

Abstract:

An accumulating body of scientific evidence supports the notion that a holistic outlook on health and life and complementary and alternative medicine health practices can promote wellness and prevent and treat prostate disease. This overview explores some of the fundamental philosophical, diagnostic, and therapeutic differences between conventional and holistic medicine, and discusses how to integrate evidence-based complementary and alternative medicine, holistic medicine, and conventional medicine for the prevention and treatment of prostate disease.

Key words: Holistic, Alternative Medicine, Complementary Medicine, BPH, Prostatitis, Prostate Cancer

An Overview Of Holistic Medicine And Complementary And Alternative Medicine For The Prevention and Treatment Of BPH, Prostatitis, And Prostate Cancer

Introduction

There has been a recent burgeoning interest among U.S. urologists in complementary and alternative medicine (CAM). Although definitions vary, the term alternative medicine refers to a broad set of health care practices that are not readily integrated into the dominant health care model because they pose challenges to diverse societal beliefs and cultural, economic, scientific, medical, and educational practices [43]. Strictly speaking, the term alternative medicine implies these health care practices are used as an alternative to conventional medicine, whereas the term CAM implies they are used to complement one another [128]. Despite the distinction in terminology, American urologists by and large regard CAM as alternative medicine. In contrast, CAM therapies are a part of everyday practice for European urologists, perhaps because they receive formal instruction in complementary and alternative medicine as part of their medical training, and European governments endorse and pay for approved CAM therapies [133][84].

Although articles about complementary and alternative medicine are now commonplace in the urologic literature, there has been little discussion about holistic medicine. The word *holistic* is derived from the Greek word 'holos', which means whole. Holistic practitioners view

health and illness as a dynamic web-like interaction between body, mind, spirit, and environment. Conventional (allopathic) physicians, on the other hand, usually equate holistic medicine with the practice of substituting herbs and other natural therapies for drugs and surgery.

This overview will explore some of the fundamental philosophical, diagnostic, and therapeutic differences between conventional and holistic medicine, and discuss how to integrate complementary and alternative medicine, holistic medicine, and conventional medicine for the prevention and treatment of prostate disease.

Differences Between Holistic Medicine and Conventional Medicine

As a rule, conventional medicine attempts to reduce disease to a malfunction of the body caused by a specific abnormality at the biochemical, cellular, tissue, or organ level, often without regard to environmental, psychosocial, and spiritual influences [33].

Conventional reductionist scientific thinking assumes unresolved differences can ultimately be explained and corrected. In contrast, holistic medicine views *dis-ease* as a unique imbalance in the body, mind, spirit, and environmental continuum; is comfortable with unresolved differences; and values uncertainty as an opportunity for personal exploration and growth.

Although practitioners of both holistic and conventional medicine weigh a patient's history, physical exam, and diagnostic tests against their own experience and awareness of known diseases to arrive at a working diagnosis, there are important differences between the two approaches. In the conventional medicine model, diagnosis is the art of distinguishing one disease from another, or discovering the nature of a disease, and health is generally regarded as the absence of disease. History taking is goal directed and greater weight is given to objective or 'hard data', and treatment algorithms are the result of hypothesis testing and linear reasoning based on logic and causation [128].

In contrast, holistic practitioners assign greater weight to careful listening and 'soft data' such as intuition and pattern recognition, and clinical outcome is more important than the mechanism of action. Furthermore, the conceptual organization of organ systems and disease causation often bears little resemblance to the Western model. For instance, in Traditional Chinese Medicine (TCM), the body, mind, and spirit are viewed as integral parts of a whole that is connected by the free flow of vital life force called *Qi* (chi). The flow and quality of *Qi* is related to health and disease. Although organs are translated with recognized Western names, they are grouped energetically, not by physiological function. Disease arises when there is an internal or external imbalance in the harmony of the whole. For example, evidence of liver disharmony may present as anger or frustration [105].

Holistic and conventional medicine also differs in their therapeutic approach to disease. Since the advent of powerful drugs and high technology, conventional medicine has primarily become a system of disease management geared to diagnose and treat disease, not promote health. In conventional medicine, the patient plays a passive role where the doctor dictates a treatment the patient is expected to follow.

Holistic medicine practitioners, on the other hand, strive to prevent disease by augmenting the natural healing power of nature (*Vis medicatrix naturae*) and teaching their patients how to access the skills and resources necessary for self-healing. Instead of merely suppressing symptoms, holistic practitioners strive to identify and treat the cause of disease (*Tolle causam*), and apply the minimum therapy necessary to restore balance. Patients are also expected to take an active role in an individualized treatment plan that is co-authored with their practitioners, and they're invited to explore the deeper meaning of illness; that is, what they experience on a physical, psychological, and spiritual level because of their disease [104].

Limitations of CAM and Conventional Medicine

Despite its purported benefits, American urologists have been reluctant to embrace holistic and complementary and alternative medicine. Lack of scientific proof is cited as one reason. The intangible benefits of holistic medicine are difficult to measure, and most CAM research studies are too short (usually less than six

months), too small (usually less than fifty patients), and rarely double-blinded or placebo-controlled.

Safety concerns are another issue. In contrast to pharmaceutical drugs, the mechanism of action of many herbal drugs and phytopharmaceuticals is unproved, which makes it difficult to accurately predict adverse herb-drug interactions. Furthermore, the quality of over-the-counter herbal products is open to question. According to independent surveys, they are often adulterated with contaminants, some of which are toxic, and contain concentrations different than the advertised amount [42].

Efficacy is another consideration. Not all CAM therapies are created equal – some work, others don't, and some can cause harm. Furthermore, treating symptoms without first knowing the cause risks a delay in diagnosis and treatment of potentially life threatening medical conditions.

On the other hand, conventional medicine has its own limitations. For instance, it isn't as scientific as most would like to believe. Urologists, for example, empirically treat BPH, prostatitis, and other urologic conditions on the basis of symptoms, not scientific fact, and off label use of pharmaceutical agents is commonplace. Similarly, the optimal treatment of prostate cancer has never been submitted to a prospective randomized controlled trial and probably never will be. Moreover, the gold standard of medical research - a randomized double-blind placebo-controlled trial – is designed to answer narrowly defined questions that may lack clinical relevance, and extrapolating

data from clinical trials to predict long-term outcomes in clinical practice is problematic [111]. Furthermore, the placebo response accounts for at least some of the positive benefits of conventional drug and surgical therapies [20]. Finally, in contrast to herbal-related side effects, which are widely publicized but rarely fatal[133], prescription-induced fatalities in hospitalized patients are the sixth leading cause of premature death in the U.S. [75].

Reasons Urologists Should Become Knowledgeable About CAM

According to surveys, nearly half of the American and European population, including a similar percentage of men with prostate cancer [81], use some form of complementary and alternative medicine to improve their general health and quality of life [128]. Nevertheless, patients usually withhold this information from their urologists unless they are directly asked about CAM usage [66]. Therefore, urologists need to inquire about CAM usage and develop a working knowledge of pertinent CAM therapies so they can properly advise their patients about the associated risks and benefits.

For instance, patients should be advised against taking vitamins, nutritional supplements, and herbal therapies that can interact with prescription medication or increase the risk for bleeding during surgery [115].

On the other hand, urologists should embrace evidence-based CAM therapies that can benefit their patients. For example, even though data are preliminary, a variety of herbal therapies compare favorably, but cost less and cause fewer side effects than prescription

medication used to treat men with prostatitis and mild to moderate LUTS [23][84][117] [86]. Furthermore, an accumulating body of scientific evidence indicates that CAM therapies can improve the quality of life and survival of men with prostate cancer by slowing prostate cancer growth, and reducing side effects and improving the efficacy of conventional cancer therapies [47][96][86] - issues that may be more important than curing cancer to some men [47].

Although theoretical, a shifting paradigm of cancer may explain how CAM therapies alter cancer biology. According to Schipper [118], cancer is a potentially reversible process that stems from a maladaptive process characterized by regulatory imbalance, not autonomy. Therefore, measures that improve regulatory balance, such as a healthy diet and lifestyle, may improve long-term outcome. Furthermore, a functional cure may not require a complete response, and a complete response may not be the best indicator of long-term survival. The results of a seminal study [80], which examined cancer incidence among a cohort of 44, 788 twins from Sweden, Denmark, and Finland, supports the hypothesis that environmental influences are a more important determinant of prostate cancer risk than genetic predisposition.

Finally, a healthy diet, lifestyle, and outlook on life can reduce the incidence of premature morbidity and mortality resulting from heart disease, diabetes, hypertension, obesity, all-cause cancer, and a variety of other chronic illnesses [94][131].

CAM Therapies for BPH, Prostatitis, and Prostate Cancer

For the sake of this overview, CAM therapies for prostate disease are divided into diet, lifestyle, vitamins and minerals, nutritional supplements, phytotherapy, mind-body medicine, and other healing traditions.

Diet

A calorie restricted diet that is low in saturated fat but high in antioxidant and fiber-containing fruits and vegetables can reduce the incidence and improve the clinical course of BPH, prostatitis, and prostate cancer. While the mechanisms vary, constituents of a healthy diet can reduce cellular inflammation, promote differentiation and apoptosis, and counteract free radical- induced DNA damage and cellular proliferation. [97][121][98][129][86][93].

Energy Intake and Fat

Although the incidence of latent BPH and prostate cancer is similar worldwide, the incidence of clinical prostate cancer, particularly advanced prostate cancer, is greatest in countries with the highest calorie and saturated fat consumption [44] [69][50]. Among other things, excessive calories and saturated fat, especially from dairy products and red meat, promote obesity and prostate cell growth by increasing the production of insulin growth factor type-I (IGF-I) and inflammatory arachidonic acid byproducts [97] [36][129].

Furthermore, meat is often contaminated with toxic bacteria, and hormone, pesticide, and antibiotic residues [127], and dairy products, which contain recombinant bovine growth hormone, stimulate increased IGF-1 production [41] .

Originating in the liver, IGF-1 causes prostate cell proliferation by promoting angiogenesis, preventing apoptosis, and increasing production of urokinase-type plasminogen activator [92] [102]. According to Chan *et al.* [26], men over the age of sixty with the highest levels of IGF-1 have an eight-fold greater risk of developing prostate cancer compared to men with the lowest levels.

Arachidonic acid metabolites prostaglandin E2 (PGE2) and series 4 leucotrienes (5-HETE and 12-HETE) stimulate prostate cell growth by increasing inflammation and inhibiting apoptosis, blocking natural killer (NK) and cytotoxic T cells function, and promoting angiogenesis and tumor cell invasiveness [54].

Although the relationship is complex and data are conflicting, animal data have shown that excess dietary ω -6 polyunsaturated acids generally stimulate tumor growth, whereas ω - 3 polyunsaturated fatty acids, especially from fish, and monounsaturated ω -9 fatty acids from olive oil have the opposite effect [121][69] [59].

The practice of substituting fat-free high carbohydrate food items for fatty foods isn't a viable solution because it simply trades one problem for another. Excessive sugar consumption promotes cell growth and increases cancer risk by contributing excess calories,

elevating insulin levels [24], and increasing arachidonic acid production [119].

Finally, regardless of the food source, excessive caloric intake promotes obesity, which increases premature mortality and overall cancer-related death rates [97].

Fruits and Vegetables

Dietary fiber and anti-oxidants found in fruits and vegetables, especially those contained in tomatoes and cruciferous vegetables, and phytoestrogens found in soy protein, prevent prostate disease by counteracting free radical damage, blocking the harmful effects of IGF-1 and excess sex hormones, lowering serum cholesterol, and preventing aromatase activity [35][44][46] [27] [73][38][51][30] [2] [19][65].

Even though the age-adjusted incidence of latent prostate cancer in native Japanese and American males is roughly the same, clinical prostate cancer is ten times higher in American males [106].

Researchers attribute this glaring discrepancy to dietary differences: Japanese males consume more soy protein and fish, but less saturated fat from dairy and red meat than American males [121]. In fact, Aldercreutz *et al.* [3] reported that Japanese males have isoflavone concentrations thirty times higher in the urine and over a hundred times higher in the blood than Western males. Soy protein

isoflavones, most notably genistein, inhibit prostate cancer cell growth by promoting apoptosis, blocking β - estrogen receptor activity in the prostate [58], inhibiting angiogenesis and endothelial cell proliferation, and blocking 5-alpha reductase, aromatase, and tyrosine-specific protein kinase activity[121][46].

Of the more than 600 carotenoids present in fruits and vegetables, lycopene has the highest concentration within the prostate, and tomatoes are one of the richest sources of lycopene [29]. Giovannucci *et al.*[52] reviewed the relationship between tomato intake and cancer and found 57 studies showed a protective benefit, 35 of which were significant. Data from the Physician's Health Study showed that eating tomatoes at least 4 times weekly lowered the risk of prostate cancer by 20%, and eating 10 weekly helpings lowered the risk by 45% [51].

Specific Diets

Studies have shown Mediterranean, vegetarian, and macrobiotic diets can reduce the incidence of prostate cancer [90] [34] [71]. A Mediterranean diet is low in meat, but high in whole grains, fruits, vegetables, and olive oil; a vegetarian diet is meat-free and rich in whole grains, fruits, and vegetables; and a macrobiotic diet, although primarily vegetarian, allows some meat and is tailored to individual needs. Although most physicians are unaware of its attributes, macrobiotics is the most popular unconventional nutritional therapy used in the U.S. [77].

Other Benefits Of A Healthy Diet

In addition to preventing prostate disease, a healthy diet can improve the efficacy and reduce the side effects of radiation and chemotherapy [77][32]. Drinking at least 6 eight-ounce glasses of water daily, and eating a diet that is rich in fruits, vegetables, and cereals can also reduce the risk of bladder cancer [25] [107].

Lifestyle

Based on results from the Health Professionals Follow-up Study, regular exercise significantly lowers the risk of BPH, regardless of age. Researchers discovered that men who watched the most television and video tapes per week (forty-one hours or more) had twice the risk of developing severe obstructive BPH symptoms when compared to men that watched less than five hours per week [112]. Furthermore, according to Finish investigators, men that smoke have a one and a half times greater risk of developing urinary symptoms than men who have never smoked [70].

Healthy lifestyle choices such as regular exercise, getting enough rest, and reducing stress can also improve prostatitis symptoms, whereas unhealthy choices have the opposite effect. Prolonged stress increases the incidence of urinary tract infections, depresses the immune system, and increases spasms of the bladder, urethral, and pelvic musculature [85] [11].

Although not specific for prostate cancer, stress can also increase the initiation, growth, and metastasis of tumors. While acute stress can enhance immune function, chronic stress has the opposite effect. Studies have shown that stressed animals had twice as many metastases as unstressed ones [12][47].

Although data are contradictory, smoking and drinking alcohol can increase the risk of prostate cancer, especially advanced prostate cancer [63] [96], whereas regular physical exercise can decrease prostate cancer risk by enabling the body to use insulin more effectively, and by reducing IGF-1 levels and obesity [97][47] [76].

Phytotherapy

Popularly known as *phytotherapy* ('phyto' means plant), plant-derived products are commonly used to prevent and treat BPH, prostatitis, and prostate cancer [64].

Buck *et al.* [23] report that phytotherapy improves BPH symptoms in up to seventy percent of patients, which may explain why fifty percent of German urologists prefer plant-based therapies to synthetic medications for men with symptomatic BPH [84].

Over thirty phytotherapeutic compounds are currently used to treat BPH. In general, these products are derived from eight plant species [21]. The active ingredient in at least fifteen of these compounds is derived from an extract made from dried berries of the American dwarf palm *Serenoa repens* [23]. Other popular preparations that have been subjected to peer-reviewed scientific research include *Prunus africana*, beta-sitosterol, rye pollen extract ,

South African star grass (*Hypoxis rooperi*), and stinging nettle (*Urtica dioica*).

Saw Palmetto (*Serenoa repens*)

Dubbed “the old man’s friend”, saw palmetto is a popular treatment for symptomatic BPH. Named after Sereno Watson, a nineteenth century Harvard botanist, saw palmetto is a small palm tree that grows along the coastal Southeastern United States and the West Indies. Standardized extracts derived from ripened saw palmetto berries contain eighty-five to ninety-five percent fatty acids and sterols.

Although the exact mechanism of action is still unclear, researchers theorize that saw palmetto improves BPH and prostatitis symptoms and inhibits prostate cancer cell growth by reducing sex hormone binding globulin levels, blocking alpha-adrenergic receptor activity and type-one and type-two 5 α -reductase enzymes, decreasing prostatic inflammation, and opposing estrogen and androgen stimulation [37][23] [49] [21].

Based on the results of a systematic review of 18 randomized controlled studies involving 2939 men, Wilt *et al.* [135] concluded that saw palmetto improves urinary tract symptoms and flow measures in men with BPH, and compares favorably with the effectiveness of finasteride, but costs less and causes fewer side effects.

Prunus africana

Commonly known as pygeum, *Prunus africana* (formally called *Pygeum africanum*) is a lipophilic extract derived from African Plum tree bark. The first recorded use of pygeum as a natural remedy dates back to the eighteenth century [49]. A popular European pygeum extract called Tadenan® contains 13% total sterols (calculated as beta-sitosterol) and 0.5% *n*-docosanol [56].

Most of the data regarding *Prunus africana*'s activity are derived from animal studies. Although the exact mechanism of action is unknown, pygeum affects the prostate by inhibiting androgen stimulation [99], blocking 5-alpha reductase[61] and aromatase activity [53], and suppressing prostatic growth factors [137], inflammation [36], and cholesterol accumulation[99].

Twelve double-blind, placebo-controlled studies showed pygeum was significantly more effective than placebo [4], and only one of ten placebo-controlled studies failed to show significant urodynamic improvement in men taking pygeum versus placebo [56].

Beta-sitosterol

Beta-sitosterol is a member of a larger family of plant steroids called phytosterols. Related to cholesterol, beta-sitosterol accounts for many of the beneficial effects of saw palmetto, pygeum, stinging nettle, and pumpkin seeds. Derived from the roots of the South African star grass (*Hypoxis rooperi*), Harzol® is one of the most popular BPH treatments in Germany [23]. Although not available in the U.S., Harzol® is

standardized to contain ten milligrams of beta-sitosterol per tablet.

Researchers theorize that *Hypoxis rooperi* has the same mechanism of action as saw palmetto and *Prunus africana* [49].

The majority of studies have shown that beta-sitosterol improves BPH-relating voiding symptoms. Two European double-blind placebo-controlled trials deserve mention. In a study involving a total of 177 men, Klippel *et al.* [68] compared 60 mg. of beta-sitosterol daily versus placebo, and in another study involving 200 men, Berges, *et al.* [13] compared 130 mg. daily versus placebo. Men in both the treatment and placebo groups had moderate BPH symptoms (mean IPSS 15). Although the dosage used in the two studies varied, they both demonstrated a significant improvement in IPSS, quality of life, peak and median urinary flow, and residual volume in the treatment versus placebo group, and the results compared favorably with alpha-blocker and finasteride medications.

Rye Pollen Extract

Derived from rye-grass pollen pollen, a popular Swedish product called Cernilton® contains a water-soluble (T60) and fat-soluble fraction (GBX) that is standardized for its alpha-amino acid and phytosterol content, and then reconstituted into capsules or tablets [23]. Cernilton® is used worldwide to treat men with BPH and non-bacterial prostatitis [22][117]. Cernilton® reportedly lowers urethral pressure, blocks alpha-adrenergic receptors and arachidonic acid metabolism, relaxes the external sphincter musculature, decreases

inflammation and swelling in the prostate, and inhibits 5 α -reductase activity [23][117]. A six month double-blind placebo-controlled trial involving a total of 57 men showed significant improvement in BPH symptoms in 69% in the treatment taking 4 tablets of Cernilton® daily versus 29% in the placebo group [22].

Nettle Root (*Urtica dioica*)

Used since ancient times, and often combined with other herbal preparations, nettle root extract is used to treat BPH, prostatitis, and prostate cancer [138]. Nettle root contains polysaccharides and lectins (N-acetyl-glucosamine-specific lectin) that inhibit sex hormone binding globulin attachment, aromatase activity, and arachidonic acid metabolism[21] [132].

A well-designed double-blind, placebo-controlled German trial studied forty-one men with moderately severe BPH symptoms (IPSS 18) [40]. After three months, the treatment group experienced twice the improvement (IPSS 18 \rightarrow 8) as the placebo group (IPSS 17 \rightarrow 12). Men treated with nettle extract also experienced an improved urinary flow.

Cranberry (*Vaccinium macrocarpon*)

Used as a folk remedy for centuries, proanthocyanidins contained in cranberries may prevent recurrent bacterial UTIs caused by pilated

bacteria such as *Escherichia coli* - the cause of 80% of bacterial prostatitis [10] [116].

Green Tea (*Camillia sinensis*)

Rich in a group of flavonoid antioxidants called catechins, especially epigallocatechin gallate, green tea may prevent the initiation, promotion, and progression of prostate cancer, including androgen-insensitive prostate cancer, by preventing DNA strand breaks, inhibiting cell proliferation, decreasing the contact of carcinogens with cells, blocking cancer initiation, and slowing cancer progression [126][79][1][91].

Milk Thistle (*Silybum marianum*)

Rich in antioxidant flavonoids known as silymarin, an extract of milk thistle seeds has been shown to inhibit prostate cancer initiation, promotion, and progression by altering signaling molecules and adaptor proteins affecting epidermal growth factor receptor [139].

Curcumin (*Curcuma longa*)

A potent antioxidant, curcumin, the major ingredient of curry powder, may inhibit prostate cancer cell growth by blocking the conversion of arachidonic acid to PGE2 and 5-HETE, inducing apoptosis, and regulating the tumor suppressor gene *p53* [15].

PC-SPES

Available over-the-counter, PC-SPES ('PC' stands for prostate cancer, and 'SPES' is Latin for hope) contains eight different Chinese herbs. Although the exact mechanism of is unclear, researchers theorize that, by working synergistically, the herbal combination PC-SPES inhibits angiogenesis, stimulates the immune system, induces an estrogenic effect, and inhibits 5-alpha reductase [60]. Small *et al.* [125] treated 37 men with androgen-dependent prostate cancer (ADPC) and 37 men with androgen-independent prostate cancer (AIPC) with a maximum dose of nine 320mg capsules of PC-SPES daily. All of the ADPC group experienced a PSA decline $\geq 80\%$, and 54% of the AIPC group experienced a PSA decline $\geq 50\%$. Furthermore, two patients with bone metastasis experienced regression of their metastatic lesions. Although effective, PC-SPES can cause a number of side effects, some of which are serious. Furthermore, PC-SPES was recently withdrawn from the market because of adulteration with a prescription medication.

Vitamins and Minerals

Water-soluble and fat-soluble vitamins and minerals are essential organic compounds our bodies use for normal metabolic function. Vitamins also counteract oxidant damage caused by infection and inflammation. Although physicians routinely advise their patients to eat a healthy well-balanced diet, they generally recommend against

taking additional multivitamins and minerals, even though government surveys show that 50% of the U.S. population has marginal nutrient deficiencies, and only 20% of individuals consume the minimum recommended daily dietary allowance of nutrients [100]. This resistance is fueled by the uncritical acceptance of bad news about micronutrient supplements [55]. Although caution is in order, if taken as directed, vitamins rarely cause serious side effects, and most side effects are reversible once the vitamins are stopped.

Taking over-the-counter antioxidants in conjunction with cancer therapies is also controversial. While opinions are divided, some physicians argue that taking antioxidant vitamins and supplements during chemotherapy or radiation therapy may exchange fewer acute side effects for a less effective therapy [72]. On the other hand, other experts argue that the vast majority of animal and human research studies have shown that antioxidants enhance the effectiveness or have a neutral effect on cancer therapies by improving detoxification of carcinogens, and cellular communication and differentiation [74][114].

Vitamin E

As a secondary endpoint of the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study, Heinonen *et al.* [62] reported that taking as little as 50 IU of dl-alpha tocopherol daily reduced the incidence of prostate cancer by a third and the death rate by forty

percent. Among other things, vitamin E prevents oxidation and peroxidation of membrane phospholipids and triggers apoptosis of prostate cancer cells [121]. Although dl-alpha tocopherol is used most frequently in research studies, dietary gamma tocopherol may be more protective against prostate cancer [95].

Vitamin D

In spite of dietary supplementation, studies have shown that > 50% of Americans are deficient in vitamin D and 22% are severely deficient [130]. In laboratory studies, vitamin D increases differentiation and decreases proliferation of prostate cancer cells [121]. In addition, vitamin D receptor polymorphisms may increase prostate cancer risk in African American males [121].

Vitamin A

Although data are mixed, in laboratory tests vitamin A can inhibit proliferation and induce differentiation of prostate cancer cells [121]. Nevertheless, clinical application is limited by dose-dependent side effects.

Beta-carotene

Brightly colored vegetables are a rich source of the pro-vitamin A beta-carotene. Although data are conflicting, findings from The Physicians Health Study suggest men with a low serum beta-carotene

level have a greater risk of developing prostate cancer [31]. Even though another highly publicized study found an increased risk of prostate cancer in smokers that supplemented with beta-carotene (but not in smokers that also supplemented with vitamin E) [62], other studies report no increased risk [51].

Vitamin C

Vitamin C regenerates vitamin E and counteracts hydroxyl-induced membrane damage. Although not specific for prostate cancer, the vast majority of over ninety epidemiological studies have found that vitamin C exerts a significant protective effect against cancer [18]. In laboratory studies, vitamin C also inhibits prostate cancer [87].

Selenium

Prostate cancer cells are deficient in selenium and glutathione peroxidase, two antioxidants that protect cells against hydroxyl radical-induced membrane damage. In a seminal study, Clark *et al.* [28] serendipitously discovered that taking 200 micrograms of yeast-derived selenium daily decreased the promotion and progression of prostate cancer, especially in selenium-deficient patients. Furthermore, the earlier in life selenium is started, the greater are the protective benefits [120]. Selenium can also protect against doxorubicin-induced heart damage and radiation-induced bladder cancer [113]

Zinc

Studies show that marginal zinc deficiency is common, especially among the elderly [103]. Concentrated in oysters, shellfish and red

meat, zinc is vital to proper immune function and wound healing. Zinc also plays an important role in preventing prostatitis. Secreted by prostate epithelial cells, zinc kills bacteria on contact [45]. Men with chronic bacterial prostatitis have extremely low prostate zinc concentrations despite normal serum zinc levels. Although taking supplemental zinc won't normalize prostate zinc levels [45], it can improve prostatitis-induced infertility [88]. Zinc can also inhibit prostate cancer cell growth and enhance apoptosis [78].

Nutritional Supplements

Quercetin

Quercetin is a naturally occurring plant flavonoid found in onions, parsley, sage, tomatoes, and citrus fruits. Quercetin significantly decreases prostatitis symptoms by decreasing prostatic inflammation. Shoskes *et al.* [122] randomized thirty men to receive either five hundred milligrams of Prosta-Q® (a proprietary blend of quercetin, bromelain, and papain) twice daily or a placebo for one month. Although few men became totally asymptomatic, two thirds of the men that were treated with Prosta-Q® experienced at least a 25% improvement in their prostatitis symptoms versus a 20% improvement in the placebo group. Furthermore, expressed prostatic secretions were improved a mean of 68% in the Prosta-Q® group versus 42% in the placebo group.

Quercetin also influences prostate cancer biology by inhibiting arachidonic acid metabolism by blocking phospholipase A2 and 5 and

12-lipoxygenase enzymes [16], and inhibiting androgen receptor mutations [136].

Melatonin

Melatonin directly and indirectly inhibits the growth of prostate cancer cells by stimulating immune function and cell differentiation, and inhibiting prolactin and IGF-1 production [82]. Italian investigators reported that >50% of men with androgen-independent prostate cancer men who took 20mg of melatonin daily restored their androgen sensitivity [82]. Furthermore, taking supplemental melatonin may enhance chemotherapy effectiveness [83] without interfering with endogenous melatonin production [89].

Probiotics

Probiotics, which means 'for life', are friendly bacteria and yeast. When taken orally, probiotic bacteria such as *Lactobacillus acidophilus* and *Bifidobacteria bifidum* can reduce bacterial overgrowth by producing antimicrobial substances, neutralizing toxins, and supporting immune function [101]. In a double-blind placebo-controlled trial involving 138 bladder cancer patients, Aso *et al.* [5] reported that patients with primary multiple bladder tumors and recurrent single bladder tumors who consumed *Lactobacillus casei* had fewer bladder tumor recurrences than did the placebo group; but there was no difference among patients with recurrent multiple bladder tumors. Taking a capsule containing 1-5 billion live bacteria (*Lactobacillus acidophilus*) twice daily with meals, but not at the same time as the antibiotic, can also prevent antibiotic-induced gastrointestinal side

effects such as bloating, stomach pain, and diarrhea [101]. Taking a capsule containing three billion *Saccharomyces boulardii* can improve gut immune function, inactivate bacterial toxins, and prevent antibiotic-induced yeast overgrowth [17].

Modified Citrus Pectin Pienta *et al.* [110] reported modified citrus pectin can slow PSA doubling time and limit prostate cancer metastases.

L-glutamine

Used selectively by the intestinal cells as fuel, the amino acid *L*-glutamine protects against radiation-induced diarrhea [67].

Co-enzyme Q-10

Co-enzyme Q-10 inhibits doxorubicin-induced cardiac damage, prevents free radical damage caused by lipid peroxidation, and spares vitamin E from oxidative degradation [74].

Alpha-lipoic Acid

Alpha-lipoic acid (ALA) is a hydrophilic and lipophilic molecule that recycles vitamin C, vitamin E, and glutathione; and is a necessary cofactor for the generation of acetyl coenzyme A [14]. Hepatitis is a rare but dangerous side effect of oral anti-androgen therapy. Alpha-lipoic acid along with milk thistle, selenium, fresh fruits and vegetables, plus other antioxidants can prevent or reverse medication-induced liver damage [14].

Mind-body medicine

Although the definition of mind-body medicine varies, broadly speaking the term refers to the body's innate healing system and any practice, treatment, or approach that influences the mind-body continuum. An accumulating body of physiological, epidemiological, and clinical research shows that mind-body medicine can prevent disease and improve treatment outcome, quality of life, and survival [77].

The quality of life for men with chronic prostatitis is on par with men suffering from chronic low back pain, heart disease, or inflammatory bowel disease [134]. Not surprisingly, men with prostatitis are prone to depression. Moreover, chronic depression can also increase the risk of developing prostate cancer risk by elevating IGF-1 levels [108]. Fortunately, psychological counseling and other mind-body interventions can alleviate depression, offer new coping skills, reduce pain and suffering, and facilitate the grieving process that accompanies any chronic illness.

A holistic approach to illness also improves quality of life and treatment outcome. Simple measures such as relaxation techniques, hypnosis, meditation, mental visualization, and guided imagery can improve surgical outcomes, shorten hospital stays, and reduce surgical and anesthetic-related side effects [109], restore hope [77], improve immune function [47] [57][77], improve quality of life [77][124], and reduce side effects associated with radiation therapy and chemotherapy [86][77][8]. Psychosocial and spiritual interventions

can also improve the survival of cancer patients [39] [8], including men with prostate cancer [123].

Other Healing Traditions

While this review focuses on specific aspects of complementary and alternative medicine, other healing traditions such as naturopathic medicine, Ayurvedic medicine, traditional Chinese medicine, homeopathy, and Native American medicine among others approach and successfully treat prostate disease differently than conventional Western medicine. Although these and other alternative therapies for prostate disease deserve further study, their discussion is beyond the scope of this overview.

Conclusion

Patients with chronic illness and those with a more holistic orientation to health and life are more likely to use complementary and alternative medicine [6] and enjoy better health outcomes as a result [7]. A growing body of scientific evidence also supports the notion that holistic and complementary and alternative health care practices improve the health and well being of men with prostate disease [96][86]. Furthermore, the popularity of complementary and alternative medicine underscores the fact that no treatment, approach, or healing system has all the answers, and our understanding of health and disease, however complete it may seem to be, is incomplete and always subject to revision [33].

Urologists have a responsibility to their patients to become knowledgeable about the advantages and disadvantages of

complimentary and alternative medicine. Based on the evidence, they should advise against therapies that are without merit or can cause harm. On the other hand, they should endorse and recommend therapies that can prevent chronic illness, reduce treatment-related side effects, improve health and well-being, forestall premature disability and mortality, and add life to years.

“The greatest challenge and the greatest promise in medicine today is not cost control, genetic engineering, or the development of new technologies . . . it’s learning how to motivate people to change their behavior.” (Leo Galland) [48]

References

1. Ahmad N, Feyes DK, Nieminen AL, Agarwal R, Mukhtar H (1997) Green Tea Constituent, Epigallocatechin-3-gallate and Induction of Apoptosis and Cell Cycle Arrest in Human Carcinoma Cells. *J Natl Cancer Inst* 89: 1881-1886
2. Aldercreutz H, Bannwart C, Wahala K, Makela T, Brunow G, Hase T, Arosemena PJ, Kellis JT Jr, Vickery LE (1993*a*) Inhibition of human aromatase by mammalian lignans and isoflavonoid phytoestrogens. *J Sterol Biochem Mol Biol* 44:147-153
3. Aldercreutz H, Markkanen H, Watanabe S (1993*b*) Plasma Concentration of Phytoestrogens in Japanese Men. *Lancet* 342: 1209-1210
4. Andro M-C, Riffaud J-P (1995) Pygeum Africanum Extract For The Treatment Of Patients With Benign Prostatic Hyperplasia: A Review Of

25 Years Of Published Experience. Current Therapeutic Research

56(8): 796-817

5. Aso Y, Akaya H, Katake T (1995) Preventive Effect of Lactobacillus Casei Preparation on the Recurrence of Superficial Bladder Cancer in a Double-blind Trial. Eur Urol 27: 104-109

6. Astin JA, Marie A, Pelletier KR, Hansen E, Haskell WL (1998) A Review of the Incorporation of Complementary and Alternative Medicine by Mainstream Physicians. Arch Intern Med 158: 2303-2310

7. Astin JA, Shapiro SL, Lee RA, Shapiro, DH, Jr. (1999) The Construct Of Control In Mind-Body Medicine: Implications For Healthcare. Altern Therap 5 (2): 42-47

8. Astin JA, Harkness E, Ernst E (2000) The Efficacy of "Distant Healing": A Systematic Review of Randomized Trials. Ann Int Med 132(11): 903-910

9. Austin JA (1998) Why patients use alternative medicine: results of a national study. JAMA 279:1548-1553

10. Avorn J, Monane M, Gurwitz JH, Glynn RJ, Choodnovskiy I, Lipsitz LA (1994) Reduction of Bacteriuria and Pyuria After Ingestion of Cranberry Juice. JAMA 271(10): 751-754

11. Bakke A, Malt UF (1998) Psychological Predictors of Symptoms of Urinary Tract Infection and Bacteriuria in Patients Treated With Clean

Intermittant Catheterization: A Prospective 7-Year Study. *Eur Urol* 34:30-36

12. Ben-Eliyahu S, Yirmiya S, Liebeskind JC, Taylor AN, Gale RP (1991) Stress increases metastatic spread of a mammary tumor in rats: evidence for mediation by the immune system *Brain Behav Immun* 5(2): 193-205

13. Berges RR, Windeler J, Trampisch H, Senge T (1995) Randomized, placebo-controlled, double-blind clinical trial of β -sitosterol in patients with benign prostatic hyperplasia. *Lancet* 345:1529-1532

14. Berkson BM (2000) A Triple Antioxidant Approach to the Treatment of Hepatitis C Using Alpha-Lipoic Acid (Thioctic Acid) Silymarin, Selenium, and Other Fundamental Nutraceuticals. *Clin Pract Altern Med* 1(1): 27-33

15. Bina J, Lokesh BR (1997) Effect of Curcumin and Capsaicin on Arachidonic Acid Metabolism and Lysosomal Enzyme Secretion by Rat Peritoneal Macrophages. *Lipids* 32(11): 1173-1179

16. Bland JS (1999) *Clinical Nutrition: A Functional Approach*. The Institute for Functional Medicine, Gig Harbor, WA

17. Bland JS, Benum SH (1999) *Genetic Nutritioneering: How You Can Modify Inherited Traits and Live a Longer, Healthier Life*. Keats Publishing, Los Angeles

18. Block G (1991) Epidemiologic Evidence Regarding Vitamin C and Cancer. *Am J Clin Nutr* 54: 1310S-14S

19. Block G, Patterson B, Subar A (1992) Fruit, vegetables and cancer prevention: a review of the epidemiological evidence. *Nutr Cancer* 18: 1-29
20. Brody H, Brody D (2000) *The Placebo Response*. Cliff Street Books, New York, pp 55-68
21. Brown D, Austin S, Reichert R (1997) *Clinical Applications of Natural Medicine: Benign Prostatic Hyperplasia and Prostate Cancer Prevention*. Natural Product Research Consultants, Seattle, pp 3-14
22. Buck AC, Cox R, Rees RW, Ebeling L, John A (1990) Treatment of Outflow Tract Obstruction due to Benign Prostatic Hyperplasia with the Pollen Extract, Cernilton: A Double-blind, Placebo-controlled Study. *Brit J Urol* 66: 398-404
23. Buck AC (1996) Phytotherapy for the prostate. *Brit J Urol* 78: 325-336.
24. Byers T, Nestle M, McTiernan A, Doyle C, Currie-Williams A, Gansler T, Thun M, et al (2002) American Cancer Society Guidelines on Nutrition and Physical Activity for Cancer Prevention: Reducing the Risk of Cancer with Healthy Food Choices and Physical Activity. *CA* (52(2)): 92-119.
25. Cantor KP (1987) Bladder Cancer, Drinking Water Source, and Tap Water Consumption: A Case-Control Study. *J Natl Cancer Inst* 79(6): 1269-1279
26. Chan JM, Stampfer MJ, Giovannuci E, Gann PH, Ma J, Wilkinson P, Hennekens CH, Pollak M (1998) Plasma Insulin-Like Growth Factor-1

and Prostate Cancer Risk: A Prospective Study," *Science* 279: 563-566

27. Chen L, Stacewicz-Sapuntzakis M, Duncan C, Sharifi R, Ghosh L, van Breemen R, Ashton D, Bowen PE (2001) Oxidative DNA Damage in Prostate Cancer Patients Consuming Tomato Sauce-based Entrees as a Whole-Food Intervention. *J Natl Cancer Inst* 93(24): 1872-1879

28. Clark LC, Combs GF Jr, Turnbull BW, Slate EH, Chalker DK, Chow J, Davis LS, Glover RA, Graham GF, Gross EG, Krongrad A, Lesker JI Jr., Park HK, Sanders BB Jr, Smith CL, Taylor JR; for the Nutritional Prevention of Cancer Study Group (1996) Effects of Selenium Supplementation for Cancer Prevention in Patients with Carcinoma of the Skin. *JAMA* 276(24): 1957-1963

29. Clinton SK (1998) Lycopene: Chemistry, Biology, and Implications for Human Health and Disease. *Nutr Rev* 56(2):35-51

30. Cohen JH, Kristal AR, Stanford JL (2000) Fruit and Vegetable Intakes and Prostate Cancer Risk. *J Natl Cancer Inst* 92 (1): 61-68

31. Cook NR, Stampfer MJ, Ma J, Manson JE, Sacks FM, Buring JE, Hennekens CH (1999) β -Carotene Supplementation for Patients With Low Baseline Levels and Decreased Risks of Total and Prostate Carcinoma. *Cancer* 86: 1783-1792

32. Copeland III EM, Daly JM, Dudrick SJ (1981) Nutrition and Cancer. *Int Adv in Surg Oncol* 4: 1-13

33. Dacher ES (1996) *Whole Healing*. Penguin Books, New York

34. deLorgeril M, Salen P, Martin JL, Monjaud I, Boucher P, Mamelle N (1998) Mediterranean Dietary Pattern in a Randomized Trial:

Prolonged Survival and Possible Reduced Cancer Rate. *Arch Intern Med* 158: 1181-1187

35. Demark-Wahnefried W, Price DT, Polascik TJ, Robertson CN, Anderson EE, Paulson DF, Walther PJ, Gannon M, and Vollmer RT (2001) Pilot Study Of Dietary Fat Restriction And Flaxseed Supplementation In Men With Prostate Cancer Before Surgery: Exploring The Effects On Hormone Levels, Prostate-Specific Antigen, and Histopathologic Features. *Urology* 58(1): 47-52

36. De Marzo AM, Coffey DS, Nelson WG (1999) New Concepts In Tissue Specificity For Prostate Cancer and Benign Prostatic Hyperplasia. *Urology* 53(Supplement 3A): 29-38

37. DiSilverio F, D'Eramo G, Lubrano C, Flammia GP, Sciarra A, Palma E, Caponera M, Sciarra F (1992) Evidence that *Serenoa repens* displays an Antiestrogenic Activity in Prostatic Tissue of Benign Prostatic Hypertrophy Patients. *Eur Urol* 21: 309-314

38. Donadio AC, Gagliano H, Remedi MM, Nowotny E, Depiante-Depaoli M (1998) Time-Course Study of Cellular Immune Response and Testosterone Metabolism in an Autoimmune Model for Chronic Prostatic Inflammation. *J Urol* 160: 1549

39. Dossey L (1993) *Healing Words*. HarperSanFrancisco, New York

40. Engelmann U, Boos G, Kres H (1996) Therapie der benignen Prostatahyperplasie mit Bazoton Liquidum. *Urologe (B)* 36: 287-291

41. Epstein SS, Steinman D. (1997) *The Breast Cancer Prevention Program*. McMillan, New York

42. Ernst E (2002) The Risk-Benefit Profile of Commonly Used Herbal Therapies: Ginkgo, St. John's Wort, Ginseng, Echinacea, Saw Palmetto, and Kava. *Ann Intern Med* 136 (1): 42-53
43. Eskinazi, DP (1998) Factors That Shape Alternative Medicine. *JAMA* 280 (18): 1621-1623
44. Evans BAJ, Griffiths K, Morton MS (1995) Inhibition of 5 α -reductase in genital skin fibroblasts and prostate tissue by dietary lignans and isoflavonoids *J Endocrinol* 147: 295-302
45. Fair WR, Couch J, Wehner N (1976) Prostatic Antibacterial Factor. Identity and Significance *Urology* 7(2): 169-177
46. Fair WR, Fleshner NE, Heston W (1997) Cancer Of The Prostate: A Nutritional Disease? *Urology* 50 (6): 840-848
47. Fair WR (1999) Back To The Future – The Role Of Complementary Medicine in Urology. *J Urol* 162: 411-420
48. Galland L (1997) *The Four Pillars Of Healing*. Randon House, New York
49. Gerber GS (1998) Phytotherapy in the Treatment of Benign Prostatic Hyperplasia. In: Carson CC, ed., *Mediguide to Urology*, Lawrence DellaCorte Publications, Inc, New York, pp 1-7
50. Giovannucci E, Rimm EB, Colditz GA, Stampfer MJ, Ascherio A, Chute CC, Willett WC (1993) A Prospective Study of Dietary Fat and Risk of Prostate Cancer. *J Natl Cancer Inst* 85(19): 1571-1579
51. Giovannucci E, Ascherio A, Rimm EB, Stampfer MJ, Colditz GA, Willett WC (1995) Intake of Carotenoids and Retinol in Relation to Risk of Prostate Cancer. *J Natl Cancer Inst* 87 (23): 1767-1775

52. Giovannucci E (1999) Tomatoes, tomato-based products, lycopene, and cancer: a review of the epidemiologic literature. *J Natl Cancer Inst* 91: 317-331
53. Gingell JC, Knonagel H, Kurth KH, Tunn UW (1995) Placebo-controlled double-blind study to test the efficacy of the aromatase inhibitor atamestane in patients with benign prostatic hyperplasia not requiring operation. *J Urol* 154: 399-401
54. Ghosh J, Myers CE (1998) Arachidonic Acid Metabolism and Cancer of the Prostate. *Nutrition* 14 (1): 48-49
55. Goodwin JS, Tangum M (1998) Battling Quackery: Attitudes About Micronutrient Supplements in American Academic Medicine. *Arch Int Med* 158: 2187-2191
56. Greenfield RH (1999) *Pygeum africanum* for the Treatment of Mild-to-Moderate Benign Prostatic Hyperplasia. *Altern Med Alert* 2(2): 13-16
57. Gruber BL, Hall NR, Hersh, Dubois P (1988) Immune System and Psychological Changes in Metastatic Cancer Patients Using Relaxation and Guided Imagery: A Pilot Study. *Scan J Behav Ther* 17(1): 25-46
58. Gruber CJ, Tschugguel W, Schneeberger C, Huber JC (2002) Production and Actions of Estrogens. *N Engl J Med* 346(5) 340-352
59. Hakim I (1998) Mediterranean Diets and Cancer Prevention. *Arch Int Med* 158: 1169-1170
60. Halicka HD, Ardelt B, Juan G, Mittelman A, Chen S, Traganos F (1997) Apoptosis and Cell Cycle Effects Induced by Extracts of the Chinese Herbal Preparation PC SPES. *Int J Oncol* 11: 437-448

61. Hartmann RW, Mark M, Soldati F (1996) Inhibition of 5 α -reductase and aromatase by PHL-00801 (Prostatonin®), a combination of PY 102 (*Pygeum africanum*) and UR 102 (*Urtica dioica*) extracts. *Phytomedicine* III(2): 121-128
62. Heinonen OP, Albanes D, Virtamo J, Taylor PR, Huttunen JK, Hartmann AM, Haapakoski J, Malila N, Rautalahti M, Ripatti S, Maenpaa H, Teerenhovi L, Koss L, Virolainen M, Edwards BK (1998) Prostate Cancer and Supplementation with Alpha-tocopherol and Beta-carotene: Incidence and Mortality in a Controlled Trial. *J Natl Cancer Inst* 90(6): 440-446
63. Hickey, K, Do, K-A, Green A (2001) Smoking and Prostate Cancer. *Epidemiol Rev* 23(1) 115-125
64. Hirsch IH (2000) Integrative Urology: A Spectrum Of Complementary And Alternative Therapy. *Urology* 56: 185-189
65. Hwang E-S, Bowen PE (2002) Can the Consumption of Tomatoes or Lycopene Reduce Cancer Risk? *Integrat Cancer Ther* 1(2) 121-132
66. Jones HA, Metz JM, Devine P, Hahn SM, Whittington R (2002). Rates Of Unconventional Medical Therapy Use In Patients With Prostate Cancer: Standard History Versus Directed Questions. *Urology* 59 (2): 272-276
67. Klimberg S (1991) Prevention of Radiogenic Side Effects Using Glutamine-enriched Elemental Diets. *Recent Results in Cancer Research* 121 (1991): 283-285
68. Klippel KP, Hiltl DM, Schipp B and the German BPHP study group (1997) Randomized double-blinded placebo controlled trial to evaluate

- the efficacy of β -sitosterol (phytosterol) in patients with obstructive and irritative symptoms due to BPH. *Brit J Urol* 80: 427-432
69. Kolonel LN, Nomura MY, Cooney RV (1999) Dietary Fat and Prostate Cancer: Current Status. *J Natl Cancer Inst* 91(5) 414-428
70. Koskimäki J, Hakama M, Huhtala H, Tammela TL (1998) Association of Smoking With Lower Urinary Tract Symptoms *J Urol* 159: 1580-1582
71. Kushi LH, Cunningham JE, Hebert JR, Lerman RH, Bandera EV, Teas J (2001) The macrobiotic diet in cancer. *J Nutr* 131 (11 Suppl): 3056S-3064S
72. Labriola D, Livingston R (1999) Possible Interactions Between Dietary and Antioxidants and Chemotherapy. *Oncology* 13: 1003-12
73. Lagiou P, Wu J, Trichopoulou A, Hsieh CC, Adami HO, Trichopoulos D (1999) Diet And Benign Prostatic Hyperplasia: A Study In Greece *Urology* 54(2): 284-290
74. Lamson DW, Brignall MS (2000) Antioxidants and Cancer Therapy II: Quick Reference Guide. *Altern Med Rev* 5 (2): 152-163
75. Lazarou J, Pomeranz BH, Corey PN (1998) Incidence of Adverse Drug Reactions in Hospitalized Patients: A Meta-Analysis of Prospective Studies. *JAMA* 279: 1200-1205
76. Lee I-M, Sesso HD, Chen JJ, Paffenbarger RS Jr (2001) Does Physical Activity Play a Role in the Prevention of Prostate Cancer? *Epidemiol Rev* 23(1):132-137
77. Lerner M (1996) Choices in Healing. The MIT Press, Cambridge, MA

78. Liang J (1999) Inhibitory effect of zinc on human prostatic carcinoma cell growth. *Prostate* 40: 200-207
79. Liao S, Umekita Y, Guo J, Kokontis JM, Hiipakka RA (1995) Growth Inhibition and Regression of Human Prostate and Breast Tumors in Athymic Mice by Tea Epigallocatechin Gallate. *Cancer Lett* 96: 239-243
80. Lichtenstein P, Holm, NV, Verkasalo, PK, Iliadou A, Kaprio J, Koskenvuo M, Pukkala E, Skytthe A, Hemminki K (2000) Environmental and Heritable Factors In The Causation Of Cancer. *N Engl J Med* 343 (2): 78-85
81. Lippert MC, McClain R, Boyd, JC, Theodorescu, D (1999) Alternative Medicine Use in Patients with Localized Prostate Carcinoma Treated with Curative Intent. *Cancer* 86 (12): 2642- 2648
82. Lissoni P, Cazzaniga M, Tancini G, Scardino E, Musci R, Barni S, Maffezzini M, Meroni T, Rocco F, Conti A, Maestroni G (1997) Reversal of Clinical Resistance to LHRH Analogue in Metastatic Prostate Cancer by the Pineal Hormone Melatonin: Efficacy of LHRH Analogue Plus Melatonin in Patients on LHRH Analogue Alone. *Eur Urol* 31: 178-181
83. Lissoni P, Barni S, Mandala M, Ardizzoia A, Palorossi F, Vaghi M, Longarini R, Malugani F, Tancini G (1999) Decreased toxicity and increased efficacy of cancer chemotherapy using the pineal hormone melatonin in metastatic solid tumour patients with poor clinical status. *Eur J Cancer* 12: 1688-1692
84. Lowe FC, Ku JC (1996) Phytotherapy In Treatment Of Benign Prostatic Hyperplasia: A Critical Review. *Urology* 48 (1): 12-20

85. Lowentritt JE, Kawahara K, Human LG, Hellstrom WJ, Domingue GJ (1995) Bacterial Infection in Prostatodynia. *J Urol* 154: 1381
86. McClure M (2001) *Smart Medicine for a Healthy Prostate*. Avery Publishing Group, New York
87. Maramag C, Menon M, Balaji KC, Reddy PG, Laxmanan S (1997) Effect of Vitamin C on Prostate Cancer Cells *in vitro*: Effect on Cell Number, Viability, and DNA Synthesis. *Prostate* 32: 188-195
88. Marmar JL, Katz S, Praiss DE, De Benedictis TJ (1975) Semen Zinc Levels In Infertile And Postvasectomy Patients And Patients With Prostatitis. *Fertil Steril* 26(11): 1057-1063
89. Matsumoto M, Sack RL, Levy AJ (1997) The Amplitude of Endogenous Melatonin Production is not Affected by Melatonin Treatment in Humans. *J Pineal Res* 22: 42-44
90. Mills PK, Beeson WL, Phillips RL, Fraser GE (1998) Cohort Study of Diet, Lifestyle, and Prostate Cancer in Adventist Men. *Cancer* 64: 598-604
91. Mitscher LA, Dolby V (1998) *The Green Tea Book*. Avery Publishing Group, Garden City Park, New York
92. Miyake H, Hara I, Yamanaka K, Gohji K, Arakawa S, Kamidono S (1999) Elevation of Serum Levels of Urokinase-type Plasminogen Activator and its Receptor in Associated with Disease Progression and Prognosis in Patients with Prostate Cancer. *Prostate* 39
93. Morton MS, Griffiths K, Blacklock N (1996) The Preventive Role of Diet in Prostatic Disease. *Br J Urol* 77: 481-93

94. Moyad MA (1999) Emphasizing and Promoting Overall Health and Nontraditional Treatments After a Prostate Cancer Diagnosis. *Semin Urol Oncol* 17(2): 119-124
95. Moyad MA, Brumfield SK, Pienta KJ (1999) Vitamin E, alpha- and gamma-tocopherol, and prostate cancer. *Semin Urol Oncol* 17 (2): 85-90
96. Moyad MA (2002) Complimentary Medicine For Prostatic Diseases: A Primer For Clinicians. *Urology* 59 (4A): 1-62
97. Moyad MA (2002) Dietary Fat Reduction To Reduce Prostate Cancer Risk: Controlled Enthusiasm, Learning A Lesson From Breast Or Other Cancers, And The Bid Picture *Urology* 59 (4A) 51-62.
98. Mukherjee, P, Sotnikov AV, Manigian HJ, Zhou J-R, Visek WJ, Clinton SK (1999) *J Natl Cancer Inst* 91(6): 512-522
99. Murray MT (1995) Chapter 29 Pygeum. In: *The Healing Power of Herbs*, 2nd ed, Prima, Rocklin, CA
100. Murray MT, Pizzorno JE (1999) Nutritional Medicine. In: L Pizzorno JE, Jr., Murray MT (eds) *Textbook of Natural Medicine*, 2nd ed. Churchill Livingstone, Edinburgh, London, New York, Philadelphia, Sydney, Toronto, pp 369-380
101. Murray MT, Pizzorno JE (1999) Probiotics. In: L Pizzorno JE, Jr., Murray MT (eds) *Textbook of Natural Medicine*, 2nd ed. Churchill Livingstone, Edinburgh, London, New York, Philadelphia, Sydney, Toronto, pp 893-898
102. Nakao-Hayashi J, Ito H, Kanayasu T, Morita I, Murota S (1992) Stimulatory Effects of Insulin and Insulin-like Growth Factor 1 on

Migration and Tube Formation by Vascular Endothelial Cells.

Atherosclerosis 92: 141-149

103. Nordstrom J (1982) Trace Mineral Nutrition in the Elderly *Am J Clin Nutr* 36: 788-795

104. Novey DW (2000) *Clinician's Complete Reference To Complementary & Alternative Medicine*. Mosby, St. Louis, Philadelphia, London, Sydney, Toronto

105. Parker MJ (2000) Traditional Chinese Herbal Medicine. In: Novey DW (2000) *Clinician's Complete Reference To Complementary & Alternative Medicine*. Mosby, St. Louis, Philadelphia, London, Sydney, Toronto, pp 203-218

106. Parkin DM, Muir CS (1992) Cancer Incidence in five continents: comparability and quality of data. *IARC Sci Publ* 120: 45-173

107. Peluso M, Airoidi L, Magagnotti C, Fiorini L, Munnina A, Hautefeuille A, Malavelle C, Vineis P (2000) White blood cell DNA adducts and fruit and vegetable consumption in bladder cancer.

Carcinogenesis 21(2): 183-187

108. Pennix BW, Guralnik JM, Pahor M, Ferucci L, Cerhan JR, Wallace RB, Havlik RJ (1998) Chronically depressed mood and cancer risk in older persons. *J Natl Cancer Inst* 90: 1888-1893

109. Petry JJ (2000) Surgery And Complementary Therapies: A Review. *Altern Ther* 6(5): 64-74

110. Pienta KJ, Naik H, Akhtar A, Yamazaki K, Replogle TS, Lehr J, Donat TL, Tait L, Hogan V, Raz A (1995) Inhibition of Spontaneous

Metastasis in a Rat Prostate Cancer Model by Oral Administration of Modified Citrus Pectin. *J Natl Cancer Inst* 87: 348-353

111. Pincus T (2000) Challenges to the biomedical model: Are actions of patients almost always as important as actions of health professionals in long-term outcomes of chronic diseases? *Adv Mind Body Med* 16: 287-294

112. Platz EA, Kawachi I, Rimm EB, Colditz GA, Stampfer MJ, Willett WC, Giovannucci E (1998) Physical Activity and Benign Prostatic Hyperplasia. *Arch Intern Med* 158:2349-2356

113. Prasad KN (1984) *Vitamins, Nutrition and Cancer*. Karger Press, Basel

114. Prasad KN, Kumar A, Kochupillai V, Cole WC (1999) High Doses of Multiple Antioxidant Vitamins: Essential Ingredients in Improving the Efficacy of Standard Cancer Therapy. *J Am Coll Nutr* 18(1): 13-25

115. Pribitkin ED, Boger G (2000) *Surgery and Herbal Therapy: Essential Guidelines on Bleeding, Skin Reactions, and Wound Healing*. *Compl Health Pract Rev* 6 (1): 29-40

116. Roberts RO, Lieber MM, Rhodes T, Girman CJ, Bostwick DG, Jacobsen SJ (1998) Prevalence of a Physician-assigned Diagnosis of Prostatitis: The Olmsted County Study of Urinary Symptoms and Health Status Among Men. *Urology* 51(4): 578-584

117. Rugendorff EW, Weidner W, Ebeling L, Buck AC (1993) Results of Treatment with Pollen Extract (Cernilton® N) in Chronic Prostatitis and Prostodynia. *Brit J Urol* 71:433-438

118. Schipper H (1995) Shifting the Cancer Paradigm: Must We Kill to Cure? *J Clin Oncol* 13 (4): 801-807
119. Schmidt MA (1997) Smart Fats: How Dietary Fats and Oils Affect Mental, Physical and Emotional Intelligence. Frog, Ltd, Berkley, CA
120. Schrauzer GN (1984) Selenium in Nutritional Cancer Prophylaxis. In: Prasad KN, ed, *Vitamins, Nutrition and Cancer*, Karger Press, Basel, p 243
121. Schulman CC, Ekane S, Zlotta AR (2001) Nutrition And Prostate Cancer: Evidence Or Suspicion? *Urology* 58: 318-334
122. Shoskes DA, Zeitlan SI, Shahed A, Rajfer J Quercetin In Men With Category III Chronic Prostatitis. *Urology* 54(6): 960-963
123. Shrock D, Palmer RF, Taylor B (1999) Effects of a Psychosocial Intervention on Survival Among Patients with Stage 1 Breast and Prostate Cancer: A Matched Case-control Study. *Altern Ther* 5(3): 49-55
124. Simonton S, Sherman AC. (1998) Psychological Aspects of Mind-body Medicine: Promises and Pitfalls From Research With Cancer Patients. *Altern Ther* 4(4): 50-64
125. Small EJ, Frohlich MW, Bok R, Shinohara K, Grossfeld G, Rozenblat Z, Kelly WK, Corry M, Reese DM (2000) Prospective Trial of the Herbal Supplement PC-SPES in Patients With Progressive Prostate Cancer. *J Clin Oncol* 18 (21): 3595-3602
126. Smith TJ, Hong JY, Wang ZY, Yang CS (1995) How can carcinogenesis be inhibited? *Ann N Y Acad Sci* 768: 82-90

127. Spake A (1997) O is for outbreak. U.S. News & World Report (November 24)
128. Spencer JW, Joseph, JJ (1999) Complementary/Alternative Medicine: An Evidence-Based Approach. Mosby, Inc., St. Lewis
129. Suzuki S, Platz EA, Kawachi I, Willett WC, Giovannucci E (2002) Intakes of energy and macronutrients and the risk of benign prostatic hyperplasia. *Am J Clin Nutr* 75: 689-97
130. Thomas MK, Lloyd-Jones DM, Thadhani RI, Shaw AC, Deraska DJ, Kitch BT, Vamvakas EC, Dick IM, Prince RL, Finkelstein JS (1998) Hypovitaminosis D in Medical Inpatients. *N Engl J Med* 338: 777-783
131. Vita AJ, Terry RB, Hubert HB, Fries JF (1998) Aging, Health Risks, and Cumulative Disability. *New Engl J Med* 338 (15): 1035-1041
132. Wagner H, Willer F, Samtelben R, Boos G (1994) Search for the antiprostatic principle of stinging nettle (*Urtica dioica*) roots. *Phytomedicine* 1: 213-214
133. Weiss RF, Fintelmann, V (2000) 2nd ed., Herbal Medicine. Thieme, Stuttgart, New York
134. Wenninger K, Heiman JR, Rothman I, Berghuis JP, Berger RE (1996) Sickness Impact of Chronic Nonbacterial Prostatitis and Its Correlates. *J Urol* 155: 965-968
135. Wilt TJ (1996) Saw Palmetto Extracts for Treatment of Benign Prostatic Hyperplasia: A Systematic Review *JAMA* 280 (18): 1604-1609

136. Xing N, Chen Y, Mitchell SH, Young CY (2001) Quercetin inhibits the expression and function of the androgen receptor in LNCaP prostate cells. *Carcinogenesis* 22: 409
137. Yablonsky F, Nicholas V, Riffaud JP, Bellamy F (1997) Antiproliferative Effect of *Pygeum Africanum* Extract On Rat Prostatic Fibroblasts. *J Urol* 157: 2381-2387
138. Yaffar, RP (1999) BPH, The Other Side of the Coin. *Life Extension Magazine* (February): 13-15
139. Zi X, Grasso AW, Kung HJ, Agarwal R (1998) A Flavonoid Antioxidant, Silymarin, Inhibits Activation of erbB1 Signaling and Induces Cyclin-dependent Kinase Inhibitors, G1 Arrest, and Anticarcinogenic Effects in Human Prostate Carcinoma DU145 Cells. *Cancer Res* 58(9):1920-1929