The Role of Nutrition in Preventing and Treating Breast and Prostate Cancer

PC-SPES and Prostate Cancer¹,²

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The American Cancer Society estimates that >184,000 American men will be diagnosed with prostate cancer in the year 2000 and ~32,000 deaths will be attributed to the disease (Greenlee et al. 2000). Prostate cancer is the most common malignancy of men in the United States and the second leading cause of cancer deaths (Greenlee et al. 2000). Because there is no cure for metastatic prostate cancer, research directed toward the development of new treatments for metastatic disease is imperative. The chemopreventive and therapeutic potential of phytochemicals is now the subject of intense research, and the molecular mechanisms of their actions are being reported (Adlercreutz 1995, Jang et al. 1997, Knight and Eden 1996, Kohlmeier et al. 1995). For example, genistein has been shown to be a protein tyrosine kinase inhibitor as well as an inhibitor of DNA topoisomerase II and angiogenesis (Fotsis et al. 1995, Peterson 1995, Planchon et al. 1995, Spinazzi et al. 1994, Traganos et al. 1992). Coumestrol is thought to be an inhibitor of 17β-hydroxysteroid dehydrogenase type 1, the enzyme that converts estrone to 17β-estradiol (Makela et al. 1995). We have shown that the chemopreventive compound indole-3-carbinol, a phytoestrogen, acts by interfering with the signal transduction pathway of the estrogen receptor in breast cancer cells (Tiwari et al. 1994). The phytoestrogens d,l-aminogluthetimide and apigenin can inhibit the enzyme aromatase, which converts testosterone to estradiol and androstenedione to estrone (Pelissero et al. 1996). Thus, several phytochemicals appear to disrupt specific biochemical functions crucial to sex hormone metabolism and cell cycle control. Intense interest has focused on these properties of phytochemicals as an alternative therapeutic approach for hormone-refractory prostate cancer.

PC-SPES is a refined herbal powder sold as an over-the-counter food supplement (Botanic Labs, Brea, CA). It is made from Glycyrrhiza glabra, Carum carvi, Carthamus tinctorius, Glycyrrhiza glabra, L., Isatis indigotica Fort, Panax pseudo-ginseng Wall, Rabdosia rubescens, Scutellaria baicalensis Georgi, and Serenoa repens. Clinical reports have indicated that dietary supplementation with PC-SPES by prostate cancer patients results in a dramatic decrease in their prostate-specific antigen (PSA) levels (de la Talle et al. 2000, DiPaola et al. 1998, Moyad et al. 1999). At least part of the dramatic effect of PC-SPES on PSA levels in patients may be attributable to the estrogenic activity of the mixture. Gynecomastia and loss of libido have been reported to be side effects of high dose PC-SPES consumption, but these side effects appear not to occur at lower doses of the herbal mixture (de la Talle et al. 2000, DiPaola et al. 1998, Moyad et al. 1999). The estrogenic activity of PC-SPES has also been demonstrated experimentally with yeast transcription activation assays and uterine weight assays in mice (DiPaola et al. 1998).

Cell culture studies by several groups have indicated that PC-SPES induces profound biochemical changes in prostate cancer cells. Hallicka et al. (1997) found that an ethanol extract of PC-SPES decreases the clonogenicity of the human prostate cancer cell lines PC-3 and LNCaP, and alters the cell cycle distribution of PC-3 cells. They found that PC-SPES also affected several other cancer cell lines, including the breast cancer cell line MCF-7, the melanoma cell line Colo 38 and the histocytic line U937. Hsieh et al. (1997) demonstrated that an ethanol extract of PC-SPES down-regulated proliferating cell nuclear antigen, and androgen receptor expression and PSA secretion in LNCaP cells. Kubota et al. (2000) found that an ethanol extract of PC-SPES inhibited clonal growth of the prostate cancer lines LnCaP, PC-3 and DU145, and altered the cell cycle distribution in these cells. Similarly, de la Talle et al. (2000) found that an ethanol extract of PC-SPES was effective in inhibiting the growth of LNCaP, PC-3 and DU145 cells.

We used a well-established rat model of prostate cancer—the highly aggressive, hormone-refractory rat prostate cancer cell line, MAT-LyLu. This prostate cancer cell line is one of several variant cell lines isolated from a heterogeneous prostate cancer lesion in a Copenhagen rat. When injected into Copenhagen rats, it forms a rapidly growing tumor and quickly metastasizes to lymph nodes and lung. MAT-LyLu cells grow rapidly, are negative for androgen and estrogen receptors and grow equally well in normal and castrated Copenhagen rats. Thus, the MAT-LyLu/Copenhagen rat is a model for hormone-independent, metastatic prostate cancer.

We have demonstrated that incorporating PC-SPES into the Copenhagen rat diet significantly protects rats from trans-
As a first step in the identification of the active components of PC-SPES, water extracts and ethanol extracts were prepared. The ethanol extract was prepared as follows: 1 g PC-SPES powder was suspended in 3 mL of 100% ethanol and shaken on an orbital shaker at full speed for 1 h at room temperature. The suspension was centrifuged at 1500 x g for 10 min; the supernatant was recovered and centrifuged at 12,000 x g for 3 min and then filtered through a 0.2-μm cellulose acetate membrane. This stock solution was designated 100% PC-SPES. The ethanol extract was stored at −20°C until used. The water extract was prepared in the same way except that 1 g of PC-SPES powder was suspended in 6 mL deionized water and the stock solution was designated 50% PC-SPES.

To assess whether ethanol extracts or water extracts of PC-SPES contain antiprostate cancer cell activity in vitro, 5 x 10^4 Mat-LyLu cells were grown for 3 d in 100-mm tissue culture plates in RPMI medium containing 0.2% ethanol or water extracts of PC-SPES. Controls consisted of medium alone or medium with vehicle (0.2% ethanol). Triplicate cultures were harvested by trypsinization and viable cells (trypan blue exclusion) were counted. Ethanol extracts (P < 0.002) and water extracts (P < 0.0009) both significantly inhibited Mat-LyLu cell growth, with water extracts of PC-SPES being slightly more inhibitory (Fig. 2).

The exact mechanism of PC-SPES action is unknown. PC-SPES was suggested to induce apoptosis in CaP cells (Halicka et al. 1997, Kubota et al. 2000). It has also been suggested that PC-SPES mediates its effect by potentiating the immune response (Hsieh et al. 1998). The finding that PC-SPES is effective in tissue culture systems and in immunodeficient mice suggests that immunopotentiation is not the only mode of action of PC-SPES (de la Talle et al. 2000, Halicka et al. 1997, Hsieh et al. 1997, Kubota et al. 2000). Several components of PC-SPES have been demonstrated to exert significant biological effects. _Ganoderma lucidum_ Karst exerts strong immunostimulatory effects in rodents and in vitro (Murasugi et al. 1991). An immunomodulatory protein, LZ-8, has been identified as a T-cell stimulator and its genomic sequence has been cloned (Murasugi et al. 1991). Baicalein, a flavonoid derived from Scutellaria baicalensis, has been shown to have antiproliferative and lipoxygenase-inhibitory activity (Huang et al. 1994). Other flavonoids from _S. baicalensis_ have been shown to inhibit mouse skin tumor promotion in two-stage carcinogenesis testing (Konoshima et al. 1992). _Serenoa repens_ is a potent phytoestrogen, and an n-hexane lipid/sterol extract of _S. repens_ has been shown to be an inhibitor of both type 1 and type 2 5α-reductase, the enzyme that converts testosterone to dihydrotestosterone, the active androgen in the prostate (Iehle et al. 1995). Rg1, a saponin derived from _Panax ginseng_, has been shown to stimulate lymphocytes (Liu et al. 1995). Similarly, a hot water extract of _P. ginseng_ is mitogenic toward T cells, both in vivo and in vitro, and the in vitro activity is comparable to that of Concanavalin A (Mizuno et al. 1994). Of particular relevance to the development of metastases, ginsenoside-Rb2 inhibits angiogenesis in B16 melanoma cells in vivo (Sato et al. 1994). Extracts of _Glycyrrhiza glabra_ have shown antimutagenic activity in the Salmonella/microsome reversion assay (Shankel and Clarke 1990, Zani et al. 1993). The progression of prostate cancer from a localized, quiescent disease to a clinically relevant and eventually metastatic cancer has been proposed to involve a series of mutagenic events (Rinker-Schaeffer et al. 1994). The antimutagenic activity of _G. glabra_ may be a significant factor in slowing or stopping the cascade of prostate cancer progression.

Thus, together, the components of PC-SPES are theoretically capable of acting on multiple targets to induce cytostatic and cytotoxic effects on cancer cells. It is perhaps this synergistic interaction and combined effect that may be unique to PC-SPES and may be critical for the observed decrease in PSA levels in prostate cancer patients and its ability to inhibit prostate cancer cell growth, both in vivo and in vitro. In fact, the combined attack on several of the aberrantly expressed metabolic and homeostatic pathways of cancerous cells may be the only way to treat cancer effectively.

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