0.639; CI 0.429–0.952; $P = .0277$), and increased overall survival (HR 0.421; CI 0.253–0.701; $P = .0009$).

A number of other medicinal mushrooms have also been tested in cancer patients, but the variable results seen may be caused in part by the phytochemical complexity and variety of extracts tested [83]. *Grifola* or *Polyporus umbellate*, also called Zhu ling in traditional Chinese medicine, was as effective as Bacillus Calmette-Guerin in preventing recurrence of bladder cancer following surgery, and was more effective than mitomycin C (34.9%, 35.1%, and 41.7% respectively) [95]. A proprietary extract (D-Fraction) of *Grifola frondosa*, also called Maitake, caused small changes in CD4+ and CD8+ counts while increasing NK cell activity in all 10 advanced cancer patients [96]. Oral polysaccharides from *Ganoderma lucidum*, also known as Ling zhi or Reishi, when given in a dose of 5.4 g per day for 12 weeks, improved the mitogenic reactivity to phytohemagglutinin, increased CD3, CD4, CD8, and CD56 lymphocyte counts, and increased NK activity, while elevating plasma concentrations of interleukin (IL)-2, IL-6, and gamma interferon, and decreasing tumor necrosis factor alpha and IL-3 in 46 subjects with a variety of advanced stage cancers [97,98]. However, a study in 30 advanced lung cancer patients showed marked variability in immune response to the *Ganoderma* extract, suggesting that certain subgroups of patients may be more responsive than others [99].

Finally, the use of an extract of the mushroom *Agaricus blazei*, given to 100 patients with gynecologic cancers (cervical, ovarian, or endometrial) undergoing conventional chemotherapy (carboplatin, etoposide, or taxol), showed a higher NK activity ($P < .002$), as well as a decrease in a variety of chemotherapy-related side effects, such as decreased appetite, alopecia, weakness, and emotional lability [100].

A proprietary fermented wheat germ extract standardized to methoxy-substituted benzoquinones (Avé or Avemar) has shown immunomodulatory and antitumor activity in a variety of preclinical studies and several human trials [101]. An open-label, matched-pair trial of pediatric cancer patients showed a decrease in the number of episodes of febrile neutropenia when compared with control (30 or 24.9% versus 46 or 43.4%) without any other differences in treatment [102]. Adult colorectal cancer patients undergoing conventional treatment were nonrandomly assigned to receive either usual care ($n = 104$) or usual care plus 9 g of Avé ($n = 66$) [103]. After 6 months of treatment, the Avé group had fewer new recurrences (3% versus 17%), new metastases (7.6% versus 23.1%), or death (12.1% versus 31.7%; all $P < .01$) with a significant increase in disease-free survival ($P = .018$) and overall survival ($P = .278$). Interim analysis of an ongoing randomized, controlled trial in Stage III

melanoma patients ($n = 42$) receiving decarbazine chemotherapy shows an increased time-to-relapse for patients treated with Avé versus placebo (8.9 versus 4.2 months) without a decrease in relapse rate and with a larger percentage of treated patients free of disease at 1 year (54.5% versus 38.9%) [104].

Probiotics have also been used clinically for their immune modulating actions. In a group of 14 leukemia patients, pretreatment before chemotherapy continuing until the resolution of severe neutropenia (absolute neutrophil count $> 1,000/\mu\text{l}$) did not prevent the development of febrile neutropenia [105]. However, no evident toxicity of the therapy was identified. Pre- and postoperative supplementation with symbiotic treatment (*Lactobacillus casei*, *Bifidobacterium breve*, and galacto-oligosaccharides) was more efficacious than postoperative treatment alone in 81 biliary cancer patients undergoing hepatectomy [106]. Subjects in the pre- and postoperative treatment group had increased NK activity and lymphocyte counts, with decreased IL-6 preoperatively, and decreased white blood cell counts, IL-6, and C-reactive protein postoperatively. Postoperative infection rates were lower in the before and after group as well (12% versus 30%; $P < .05$). However, given the recent unexpected and as yet unexplained deaths in a trial using probiotics in patients with severe pancreatitis, caution may be advised [107].

In summary, medicinal mushroom extracts tested in a variety of cancers have shown benefit by improving immune parameters, increasing disease-free survival, and sometimes by enhancing tumor response. Data is strongest for the proprietary Coriolus extract PSK at a dose of 3 g per day, but positive data was also seen for other extracts, including AHCC, Maitake, and Agaricus. Benefit was also shown for a proprietary wheat germ extract Avé and probiotic preparations. No significant toxicities were reported in any of the trials reviewed, but adverse events in a recent probiotic trial (though not with cancer patients) require caution.

Stomatitis/Mucositis

Mucositis, a common side effect of both chemotherapy and local radiation, contributes significantly to patient morbidity through decreased quality of life and interference with proper nutrition. It is often the dose-limiting side effect for treatment [108,109]. A number of natural products have shown promise in preventing or alleviating oral mucositis, beginning with even the simplest therapy, such as ice chips (plain or flavored) or honey [110,111].

Glutamine is the DS that has been most often studied to prevent and treat oral mucositis resulting from either chemotherapy or radiation. The effects were strongest when head and neck patients were given intravenous glutamine (dose 0.4 g/kg per day) [112]. Clear improvements in chemotherapy-related mucositis were seen, with patients reporting a lower incidence of mucositis ($P = .035$), less severe mucositis ($P = .007$), and less pain ($P = .008$), as well as less need to insert a feeding tube ($P = .02$). Positive results were also seen in a number of trials using oral glutamine as a swish and swallow mouthwash. A phase I trial of oral glutamine (dose of 0.5 g/kg per day) was performed on

nine subjects with inflammatory breast cancer receiving neoadjuvant methotrexate followed by adriamycin [113]. Only one subject reported any mucositis (grade I), with a good response to chemotherapy for eight of the nine subjects and without any glutamine related toxicity. Similarly, a placebo controlled trial of adults and children using glutamine (2 g/m² twice a day during chemotoxic therapy) showed significant reductions in both severity ($P = .002$) and duration of mucositis pain (decreased by 4.5 days, $P = .0005$) [114]. Even subjects who had pre-existing mucositis developed during an initial course of chemotherapy responded well when 4-gm glutamine twice a day was given in subsequent sessions [115]. Twelve of 14 subjects decreased their maximum grade of mucositis ($P < .001$) and the total number of days with mucositis decreased by more than two thirds ($P \geq .001$) following treatment.

Glutamine was also beneficial for children undergoing autologous bone marrow transplant when given at a dose of 1 g/m² four times a day throughout the transplant and for 28 days afterwards [116]. Subjects reported less pain and used morphine half as many days ($P = .005$). A second trial of children taking 2 g/m² to 4 g/m² of glutamine twice a day during stem cell transplant showed decreased use of pain medication and fewer number of days using total parenteral nutrition as well [117]. In a retrospective chart review, adult breast cancer patients ($n = 21$) undergoing autologous stem cell transplant following high-dose paclitaxel showed similar positive results when given 24 g per day of glutamine administered as a swish and swallow preparation around the clock [118]. Treated women had fewer total days of narcotic pain relief and did not require patient-controlled analgesia (PCA) morphine, while the untreated group used PCA for 5.22 days. The women in the glutamine group also had less oral ulceration and bleeding and were able to ingest liquids sooner than the untreated group.

Radiation-induced mucositis in 17 head and neck cancer patients showed a response to 16 gm of glutamine delivered four times a day by swish and swallow [119]. After randomization to either glutamine or placebo, objective evaluation showed a reduction of mean maximum grade of mucositis ($P = .0058$) and duration of mucositis at all grades (grade 1, $P = .0097$; grade 2, $P = .0232$; grade 3, $P = .0168$). Subjective evaluations did not show the same positive effect, except for the most severe mucositis (grade 3 or worse, $P = .0386$). No changes in medication use or body weight were found.

However, despite the previous positive trials, a large phase III trial testing oral glutamine with 5-fluorouracil (5-FU) chemotherapy did not show benefit [120]. One hundred and thirty four subjects, randomized to receive 4 g of glutamine twice a day, were instructed to retain the glutamine mouthwash in their mouths for only 10 seconds. No significant differences between groups were seen regarding pain or severity of symptoms as assessed by either subjects or physicians. The investigators speculated that the pretreatment with ice may have blunted the expected positive effects of glutamine, but the short retention time in the mouth was a possible factor in the poor response as well. In the final analysis, it may be that glutamine is less effective for 5-FU chemotherapy, as an

additional small pilot study examining the effect of 16 g of glutamine for 8 days during treatment for gastrointestinal cancer also showed no benefit [121].

None of the glutamine studies reviewed demonstrated any toxicity, and the treatment was generally well tolerated. In one study where it was examined [116], glutamine did not increase the relapse rate, progression of malignancy, or incidence of graft-versus-host disease.

Vitamin E (formulation not reported), when given in a dose of 100 mg applied topically in the mouth of children who were receiving a variety of different chemotherapeutic agents, significantly improved their mucositis [122]. However, 16 children undergoing doxorubicin chemotherapy, given 800 mg of topical vitamin E or placebo using an N-of-1 study design, showed no advantage for vitamin E [123]. In a small trial of adults ($n = 18$) receiving a variety of different chemotherapeutic regimens, swishing a vitamin E oil containing 400 mg/mL around the oral cavity twice a day resolved pre-existing mucositis in all but one subject [124]. Vitamin E also appears to have benefit in radiation-induced mucositis as well, as shown in a study where 54 patients with head and neck cancer undergoing radiation therapy were randomly assigned to rinse the oral cavity with either an oil containing 400 mg of vitamin E twice a day or an equivalent volume of evening primrose oil [125].

Zinc supplementation, 25 mg given three times a day during radiation therapy, delayed the development of grade 2 and reduced the number of grade 3 mucositis in a group of 50 head and neck cancer patients [126]. Concurrent administration of chemotherapy decreased the degree of benefit observed. In a similar group of subjects using a dose of 50 mg of zinc sulfate three times a day, not only was the incidence of mucositis less, but improvement after the development of mucositis started sooner in the treated group [127]. Two subjects of the treated group had no mucositis and none had grade 3 or 4 symptoms ($P = .05$).

Herbal therapy showed mixed results. Aloe vera mouthwash did show a non-statistically significant improvement in quality of life for 58 head and neck cancer patients during radiation treatment, but there was no difference in the number of patients with mucositis, the severity of symptoms, or weight [128]. Utility of chamomile extract mouthwashes was supported in some but not all of the trials. In an uncontrolled case series, a heterogeneous group of chemotherapy and radiation therapy subjects, treated with a commercial chamomile extract (Kamillosan), were reported to develop less mucositis if treated prophylactically and to heal faster if treated after symptoms developed [129]. A case report of a patient with severe mucositis following a methotrexate overdose reported resolution after rinsing with chamomile tea instead of using conventional treatments [130]. However, results from one large phase III study of 164 subjects receiving 5-FU and chamomile [131] did not show a benefit different from placebo. Unfortunately, the material used in this trial was not well described, so it is not possible to determine if the lack of response was because of a difference in materials.

A homeopathic remedy (Traumeel) containing *Arnica Montana* and other substances, when given as a mouthwash to 32 chemotherapy patients, significantly

reduced the mean AUC of the stomatitis score ($P < .01$) compared with placebo [132]. In addition, more subjects in the treatment group did not develop any stomatitis (five versus one) and fewer subjects worsened during treatment with Traumeel (47% versus 93%).

Proteolytic enzymes decreased mucositis resulting from radiation therapy in a randomized open trial involving 100 head and neck patients [133]. From 3 days before until 5 days after radiation, subjects were given three tablets three times a day of a proprietary product containing 100 mg of papain, 40 mg of trypsin, and 40 mg of chymotrypsin. The maximum degree of mucositis was less in the treatment arm ($P < .001$). An additional smaller, randomized study of head and neck patients ($n = 50$) undergoing radiation therapy also demonstrated the effect of the same proteolytic enzyme supplement regimen [109]. Decreases in severity of mucositis was noted, as well as decreased skin reactions, both highly statistically significant ($P < .001$). In addition, biopsies taken of the buccal mucosa before and after radiation therapy showed striking differences between the enzyme-treated and control groups.

In summary, simple interventions, such as ice, honey, and topical vitamin E oil can decrease stomatitis. The largest body of evidence supports the use of glutamine as an oral rinse, which is then swallowed to decrease stomatitis. Amounts of up to 30 g per day have been used without toxicity, but results with 5-FU chemotherapy were generally negative. Zinc, a proprietary homeopathic remedy, and proteolytic enzymes also showed benefit. Evidence for herbal therapies, such as aloe or chamomile mouthwashes, were mixed.

Intestinal Toxicity

Inflammation of the mucous membranes in the mouth is often associated with disruption of the gut mucosa, leading to gastrointestinal toxicity, such as leaky gut or diarrhea. In ten patients with chemotherapy-induced stomatitis, an oral challenge test demonstrated marked elevation in lactulose excretion when compared with 21 control subjects who did not have mucositis [134]. The degree of mucositis, not unexpectedly, is directly correlated with the severity of intestinal permeability (IP) [135]. Lactose intolerance increases during chemotherapy with 5-FU, and although it is reversible with the cessation of chemotherapy, it is accompanied by flatulence, diarrhea, and poor nutritional status [136]. Not unexpectedly, agents demonstrated to be helpful with stomatitis have also been tested for intestinal toxicity.

Glutamine showed benefit for chemotherapy-related intestinal toxicity in some studies [137]. A trial of 51 subjects receiving 5-FU chemotherapy with leucovorin rescue showed a significant correlation between the degree of stomatitis and abnormality of an oral challenge test for IP ($r = 0.898$, $P < .001$) [135]. Approximately half of the subjects in this trial were treated with 30 g per day of oral glutamine, while the control group received best supportive care. The glutamine-treated group showed a significantly lower IP score ($P < .001$) and had fewer subjects with a grade 2 to 4 mucositis than the control group (9% versus 38%; $P < .001$). A second trial of glutamine (18 g per day for

5 days before and until 15 days after chemotherapy) was compared with placebo in 70 gastrointestinal cancer subjects receiving 5-FU [138]. Reduction in intestinal absorption and increase in permeability were significantly greater in the placebo arm ($P = .02$), while the incidence of diarrhea and use of loperamide tablets was decreased in the glutamine patients ($P = .09$ and $P = .002$, respectively). A small case series ($n = 6$) showed benefit using a proprietary oral glutamine product in metastatic colon cancer patients who had irinotecan-induced diarrhea unresponsive to loperamide and severe enough to require the suspension of therapy [139]. All patients restarted on chemotherapy with the addition of 10 g of glutamine three times a day beginning the day before irinotecan infusion and continuing until 4 days afterwards were able to tolerate full doses of chemotherapy.

When used in a randomized, controlled trial for breast cancer patients receiving neo-adjuvant chemotherapy, glutamine given for a single round of chemotherapy did significantly decrease IP ($P < .05$) but did not decrease the severity of stomatitis or diarrhea [140]. Perhaps, with a longer trial, differences in symptoms would have followed the changes in permeability. However, breast cancer patients with advanced disease ($n = 33$) also did not decrease their diarrhea after taking 30 g of glutamine given in three divided doses for 8 days during the interval between doxifluridine chemotherapy [141].

Used in conjunction with pelvic radiation therapy, glutamine did not prevent gastrointestinal toxicity in a trial of 129 subjects with gynecologic cancers [142]. Subjects were randomly assigned to receive either a relatively low dose of glutamine (4 g twice a day) or placebo from the onset of radiation until 2 weeks after completion of the course of treatment. There were no differences between groups with respect to high-grade diarrhea (20% versus 19%) or maximum number of stools per day (5.1 versus 5.2).

Despite mixed evidence for efficacy, there was no evidence of decreased response to chemotherapy. In the Li and colleagues [140] study, the neoadjuvant breast cancer patients did not show any adverse effect on tumor response, with no change in tumor size, the Ki 67 index, or proliferating cell nuclear antigens (PCNA). Similarly, the Bozzetti and colleagues [141] trial of advanced breast cancer patients showed similar response rates to chemotherapy between the glutamine and the placebo groups (21% versus 28%).

Probiotics have been used to decrease gastrointestinal toxicity resulting from both chemotherapy and radiation. Colorectal cancer patients receiving one of two 5-FU chemotherapy regimens were also randomized to receive either *Lactobacillus rhamnosus* GG at a dose of 1 to 2×10^{10} organisms or 11 g of guar gum per day [143]. Subjects receiving the probiotic had fewer episodes of high-grade diarrhea (22 versus 37%, $P = .027$) and less abdominal discomfort. They also needed less hospital care and had fewer reductions in chemotherapy because of bowel toxicity. No toxicity was noted with the *Lactobacillus* therapy. A different *L. rhamnosus* strain, also called Antibiohilus, was given in a randomized, double-blind fashion to 206 subjects receiving abdominal and pelvic radiation [144]. Subjects receiving the probiotic had

fewer bowel movements with a trend toward statistical significance ($P < .1$), with a significantly better consistency of fecal material ($P < .05$). In addition, subjects reported fewer episodes of high-grade diarrhea in the probiotic group. Similar benefits were seen for 190 subjects receiving adjuvant radiotherapy for sigmoid, rectal, or cervical cancer [145]. Subjects received three times a day either a packet of a proprietary blend of eight species of lyophilized bacteria (VPL#3) containing 450 billion live bacteria per gram or placebo. The treated subjects reported significantly less diarrhea ($P < .001$), lower grades of diarrhea when they did develop it ($P < .001$), and fewer bowel movements (4.6 versus 12.3; $P < .05$). Two subjects in the placebo group needed to stop therapy because of gastrointestinal side effects, while none in the treatment group modified therapy on this basis. No treatment-related toxicity was reported from the probiotic group. A larger cohort of similar subjects ($n = 490$) from the same research team, using the same intervention, showed similar benefit [146]. Treated subjects showed a lower incidence of radiation-induced diarrhea (32% versus 52%; $P < .001$), less severe high grade diarrhea (1% versus 33%; $P < .001$), and fewer number of bowel movements (15 versus 5; $P < .05$). Again, the therapy was well tolerated.

In summary, glutamine in similar doses as used for stomatitis showed more mixed results for prevention or treatment of chemotherapy and radiation-induced intestinal toxicity. Again, no evidence for significant toxicity was found. Probiotics given concurrently with chemotherapy or radiation decreased the severity of diarrhea without reports of toxicity. Theoretic cautions with probiotics were noted previously.

Neuropathy

Peripheral neuropathy is a potentially debilitating side effect caused by a number of chemotherapeutic agents, especially the platinum-based drugs and taxanes. Several dietary supplements have shown promise in ameliorating chemotherapy-induced neuropathy in human clinical trials [147].

In a nonrandomized, controlled clinical trial, patients receiving high-dose paclitaxel ($n = 45$) were given either usual care ($n = 12$) or glutamine ($n = 33$) at a dose of 10 g, three times a day for 4 days starting 24 hours after chemotherapy [148]. The glutamine-treated group showed a statistically significant decrease in the severity of sensory neuropathy both for dysesthesia and numbness ($P < .05$), as well as better motor function with a lower incidence and severity of motor weakness ($P = .04$) and less disturbance in gait ($P = .016$), resulting in less interference with the activities of daily living for the glutamine group ($P = .001$). A second nonrandomized, controlled trial in 46 subjects receiving high-dose paclitaxel showed that the glutamine-treated group ($n = 17$), after an average of 32 days of treatment, had significantly less weakness ($P = .02$), better vibratory sensation ($P = .04$), and less toe numbness ($P = .004$) [149]. Nonstatistically significant improvements were seen in compound motor action potential and sensor nerve action potential measurement in the treatment group. Eighty-six metastatic colon cancer patients in

a pilot study of the effect of glutamine on the neurotoxicity of oxaliplatin/5-FU chemotherapy showed that glutamine ($n = 44$), given at a dose of 15 g twice a day for the first 7 days of chemotherapy, reduced the incidence of moderate grade neuropathy after two (17% versus 39%), four (5% versus 18%), and six cycles (12% versus 32%) of treatment [150]. The benefit continued to accrue to the glutamine group despite a lack of difference in electrophysiologic abnormalities, which translated into less interference with activities of daily living (17% versus 41%) and less reduction in chemotherapy (7% versus 27%) because of neuropathy. There was no difference in response to chemotherapy or survival between the two groups.

Vitamin E (alpha-tocopherol), given concurrently with platinum or taxane-based chemotherapy, has shown benefit in preventing chemotherapy-related neuropathy. A small, randomized trial enrolled 47 subjects to either usual care or to 300 mg of alpha-tocopherol twice a day throughout treatment with cisplatin chemotherapy, and for 3 months after completion [151]. Of the 27 subjects who completed the trial, the vitamin E group ($n = 13$) showed a decreased incidence (31% versus 86%; $P < .01$) as well as decrease in severity ($P < .01$) of neurotoxicity. No differences were seen in tumor weight, growth delay, or survival between the two groups. An additional three reports on the use of vitamin E to reduce chemotherapy toxicity were found [152–154]. They were all performed by the same research group and may represent multiple reports on the same patient population, so they will be discussed in aggregate. Subjects were given cisplatin, paclitaxel, or a combination of both, usually for six cycles, and were also randomly assigned to either a usual care group or to receive 600 mg of vitamin E per day during chemotherapy and for 3 months afterwards. The incidence of neuropathy was less in the treated group ($P = .019$ – 0.03) and the relative risk of developing neurotoxicity was found to be significantly higher in the control group (RR = 0.25–2.51). No adverse events or death were attributed to vitamin E use.

In summary, glutamine in doses of up to 30 g per day decreased the incidence and severity of chemotherapy-related neuropathy. Despite previously cited risks from vitamin E, doses of 300 mg to 600 mg decreased neuropathy during chemotherapy without any evidence of adverse events in these trials.

Nausea

Ginger has been suggested to treat nausea from multiple causes, including those associated with cancer treatment, although the literature in this area is more limited. Subjects ($n = 120$) undergoing major gynecologic surgery for malignant conditions were randomized to receive either 1 g of ginger or placebo an hour before surgery [155]. A visual analog scale of nausea and incidence of vomiting were lower in the treated group throughout the first 24 hours after surgery. No adverse events were reported. An early trial suggested that ginger could also help relieve nausea associated with 8-methoxsalen chemotherapy, but this trial was not randomized [156]. The ability of ginger to reduce acute and delayed nausea associated with cisplatin-based chemotherapy was tested

in a randomized, double-blind placebo-controlled crossover trial [157]. Forty-eight subjects with gynecologic malignancies treated with cisplatin therapy were randomized to receive either placebo or 1 g per day of ginger orally for the first 5 days of the chemotherapy cycle on the first day, and metaclopramide daily for the next 4 days. All subjects received standard antiemetics on the first day. After the first cycle, patients were crossed over to the alternate protocol. Ginger performed as well as metaclopramide for delayed nausea with less restlessness, but the addition of ginger to conventional antiemetics did not improve acute efficacy.

In summary, ginger in doses as low as 1 gram of powdered herb per day showed benefit by reducing chemotherapy-related nausea. No serious adverse events were seen and ginger had fewer side effects than metaclopramide, a standard drug used for the same indication.

Radiation-Induced Dermatitis

Skin changes that occur commonly during radiation therapy usually don't limit treatment, but they do contribute to morbidity for patients. Unfortunately, most natural products tested to relieve radiation-induced dermatitis, with a few exceptions, did not show benefit. Aloe vera is one of the most commonly used topical agents used by cancer patients for radiation therapy-induced burns. Clinical trials and systematic reviews have not, unfortunately, been able to confirm a robust benefit [158]. A small controlled trial added aloe vera (product composition not fully described) to usual skin prophylaxis in patients receiving radiation therapy [159]. The aloe vera was applied "liberally to the [treated] area at various intervals throughout the day." At higher doses of radiation ($>2,700$ cGy), aloe treatment delayed the onset of skin changes by 2 weeks, from 3 to 5 weeks. A larger phase III trial ($n = 194$) of breast cancer patients receiving radiation to the chest wall were randomized to apply either 98% pure aloe vera gel or an inert control gel to the treated area twice a day throughout treatment [160]. Groups, identical at the start of the experiment based on age, surgery, radiation dose, and skin type still showed no difference after treatment. The only toxicities noted were three cases of aloe allergy and one allergic reaction in the control group. A second unblinded study of 108 women, reported in the same article, compared aloe vera gel to no therapy and again, there was no discernable difference between the two groups with respect to dermatitis [160].

Other herbal preparations have shown some benefit. A controlled clinical trial comparing a proprietary chamomile skin cream to almond oil, a standard therapy in the center conducting the trial, was undertaken in 48 women with breast cancer [161]. They were randomly assigned to apply either the chamomile cream or the almond oil to the area above and below the scar. Although the results were not statistically significant, the researchers concluded that chamomile cream delayed the onset of dermatitis and had a mitigating effect on severity. Allergic reactions occurred in two chamomile-treated patients and one almond oil patient. A large phase III clinical trial tested the efficacy

of a calendula or trolamine in preventing grade II or higher dermatitis in breast cancer patients during radiation [162]. Subjects ($n = 254$) were randomized to apply either to a proprietary calendula homeopathic lotion or trolamine to the skin at least twice a day throughout the course of radiation. The incidence of grade II or higher dermatitis was significantly less in the calendula group (41% versus 63%; $P < .001$). Subjects reported greater satisfaction with the calendula lotion as well, despite rating it as being harder to apply.

In summary, topical aloe did not show consistent benefit in preventing or treating radiation dermatitis. One large trial of a calendula homeopathic lotion showed that it was effective and well tolerated in preventing skin changes because of radiation therapy.

Cachexia

Several systematic reviews and meta-analyses have examined the role of omega-3 fatty acids in preventing cancer-related cachexia [163–165]. The strictest of the three only includes five studies and suggests that the literature is insufficient to judge whether eicosapentaenoic acid (EPA) is superior to placebo in treating cachexia. However, two other reviews with broader inclusion criteria come to different conclusions. When the results of an analysis that included all controlled trials was presented to a panel of experts, they concluded that patients with advanced malignancies of the pancreas and upper digestive tract accompanied by weight loss benefited from oral supplementation with omega-3 fatty acids (ω 3FA) [164]. These benefits included increases in weight and appetite, especially if ω 3FA (a combination of EPA and docosahexaenoic acid or DHA) were given in a dose of 1.5 g per day. Heterogeneity existed in the composition of the ω 3FA supplements and the mode of delivery, but lower fat formulas appeared to be better tolerated. Looking specifically at radiation therapy patients, pooling of available data suggested that use of ω 3FA-rich nutritional formulas lead to a significant increase in dietary intake of approximately 380 kcal per day when compared with routine care [165]. A closer examination of some individual studies provides clinically useful information.

A phase I trial in 22 subjects with advanced disease established the upper limit of tolerance for oral fish oil capsules as 0.3 g/kg per day [166]. The capsules tested contained 378-mg EPA and 249-mg DHA per gram of fish oil, suggesting that the maximal dose of ω 3FAs for a 70-kg man was 13.1 g per day (0.19 g/kg). Doses were limited by gastrointestinal toxicity, mainly diarrhea, without any reports of serious adverse effect on coagulation or tumor response. However, for acceptable compliance over time, a much lower dose of fish oil, approximately 6 g per day, was found to be the maximum tolerated in a trial of subjects with advanced lung cancer [167].

Burns and colleagues [168] suggested that a relatively high dose of EPA is required for effect. In a follow-up phase II trial they tested a dose (7.5 g of EPA for a 70-kg patient or 0.11 g per day), which was approximately half of the maximally tolerated dose in their prior phase I trial. Only 6 subjects showed any weight gain, but the majority of the enrolled subjects did show

stabilization of their weight (24 of 36 subjects). The investigators noted that this dose was double the dose tested in most other phase III trials and may have accounted for poor effect seen in some published studies.

Fish oil has also been tested in combination with other conventional medications. When combined with megase, the conventional treatment for cancer-related anorexia, no additional benefit was seen by adding 2.18 g of EPA per day [169]. However, combining fish oil (2 g three times a day) with celecoxib (200 mg twice a day) showed significantly greater improvements in appetite, fatigue, body weight, and muscle strength than with fish oil alone in a small group of subjects with advanced lung cancer [167]. C-reactive protein levels were also significantly lower in the combination group, suggesting that fish oil, as well as celecoxib, may have their benefit through interference with inflammation. A complex intervention involving a number of products (300-mg alpha lipoic acid; 400-mg vitamin E; 30,000-IU vitamin A, 500-mg vitamin C; omega-3 fatty acids) as well as the pharmaceuticals medroxyprogesterone (500 mg) and 200-mg celecoxib daily showed significant improvement on two different measures of quality of life [170].

In summary, fish oil, rich in ω 3FAs, showed benefit in stabilization or reduction of cancer-related cachexia, but relatively high doses were required for effect. Weight stabilized or improved at 7.5-g EPA or fish oil. Combining fish oil with cyclooxygenase-2 inhibitors but not megase improved efficacy. Adherence was limited by gastrointestinal toxicity (diarrhea and nausea).

Lymphedema

Edema following conventional cancer care can be very problematic for patients and difficult to treat. Although a trial with vitamin E and pentoxifylline did not show benefit [171], one randomized trial with selenium selenite did reduce the upper extremity edema and improve the function of breast cancer patients enrolled in a decongestive physical therapy program [172]. Subjects were given 1,000 mcg of selenium selenite for the first week of the trial, 300 mcg for next 2 weeks, and then took a maintenance dose of 100 mcg for 3 months. A positive effect of selenium selenite was also reported in 10 of 12 patients with lymphedema following breast cancer treatment [173].

In addition, a number of small studies using flavinoid-rich preparations have also shown benefit. A proprietary ginkgo formula was given to 48 women with upper extremity edema following breast cancer treatment, and showed a reduction in the symptoms of limb heaviness as well as an increase in lymph migration speed [174]. Following a successful pilot using a proprietary micronized flavinoid fraction [175], a larger randomized controlled trial was performed on 104 women with lymphedema following breast cancer treatment [176]. Despite showing improvements in lymphatic migration speed by scintigraphy, subjects reported a nonstatistically significant improvement in symptom relief. Greatest benefit accrued to the more severely affected women. A second small randomized, placebo-controlled pilot by a different research group also showed benefit in postmastectomy patients with edema when given 500 mg twice a day

of a micronized, purified flavinoid fraction [177]. Fifty seven patients treated with either a proprietary formula of ruscus and hesperidin methyl chalcones or placebo for 3 months showed a 12.9% reduction in limb volume in the treatment group ($P = .009$) [178]. Conversely, a randomized phase II trial of 66 women with breast induration following radiation did not show benefit from a grape seed extract at a dosage of 100 mg three times a day for 6 months [179].

Head and neck patients also develop bothersome edema and tissue induration during radiotherapy, and selenium has shown some benefit in clinical trials [180]. Thirty-six patients with edema after radiotherapy, including 20 who had endolaryngeal edema with stridor and dyspnea, were included in an uncontrolled trial [173,181]. Patient self-assessment of symptoms on a visual analog scale showed statistically significant improvement after treatment ($P < .05$). Head and neck cancer patients ($n = 20$), given 1,000 mcg of selenium selenite per day orally or intravenously for three weeks in the perioperative period, had reduction in edema [182].

In summary, selenium at a dose of 300 mcg per day (perhaps with a loading dose of 1,000 mcg for 1 week), decreased lymphedema in breast and head and neck cancer patients without reported toxicity. A number of proprietary flavinoid-rich extracts, such as ginkgo or bioflavinoid extracts, also improved symptoms with noticeable side effects.

Fatigue

Fatigue, one of the most common and debilitating side effects of conventional cancer care, has been ameliorated to only a limited degree by dietary supplements. In fact, a randomized, double-blind trial of a common proprietary multiple vitamin did not relieve fatigue in 40 breast cancer patients undergoing radiation therapy [183]. More promising was a pilot study of cancer patients with fatigue and carnitine deficiency [184]. After 1 week of supplementation, 13 of 15 subjects increased total and free carnitine along with decreases in fatigue, as measured by Brief Fatigue Inventory scale, and Karnofsky performance status. Similar responses were seen in a group of patients receiving cisplatin or ifosfamide chemotherapy [185]. After 1 week of 4 g of carnitine daily, 45 of 50 subjects with abnormal fatigue significantly improved ($P < .001$) and they maintained their gains through the next cycle of chemotherapy. Longer administration of L-carnitine was tested in a small ($n = 12$), uncontrolled clinical trial. Subjects with advanced disease undergoing cytotoxic chemotherapy were given 6 g per day of L-carnitine with a measurable improvement in fatigue and quality of life [186]. A formal phase I/II study was undertaken to assess the safety of carnitine supplementation [187]. Subjects with advanced cancer, significant fatigue, and compromised activity (Karnofsky performance status of greater than or equal to 50) were enrolled in a dose-ranging study of L-carnitine. Of the screened patients, 77% (29 of 38) had deficient levels of carnitine at baseline. Of the 21 subjects who participated in the study, 17 raised their carnitine levels to normal with oral supplementation. Dosing

started at 250 mg per day and increased to a maximum of 3,000 mg per day in divided doses. No toxicities were observed and in the 17 responders, a dose response effect was seen for carnitine levels and fatigue scores ($P = .01$). Positive effects were more likely at higher dose ranges.

In summary, DS for cancer-related fatigue were generally ineffective. Carnitine supplementation (up to 3,000 mg per day) decreased fatigue and improved quality of life in carnitine-deficient patients during chemotherapy.

Vasomotor Symptoms

Vasomotor symptoms related to natural menopause or cancer therapy, especially in younger women, cause significant morbidity for high-risk patients unable to take estrogen replacement therapy or for breast cancer survivors on hormonal therapy. Black cohosh extract has been suggested as a possible therapy to moderate vasomotor symptoms in this group.

Not all clinical trials have shown benefit in women with breast cancer, but some of the differences in response may be because of variations in the material used or the duration of the trial, as well as large, variable placebo effects commonly seen in menopausal studies. Breast cancer patients, after completion of conventional therapy (59 on tamoxifen; 26 on no hormonal therapy), were enrolled in a randomized, placebo-controlled trial of 8 weeks duration [188]. Both groups (placebo and proprietary black cohosh extract of Remifemin, 40 mg per day) showed similar improvements in number and intensity of hot flashes. The same extract studied in a small pilot study ($n = 21$) at the same dose showed a 56% reduction in hot flash frequency at the end of a 4-week open-label trial [189]. A follow-up phase III trial based on this pilot did not show any benefit [190]. However, the study medication was not the previously used proprietary product, but an extract prepared by the study team, which attempted to approximate the composition of the original. Perhaps this contributed to the marked difference in outcome of the two trials. Finally, a different proprietary product (Klimadynon) was used in the largest and longest study, an open-label trial of 136 women with breast cancer who had completed all conventional therapy and were being maintained on tamoxifen [191]. Two-thirds of the women were given a proprietary BCE (20 mg of herbal drug per day) for 12 months. At the end of that time, almost half of the intervention group were free of hot flashes, with severe hot flashes being reported in only 24% of the treatment group versus 74% of the control group ($P < .01$). No serious adverse events were reported.

Far from being detrimental to women with respect to breast cancer risk, two case controlled studies recently published suggest a protective effect. A case-controlled study of menopausal women identified 949 breast cancer patients and 1,524 controls [192]. Women who took BCE had more than a 50% reduction in risk of developing breast cancer (adjusted OR of developing breast cancer of 0.47; CI 0.27–0.82). Protective effects were also seen in a cohort of breast cancer subjects examined in a retrospective cohort study [193]. The effect of BCE on disease free survival was tested in 1,102 breast cancer survivors

who took BCE, compared with a control group who did not. Use of BCE, after correction for other confounders such as tamoxifen use, showed a prolongation of disease-free survival. After 2 years, the group without BCE had a 14% recurrence rate. It took the BCE group until 6.5 years to achieve the same level of recurrence. The hazard ratio for recurrence was 0.83 (CI 0.69–0.99). These data suggest that BCE is unlikely to cause an increase risk of breast cancer recurrence and may in fact provide protection from recurrence.

In summary, proprietary BCEs have shown variable efficacy. Current safety data does not suggest estrogenic activity for BCEs, nor serious risk of hepatotoxicity. Preliminary cohort data suggests that BCEs may modify risk of recurrence.

Treatment of Pre-cancerous or Specific Lesions

Although dietary supplements are not appropriate as primary treatment in cancer, interesting data are emerging regarding selective use in treating premalignant lesions, some early cancers usually treated with watchful waiting, or specific treatment-resistant cancers. Fifty-nine subjects with oral leukoplakia were treated with either 3 gm of tea or placebo [194]. After 6 months, the treatment group showed a decrease in lesion size (38% versus 10% of subjects) and a lower number of micronucleated exfoliated cells (5.4 per 1,000 cells versus 11.3 per 1,000 cells; $P < .01$). Clinical improvement, decreases in micronuclei frequency in exfoliated cells, and reduction in chromosome abnormality was also seen in men treated orally with black tea in second study after 1 year of treatment [195].

High-grade intraepithelial neoplasia of the prostate (HG-PIN) has responded well to oral administration of a green tea extract [196]. When given 600 mg per day of a high catechins extract (total catechins 75.7%) or placebo for 1 year, progression to frank prostate cancer was 30% in the placebo group and only 3% in the treated group. Total prostate specific antigen (PSA) did not change, and men with symptomatic benign prostatic hyperplasia reported symptom reduction. Pomegranate juice (8 oz of concentrate, POM Wonderful variety), when given to men with a rising PSA following surgery or radiation, increased the mean PSA-doubling time from 15 months to 54 months ($P < .001$) without reports of adverse events [197]. When given a dietary supplement containing soy, lycopene, silymarin, and antioxidants (formulary details not given) following surgery or radiation for 10 weeks, 49 men showed an increase of PSA-doubling time from 445 days to 1,150 days, along with significant decreases in PSA slope ($P = .03$) [198].

Hormone-resistant or refractory prostate cancer (HRPC) can be very difficult to treat and there is interest in finding less toxic alternatives. A small trial ($n = 20$) studied the effect of 10 mg per day for 3 months of lycopene supplementation (Lycored brand) in patients with metastatic HRPC [199]. Tumor responses were seen (5% complete; 30% partial; 50% stable; 15% progression) in some of the study group, but the majority of patients (62%) were able to reduce amount of daily analgesics used, showing an improvement in bone pain. No toxicity from the lycopene supplementation was noted. Furthermore, the

Table 1
Safety dietary supplements in cancer care

Supplement	Action	Reference
Alternative therapy for sole treatment of breast cancer	Early death and higher rates of recurrence	[23]
Garlic extract with docetaxel	No change in pharmacokinetics	[45]
Milk thistle with irinotecan	No change in pharmacokinetics	[46]
St. John's wort with imatinib and irinotecan	Reduced serum levels	[47–49]
Black cohosh extracts	No evidence estrogenic activity	[56–60]
Beta-carotene and alpha tocopherol in head and neck patients during radiation	Increased rate local recurrence and high all cause mortality at 6.5 years	[68]
Vitamin C, beta-carotene, alpha tocopherol in non-small cell lung cancer patients during chemotherapy	No change in response rate; no increase in toxicity	[71]
Glutamine in bone marrow transplant	Did not increase relapse rate, progression of malignancy or incidence of graft versus host disease	[116]
Glutamine in breast cancer patients	No adverse effect on tumor response	[140,141]
Vitamin E in variety of solid tumors with cisplatin chemotherapy	No change in tumor response or survival	[151]

addition of lycopene (4 mg per day) to orchiectomy was also shown to improve the outcome of men with metastatic hormone-responsive cancer [200]. PSA, lower in the lycopene group from 6 months, was significantly lower by 2 years (3.01 ng/mL versus 9.02 ng/mL; $P < .001$), and almost twice as many lycopene treated subjects had a complete response (78% versus 40%). Formulation of the lycopene product may affect response, as a clinical trial of 46 subjects with HRPC did not respond to 15 mg of lycopene supplementation given twice a day in the form of tomato paste or juice [201].

In summary, preliminary data suggests that selected dietary supplements may play a role in treating precancerous lesions, such as tea for leukoplakia. Early cancerous lesions of the prostate (HG-PIN) that are conventionally treated by watchful waiting, may also benefit from the use of green tea extracts, pomegranate concentrates, or complex dietary supplements. The use of lycopene for hormone refractory prostate cancer showed mixed results. However, because of its low toxicity, it might be worth trying in doses of 4 mg to 30 mg per day.

SUMMARY

To meet the needs of the large number of cancer patients who are using DS, physicians and other health care providers must adopt strategies that encourage

Table 2
Efficacy dietary supplements in cancer care

Supplement	Action	Reference
Vitamin C, E, and selenium in chemotherapy patients	Decreased rate nephro and ototoxicity	[78]
Coenzyme Q10 with anthrocyline chemotherapy	Decrease cardiotoxicity	[79]
<i>Trametes versicolor</i> extract in variety of solid malignancies	Increased percentage of 5-year disease-free survival; decreased relative risk of regional metastases; improvement in overall survival	[85–89]
<i>Basidiomycotina</i> extract in variety of solid malignancies	Increased NK cell activity; improvement in activities of daily living (ADL); longer disease-free survival interval	[92–94]
<i>Grifola umbellatae</i> in bladder cancer	More effective than mitomycin C in preventing recurrences after surgery	[95]
<i>Agaricus blazei</i> extract in variety gynecologic cancers with chemotherapy	Increased NK cell activity and decreased general symptoms	[100]
Fermented wheat germ extract in pediatric cancer patients	Decreased episodes of febrile neutropenia	[101]
Fermented wheat germ extract in colorectal or melanoma cancer patients	Lower incidence of new disease, new metastases, or death; increased time to relapse	[102,103]
Probiotics in biliary cancer patients undergoing surgery; colorectal cancer patients undergoing chemotherapy; patients receiving abdominal and pelvic radiation	Lower postoperative infection rates; decreased gastrointestinal toxicity (diarrhea) with less hospital care and less reduction in chemotherapy; decreased incidence of diarrhea	[106,143–146]
Glutamine in variety of cancer patients undergoing chemotherapy and radiation	Decreased rates and severity of mucositis, neuropathy, and intestinal toxicity; decreased use of pain medication in stomatitis patients; improved nutrition in stomatitis patients; improved ADL in neuropathy patients	[112–119, 137–139, 148–150]
Vitamin E topically in children undergoing bone marrow transplant; in adults undergoing chemotherapy or radiation to head and neck area	Improved stomatitis	[122,124,125]
Zinc in head and neck patients during radiation therapy	Improved stomatitis	[126,127]

(continued on next page)

Table 2
(continued)

Supplement	Action	Reference
Chamomile extract as mouthwash in chemotherapy and radiation	Improved stomatitis sometimes	[129,130]
Homeopathic remedy including <i>Arnica montana</i> in chemotherapy	Improved stomatitis	[132]
Proteolytic enzymes in head and neck patients with radiation	Improved stomatitis	[109,133]
Vitamin E orally in variety of cancers during cisplatin chemotherapy; patients with cisplatin and paclitaxel chemotherapy	Decreased rate of neuropathy	[151–154]
Ginger postoperatively in surgical cancer patients; with MOPP chemotherapy; with cisplatin chemotherapy	Decreased nausea	[155–157]
Calendula homeopathic lotion in radiation therapy	Decreased dermatitis	[162]
Chamomile skin cream	Decreased dermatitis	[161]
Fish oil in patients with cancer induced cachexia	Increased dietary intake, maintenance of weight, decreased fatigue	[163–170]
Selenium selenite in breast cancer and head and neck cancer patients	Decreased lymphedema	[171–173, 180–182]
Ginkgo in breast cancer patients	Decreased lymphedema	[174]
Variety of high flavinoid extracts	Decreased lymphedema	[175–179]
Carnitine in cancer patients following chemotherapy; benefit most pronounced in patients with carnitine deficiency	Decreases fatigue	[184–187]
Black cohosh extracts in breast cancer patients with menopausal symptoms	Decreases vasomotor symptoms in some trials	[189,191]
Green or black tea in leukoplakia	Improved abnormality	[194,195]
Green tea extract in high-grade intraepithelial neoplasia of the prostate without conventional therapy	Decreased progression to frank prostate cancer	[196]
Pomegranate juice in prostate cancer patients with rising PSA after radiation or surgery	Increased PSA-doubling time	[197]
Soy in complex formula in prostate cancer patients with rising PSA after radiation or surgery	Increased PSA-doubling time	[198]
Lycopene in hormone refractory prostate cancer; in hormone responsive patients following orchiectomy	Limited clinical response in some patients; Improved clinical response	[199–201]

Box 1: Recommendations to maximize gain and minimize risk in use of dietary supplement during cancer care

- Encourage full disclosure from patients.
- Assist patients to establish reasonable goals.
- Develop a nuanced message about dietary supplement use.
- Develop knowledge base regarding dietary supplements.
- Favor dietary supplements from well-known, reputable companies.
- Favor simpler over more complex dietary supplements.
- Favor products that have been tested in human clinical trials.
- Ask to see the actual products that patients are using.
- Ask to see the resources patients use to guide decisions.
- Collaborate with patients to form a treatment plan.
- Monitor patients during use of dietary supplements.

full disclosure of use. Nonjudgmental questioning and demonstration of greater knowledge of the research concerning dietary supplements by physicians should aid in this endeavor. If the individual practitioner does not have this expertise, resources and referral sources should be identified to supplement their expertise.

Risks may be associated with the use of DS. These should be discussed specifically, based on evidence where possible (summary of evidence for risk or lack of harm is in [Table 1](#)). Caution should be urged when DS use substitutes for or delays the start of conventional care. Use of St. John's wort with chemotherapy and vitamin E in head and neck cancer patients should be discouraged. The use of blanket negative statements about DS to patients who perceive benefit from their use and have identified sources that support such use does not foster open communication.

Familiarity with the literature supporting safe dietary supplements, especially those used to relieve symptoms related to treatment, would help the clinician guide the patient toward supplements that are most likely to benefit them (summary of evidence for efficacy is in [Table 2](#)). A number of products reviewed here suggest benefit, including medicinal mushrooms and other immunomodulators, glutamine, ginger, black cohosh, and ω 3FA, among others. Use of products that have been tested in clinical trials should be preferred where such products are available. Steering patients toward well-characterized products from reputable sources can address concerns regarding the quality of dietary supplements. Specific strategies to aid patients in deriving maximal benefit from their use of dietary supplements while minimizing risk are listed in [Box 1](#). Finally, it is critical that further research on the combined use of DS and conventional cancer treatments be given higher priority. As our knowledge improves, so will our ability to advise our patients.

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