

Treatment of Prostate Cancer with Natural Therapeutics

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Introduction:

The prostate is a gland in the male reproductive system that helps produce semen, the thick fluid that carries sperm cells. The prostate is a walnut-sized structure located beneath the bladder of males. It surrounds the upper part of the urethra. The urethra is the tube that carries urine from the bladder. Prostate function is regulated by testosterone, the male sex hormone produced primarily in the testicles.

Prostate cancer represents a significant number of malignancies in men over the age of 50 years. The incidence of prostate cancer has been increasing each decade in the United States. About 200,000 new cases and 38,000 deaths are related to prostate cancer each year in the United States. African-American males have the highest incidence of prostate cancer in the world.¹ The disease is rare in Asia, Africa, and Latin America.

Prostate cancer typically has a strange course. It often is inactive for many years. Once activated, it tends to progress slowly. The disease is often fatal if it spreads beyond the prostate gland. The cause of prostate cancer is still unknown, but it is likely related to hormonal factors. In particular, the conversion of testosterone to dihydrotestosterone (DHT) is recognized as an important factor in the development of disease. Adenocarcinoma is the primary type of prostate cancer, but sarcoma, squamous cell carcinoma, ductal transitional carcinoma, and undifferentiated prostatic carcinoma also occur.

Signs and Symptoms:

Prostate cancer is typically a progressive disease that develops at a slow rate. It can also develop with no significant symptoms, particularly in the early stages of the disease. As the disease progresses, however, symptoms such as the following begin to appear:

- The need to urinate frequently, particularly at night
- Problems in the initiation and cessation of urination
- The complete inability to urinate
- Blood in the urine
- Painful ejaculation
- Burning or painful urination
- Persistent pain in the upper thighs, lower

back, or hips

It is important to note that benign conditions involving the prostate such as enlargement (benign prostatic hypertrophy, BPH), infections, and stones can mimic the symptoms of cancer, so a professional consultation is important. When the cancer metastasizes to the ribs, pelvis, or vertebral bodies it can lead to bone pain in prostate cancer patients.

Diagnosis

Prostate cancer diagnosis begins with a digital rectal examination by the health care professional. Additional tests such as a transrectal or transperineal needle biopsy can detect small prostatic nodules or more advanced cancerous growth. Transrectal ultrasound is also used for both diagnosis and to help guide needle biopsy. Serum acid phosphatase levels can be elevated when there is local extension or metastasis of disease. However, other conditions such as benign prostatic hyperplasia, multiple myeloma, Gaucher's disease, and hemolytic anemia can also raise these levels. Radioimmunoassay analysis of prostate-specific antigen (PSA) has become a standard test for diagnosing both localized as well as metastasized stages of the prostate cancer. Though controversial, PSA is the most sensitive marker for monitoring disease and is elevated in 25 to 92% of patients with prostate cancer. However, it is also raised in 30 to 50% of those with BPH. Prostate cancer often leads to osteoblastic (bone-formation cells) bony metastases, which are often detected on bone scans or x-rays of prostate cancer patients. Physicians often have difficulty in identifying what types of prostate cancers will spread and become dangerous. A new protein called KAI-1 has been identified as a marker for disease. If significant levels of KAI-1 are found in cancerous tissues, the cancer is not likely to spread. If the protein is not found, cancer typically spreads.

Prostate cancer has been classified into four stages:

- Stage A. The tumor is not found by normal tests but during surgery for a different prostate condition.
- Stage B. The tumor can be palpated during rectal examination but it has not spread beyond the prostate

- Stage C. Cancer has spread to tissues outside of the prostate.
- Stage D. The cancer has metastasized to the lymph nodes of the pelvis or to other parts of the body, especially the bones.

Conventional Therapy

Prostate cancer that is localized is typically treated with radiation therapy or radical prostatectomy (excision of part or all of the prostate gland). This operation is performed through incision in the perineum, into the bladder, or through the urethra. Libido is typically unaffected by prostatectomy but some 30% of patients become impotent after the procedure. A more common complication following a radical prostatectomy is the development of urinary incontinence. When disease has significantly progressed beyond this stage, or when the patient is very old or in poor health, these treatment approaches may not be used. These patients may be treated with irradiation, hormone therapy, or the surgical removal of the testicles. One of the hormonal therapies, oral diethylstilbestrol, has been given to prostate cancer patients in doses of 1 to 3 mg/day and has demonstrated some success over long periods of time. Long-term use of such estrogen therapies increases the risk of developing thromboembolic (blocking of a blood vessel by a thrombus) complications. Additional adverse effects caused by estrogen therapies can include breast tenderness, breast enlargement, nausea, vomiting, loss of sexual desire, impotence, and water retention. Short-term use of agents such as high-dose diethylstilbestrol diphosphate can lead to substantial relief in patients within days. A variety of agents are used to decrease testosterone levels circulating in the body. These agents include flutamide, cyproterone acetate, ketoconazole, aminoglutethimide, and analog agents of luteinizing hormone-releasing hormone. Surgical removal of the testicles is sometimes performed when the disease has advanced or when hormone therapy has failed. The use of local radiation therapy has been found to be effective in relieving pain associated with cancer metastasis into the bones. Local radiation therapy can also help limit disease to the prostate. Chemotherapy has generally not been effective once hormonal therapy has failed. It is also associated with severe adverse effects such as nausea, vomiting, lowered blood and immune system factors, and hair loss.

Benign Prostatic Hypertrophy

While BPH and prostate are not the same condition and are not believed to be related to each other, they do have many common factors. As mentioned previously, both produce elevated PSA levels and a variety of problems relating to urination. In addition, both are believed to develop from hormonally-related factors. BPH occurs in more than half of all men in their 60s and in as many as 90 percent of all men in their 70s and 80s. BPH may develop from the growth of cells from the relatively increased levels of estrogen that occur in men as they age. Another line of thought states that the testosterone-derivative DHT⁹⁵ is involved with the increased cellular growth associated with BPH. The drug called finasteride (Proscar), a 5-alpha-reductase inhibitor has reduced the size of the prostate in some patients, resulting in improved urination. BPH does not increase the risk of developing prostate cancer, and these two conditions develop in different parts of the prostate gland.

Risk Factors

Age, as previously mentioned, is a significant risk factor for disease development. Men with a family history of prostate cancer have a significantly increased risk for the development of the disease. A man whose father had prostate cancer is 2.3 times more likely to develop the disease than if his father never developed the disease. A man is also more likely to develop prostate cancer if his sister or mother develops breast or ovarian cancer. This suggests an important genetic relationship in the development of prostate cancer. Some 15% of inherited cases may be transmitted through the mother's X chromosome. A different gene called HPC1 has been associated with about 30% of all inherited cases of prostate cancer. Some association between viral and bacterial infections of the prostate and the later development of prostate cancer has been seen.

Levels of sexual activity do not appear to have a significant effect on the risk of developing disease. Despite some discussion to the contrary, there is no evidence that a vasectomy will alter prostate cancer risk. Occupational factors may be a small factor in the development of disease. There is some evidence that working around metals and chemicals, such as acrylonitrile, dimethylformamide, and cadmium, may increase the risk of developing prostate cancer.

cer. There is also limited evidence that a history of nonmelanoma skin cancer may increase the risk of developing disease.

Apart from genetic and age factors, the strongest evidence of risk association comes from dietary patterns. Research has suggested that men who consume high levels of fat are more likely to develop prostate cancer. Prostate cancer is more common in countries where meat and dairy products are consumed in large quantities than in regions where the diet contains large quantities of vegetables, rice, and soybean products. Fat has been found to stimulate testosterone and other hormone production. High testosterone levels may also stimulate dormant prostate cancer cells into action. Eating meat cooked at high temperatures can produce carcinogens that directly affect the prostate. Smokers who develop prostate cancer tend to have poorer outcomes than those who do not smoke.² Studies have also shown that the ingestion of 22 to 56 alcoholic drinks per week also increases risk of developing the disease.³

Obesity as a Risk Factor

Obesity has been associated with an increased risk of developing prostate cancer. A study of 5,212 men who died from prostate cancer and others who did not develop the disease found that obese (body mass index greater than 30) were 1.27 times more likely to develop and die from the disease than non-obese men.¹²⁸ A study from China found that men with the highest waist-to-hip ratios were nearly three times more likely to develop prostate cancer as those with the smallest waist-to-hip ratios.¹²⁹ This may be due to the fact that greater fat deposits in the abdomen may increase hormonal activity. A study of 101 men who developed prostate cancer in Iowa found that obesity was associated with more aggressive and late-stage prostate tumors.¹³⁰ A different study found an association between childhood obesity and an increased risk of prostate cancer late in life.¹³¹

Prostate Cancer Prevention

The prevention of prostate cancer has just begun to be studied. At the microscopic level, men throughout the world appear to have the early stage of the disease. However, the large variations in the progression of the disease among populations in particular regions are the focus of researchers. For

example, Asians who move to the United States have a higher incidence of prostate cancer than those who live in Asia.⁴ This suggests a role for nutrition in the prevention of the disease. Animal fats and certain vegetable oils appear to be critical factors in disease development. Diets that involve the ingestion of large amounts of fresh fruits and dark-colored vegetables have been shown, in general, to have cancer-prevention effects.

Phytonutrients

Even though there is evidence that supplementation of various nutrients to the diet can provide benefits in the prevention and therapy of prostate cancer, more benefit may be derived from obtaining various nutrients from natural sources in the diet. In fact, the National Cancer Institute recommends the ingestion of at least five servings daily of fruits and vegetables to fight the development and progression of prostate cancer.¹⁴⁵ In addition, scientists have discovered that not all nutrients have been identified in some foods. The phytochemicals known as silymarin, genistein, and epigallocatechin 3-gallate have been shown to inhibit prostate cancer cells from multiplying.¹⁴⁶ Several studies have found that vegetables, fruits, and whole grains contain numerous phytonutrients that modulate cancer development. These foods contain anticarcinogenic compounds such as chlorophyll, carotenoids, flavonoids, indole, polyphenols, and protease inhibitors.¹⁴⁷ Researchers have found that the foods and herbs with the highest anticarcinogenic activity are licorice, garlic, soybeans, cabbage, ginger, citrus, and the umbelliferous vegetables.¹⁴⁸

Lycopene

Lycopene is a chemical in some fruits and vegetables that has demonstrated some potential in the prevention of prostate cancer.⁵ Lycopene is being thoroughly studied in a number of ongoing trials. Lycopene is a carotenoid present in blood that has proven antioxidant activity.⁶ In vitro and in vivo studies have shown that lycopene has protective effects against some types of cancers. Lycopene ingestion has been shown to reduce some types of digestive system cancers but has been primarily studied in association with prostate cancer.⁷ Lycopene is found primarily in nature in tomatoes and tomato products but is also found in carrots, green peppers, apricots, watermelon, and pink grapefruit. A case-control

study that analyzed plasma levels of lycopene in men with prostate cancer and in healthy men found that men with the highest levels of lycopene in plasma were less likely to develop prostate cancer.⁸ An additional study of 12 prostate cancer patients and 12 age-matched healthy subjects found significantly lower lycopene serum and tissue levels in cancer patients than in controls.⁹ A study of mortality from prostate cancer in 41 countries found that men who ingest more than 6 Kcal per day of tomatoes and tomato products have a significantly reduced risk of developing prostate cancer.⁵ A population-based case-control study of 317 prostate cancer cases and 480 controls in New Zealand found that the intake of lycopene and tomato-based foods was weakly associated with prostate cancer risk reduction.¹⁰ A prospective cohort study of 47,894 subjects found lycopene intake from tomato products was inversely associated with the risk of prostate cancer.¹¹ A study found that lycopene obtained by eating tomato sauce is associated with a decreased risk of prostate cancer development.⁹⁵ A new study in mice found that lycopene has the ability to inhibit tumor formation in the prostate and that these effects are organ-specific.⁹⁶ It is generally believed the antioxidant effects of lycopene are responsible for the tumor-inhibiting properties of lycopene, but other mechanisms may also be involved.⁹⁷

Newer evidence is coming in on how lycopene produces positive effects on the prevention and control of prostate cancer. This evidence has identified how lycopene alters events at the cellular level to produce these beneficial effects.¹⁴⁹ Another study found that lycopene, when combined with vitamin E, down regulates the levels of 5-alpha-reductase, the key enzyme involved in the progression of prostate cancer.¹⁵⁰ A new large meta-analysis of several observational studies found that lycopene, especially in natural form such as tomato products, reduced the relative risk of developing prostate cancer.¹⁵¹ An additional prospective study found further evidence that consumption of lycopene, especially in the form of tomato sauce, significantly reduced the risk of developing prostate cancer over a lifetime.¹⁵²

A case-control study of patients with and without prostate cancer found that the administration of lycopene increased the level of apoptosis, or cell destruction, of prostate cancer cells in the afflicted

group.¹⁵³ A similar study of patients about to undergo surgery for prostate cancer found that those who supplemented their diet with lycopene before the surgery had lower PSA levels than those who did not supplement when the prostate cancer tissue was analyzed after surgery.¹⁵⁴ A similar randomized study found that lycopene supplementation led to positive effects on prostate cancer cells in patients with localized diseases.¹⁵⁵ A study of men with advanced prostate cancer who underwent castration found that men who received lycopene had better outcomes than those men who did not receive lycopene supplementation.¹⁵⁶ The men who received lycopene had lower PSA levels, lower pain levels, and greater tumor shrinkage than those who did not receive lycopene.

Selenium

Selenium has been shown to have anti-carcinogenic effects both in vitro and in clinical studies.¹² An in vitro study of both human and mouse tumor cell lines found that selenium reduced human prostate carcinoma cell growth by 50% compared to controls.¹³ A case-control study of 164 prostate cancer patients and 152 controls with BPH found that plasma selenium levels were significantly higher in the BPH group compared to the cancer group.¹⁴ High levels of selenium have been found to counteract the prostate cancer cell-stimulatory effects of cadmium in vitro.¹⁵ A case-control study of 181 prostate cancer cases and 181 matched controls found that selenium levels in the body, as gauged by levels in the toenails, are associated with the risk of prostate cancer.¹⁶ In these cases, high selenium levels were associated with significantly reduced risk of advanced prostatic cancer. This held up even after controlling for a variety of factors, such as family history of prostate cancer, saturated fat intake, vasectomy, geographical region, body mass intake, and calcium intake. A study of 9345 Japanese-American men who had serum samples drawn and frozen in the 1970s and were assessed for prostate cancer incidence 20 years later found that those with selenium levels in the highest quartile were only half as likely to have disease as those in the lowest quartile.¹⁷ A similar study collected samples from 111 subjects in 1973 and found that the mean serum selenium levels of those with prostate cancer were significantly lower than those in 210 matched controls.¹⁸ A different study evaluated the effects of oral selenium supplementation

on general cancer risk reduction in patients with a history of skin cancer.¹⁹ The researchers found no evidence that selenium supplementation affected skin cancer outcomes. However, they did find that supplementation reduced the incidence of all cancers combined, including lung, colorectal, and prostate. Selenium supplementation also reduced mortality from all cancers combined and total mortality. An additional study of 974 men with a history of basal or squamous cell carcinoma evaluated whether supplemental selenium affects the incidence of prostate cancer.²⁰ The men were randomized either to 200 micrograms of selenium daily or placebo for a mean length of 4.5 years. After an overall follow-up period of 6.5 years, the researchers found that the group receiving selenium had a significantly lower (63%) incidence of prostate cancer. The selenium group also had significantly lower total cancer incidence and overall mortality. A new study has shed some light on the mechanism by which selenium may produce some of its anti-tumor effects.⁹⁸ This study strongly suggests selenium plays a key role in the induction of apoptosis, or programmed cell death, of prostate cells. Several ongoing trials are evaluating the ability of selenium supplementation to reduce the risk of prostate cancer.

A new prospective study of 586 men diagnosed with prostate cancer found that high levels of selenium in the blood were associated with a lower risk of disease progression.¹⁵⁷ A new study found that selenium destroys prostate cancer cells by interfering with the metabolism of a compound called 5-lipoxygenase that is critical in the growth of prostate cancer cells.¹⁵⁸ Another new study found that the combination of selenium and vitamin E has powerful additive effects on the destruction of enzymes that are important in the progression of prostate cancer.¹⁵⁹

Vitamin E

A study based on a cohort of 29,133 men found 317 developed prostate cancer during 9 years of follow-up. Baseline serum vitamin E levels were not important in prostate cancer development, but those who received high levels of vitamin E supplementation had a significantly reduced risk of developing prostate cancer.²¹ Alpha-tocopherol combined with lycopene has been shown to have strong inhibitory effects on prostate cell proliferation in vitro.²² A

new study has discovered that long-term vitamin E supplementation is associated with decreased levels of male hormones in the blood.⁹⁹ The lower level of hormone in the blood may be the critical factor in the found association between vitamin E supplementation and reduced risk of developing prostate cancer. A recently completed study of 145 men who developed prostate cancer found that these men had lower plasma levels of selenium, alpha-tocopherol (a component of vitamin E), and gamma-tocopherol (another component of vitamin E) than a control group that did not have the disease.¹⁰⁰ A new study discovered that vitamin E produces these anti-tumor effects on prostate cells by way of apoptosis (programmed cell death).¹⁰¹

A new study found that the inhibitory effects of vitamin E on prostate cancer cells are due to its suppression on male hormones (androgen).¹⁶⁰ A new clinical trial has found that men who took 5 mg per day of vitamin E for up to eight years had a reduced incidence of prostate cancer compared to those men who did not supplement with vitamin E.¹⁶¹ A new randomized, double-blind study is being conducted to determine if vitamin E can prevent and treat prostate cancer.¹⁶² This study is being conducted because of the strong evidence in epidemiological and other type of studies that suggest vitamin E can prevent and treat prostate cancer. A new study has demonstrated that a derivative of vitamin E inhibits the progression of prostate cancer.¹⁶³

Vitamin D

A study in rats found that an analog of vitamin D suppressed tumor development in the animals.²³ A different study in rats found that the administration of hormonal analog of vitamin D, 1, 25-dihydroxyvitamin D (calcitriol) and a different vitamin D analog called EB1089 led to significantly smaller prostate tumor volumes than a control solution.²⁴ An additional study also found evidence that 1,25-dihydroxyvitamin D inhibits the growth of both primary cultures of human prostate cancer cells and cancer cell lines.²⁵ Yet another study found that 1 alpha, 25-dihydroxyvitamin D can inhibit the invasive growth properties of the human prostate carcinoma lines, DU 145, PC-3, and LNCaP, in vitro.²⁶ Epidemiological studies in humans have suggested vitamin D deficiency is an important factor in the development of prostate cancer.²⁷ A new study has

found that prostate cancer cells lack a component of vitamin D that is typically present in healthy prostate cells.¹⁰² The same component found in this study, 1 alpha, 25(OH)(2)D(3), may be a useful prostate cancer treatment when combined with previously-used therapies.¹⁰³ Another new study has found further evidence that this component of vitamin D can inhibit the growth of prostate cancer cells.¹⁰⁴

Vitamin D is increasingly being recognized for its inhibitory effects on the growth of prostate cancer. A new case-control study has found that vitamin D and its metabolites produce their inhibitory effects on specific receptors in prostate cancer cells.¹⁶⁴ Another study found that sufficient amounts of vitamin D and its metabolites are necessary for the inhibition of prostate cancer.¹⁶⁵ One of the most interesting facts to emerge from this study is the need for vitamin E and its metabolites to be present for any cancer inhibition to occur, regardless of the type of therapy being used. A new study found that vitamin D3 obtained from sunshine improved the prognosis of patients with prostate cancer.¹⁶⁶ Yet another study has recently found that a key metabolite of vitamin D directly inhibits key processes in the development of prostate cancer.¹⁶⁷ A new study of prostate cancer cells found that a combination of radiation therapy with vitamin D produced greater reduction of cancer cells than those cells that did not receive vitamin D.¹⁶⁸ A new study of men with prostate cancer found that a combination of chemotherapy with a form of vitamin D produced better outcomes than chemotherapy alone.¹⁶⁹

Zinc

Zinc plays a major role in androgen metabolism. Estrogens appear to reduce the uptake of zinc in the intestines. Estrogen levels are increased in men with BPH and sometimes in men with prostate cancer. Zinc has been shown to decrease the size of the prostate and to decrease symptomology in BPH patients.^{28,29} This could have implications for prostate cancer prevention and the patient recovery after prostatectomy. Zinc has also been shown to inhibit 5-alpha-reductase activity, which reduces the conversion of testosterone to the dangerous DHT form.^{30,31} Zinc, like saw palmetto, has been shown to prevent the specific binding of androgens to nuclear and cytosol androgen receptors.³² Zinc has also been shown to inhibit prolactin secretion.³³ As mentioned

before, prolactin increases the uptake of testosterone by the prostate. This increased prolactin secretion leads to greater levels of DHT because of increased levels of substrate.³⁴ Cadmium is an antagonist of zinc and is also a stimulant of 5-alpha-reductase activity. Zinc has been shown to selectively inhibit prolactin secretion from the pituitary.³⁵ Prolactin secretion directly stimulates increased production of testosterone and the conversion to the more dangerous form, DHT. A new study has determined that zinc is absolutely vital to the apoptosis of prostate cancer cells through its effects on the compound known as fetuin.¹⁰⁵ A different study discovered that zinc plays an important role in the regulation of tumor cell invasion of various tissues in the prostate.¹⁰⁶ An additional study confirmed these tumor-inhibiting effects of zinc.¹⁰⁷

A new study found that there is decreased zinc uptake into the prostate gland in patients who have a more rapid progression of prostate cancer compared to those with higher levels of zinc uptake.¹⁷⁰

Essential Fatty Acids

Many BPH patients have received benefit from the administration of essential fatty acids (EFA) containing linoleic, linolenic, and arachidonic acids.³⁶ For reasons stated earlier, this could have implications for prostate cancer prevention or following conventional treatment for prostate cancer such as prostatectomy. An uncontrolled study of 19 subjects found reduction in residual urine in 12 of the subjects after several weeks of treatment.³⁷ This study confirmed other research that suggests EFA deficiencies in BHP and prostate cancer patients.³⁸ The combination of linoleic, linolenic, and arachidonic acids appears to be a critical factor in producing beneficial therapeutic effects.¹⁰⁸

A new prospective study has found that increased intake of eicosapentaenoic acid and docosahexaenoic acid decrease the risk of developing prostate cancer, in general, and reduce the risk of developing advanced disease in those already with prostate cancer.¹⁷¹ A new study has found that eicosapentaenoic acid and gamma-linolenic acid inhibit the conversion of testosterone to dihydrotestosterone, a key factor in the development and progression of prostate cancer.¹⁷²

Corn Oil

Evidence is emerging that the ingestion of large quantities of corn oil may increase the risk of developing prostate cancer and stimulating the growth of prostate cancer cells once developed. A study in mice found that corn oil and linoleic acid stimulated the growth of prostate cancer cells called DU145.¹²⁷ Rats fed a diet rich in corn oil (20% of fat intake) were more likely to have fast-growing prostate cancer cells than those on a fat-free diet.¹⁰⁹ An additional study found that rats fed a diet rich in fats obtained from corn oil (20%) were significantly more likely to develop carcinoma of the prostate than those fed a low-fat diet with low levels (5%) of corn oil.¹¹⁰ An additional study in mice using human prostate cancer cells that had been placed in the animals found that a diet rich (18%) in corn oil stimulated the growth of the cancerous cells to a greater extent than in mice who were fed a diet low in corn oil (5%).¹¹¹ Additional evidence has come in that increased consumption of alpha-linolenic acid may increase the risk of developing prostate cancer.¹⁷³

Amino Acids

A combination of amino acids that includes glutamic acid, alanine, and glycine given in the form of two 6 grain capsules three times daily for 2 weeks followed by one capsule three times daily has led to BPH symptom improvement in several studies.³⁹ A controlled study of 45 men with BPH found that delayed micturition occurred in 70% of cases, urine frequency was reduced in 73% of cases, nocturia was improved in 95% of cases, and urgency was reduced in 81% of cases.⁴⁰

Cholesterol

Cholesterol is an important factor in the formation of sexual hormones. Evidence indicates that cholesterol-lowering drugs have a beneficial effect on androgen formation in the prostate. A diet low in saturated fat coupled with regular aerobic exercise can reduce cholesterol levels in most individuals.

Soy

As previously noted, Asian populations have a reduced prevalence of progressive prostate cancer compared to Western populations. This may be due to generally high dietary soybean ingestion in these populations. Soybeans have abundant quantities of phytoesters. Phytoesters are known to have cholesterol-lowering properties.⁴¹ Phytoesters have

demonstrated positive effects in treating BPH. A double-blind study evaluated the administration of 20 mg beta-sitosterol, a phytoesterol in soy, three times daily or placebo to 200 men with BPH.⁴² Beta-sitosterol increased maximum urinary flow rates from 9.9 ml/s to 15.2 ml/s and decreased mean residual urinary volume from 65.8 ml to 30.4 ml. The placebo group had no significant changes. Typical Western diets provide only about 80 mg/day of phytoesters compared to a traditional Japanese diet, which provides about 400 mg/day.⁴⁸ A three-and-a-half ounce serving of soybeans or tofu contains about 90 mg of beta-sitosterol. Higher consumption of soy and soyfoods has also been associated with a reduced risk of prostate cancer.⁴³ Two separate studies have attributed this effect to the isoflavonoids called daidzein and genistein.⁴⁴ Both of these agents have demonstrated 5-alpha-reductase reduction activity.

Saponins are another class of compound found in soybeans. Saponins are also found in many other types of plants. They are known to have a variety of anti-cancer properties.⁴⁵ Phytates are another compound found in soybeans and in other plants. Phytates have been shown to increase natural killer cell activity in the body.⁴⁶ The phytoestrogens found in soy are known to have anti-estrogenic effects.⁴⁷ Again, this can have important effects in the prevention of prostate cancer. It has been suggested that, in general, phytoestrogens have enzyme inhibition action, which could lead to inhibition of 5-alpha-reductase activity.⁴⁸

Asian cultures are believed to consume about 20-80 mg/day of genistein, whereas Western populations consume about 2-3 mg/day.⁴⁹ Messina and colleagues performed a review of 26 animal studies involving genistein and found that 17 (65%) of them demonstrated evidence of anti-carcinogenic activity from this compound.⁵⁰ It is believed that genistein is a natural PTK inhibitor.⁵¹ PTK inhibition has been found to be major factor in the inhibition of cancer.⁵² In vitro research has suggested genistein is a strong inhibitor of angiogenesis, a major factor in the growth of cancer cells.⁵³ Studies involving human volunteers who consumed soy beverages that contained 42 mg of genistein and 27 mg of daidzein daily produced peripheral blood concentrations of 0.5-1.0 μ M.⁵⁴ This is known to be an insufficient quantity to inhibit the growth of cultured cancer

cells.⁵⁵ This suggests that these compounds may have a more important role as chemopreventative rather than chemotherapeutic agents.¹⁴⁷

Additional epidemiological data has found that Japanese men have plasma levels of these isoflavone compounds that are 7 to 110 times higher than those in Finnish men.⁵⁶ The major constituent of these isoflavone concentrations is genistein. Researchers have suggested genistein may have a variety of mechanisms that prevent cancer formation, including direct growth inhibition, apoptosis induction, and cancer cell adhesion.⁵⁷ An in vitro study suggests that equol, biochanin A, and genistein are all potent inhibitors of 5-alpha-reductase.⁵⁸ Animal studies have suggested a diet high in genistein and daidzein resulted in a lower incidence of prostate cancer and longer disease-free periods after exposure to carcinogenic materials compared to a low isoflavone diet.⁵⁹ The isoflavones genistein and biochanin A inhibited many different human prostate cancer cell lines, but this effect did not occur with daidzein.⁶⁰

A new study found that 50 healthy men who received 50 mg of soy isoflavone twice daily for three weeks had an increase in antioxidant activity in prostate cells that could inhibit the formation of prostate cancer cells.¹¹² A different study found that the administration of genistein to prostate cancer cells already receiving radiation therapy increased the therapeutic effect of the therapy.¹¹³ An additional study has found that low doses of genistein can induce apoptosis in human prostate cancer cells.¹¹⁴

A new case-control study in Japan, Korea, and the United States has found that men who have the ability to properly metabolize daidzein have a reduced incidence of prostate cancer.¹⁷⁴ An additional case-control in Japanese men found that relative levels of daidzein, genistein, and equol in the blood were more important than sex hormone levels in the development of prostate cancer.¹⁷⁵ Men with higher levels of these soy components were less likely to develop prostate cancer than those with low levels of the compounds. A case-control study of men in China found that men with the highest consumption of tofu had the lowest risk of developing prostate cancer.¹⁷⁶ A new study has found that genistein and daidzein counteract the negative effects of dihydrotestoster-

one on the prostate gland and prostate cancer cells.¹⁷⁷ An additional study found that daidzein metabolism is an important factor in the prevention of prostate cancer.¹⁷⁸

Drug and Pesticide Avoidance

A variety of pesticides have been shown to produce changes that increase the activity of 5-alpha-reductase. Some of these compounds include dioxin, polyhalogenated biphenyls, hexachlorobenzene, diethylstilbestrol (DES), and dibenzofurans.⁶¹ A diet that avoids exposure to these agents is recommended for the prevention and treatment of prostate cancer.

Alcohol Avoidance

Beer ingestion has been associated with increased secretion of prolactin, which increases both testosterone formation and dihydrotestosterone conversion. Alcohol intake, in general, has negative effects on the prostate as evidenced by a 17-year study of 6,581 men in Hawaii. This study found that alcohol intake of at least 25 ounces per month was directly correlated with the development of BPH.⁶²

Saw Palmetto (*Serenoa repens*)

As mentioned earlier, there is no known connection between BPH and prostate cancer other than the fact that they have some similarities in etiology and symptoms. In both cases, the conversion of serum testosterone to DHT in the prostate gland appears to be an important part of the disease process. The drug finasteride has been used to treat BPH and is being studied in prostate cancer prevention trials. Finasteride works by inhibiting the conversion of testosterone to DHT. It accomplishes this by blocking the effects of 5-alpha-reductase, which converts testosterone to DHT.

Saw palmetto is the fat-soluble medicinal fraction obtained from the small palm tree called *Serenoa repens*, which grows in the West Indies and southeast Atlantic coast of North America.⁶³ Saw palmetto extract has been found to inhibit the conversion of testosterone to DHT in the prostate.⁶⁴ It has also demonstrated anti-estrogenic and receptor site-binding effects.⁶⁵ Surprisingly, estrogen has been found to contribute to the effects of BPH and possibly prostate cancer because it reduces the ability of the

prostate to clear DHT levels.

A double-blind study of 35 men with BPH found that men given 160 mg of saw palmetto extract daily for 90 days had lower receptor values for estrogen and progesterone than those in a placebo group.⁶⁶ The researchers also found that saw palmetto extract blocks the translocation of the cytosol androgen receptor to the nucleus. The overall implications of the study are that saw palmetto extract has both anti-estrogenic and anti-androgenic effects. A double-blind, placebo-controlled study involving 110 BPH patients over 28 days found that saw palmetto administration significantly improved BPH symptoms, such as dysuria, nocturia, prostate volume, and residual urine.⁶⁷

Finasteride has had similar positive effects in the control of BPH but can take up to a year for the effects to occur, whereas saw palmetto generally produces positive effects in as little as 30 days and without serious adverse effects. Saw palmetto does not appear to effect PSA levels.

New research has discovered that men treated with saw palmetto had greater improvement in urinary tract symptoms associated with BPH than those who received placebo.¹¹⁵ A new randomized study of 44 men aged 45-80 years found that men receiving saw palmetto had improvement in symptoms associated with BPH, though this improvement did not reach statistical significance.¹¹⁶ A new microbiological study found that the application of an extract of saw palmetto to prostate cells led to increased rates of cell apoptosis.¹¹⁷

A new study has found that saw palmetto reduces the expression of cyclooxygenase-2, a newly-recognized factor in the development of prostate cancer and many other diseases.¹⁷⁹ Newer research has found that Permixon, a commercial product derived from saw palmetto, is an inhibitor of 5-alpha-reductase.¹⁸⁰ However, the researchers found that Permixon does not inhibit 5-alpha-reductase as much as the commonly-used drug, finasteride, but is probably safer. Newer research has shown how saw palmetto produces these positive effects at a deeper cellular level.¹⁸¹

Bitter Almond (*Pygeum Africanum*)

Pygeum africanum is an evergreen tree native to Africa. The fatty acids of the extract have similar properties to those of saw palmetto.⁶⁸ The tree also contains esters of ferulic acid, which have effects on the endocrine system. Studies have shown that docosanol reduces levels of testosterone and leutinizing hormone.⁶⁹ Docosanol is a compound that has been found in *Pygeum africanum*. Docosanol has been found to reduce prolactin levels in the body.⁷⁰ Prolactin increases the uptake of testosterone and increases the conversion of testosterone to DHT in the body. Pygeum contains quantities of docosanol but the esters of ferulic acid have similar activity and are found in greater concentrations and are more bioavailable in pygeum than docosanol.⁷¹ Ferulic acid esters have been shown to reduce the cholesterol content in the prostate.⁷² Cholesterol end-products in the prostate have been associated with both BPH and cancer.⁷³ The sterolic portion of pygeum also works against the accumulation of testosterone in the prostate.⁷⁴

Double-blind studies have found that standardized pygeum extract, like that of saw palmetto, improved a variety of urinary symptoms associated with BPH, such as urinary frequency, nocturia, flow interruption, after-dribbling, weak stream, and hesitation.⁷⁵ Pygeum has also been found to increase prostatic secretions and improve the composition of the seminal fluid.⁷⁶ Standardized pygeum extract has also been found in double-blind clinical trials to improve the capacity of BPH patients to achieve erections.⁷⁷ All of these factors suggest a role for pygeum in prostate cancer patients who have received a prostatectomy, and possibly a role in the prevention of disease. A double-blind study found that saw palmetto was more effective than pygeum extract in most measures of BPH, but pygeum has better proven effects on prostate secretion.⁷⁸ The standardized extract of pygeum is 14% triterpenes including betasitosterol and 0.5% n-docosanol. The typical dose is 100-200 mg per day in divided doses. The crude herb is not used therapeutically.

New research in rat prostate tissues suggest pygeum africanum extract has positive effects on processes associated with BPH development.¹¹⁸ An additional study in animal tissues found further evidence of positive effects from pygeum africanum administration on inflammatory effects associated

with the development of BPH.¹¹⁹ A review of 18 controlled clinical trials involving 1,562 men found that men treated with pygeum africanum for at least 30 days were more than twice as likely as controls to have symptom improvement associated with BPH than those receiving placebo.¹²⁰ New research suggests pygeum africanum can inhibit the progression of benign prostatic hyperplasia prostate cancer.¹⁸²

Cernilton

Clinicians in Europe have used an extract of flower pollen called Cernilton for more than 35 years to treat prostatitis and BPH.⁷⁹ Double-blind clinical trials have shown that Cernilton improved BPH patients at an overall success rate of 70%.⁸⁰ Nocturia and diurnal frequency symptoms improve in about 70% of patients.⁸¹ Researchers have found evidence that Cernilton contains a substance that can inhibit the growth of prostate cells.⁸³ A study of 79 males aged 62-89 evaluated the effects of the administration of 63 mg Cernilton pollen extract daily for 12 weeks.⁸⁴ The mean baseline prostatic volume was 33.2 cm. During the study period, maximum urinary flow rate increased from 5.1 to 6.0 ml/sec. Average flow rates increased from 9.3 to 11 ml/sec. In addition, residual urinary flow rates decreased from 54.2 ml to below 30 ml. Furthermore, all of the following measures improved in these patients: urgency, intermittency, delayed voiding, post-void dribbling, prolonged voiding, incomplete emptying, dysuria, and nocturia. Cernilton demonstrated 50% inhibition on DU145 cell line growth after 2 days exposure at 5 mcg/ml.⁸⁵ A recent review of studies involving cernilton for the treatment of BPH found that cernilton modestly improves urologic symptoms associated with BPH.¹²¹

***Urtica dioica* (stinging needles)**

Urtica dioica has also been found to have beneficial effects in the treatment of BPH. Two double-blind studies have shown it to have greater efficacy in treating BPH than placebo.⁸⁶ The range of efficacy in this plant appears to be comparable to that of pygeum. This ranks it lower than saw palmetto for the treatment of BPH and in prostate cancer prevention potential.⁸⁷ The effects of *Urtica dioica* are similar to those of saw palmetto in that its main activity appears to be the interference of dihydrotestosterone binding to both cytosolic and nuclear receptors.⁸⁸ This suggests a role in the prevention

of prostate cancer. A study of 431 patients with BPH found that a combination therapy composed of extracts from saw palmetto and *urtica dioica* was as effective as finasteride in treating the symptoms of disease.¹²²

A new randomized, double-blind study over a one-year period found that daily ingestion of 459 mg of a dry extract of stinging nettle root improved the objective disease and symptoms of benign prostatic syndrome in the group of treated men compared to controls.¹⁸³ A newer study found that an extract of stinging nettle root inhibits some key enzymes that are important in the development of prostate cancer.¹⁸⁴

Garlic

A compound in aged garlic significantly inhibited the growth of human prostate cancer cells in vitro.⁹² A new study has demonstrated that garlic has properties that can detoxify cancer-producing factors.¹²³ Preliminary studies with allium, a component of garlic, suggest this compound has strong anti-tumor properties in both prostate and breast cancer cells.¹²⁴ A different study found evidence that a constituent of garlic called S-allylmercaptocyste has anti-tumor effects in prostate cells by converting the breakdown products of testosterone into less harmful substances.¹²⁵

New research suggests garlic compounds inhibit the kinase enzymes that are important in the progression of prostate cancer.¹⁸⁵ A new population study of 238 men with prostate cancer and 471 disease-free controls found that the consumption of garlic and other allium vegetables is associated with a significant reduction in the risk of developing prostate cancer.¹⁸⁶

Citrus Pectin

Citrus pectin is a soluble component of plant fiber that is derived from citrus fruit. There is some evidence that citrus pectin can inhibit prostate cell formation and growth. A study in rats found that animals given 1.0% by volume citrus pectin in their drinking water had statistically significant reductions in the metastasis of prostate carcinoma compared to control animals.¹³² A study involving mice found that the administration of high-dose (1.6 mg/ml)

modified citrus pectin inhibited the tumor size after 20 days compared to controls.¹³³ A study of cancerous human prostate cells found that the addition of modified citrus pectin to the culture interfered with the mechanisms necessary for the cancer cells to multiply.¹³⁴ There is a significant amount of interest in studying modified citrus pectin for its anti-metastatic effects.¹³⁵ A new study of 13 men with prostate cancer found that the ingestion of modified citrus pectin reduced the progression of disease as assessed by PSA levels.¹⁸⁷

Green Tea

Green tea has been shown to have inhibitory effects on prostate cancer cell growth. Studies in rats suggest that compounds contained in green tea inhibit the activity of 5-alpha-reductase, the enzyme that converts testosterone to dihydrotestosterone, which has carcinogenic effects in the prostate.¹³⁶ Researchers have found that the most potent of these compounds is called epigallocatechin-3-gallate (EGCG).¹³⁷ A study in rats found that green tea has inhibitory effects on other enzymes associated with the growth of prostate cancer cells.¹³⁸ EGCG has been found in high concentrations in the serum of green tea drinkers. EGCG and other compounds in green tea inhibit the activity of the enzyme called proteasome, a key factor in the formation of prostate cancer.¹³⁹

A new study has found that the green tea compound epigallocatechin-3-gallate inhibits the activity of the enzyme cyclooxygenase (COX)-2, which, as previously mentioned, is involved in the progression of prostate cancer.¹⁸⁸ A newer epidemiological study has found further evidence that green tea can reduce the risk of prostate cancer.¹⁸⁹ Epigallocatechin gallate has been shown to inhibit prostate cancer in another study.¹⁹⁰ A case-control study of 130 cases and 274 controls in China found that green tea consumption significantly reduces the risk of developing prostate cancer over a lifetime.¹⁹¹ Epigallocatechin-3-gallate has been shown to destroy prostate cancer cells in another study.¹⁹² A new clinical trial involving 42 patients with prostate cancer found that green tea has some anticancer activity in patient with androgen-independent prostate carcinoma.¹⁹³ The degree of anticancer activity was determined using PSA tests.

Spices

Spices add flavor to food but also may have cancer-fighting properties. India has one of the lowest cancer rates in the world, and the people there typically eat a diet containing a wide variety of spices. There is some limited evidence that capsaicin, the component of chile peppers that makes them hot, has some anti-cancerous properties. Both curry and cumin contain turmeric, which has been found to have anti-carcinogenic properties in cell cultures.¹⁴⁰ In studies involving mice, curcumin has demonstrated anti-carcinogenic activity in a variety of cancers.¹⁴¹ While the mechanisms of its action are still unknown, curcumin has also demonstrated anti-carcinogenic effects in human cancer cell lines.¹⁴² A new study involving curcumin found that this spice inhibits prostate cancer growth by making natural cancer-fighting processes within the cell more effective.¹⁹⁴ A new study found that curcumin inhibits the metastasis of prostate cancer to the bones.¹⁹⁵ Another study found that curcumin increases the susceptibility of prostate cancer cells to radiation therapy.¹⁹⁶

Research from animal studies in Asia has suggested capsaicin has anti-tumor effects.¹⁴³ A study at Yale University found that capsaicin interferes with the tumor-formation process in mice.¹⁴⁴

Other Agents

A commercial eight-herb formulation called PC-SPES fed to rats in 0.05% and 0.025% levels in the diet led to dose-dependent effects on both tumor incidence and tumor growth rate.⁸⁹ PC-SPES decreased serum testosterone in six men with prostate cancer. An additional eight of eight patients had reduced PSA levels after using PC-SPES. PC-SPES has strong estrogenic activity that could cause adverse effects.⁹⁰ A study among 16 men with hormone-refractory prostate cancer led to significant improvement in quality-of-life measures, reduction in patient pain ratings, and decreased PSA levels.⁹¹

A new study found that silibinin, a flavolignan derived from the fruit of *Silybum marianum*, inhibits the conversion of testosterone to DHT.¹⁹⁷ The herbal agent from Traditional Indian Medicine, rasagenthi lehyam (RL), is used to treat cancer in some areas of India. A new study has found some positive effects of RL on the inhibition of prostate cancer

progression.¹⁹⁸ A new study of a new Amazonian plant extract called BIRM found that this compound inhibits prostate cancer growth and metastasis.¹⁹⁹ A new study of dietary isoflavones obtained from the red clover plant found that these compounds increased apoptosis in prostate cancer cells.²⁰⁰ New research that assessed the effects of an extract of the Terminalia chebula fruit found that this compound inhibited prostate cancer cell growth.²⁰¹

Biofeedback therapies can help men with prostate cancer and prostatectomy restore pelvic muscle function.⁹³ A treatment group regained continence after 51 days compared to 56 days in the control group. Acupuncture was used on 7 men who developed hot flushes after receiving castration therapy for prostate cancer.⁹⁴ Six of the men completed 10 weeks of acupuncture therapy and had an average symptom decrease of 70%. A new study of ginseng found that a constituent called ginsenoside Rg3 demonstrated inhibitory action against a human prostate carcinoma cell line.¹²⁶

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