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The Use of Complementary and Alternative Medicine in Prostate Cancer Patients

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Regardless of the level of acceptance by the mainstream medical community, the use of complementary and alternative medicine (CAM) in cancer patients has been increasing both worldwide and in the United States.[1] People are using CAM as an alternative to conventional therapies or in addition to conventional therapies as complementary care.[2]

Among cancer patients, vitamins and herbs are the second most popular types of CAM, according to a study by Richardson and colleagues.[3] (Spiritual practices lead the list.) The researchers found that two-thirds of vitamin and herb users were also receiving chemotherapy, radiotherapy, or surgery.

Nam and colleagues[4] reported that the prevalence rates of CAM use among patients with prostate cancer and those at high risk were 27.4 to 38.9 percent and 25.8 to 80 percent, respectively. A significant number of patients who used CAM did not report its use to physicians. Vitamin E was found to be the most popular form of CAM in this study.

Since the passage of the 1994 Dietary Supplement Health and Education Act, which permitted herbal products and vitamins to be sold over the counter as dietary supplements, the use of CAM has dramatically increased in the United States, and CAM has become a multibillion-dollar business.[2] Despite little clinical data for their efficacy and safety, CAMs are widely available, and claims of their effectiveness have been based largely on anecdotal reports. Neither the Food and Drug Administration (FDA) nor any other government agency oversees the evaluation of effectiveness or safety of CAM.

As a result of congressional action, the Office of Alternative Medicine (OAM) was established at the National Institutes of Health in 1992. The OAM subsequently expanded to the National Center for Complementary and Alternative Medicine in 1998 to advocate for quality science and assess the scientific validity of CAM. Separately, the Office of Cancer Complementary and Alternative Medicine was established in 1998 at the National Cancer Institute to address similar issues primarily in cancer therapy.

Despite questionable anecdotal reports, quality scientific studies are showing the promise of CAM among cancer patients. In this article, we examine the effectiveness, safety, and role of PC-SPES (a recently publicized herbal product), vitamin E, selenium, lycophene (a powerful antioxidant found in tomatoes), genistein (a phytochemical found in soybeans), and saw palmetto (a fruit extract) in prostate cancer therapy.

PC-SPES

An extract mixture from eight different herbs, PC-SPES is used by patients with prostate cancer at different stages as a supplement or alternative to their traditional therapy. PC-SPES is the commercial name of an herbal supplement sold by Botanic Lab of Brea, Calif., since November 1996. Each capsule contains 320 mg of the herbal combination powder with an unknown ratio of each herbal extract.[5] Its out-of-pocket cost ranges from $162 to $486 each month.[5]

PC-SPES is promoted as a food supplement that contains no estrogen; however, it does exhibit some estrogenic effects, including loss of libido and extreme breast enlargement. The degree of estrogenic activity of PC-SPES was found to be inconsistent from batch to batch, indicating problems in standardization.[6]

A recently reported Phase II study[7] tested the efficacy and toxicity of PC-SPES (nine capsules daily) in 34 prostate cancer patients. Twenty of these patients were hormone naïve (the cancer had not yet been treated with hormones), and 14 were androgen independent (having hormone-insensitive disease and not responding to androgen therapy). The study showed a greater than 50 percent decline in prostate-specific antigen (PSA) in 9 of 12 hormone-naïve patients and in 9 of 12 androgen-independent patients. Testosterone levels decreased in almost all patients. Adverse reactions included extreme breast enlargement in 71 percent, mild (grade 1) nausea in 12 percent, and mild (grade 1) diarrhea in 33 percent of the patients. One patient developed a pulmonary embolism, and 60 percent of patients with previous normal testosterone level experienced loss of libido.

Another recent study of 33 patients with hormone-naïve prostate cancer found that PSA fell by more than 80 percent in all

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patients.[8] There was a greater than 50 percent decrease in tumor volume in 14 of 19 patients whose disease was assessable by ultrasound. And, of 2 patients with positive bone scans, one patient improved and one patient stabilized. Adverse reactions included extreme breast enlargement in all patients, loss of libido and potency in all who were sexually active prior to treatment, and deep vein thrombosis in 6 percent of the patients.

PC-SPES has antitumor effects in several prostate cancer cell lines.[9] PC-SPES promotes programmed cell death (apoptosis), decreases the expression of the androgen receptor (where testosterone binds and activates prostate cell growth), and reduces PSA levels in an androgen-dependent prostate cancer cell line.[10-12] Other clinical studies[5-8,13,14] have shown that PC-SPES reduces PSA levels in patients with hormone-naïve and androgen-independent prostate cancer. PSA concentrations increased to baseline within two to six weeks after discontinuation of PC-SPES. The studies showed a decrease in pain medication requirements, and improvement in quality-of-life measures in patients with hormone-independent prostate cancer. Common side effects were hot flushes, extreme breast enlargement, loss of libido, and dyspepsia. Rare but potentially serious side effects include venous thrombosis, pulmonary embolism, and allergic reactions.

Little data exist on the long-term efficacy and toxicity of this product. Clinical activity and adverse effects of the PC-SPES are strikingly similar to those in previous clinical trials using high-dose estrogen (diethylbesterol),[15,16] and it is unknown if PC-SPES provides a significant additive benefit. Studies are being planned to test the efficacy of PC-SPES in prostate cancer patients who have failed estrogen therapy.

Due to its estrogenic activity, the risk of venous thrombus and pulmonary embolism, and alteration of PSA levels, use of PC-SPES may be inappropriate for patients receiving other hormonal or antineoplastic agents. PC-SPES should be used with careful medical supervision. Nevertheless, PC-SPES has shown considerable antitumor activity in preclinical and clinical studies, and further study is clearly warranted.

VITAMIN E

Vitamin E is an essential vitamin with a recommended dietary allowance of 15 mg per day for adults.[17] Vitamin E is actually a general name for a group of compounds called "tocopherols" and "tocotrienols." Typically, oral supplements of vitamin E are given in the alpha-tocopherol form.[18]

When making clinical recommendations for patients, health care professionals must be aware of the potential for side effects in oral doses of vitamin E greater than 800 IU daily.

Vitamin E has potent antioxidant properties and may also protect against cancer by enhancing immune functions, lowering the activity of protein kinase C (involved in regulating cellular proliferation), and inducing apoptosis.[19-21] This vitamin has been shown to inhibit the growth of several prostate cancer cell lines.[20]

The most convincing study on the role of vitamin E in prostate cancer was the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) trial.[22] In this study, Finnish male smokers receiving 50 mg of vitamin E (approximately equal to 75 IU of vitamin E) had a 33 percent reduction in prostate cancer incidence and a 41 percent reduction in prostate cancer mortality. This group of men experienced a reduction in clinically detectable prostate cancer within two years of taking the supplement. While this result is promising, additional studies are needed to confirm the results since prostate cancer incidence was a secondary end point in this study.

When making clinical recommendations for patients, health care professionals must be aware of the potential for side effects in oral doses of vitamin E greater than 800 IU daily. Side effects of such large doses of vitamin E include, among others, delayed bloodclotting and an increased requirement of vitamin K in vitamin K-deficient patients.[18]

SELENIUM

Selenium, an essential trace element in humans, is found in grains, fish, and meats. Large variation exists in dietary selenium consumptions across the population because the availability of selenium critically depends on selenium concentration in the soil.[17]

Higher selenium levels were found to be associated with a reduced risk of prostate cancer as determined by serum selenium concentrations, measure of short-term selenium intake, or amount of selenium in toenail clippings, a surrogate marker for long-term selenium intake.[23,24] Selenium at different doses may affect several types of anticarcinogenic activities including antioxidant protection, carcinogen metabolism, immune enhancement, and apoptosis.[25] Selenium works synergistically with vitamin E to inhibit carcinogenesis, and vitamin E reduces the oxidative damage seen in selenium deficiency.[26-28]

The most profound evidence of protective effect of selenium on prostate cancer so far has been from a double-blind and placebo-controlled clinical trial by Clark and colleagues.[29] A total of 1,312 patients with a history of basal or squamous cell skin cancer were randomized to take either placebo or daily dose of 200 µg selenium, as a selenium-enriched yeast tablet for

a mean of 4.5 years. Although the researchers failed to detect the protective effect of selenium on the recurrent skin cancer, the risk of prostate cancer rate was found to be reduced by two-thirds of that of men receiving placebo.

In light of the encouraging findings by Clark and colleagues[29] and the Finnish ATBC trial,[22] the SELECT study—Selenium and Vitamin E Cancer Prevention Trial—will be launched in late 2000. The SELECT study is a multicenter, placebo-controlled large Phase III study to evaluate the effect of selenium and vitamin E on prostate cancer incidence. Funded by the NCI's Division of Cancer Prevention and coordinated by the Southwest Oncology Group, the SELECT study will randomize at least 32,400 healthy males age 55 and older (for African-Americans, age 50 and older) to either placebo, 200 µg of selenium per day, 400 mg of vitamin E per day, or both for up to 12 years.[30,31] This study is expected to provide confirmatory data on the role of selenium and vitamin E in the prevention of prostate cancer, because neither trial by Clark nor the ATBC was designed to evaluate prostate cancer prevention as a primary end point.

Two clinical trials—Phase II Chemoprevention Trial of Selenium and Prostate Cancer, and Chemoprevention Trial of Selenium and Prostate Cancer—are already underway at the University of Arizona.[32]

For American adults, the recommended daily allowance of selenium is 55 µg,[17] and typical daily selenium intakes fall in the range of 80 to 165 µg.[33,34] The Institute of Medicine recently reported selenium can be toxic above 400 µg/day, resulting in characteristic garlicky breath and brittle fingernails and hair.[17] Whether individuals with nutritionally adequate selenium intake may benefit from selenium supplementation still remains to be proven.

LYCOPENE

Lycopene is a carotenoid phytochemical and a powerful antioxidant. Tomatoes are the major source of lycopene. It reduces cellular proliferation of various cancer cell lines induced by insulin-like growth factor-I (IGF-I), which may

Whether individuals with nutritionally adequate selenium intake may benefit from selenium supplementation still remains to be proven.

be associated with a higher risk of prostate cancer.[35] Lycopene was found in relatively high concentrations in the prostate. The presence of lycopene in the prostate at concentrations that are biologically active supports a hypothesis that dietary carotenoids might be related to prostate function and disease processes, particularly reducing prostate cancer risk.[36]

Although tomatoes are the major source of lycopene, in the Auckland Prostate study consumption of raw tomatoes was not associated with a reduced prostate cancer risk. Interestingly, many of the processed foods such as spaghetti sauce, tomato soup, salsa, ketchup, and tomato paste are better sources of bioavailable lycopene than the fresh tomatoes.[37] In a study of 14,000 Seventh-Day Adventist men, high intake of tomatoes and tomato products, which accounted for 82 percent of lycopene, reduced the risk of total prostate cancer by 35 percent and aggressive prostate cancer by 53 percent.[35] A review of the Health Professionals Follow-Up Study of more than 50,000 men revealed a significant reduction in prostate cancer risk in those men whose diet was high in consumption of tomatoes and tomato-containing products, such as tomato paste and pizza.[36] Further clinical studies are needed to better understand the role of lycopene in the prevention and/or treatment of prostate cancer. An ongoing NCI-sponsored clinical trial, Phase I Study of Lycopene for the Chemoprevention of Prostate Cancer, started in June 2000 to determine dose-limiting toxicities and the maximum tolerated dose of lycopene in healthy male subjects.

GENISTEIN

Genistein is a phytochemical found in soybeans.[38] Soybeans contain a variety of phytochemicals, and in particular they are the only source with nutritionally significant amounts of one type of phytochemical called isoflavones. Foods that contain large amounts of soy are tofu, soy milk, and miso. In soy consuming populations, the concentrations of genistein average 0.28 µM, which is ten-fold higher than that seen in non-soy consuming populations.[39] Much interest has been shown recently in genistein as a chemopreventive agent in prostate cancer. Both epidemiological and migrant studies have demonstrated a correlation between increased isoflavone levels in the serum and urine of Asian men with decreased levels of prostate cancer.[40] Also, in a cross-national study for which data was available from 42 countries, soy products were identified as having a significant protective effect against prostate cancer.[41]

Genistein is a potent inhibitor of protein-tyrosine kinase and topoisomerase II, enzymes which are crucial to cellular proliferation. Genistein is also an inhibitor of angiogenesis and several steroid metabolizing enzymes, such as aromatase and 5 alpha-reductase.[42] A NCI-sponsored placebo-controlled clinical trial, Phase I Randomized Study of Genistein in Patients with Stage III or IV Prostate Cancer, has been underway since December 1999 to determine the safety and pharmacokinetics of genistein.

SAW PALMETTO

Saw palmetto is an extract derived from the fruit of *Serenoa repens*. The German Commission E, a committee established by the German government to evaluate the safety

and efficacy of herbs and herb combinations sold in Germany, has listed saw palmetto as an approved herb for use in urination problems associated with benign prostate hyperplasia (BPH) stages I and II. The mechanism of action by saw palmetto in BPH symptoms is unknown, but thought to be primarily by inhibiting type I and type II 5 alpha-reductase, which converts testosterone to dihydrotestosterone, an important promoter of prostatic growth.[43,44] Although several studies have shown that saw palmetto improves urologic symptoms and flow measures in patients with BPH symptoms,[45,46] there is no evidence to date to support that it has any indication in prostate cancer prevention or treatment. No changes in PSA levels were observed in patients with saw palmetto when followed up to six months;[47] however, the long-term effect or effect at increased doses of saw palmetto on PSA levels is unknown. Furthermore, due to its potential effect on PSA levels, unsupervised use of saw palmetto may further delay prostate cancer diagnosis or confound the follow-up of the disease.

CONCLUSIONS

While herbal products, phytochemicals, and vitamins may provide beneficial options in prostate cancer prevention or treatment, assessment in their efficacy and safety still awaits rigorous scientific testing before approval or dispute of their use in prostate cancer. Many herbal products lack information regarding characterization of the products, the nature of specific components responsible for their biological activity and toxicity, standardization, and variability in their manufacturing process. Also missing from many of these products is information on the measure of stability; appropriate dose, dosing interval, and duration; a safety profile across differing doses in animals and humans; contraindications to their use; and potential drug-herbal interactions. These issues will likely remain as long as the government does not require regulation in the effectiveness and safety of these products. Despite the efforts to standardize the consistency of herbal products, variability seems to be unavoidable in view of the complex nature of herbal components.

The use of herbal agents by prostate cancer patients must be under careful medical supervision because of safety concerns and the risk of disease/herb or drug/herb interactions.

Variability will continue as long as we remain unclear as to the active ingredients responsible for an herbal product's clinically relevant activity and toxicity. The use of herbal agents by prostate cancer patients must be under careful medical supervision because of safety concerns and the risk of disease/herb or drug/herb interactions.

PC-SPES seems to have substantial clinical effects in prostate cancer patients, and its mechanism of action appears to be hormonal in nature. Further studies are required to evaluate its long-term effects, any beneficial effects compared to estrogen or other existing therapies, and to elucidate the active components responsible for its effects.

For vitamin E, selenium, lycopene, and genistein, it is premature to conclude if their supplementation in nutritionally adequate individuals is beneficial in prostate cancer prevention or treatment.

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