The term “complementary and alternative methods” (CAM) refers to products and regimens that individuals may employ either to enhance health and well being or to cure disease. Complementary therapies are used along with mainstream care to manage symptoms, relieve stress, and enhance quality of life. In contrast, alternative methods are used instead of evidence-based medical therapy. The dangers inherent in bogus alternatives are two-fold: First, they may cause direct harm, and second, they may be ineffective, resulting in disease progression. In this section, we hope to help providers guide patients toward CAMs that might improve quality of life and away from those that are ineffective, toxic, and wasteful of time and money.

—David Rosenthal, MD and Terri Ades, RN, MSN, AOCN, Section Editors

**VITAMIN C PROMOTES GENOTOXIC LIPID METABOLITES IN VITRO — IN VIVO SIGNIFICANCE REMAINS UNCERTAIN**

New *in vitro* research indicates that vitamin C can promote formation of highly reactive lipid metabolites that can lead to DNA mutations that might increase cancer risk. The report, published in *Science* (2001;292:2083-2086)\(^1\), is raising questions about the increasingly common use of vitamin C supplements.

“[One] thing which has captured people’s imaginations is the fact that there’s never been a negative effect of vitamin C reported before,” says Ian Blair, PhD, co-author of the study, and A. N. Richards, professor of pharmacology and director of the center for cancer pharmacology at the University of Pennsylvania in Philadelphia.

Vitamin C is necessary to health and functions as a scavenger of free radicals—highly reactive compounds that can cause mutations. For this reason, many scientists and lay people have speculated that high doses of the vitamin should be useful for cancer chemoprevention. However, most observational and interventional studies have not supported this hypothesis. In a surprising twist, Blair and his colleagues found that vitamin C, like free radicals, also can promote the formation of harmful genotoxins.

The *in vitro* experiments started with linoleic acid, a polyunsaturated fatty acid found in sunflower, corn, and safflower oils. Linoleic acid is the major fatty acid found in blood and is normally broken down into a compound called lipid hydroperoxide. When vitamin C was added to lipid hydroperoxide under conditions found in the body, the dangerous genotoxins formed within hours.

**Report No Cause for Alarm**

However, David Ringer, PhD, MPH, a scientific program director for the American Cancer Society (ACS), believes that the report presents no cause for alarm. “They’re very interesting, preliminary results,” says Ringer. “They definitely demonstrate that, *in vitro*, vitamin C can participate in the creation of a compound known to be genotoxic. Whether that actually occurs in the body or not—obviously they don’t have data that speak to that. But they raise the interesting question, ‘does it happen and should we be concerned about it?’”

Epidemiological studies have not found a link between taking vitamin C supplements and risk of developing cancer. In other words, the supplements do not appear to be either causing or preventing cancer. Perhaps the reason is that vitamin C has both beneficial antioxidant and harmful genotoxic effects *in vivo*, which balance each other out. The practical significance of this hypothesis is that if the lipid hydroperoxide pathway could be blocked, the chemopreventive potential of vitamin C might be realized.
The More the Better?

Blair speculates that megadosing with vitamin C may constitute the highest risk. “People will take one [vitamin C] tablet and then think, ‘well, if I take five I’ll be even more protected,’” Blair says. “When you examine the scientific literature, you’ll see that there’s absolutely no scientific evidence that more is better. Now there’s a potential for more to be worse. It seems to have reawakened this notion that it’s better to get your vitamin C from your diet than from supplementation.”

This study and Blair’s interpretation provide additional support for the ACS view on the issue. According to the ACS Guidelines on Diet, Nutrition, and Cancer Prevention, “strong evidence associates a diet rich in fruits, vegetables, and other plant foods with reduced risk of cancer, but there is no evidence at this time that supplements can reduce cancer risk. The few studies in human populations that have attempted to determine whether supplements can reduce cancer risk have yielded disappointing results.”

BLACK COHOSH NO BETTER THAN PLACEBO FOR BREAST CANCER SURVIVORS WITH HOT FLASHES

Many advocates of herbal medicine claim that black cohosh (Cimicifuga racemosa) reduces the intensity of hot flashes associated with menopause, but researchers at Columbia University in New York found that for women with breast cancer, the herb was no more effective than placebo for relieving most menopausal symptoms. The Columbia study appeared in the May 15 issue of the Journal of Clinical Oncology (2001;19:2739-2745).2

“We initiated this trial because hot flashes have an adverse effect on breast cancer survivors’ quality of life, and a number of patients have said that black cohosh relieved symptoms,” said study co-author Judith S. Jacobson, DrPH, assistant professor of clinical public health at Columbia University’s Mailman School of Public Health.

During the study, breast cancer patients who had completed primary therapy were randomly assigned, after stratification by Tamoxifen use, to receive either black cohosh or placebo. To gauge the intensity of hot flashes and other menopausal symptoms, subjects recorded the number and the intensity (on a scale of 1 to 3) of hot flashes, and completed a detailed menopausal symptom survey.

Those who received black cohosh reported significantly less sweating than those who received placebo (p < 0.04). However, there was no comparable decrease in other menopausal symptoms, including heart palpitations, headaches, poor sleep, depression, irritability, or nervousness. There were no significant differences in number or intensity of hot flashes between the placebo and study groups, although both groups showed a reduction in number and intensity of hot flashes during the course of the study. The observations applied to women taking Tamoxifen and to those not using the medication. Black cohosh did not have any estrogen-like effects on luteinizing hormone or follicle-stimulating hormone levels. No adverse effects were attributed to the herbal treatment.

The study outcome does not mean that black cohosh has no medicinal value for menopausal women, according to Jacobson. “We asked only what we can learn about the effects of 40 mg of black cohosh daily for two months on breast cancer patients,” she says.

Jacobson says the study illustrates the importance of controlled clinical trials in testing herbal treatments to determine if they are harmful or live up to claims made by
manufacturers. Writing in the *JCO* article, Jacobson and colleagues note that “…the placebo effects in our study were significant; without a control group, we might easily have attributed all the improvement in menopausal symptoms to black cohosh.”

“I’m glad researchers are conducting these kinds of studies,” says David Rosenthal, MD, professor of medicine at Harvard Medical School and chair of the ACS’s Advisory Group on Complementary and Alternative Methods of Cancer Management. “We want an answer to the question of whether herbal substances work. They need to be tested because people are using them whether we like it or not.”

Rosenthal adds that though the study was small, involving fewer than 70 participants, the results shift the burden of proof to practitioners who claim that black cohosh is an effective remedy for hot flashes.

Jacobson says that another larger and longer randomized trial of black cohosh for women who do not have cancer is underway at Columbia.

**STUDY SUGGESTS FLAXSEED AND LOW-FAT DIET MIGHT HELP IN PROSTATE CANCER PREVENTION OR TREATMENT**

In a short-term pilot study of prostate cancer biomarkers, a low-fat diet supplemented with ground flaxseed reduced total serum testosterone, free androgen index, and tumor proliferation index, and increased apoptosis. Reported in the July issue of *Urology* (2001;58:47-52), these results warrant further study of this dietary intervention as a strategy for prostate cancer risk reduction or as a complementary method for men with prostate cancer.

Flaxseed is high in lignans, fiber-related compounds that can bind androgens and increase their elimination during enterohepatic circulation. Lignans also act as phytoestrogens, and this combination of endocrine effects might be reasonably expected to inhibit prostate cancer formation and growth. In addition, flaxseed is a rich source of omega-3 fatty acids, which have been linked in some epidemiological studies to a lower incidence of prostate cancer.

Wendy Demark-Wahnefried, PhD, RD, LDN, and colleagues from Duke University Medical Center and Durham Veterans Affairs Medical Center, tested this dietary intervention in 25 men who were recently diagnosed with prostate cancer and were awaiting radical prostatectomy. Men in the study followed a low-fat (≤ 20% of total calories) diet supplemented daily with 30 grams of ground flaxseed for an average period of 34 days.

During this time, the participants’ serum testosterone levels and their free androgen index decreased significantly, by 15% and 19%, respectively. Compared with historical controls (matched by age, race, PSA level at diagnosis, and biopsy Gleason score) prostatectomy specimens of the subjects in the study had a significantly lower tumor proliferation index and significantly higher apoptotic index, measured by MIB-1 labeling and TdT-mediated dUTP-biotin nick end-labeling, respectively.

In their discussion, the authors point out that this exploratory study was intended as an initial look at their hypothesis and was limited by its use of historical controls and by its short duration. They were still able to conclude, “These findings suggest that a flaxseed-supplemented, low-fat diet may have an effect on prostate cancer biology that may be mediated through a hormonal mechanism.”

Tim Byers, MD, MPH, co-chair of the ACS Workgroup on Nutrition and Physical Activity for Cancer Survivors, and professor of preventive medicine, University of Colorado School of Medicine, agrees with the authors’
conclusion but notes that it would be premature to make any firm recommendations for men with prostate cancer based on this small, uncontrolled study of intermediate biomarkers. Byers says one needs data on clinical outcomes. “This was a study in which two dietary changes were tested at the same time—a diet very much lower in total fat than most men consume (20% of calories from fat), and flaxseed oil supplements. The reductions in cholesterol and testosterone levels observed may be due as much to the low-fat diet as to the flaxseed. If this dietary intervention does have effects on testosterone metabolism it would likely not be a more effective alternative to conventional anti-androgen therapy and would probably have little impact as a complementary therapy for men already taking conventional hormonal therapy. On the other hand, as a complementary dietary intervention, this combination of substantial reduction in dietary fats along with flaxseed supplements might eventually turn out to be useful for men who have surgery, radiation, or expectant management without undergoing conventional hormonal therapy. Low-fat diets of this type might also be effective in reducing the risk of getting prostate cancer. The side effects of this type of intervention are minimal, and this is a very heart-healthy, low-fat diet. I look forward to continued research in this important area in which the interventions might be evaluated in the context of randomized, controlled trials.”

HERBAL DIETARY SUPPLEMENTS MAY INCREASE RISK OF PERIOPERATIVE PROBLEMS

Unlike conventional over-the-counter or prescription drugs, which cannot be marketed without submitting laboratory and clinical data to document safety and efficacy, dietary supplements are exempt from these pre-market requirements. Instead, availability of such information depends on voluntary research efforts by health care professionals.

An article in the July 11 issue of *JAMA* (2001;286:208-216) reviews the literature on the use of herbal remedies as a factor contributing to perioperative complications. In their discussion, Michael K. Ang-Lee and colleagues from the Pritzker School of Medicine, University of Chicago, highlight the importance of good patient-physician communication in helping to prevent such adverse effects.

Ang-Lee, et al. note concerns regarding perioperative use of eight common herbs—echinacea, ephedra, garlic, ginkgo, ginseng, kava, St. John’s Wort, and Valerian—and provide recommendations for their perioperative discontinuation. They note, “Complications may arise from the herbs’ direct and pharmacodynamic or pharmacokinetic effects. Direct effects include bleeding from garlic, gingko, and ginseng; cardiovascular instability from ephedra; and hypoglycemia from ginseng. Pharmacodynamic herb-drug interactions include potentiation of the sedative effects of anesthetics by kava and Valerian. Pharmacokinetic herb-drug interactions include increased metabolism of many drugs used in the perioperative period by St. John’s Wort.”

Dr. Barrie Cassileth, chief of integrative medicine service at Memorial Sloan-Kettering Cancer Center and member of the American Cancer Society Advisory Group on Alternative and Complementary Methods of Cancer Management, says, “Although the increasing prevalence of dietary supplement use has received considerable attention in medical journals and in the popular media, the issue is often not discussed by physicians and their patients.”

“Patients may be reluctant to talk about over-the-counter remedies,” Cassileth says. “They may assume that these remedies do not ‘count,’ or are irrelevant, because they are natural products rather than prescription drugs.
Concern about physician disapproval may play a role. On the other hand, physicians typically fail to ask about non-prescription therapies that patients are taking. They may not have the time to do so, and lack of knowledge about herbal remedies may make some reluctant to bring up a topic about which they can offer little in the way of informed advice.

“Patients often incorrectly assume that herbal products are benign,” Cassileth says. “Several herbs, including those mentioned in the study, have anticoagulant activity that may be further exacerbated in cancer patients with concomitant coagulopathies.”

Cassileth says, “Ang-Lee et al. effectively reviewed the available literature and raised awareness about herbs during the perioperative period. Radiation, chemotherapy, and surgery are three primary treatment modalities for cancer patients. Most oncologic surgery is scheduled well in advance, and disclosure of dietary supplement use should be requested and documented by all physicians caring for cancer patients.”

Cassileth concludes, “Herb use has important implications for radiation and chemotherapy as well as for surgery. Communication is a two-way street; physicians as well as patients have a responsibility to discuss patients’ self-prescribed remedies. They should ask direct, open-ended questions to initiate communication and protect patients against disapproving reactions.”

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Errata

In the July/August 2001 issue, in the article “Nausea, Vomiting, and Retching: Complex Problems in Palliative Care” (Rhodes VA, McDaniel RW. CA Cancer J Clin 2001;51:232-248), an error occurred in Table 2 (page 242).

The correct IV dosage for Granisetron is 10 mcg/kg of body weight. We apologize for the error and any confusion this may have caused.

In the May/June 2001 issue, in the article “Nutrition During and After Cancer Treatment: A Guide for Informed Choices by Cancer Survivors” (Brown J, Byers T, Thompson K, et al. CA Cancer J Clin 2001;51:153-187), an error occurred on page 173.

The statement “Using a high-protein, low-fat, high-carbohydrate regimen helps decrease lower esophageal sphincter pressure, whereas chocolate, fat, alcohol, coffee, and compounds containing carminatives (e.g., oil of spearmint, peppermint, garlic, and onion) may increase lower esophageal sphincter pressure, and should be avoided,” was printed incorrectly.

The statement should have read: “Using a high-protein, low-fat, high-carbohydrate regimen helps decrease lower esophageal sphincter pressure, whereas chocolate, fat, alcohol, coffee, and compounds containing carminatives (e.g., oil of spearmint, peppermint, garlic, and onion) may decrease lower esophageal sphincter pressure, and should be avoided.” We apologize for the error and any confusion this may have caused.