



Several nutrients and phytochemicals are being evaluated in prospective trials to evaluate their potential as cancer chemopreventive agents for prostate cancer.

A. Griffin (Alice Griffin Myers), North Carolina. *Osprey Point, Maine*. Oil monotype, 14-1/2" × 20-1/2".

Nutrients in the Chemoprevention of Prostate Cancer: Current and Future Prospects

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Background: *External factors such as diet and lifestyle may be important in the etiology of invasive prostate cancer. Specific features of prostate cancer, including high prevalence, long latency, and significant mortality and morbidity, provide the opportunities for chemoprevention.*

Methods: *The authors examine the experimental and epidemiological data demonstrating the chemopreventive activity, safety, and toxicity of chronic administration of these specific nutrients as chemopreventive agents in prostate cancer.*

Results: *Several nutrients have been identified as agents that inhibit mutagenesis and hyperproliferation or induce apoptosis or differentiation, which are critical characteristics for chemoprevention. Successful chemopreventive strategies require well-characterized agents, suitable cohorts, and reliable intermediate biomarkers of cancer for evaluating efficacy. Phytoestrogens/isoflavones, vitamins D and E, selenium, and lycopene have been identified as promising nutrients in the role of chemoprevention of prostate cancer.*

Conclusions: *Clinical studies to evaluate the safety and effectiveness of these agents as future prospects in cancer chemoprevention, both individually and in combination, are warranted.*

Introduction

It is estimated that 179,300 new cases of prostate cancer will be diagnosed in the United States in 1999. An estimated 37,000 deaths due to this disease are expected in 1999, making prostate cancer the second leading cause of cancer death in men in the United States.¹ The initiation and progression of prostate cancer involve a complex series of both exogenous and endogenous factors. Although clinical prostate cancer incidence and mortality vary greatly among popula-

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tions,^{1,3} the frequency of latent prostate cancer is evenly distributed. This suggests that external factors are important in the transformation from latent into more aggressive clinical cancer.^{4,6} Geographic variations and increasing incidence in populations migrating to high-incidence areas, demonstrate an increasing evidence that lifestyle factors such as diet, physical activity, smoking, and other environmental factors may be important in the etiology of invasive prostate cancer.^{1,2,7-9}

Most cancers have a latency period of 10 to 20 years, which provides ample time for preventive measures.¹⁰ In most epithelial tissues, including the prostate, genetic progression and loss of cellular control functions occur as the cell and tissue phenotype changes from normal to dysplasia (prostatic intraepithelial neoplasia [PIN]), to increasingly severe dysplasia high-grade PIN (HGPIN), then to superficial cancers, and finally to invasive disease. These changes occur over a long time period.¹⁰ Specifically in the prostate, PIN develops over approximately 20 years. Progression from PIN to HGPIN and early latent cancer may take 10 or more years, and clinically significant carcinoma may not occur for another three to 15 years.¹¹ These features of prostate cancer — high prevalence, long latency, significant mortality and morbidity — provide the most opportunistic and promising approach for chemoprevention.

The development of chemopreventive agents is the major objective of the Chemoprevention Branch of the Division of Cancer Prevention at the National Cancer Institute. Chemoprevention is the administration of natural and synthetic agents to prevent induction and to inhibit the development of preinvasive and invasive neoplasia and its progression. Some of the chemopreventive agents that demonstrate potential for prostate cancer are drugs, biologics, and micronutrients. For the prostate, as for all other cancer targets, successful chemopreventive strategies require well-characterized agents, suitable cohorts, and reliable intermediate biomarkers of cancer for evaluating chemopreventive efficacy. Agent requirements include experimental or epidemiological data that show chemopreventive efficacy, safety on chronic administration, and a mechanistic rationale for the observed chemopreventive activity.¹²

In recent years, attention has focused on the role of nutrients as chemopreventive agents. The concept of using micronutrients for the chemoprevention of cancer is based on the evidence from human epidemiology, the results of a few clinical trials, and studies of animal carcinogenesis models for cancer-inhibiting potential of these substances.¹³ Basic research has identified nutrients as agents that inhibit mutagenesis and hyperproliferation, as well as those that induce apoptosis or differentiation as critical characteristics for chemopre-

vention regardless of their specific molecular targets.¹⁰ Some of the most promising nutrients identified as chemopreventive agents in prostate cancer include phytoestrogens/isoflavones, vitamins D and E, selenium, and lycopene.

The objective of this paper is to examine (1) the experimental and epidemiological data demonstrating chemopreventive efficacy, (2) the mechanistic rationale for observed chemopreventive activity, and (3) the safety/toxicity of chronic administration of these specific nutrients identified in the chemoprevention of prostate cancer. We also provide a discussion of future prospects in nutrients and cancer chemoprevention and the obstacles to overcome prior to use of these agents in clinical practice.

Soy Isoflavones

The interest in soy isoflavones and their effect on prostate cancer originated with the epidemiological studies supporting the theory that soy products and their constituents, primarily isoflavones, are partly responsible for the lowered rates of incidence and mortality of prostate cancer. Four to five times more men die of prostate cancer in the United States than in Japan.¹ It appears that the onset of prostate cancer occurs later in life and/or prostate cancers grow more slowly in Japanese populations compared with Western populations. As in the case of breast cancer, lower incidence and mortality from prostate cancer may be attributed to the consumption of soy and soy products. There is increasing evidence that, in addition to possessing antiproliferative properties, soy isoflavones may alter the plasma concentration, production, metabolism, and excretion of testosterone and estrogens and their impact on target tissues. It has been demonstrated that components of plants and fiber-rich foods containing lignans and isoflavonoids, with molecular structures similar to those of steroids, could be critical modulators of the human hormonal system and hormonal action on target tissues.^{2,6}

Several natural anticarcinogens (eg, protease inhibitors, phytate, phytosterols, saponins, lignans, and isoflavones) have now been identified in soybeans.^{14,15} After structural modifications by intestinal bacteria, isoflavones are converted to compounds that possess weak estrogenic and antiestrogenic properties.^{3,16} Phytoestrogens found in soy products increase serum sex hormone binding globulin (SHBG) via increased hepatic synthesis, which then decreases the bioavailability of testosterone.¹⁶ In addition, although phytoestrogens have been shown to have an antiestrogenic effect in a high estrogenic environment, it has been postulated

that they exert a proestrogenic effect in a low estrogenic environment.⁶

Isoflavones have been shown to influence not only hormonal metabolism, but also intracellular enzymes, protein synthesis, growth factor action, cell proliferation, and angiogenesis.^{14,15,17} Genistein, an isoflavone, has received much attention due to its interesting antiproliferative, estrogenic, and antiestrogenic effects¹⁸⁻²¹ and most recently for induction of p53-independent apoptosis in lung cancer. Genistein also showed the highest concentration of all phytoestrogens present in the urine of Japanese men and women consuming their typical diet, which is rich in soy products.²² In a recent review of research regarding the effect of genistein on in vitro and in vivo models of cancer, it was found that in 74% of the studies using animal models, the proliferation of mammary and prostatic tumors was significantly reduced with genistein.²³⁻²⁵ In vitro, genistein also had an inhibitory effect on human tumor cell lines.²³ The mechanism may be due to apoptotic cell death as well as inhibition of cell proliferation, indicating its potential use as a chemopreventive agent. In another study of plant estrogens on estrogen-sensitive cancer cells, genistein was found to compete with estradiol binding to estrogen receptors. It has also been postulated that plant lignans and isoflavonoid phytoestrogens may decrease aromatase activity, a cytochrome P450 enzyme, thus decreasing conversion of androgens to estrone and estradiol, which may then play a protective role in the development of hormone related cancers, including prostate cancer.²⁶ Collectively, these isoflavones, specifically genistein, have provided enough evidence to warrant use in a number of clinical trials to examine their efficacy as potential chemopreventive agents for prostate cancer.

Lycopene

Lycopene is a carotenoid found primarily in tomatoes and tomato products. It is the prevalent carotenoid in the Western diet and the most abundant carotenoid in human serum.²⁷ Lycopene ranks highest among major natural carotenoids in its capacity for quenching singlet oxygen and scavenging free radicals.²⁸ In addition to its antioxidant activity, biological activities include induction of cell-cell communications and growth control. However, lycopene does not have provitamin A activity like other carotenoids. In vitro and in vivo studies on the growth of tumor cells suggest protective effects of lycopene on specific cancers, including prostate cancer.^{29,30}

In epidemiological studies, dietary consumption of lycopene has been associated with lower risk of

prostate cancer. In a review of 72 epidemiological studies that investigated a link between cancer risk and consumption of tomato products, 57 linked tomato intake with a reduced risk; in 35 of those studies, the association was considered statistically significant.³¹ A major prospective study by Gann et al³² examined the relationship between the plasma concentration of several antioxidants and the risk for prostate cancer, using plasma samples obtained in the Physician's Health Study. They reported that lycopene was the only antioxidant found at significantly lower mean levels in prostate cancer cases than in matched controls. Another study by Rao et al³³ investigated the levels of serum and prostate tissue lycopene and other major carotenoids in cancer patients and controls. They found that while the serum and tissue beta-carotene and other major carotenoids did not differ between the two groups, serum and tissue lycopene levels were significantly lower in the cancer patients than in their controls. These findings support other study results that identify lycopene as the carotenoid with the clearest inverse relation to the development of prostate cancer. In a more recent study,³⁴ 33 men were randomly assigned to take lycopene or no supplement for 30 days before their prostatectomies; postoperatively, researchers found that in the lycopene-supplemented group, prostate-specific antigen (PSA) levels fell 20% and cancer had spread in only 33% of the subjects. However, in 75% of the control group, cancer had spread and their PSAs remained unchanged.³⁴ Although the sample size in this study is small, these results warrant further examination of the role of lycopene in the progression of prostate cancer.

Although research results appear promising, findings are preliminary. Most have been based on epidemiological studies that focus on the association of prostate cancer risk and consumption of lycopene-rich foods. Optimal therapeutic dosage and the effects of chronic use and potential toxicity of lycopene supplementation on intermediate biomarkers of prostate cancer are currently unknown. Like genistein, there is enough evidence to warrant use of lycopene in a number of clinical trials to examine its efficacy as a potential chemopreventive agent for prostate cancer.

Vitamin E

Vitamin E is a fat-soluble vitamin. The term *vitamin E* applies to a family of eight related compounds, the tocopherols and the tocotrienols in four forms (alpha, beta, delta, and gamma) based on the number and position of methyl groups on the chromanol ring.³⁵ Although several forms of vitamin E exist, the most common form is α -tocopherol, which is the most biological-

ly active form of the vitamin and the most common source of this vitamin in food.³⁵ The major physiological function of vitamin E is its role as a scavenger of free radicals that has the potential to decrease DNA damage and inhibit malignant transformation through its antioxidant function. Because vitamin E is a fat-soluble vitamin, it can directly protect cell membranes. In addition, vitamin E affects the immune system, specifically the function of T lymphocytes. Decreased vitamin E intake has been associated with decreased immune function, while high levels have a stimulatory effect on immune function.³⁵

In the past decade, case-control studies³⁶⁻³⁹ that examined prediagnostic levels of α -tocopherol or vitamin E intake and prostate cancer risk produced conflicting results. Two of the studies^{37,39} demonstrated decreased risk of prostate cancer, and the other two^{36,38} showed no statistical reduction in prostate cancer risk. Although one previous case-control study failed to show alteration in risk of prostate cancer with intake of vitamin E, three recent major well-designed, prospective studies^{38,40,41} reported the role of supplementation of α -tocopherol in prostate cancer progression. One of these studies⁴¹ compared the incidence of prostate cancer in smokers in an α -tocopherol group and a control group. In the α -tocopherol group, the incidence of prostate cancer was 32% lower (95% confidence interval [CI] = 47% to -12%) than the control group, and the mortality was 41% lower (95% CI = -65% to -1%) compared with the placebo group. In this study, a reduction in clinically overt cancers appeared soon after the onset of supplementation, suggesting that α -tocopherol influences the progression phase of cancer from latent to clinical. However, no effect was observed in advanced prostate cancer; the time from clinical diagnosis to death remained the same as that of nonrecipients of the supplements. Similarly, a suggestive inverse correlation between supplementation with vitamin E and risk of metastatic prostate cancer among current smokers and recent quitters was observed by Chan et al.³⁸

Based on the above studies, it can be theorized that the effect of vitamin E was limited to the prevention of clinically evident cancers of stages II to IV, thereby suggesting inhibition of the progression of latent tumors to more invasive disease.^{38,41} The antioxidant property of vitamin E prevents the propagation of free radical damage in biologic membranes and to critical cellular structures like DNAs and proteins. Vitamin E may also protect by enhancing immune function. In addition, vitamin E has been reported to lower the activity of protein kinase C, a cellular signal transducer that regulates cell proliferation.⁴²

A more recent study⁴² reported data suggesting that supplemental vitamin E is beneficial in inhibiting

growth of human prostate cancer cells induced by a high-fat diet in a mouse xenograft model. The study suggests that oxidative stress is important in the genesis of clinical prostate cancer and raises the possibility of the role of antioxidants as preventive agents. Recent findings of Ripple and colleagues⁴³ demonstrated that physiological levels of androgens exerted their effect in part by increasing oxidative stress, raising the possibility that antioxidants can blunt the mitogenic effects of endogenous androgens and thus limit the growth of androgen-sensitive tissues such as the prostate. This mechanism, although interesting and plausible, remains hypothetical.

The allowance of vitamin E for adult men recommended by the United States Department of Agriculture is 10 mg α -tocopherol per day. A dose of 50 mg was used in a Finnish study.⁴⁴ It has been reported that intakes of more than 1,200 mg of tocopherol equivalents per day can interfere with metabolism of vitamin K, thus potentiating the anticoagulation effect of drugs such as warfarin.⁴⁵ In adults, 200 to 800 mg of α -tocopherol equivalents per day are well tolerated without adverse effects. However, large doses of over 800 to 1,200 mg per day may decrease platelet adhesion to some extent and thus may lead to postsurgery bleeding.⁴⁵ Due to the effect of α -tocopherol on platelet function, an increased risk of hemorrhagic stroke was observed in one large trial of adults⁴⁶ but no such increased risk or other bleeding problems was observed in others similar trials.⁴⁷

Selenium

The potential anticarcinogenic property of selenium, an essential trace mineral, may relate to its antioxidant properties, which is a function of its role in maintaining the enzyme glutathione peroxidase. Selenium is an essential part of the enzyme glutathione peroxidase that neutralizes or catabolizes peroxides to prevent the formation of free radicals that cause oxidative damage. When present in high doses, selenium has also been shown to suppress cell proliferation and enhance immune response, thus functioning similarly to vitamin E. An additional function of selenium is to spare vitamin E.

Although previous studies did not show any promise with selenium supplementation to reduce cancer risk,^{44,48} the most provocative results to date come from a prospective clinical trial by Clark et al.⁴⁰ They reported that prostate cancer incidence was reduced by 60% among those supplemented with selenium compared with a placebo group. The relationship between prostate cancer and selenium is further sup-

ported in a recent study by Yoshizawa et al.⁴⁹ They suggest a 50% to 66% reduction in risk for advanced cancer in men with the highest selenium status as determined by the level of selenium in toenails. Other potential antitumorigenic mechanisms of selenium are an apoptosis inducer, amino acid metabolism inhibitor, catalase enhancer, cytochrome P450 modifier, glutathione-s-transferase/glutathione enhancer, immunostimulant, and UDP-glucuronyl-transferase enhancer.¹⁰ The recommended dietary allowance for selenium is 55 to 70 µg/day. A selenium dose of 200 µg/day for a mean period of 4.5 years was safely used in the clinical trial reported by Clark et al.⁴⁰ This dose provided approximately twice the projected intake level of typical Americans and was two or three times above the recommended daily allowances. There was no dermatological signs of selenosis, and plasma selenium concentration remained below 1,000 ng/mL in whole blood as established by the Environmental Protection Agency.⁴⁰

Vitamin D

The primary role of vitamin D is in bone and mineral metabolism. However, more recent studies have shown that vitamin D metabolites induce differentiation and/or inhibit cell proliferation of a number of cell types, specifically prostate cancer cells. The active metabolite of vitamin D inhibits the growth of both primary cultures and other cancer cell lines. Initial studies suggest the mechanism may include alteration of cell cycle progression and initiation of apoptosis.⁵⁰⁻⁵² The presence of vitamin D receptors in prostate cancers and the low level of vitamin D in the sera of prostate cancer patients⁵³ suggest that vitamin D may have potential as a chemopreventive agent. Other research has demonstrated that high intake of dairy products and meats are related to higher risk of prostate cancer incidence in most ecologic, case-control, and prospective studies. Recent laboratory and epidemiological studies indicate that a high circulating level of 1,25(OH)₂D vitamin D, the biologically active form of vitamin D, inhibits prostate carcinogenesis. It is speculated that the mechanism may be higher levels of calcium and phosphorous, largely from dairy products, that lower circulating vitamin D. Similarly, sulfur-containing amino acids from animal proteins lower blood pH, which in turn suppresses the production of 1,25(OH)₂D.

The current recommended dose for vitamin D is 10 µg/day. Using vitamin D at doses above physiological levels may cause hypercalcemia.⁵⁰ Analogs of this vitamin have been developed that are more potent and less calcemic. The optimal therapeutic dosage, the effects of chronic use, and the potential toxicity of vitamin D supplementation are currently unknown.

Conclusions

It is increasingly evident that the development and use of chemopreventive agents in cancer prevention and treatment must have a multidisciplinary scientific base. Epidemiological studies not only explain variations in incidence and mortality in populations, but also link lifestyle factors to explain these general variations, thus identifying cohorts and leads to these agents. Pathology studies describe the phenotypic changes at the cellular and tissue levels that mark the progression of cancer and define precancerous target lesions for chemoprevention intervention. Studies in molecular and cellular biology, genetics, and experimental carcinogenesis explain the potential mechanisms of chemoprevention. Supporting these research efforts are the disciplines of pharmacology, toxicology, medicine, and chemistry, which are required to develop and evaluate strategies that address the four goals of chemoprevention: inhibition of carcinogens, logical intervention for persons at genetic risk, treatment of precancerous lesions, and confirmation and translation of leads from dietary epidemiology into intervention strategies. Epidemiological studies and experimental efficacy studies in animal tumor models have identified several nutrients that have potential as chemopreventive agents.

The nature of cancer prevention requires the use of chemopreventive agents with little or no toxicity. It is critical to evaluate the chronic administration of these agents and to establish dosage regimens for chemoprevention. Vitamins D and E and other antioxidants are essential micronutrients in many species, including humans. These nutrients and others have been reported to function as antioxidants and to inhibit carcinogenesis. In clinical settings, the deficiency symptoms of these micronutrients can be confused with the deficiency symptoms of others. Similarly, nutrients such as vitamins A and C function as antioxidants and may act individually or synergistically to inhibit carcinogenesis while compensating for the deficiency of the other. In addition, some of these nutrients spare others for different critical metabolic functions. The efficacy of this "cocktail" of agents cannot be ignored. Therefore, designing clinical studies to evaluate these agents individually and in combination is warranted.

Whether the prevention of DNA oxidative damage is as relevant to tumor progression as is the inhibition of cell proliferation or the promotion of apoptosis is unknown. Therefore, it is critical to identify the cellular and molecular mechanisms that are operational in prostate cancer and to determine how these pathways may be modified by agents. It is also critical to evaluate intermediate biomarkers as surrogates for cancer in the

context of carcinogenesis at the target site to ensure that the biomarker is a precursor to cancer and not just indirectly associated.¹⁰ Thus, it is imperative that research demonstrate that the chemopreventive agents can modulate the biomarkers chosen as surrogate endpoints. On this basis, PIN is regarded as a surrogate endpoint in prostate cancer because it has a short latency compared with prostate cancer. Phase II and III trials are needed to evaluate chemoprevention efficacy in suitable cohorts, as defined by risk factors, and particularly to establish intermediate endpoints as surrogate cancer endpoints.¹⁰

Prior to recommending supplemental doses for cancer prevention or treatment above the doses required to prevent deficiency, practitioners must await the results of empirical research that demonstrate the safety and efficacy of the agents in chemoprevention.

References

1. *Cancer Facts & Figures, 1999*. Atlanta, Ga: American Cancer Society; 1999.
2. Adlercreutz H. Western diet and Western diseases: some hormonal and biochemical mechanisms and associations. *Scand J Clin Lab Invest*. 1990;201:3-23.
3. Setchell KD, Borriello SP, Hulme P, et al. Nonsteroidal estrogens of dietary origin: possible roles in hormone dependent disease. *Am J Clin Nutr*. 1984;40:569-578.
4. Adlercreutz H, Mousavi Y, Clark J, et al. Dietary phytoestrogens and cancer: in vitro and in vivo studies. *J Steroid Biochem Mol Biol*. 1992;41:331-337.
5. Adlercreutz H, Gorbach S, Goldin B, et al. Diet and urinary estrogen profile in various populations: a preliminary report. Presented at the 14th International Meeting on Polycyclic Aromatic Hydrocarbons; 1993.
6. Adlercreutz H, Mazur W. Phyto-estrogens and Western diseases. *Ann Med*. 197;29:95-120.
7. Carlstrom K, Stege R. Testicular and adrenocortical function in men with prostatic cancer and in healthy age-matched controls. *Br J Urol*. 1997;79:427-431.
8. Gann PH, Hennekens CH, Ma J, et al. Prospective study of sex hormone levels and risk of prostate cancer. *J Natl Cancer Inst*. 1996;88:1118-1126.
9. Nomura AM, Kolonel LN. Prostate cancer: a current perspective. *Epidemiol Rev*. 1991;13:200-227.
10. Kelloff GJ, Lieberman R, Steele VE, et al. Chemoprevention of prostate cancer: concepts and strategies. *Eur Urol*. 1999;35:342-350.
11. Bostwick D. Prostatic intraepithelial neoplasia: current concepts. *J Cell Biochem*. 1992;16(suppl H):10-19.
12. Kelloff GJ, Hawk ET, Karp JE, et al. Progress in clinical chemoprevention. *Semin Oncol*. 1997;24:241-252.
13. Reddy BS. Micronutrients as chemopreventive agents. *IARC Sci Publ*. 1996;139:221-235.
14. Messina M, Barnes S. The role of soy products in reducing risk of cancer. *J Natl Cancer Inst*. 1991;83:541-546.
15. Adlercruetz H, Fotsis T, Schweigerer L, et al. Isoflavonoids and 2-methoxyestradiol: inhibitors of tumor cell growth and angiogenesis. *Proc Annu Meet Am Assoc Cancer Res*. 1994;35:693-694.
16. Adlercreutz H, Höckerstedt K, Bannwart C, et al. Effect of dietary components, including lignans and phytoestrogens, on enterohepatic circulation and liver metabolism of estrogens and on sex hormone binding globulin (SHBG). *J Steroid Biochem*. 1987;27:1135-1144.
17. Fotsis T, Pepper M, Adlercruetz H, et al. Genistein, a dietary-derived inhibitor of in-vitro angiogenesis. *Proc Natl Acad Sci U S A*. 1993;90:2690-2694.
18. Fotsis T, Pepper M, Adlercruetz H, et al. Genistein, a dietary ingested isoflavonoid, inhibits cell proliferation and in vitro angiogenesis. *J Nutr*. 1995;125(3 suppl):790S-797S.
19. Molteni A, Brizio-Molteni L, Persky V. In vitro hormonal effects of soybean isoflavones. *J Nutr*. 1995;125(3 suppl):751S-756S.
20. Wang TT, Sathyamoorthy N, Phang JM. Differential effects of genistein on p52 expression and proliferation in MCF-7 cells are concentration-dependent. *Proc Annu Meet AICR*. 1994;35:A503.
21. Pagliacci MC, Smacchia M, Migliorati G, et al. Growth-inhibitory effects of natural phyto-estrogen genistein in MCF-7 human breast cancer cells. *Eur J Cancer*. 1994;30A:1675-1682.
22. Adlercreutz H, Honjo H, Higashi A, et al. Urinary excretion of lignans and isoflavonoid phytoestrogens in Japanese men and women consuming a traditional Japanese diet. *Am J Clin Nutr*. 1991;54:1093-1100.
23. Barnes S. Effect of genistein on in vitro and in vivo models of cancer. *J Nutr*. 1995;125(3 suppl):777S-783S.
24. Hempstock J, Kavanagh JP, George NJR. Growth inhibitors of human prostatic cell lines by phytoestrogens. Proceedings from the 2nd International Symposium on the Role of Soy in Preventing and Treating Chronic Disease. Belgium; 1996.
25. Schleicher R, Zheng M, Zhang M, et al. Genistein inhibition in prostate cancer cell growth and metastasis in vivo. Proceedings from the 2nd International Symposium on the Role of Soy in Preventing and Treating Chronic Disease. Belgium; 1996.
26. Adlercreutz H, Bannwart C, Wähälä K, et al. Inhibition of human aromatase by mammalian lignans and isoflavonoid phytoestrogens. *J Steroid Biochem Mol Biol*. 1993;44:147-153.
27. Nguyen ML, Schwartz SJ. Lycopene: chemical and biological properties. *Food Technol*. 1999;53:38-45.
28. Gester H. The potential role of lycopene for human health. *J Am Col Nutr*. 1997;16:109-126.
29. Stahl W, Seis H. Lycopene: a biologically important carotenoid for humans? *Arch Biochem Biophys*. 1996;336:1-9.
30. Giovannucci E, Clinton SK. Tomatoes, lycopene and prostate cancer. *Proc Soc Exp Biol Med*. 1998;218:129-139.
31. Giovannucci E. Tomatoes, tomato-based products, lycopene, and cancer: review of the epidemiologic literature. *J Natl Cancer Inst*. 1999;91:317-331.
32. Gann PH, Ma J, Giovannucci E, et al. Lower prostate cancer risk in men with elevated plasma lycopene levels: results of a prospective analysis. *Cancer Res*. 1999;59:1225-1230.
33. Rao AV, Fleshner N, Agarwal S. Serum and tissue lycopene and biomarkers of oxidation in prostate cancer patients: a case-control study. *Nutr Cancer*. 1999;33:159-164.
34. Kucuk O, Sakr W, Sarkar FH, et al. Lycopene supplementation in men with localized prostate cancer (PCa) modulates grade and volume of prostatic intraepithelial neoplasia (PIN) and tumor, level of serum PSA and biomarkers of cell growth, differentiation and apoptosis. *Proc Annu Meet Am Assoc Cancer Res*. 1999;40:409. Abstract.
35. Meydani M. Vitamin E. *Lancet*. 1995;345:170-175.
36. Hsing AW, Comstock GW, Abbey H, et al. Serologic precursors of cancer: retinol, carotenoids, and tocopherol and risk of prostate cancer. *J Natl Cancer Inst*. 1990;82:941-946.
37. Hayes RB, Bogdanovic JF, Schroeder FH, et al. Serum retinol and prostate cancer. *Cancer*. 1988; 62:2021-2026.
38. Chan JM, Stampfer MJ, Ma J, et al. Supplemental vitamin E intake and prostate cancer risk in a large cohort of men in the United States. *Cancer Epidemiol Biomarkers Prev*. 1999;8:893-899.
39. Kristal AR, Stanford JL, Cohen JH, et al. Vitamin and mineral supplement use is associated with reduced risk of prostate cancer. *Cancer Epidemiol Biomarkers Prev*. 1999;8:887-892.
40. Clark LC, Combs GF Jr, Turnbull BW, et al. Effects of selenium supplementation for cancer prevention in patients with carcinoma of the skin: a randomized controlled trial. Nutritional Prevention of Cancer Study Group. *JAMA*. 1996;276:1957-1963.
41. Heinonen OP, Albanes D, Virtamo J, et al. Prostate cancer and supplementation with alpha-tocopherol and beta-carotene: incidence and mortality in a controlled trial. *J Natl Cancer Inst*. 1998;90:440-446.
42. Fleshner N, Fair WR, Huryk R, et al. Vitamin E inhibits the high-fat diet promoted growth of established human prostate LNCaP tumors in nude mice. *J Urol*. 1999;161:1651-1654.
43. Ripple MO, Henry WF, Rago RP, et al. Prooxidant-antioxidant shift induced by androgen treatment of human prostate carcinoma

cells. *J Natl Cancer Inst.* 1997;89:40-48.

44. Knekt P, Aromaa A, Maatela J, et al. Serum selenium and subsequent risk of cancer among Finnish men and women. *J Natl Cancer Inst.* 1990;82:864-868.

45. Corrigan JJ Jr. Coagulation problems relating to vitamin E. *Am J Pediatr Hematol Oncol.* 1979;1:169-173.

46. The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. The Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group. *N Engl J Med.* 1994;330:1029-1035.

47. Bendich A, Machlin LJ. Safety of oral intake of vitamin E. *Am J Clin Nutr.* 1988;48:612-619.

48. Coates RJ, Weiss NS, Daling JR, et al. Serum levels of selenium and retinol and the subsequent risk of cancer. *Am J Epidemiol.* 1988;128:515-523.

49. Yoshizawa K, Willett WC, Morris SJ, et al. Study of prediagnostic selenium level in toenails and the risk of advanced prostate cancer. *J Natl Cancer Inst.* 1998;90:1219-1224.

50. Blutt SE, Weigel NL. Vitamin D and prostate cancer. *Proc Soc Exp Biol Med.* 1999;221:89-98.

51. Konety BR, Johnson CS, Trump DL, et al. Vitamin D in the prevention and treatment of prostate cancer. *Semin Urol Oncol.* 1999;17:77-84.

52. Giovannucci E. Dietary influences of 1,25(OH)₂ vitamin D in relation to prostate cancer: a hypothesis. *Cancer Causes Control.* 1998;9:567-582.

53. Corder EH, Guess HA, Hulka BS, et al. Vitamin D and prostate cancer: a prediagnostic study with stored sera. *Cancer Epidemiol Biomarkers Prev.* 1993;2:467-472.