

Treatment of Prostate Cancer with Natural Therapeutics

— FIFTH EDITION —

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antigen.^{7,8}

Introduction

The prostate is a walnut-sized gland located just beneath the urinary bladder. It is part of the urinary system and the reproductive system. There are passages through the prostate that carry either urine or semen. In fact, the prostate also helps produce semen, the thick fluid that carries sperm cells produced in the testicles. The prostate surrounds the upper part of the urethra, which is the tube that carries urine from the bladder. Prostate function is regulated by testosterone, the male sex hormone, which is produced primarily in the testicles. Prostate cancer is a cancer that starts in the prostate gland, but may spread to other organs and tissues of the body.

Prostate cancer is the second most common cancer in men worldwide. In 2012, for example, there were 1.1 million cases of prostate cancer and over 300,000 men died from the disease. In the United States, the National Cancer Institute estimates that 233,000 men will be diagnosed with prostate cancer in 2014 and the disease will kill almost 30,000 American men.¹ Despite research developments and innovations, the annual number of new cases of prostate cancer has remained constant over the past two decades. The lifetime risk of prostate cancer for American men (living in the United States) is one in six.²

The risk of prostate cancer is strongly correlated with age, so the risk of prostate cancer increases dramatically between age 40 and age 75.³ Prostate cancer occurs more often in African Americans than in Caucasian or Hispanic men. For reasons that are unclear, the disease is relatively rare in Asia, Africa, and Latin America. Sadly, prostate cancer tends to be more advanced in African American men at the time of diagnosis. There is considerable evidence that prostate cancer runs in families, but it has been a challenge for researchers to determine the specific genes that cause the disease. To date, the only genes that seem to help predict prostate cancer are those that are used for breast and ovarian cancer, namely BRCA1 or BRCA2 mutations.⁴ Importantly, simply having a mutation in BRCA does not necessarily mean that a person will develop prostate cancer.

Prostate cancer screening

Prostate cancer usually grows at a slow rate. In the early stages of the disease, prostate cancer is considered “silent,” which means that it does not cause any noticeable symptoms. This can be a dangerous aspect of the disease because men can have prostate cancer and not know it for months to years. Therefore, screening tests for prostate cancer may be helpful.

Digital rectal examination

Digital rectal examination is a key screening test for prostate cancer. In a digital rectal examination, the physician places a gloved and lubricated finger into the rectum to feel the shape and size of the prostate gland. Findings that would indicate or suggest prostate cancer during a digital rectal examination are abnormal or asymmetric borders of the prostate gland, hard areas of the prostate called in duration, or nodules in the gland. While digital rectal examination is important, it is not foolproof. Only 85% of prostate cancers start in the area that they could be felt during the examination. Also, by the time that a prostate tumor has grown to the size that it can be felt by a physician, it is likely to be fairly advanced.⁵ Nevertheless, digital rectal examinations can double the chances of detecting prostate cancer⁶, so this screening is still important. However, digital rectal examination is likely more accurate when combined with another prostate cancer screening test called prostate specific

Prostate specific antigen (PSA)

Prostate specific antigen, better known as PSA, is a molecule that is produced by the prostate gland. Men with prostate cancer may have increased levels of PSA in their blood because the prostate gland is enlarged and/or the cancer has partially destroyed the prostate gland allowing more PSA to leak into the blood. As with digital rectal examination, there are benefits and limitations to this prostate cancer screening test. On the positive side, PSA levels may be abnormally elevated very, very early in prostate cancer.⁹ This means that prostate cancer may be detected long before it has spread and long before it is detectable by digital rectal examination. On the other hand, some illnesses can increase the level of PSA in the blood such as benign prostatic hyperplasia and bacterial prostatitis. Even relatively minor events can raise PSA such as holding onto urine to the point of discomfort, a recent ejaculation, or even digital rectal examination itself.^{10,11} Therefore, simply having an abnormally high PSA test does not make the diagnosis of prostate cancer. Tracking PSA levels over time may help physicians distinguish between minor illness and prostate cancer.

Limitations of prostate cancer screening

Neither digital rectal examination nor prostate specific antigen testing are very sensitive or specific for prostate cancer. Because screening can be abnormal in people without prostate cancer. An abnormal PSA and/or digital rectal examination usually requires a prostate biopsy has follow-up. During a prostate biopsy, a needle is passed into the prostate gland and a piece of prostate is removed for analysis. There are risks associated with prostate biopsy including bleeding, infection, and prolonged pain (longer than one week).¹² In a European study, only one man in 1000 actually benefited from more than a decade of PSA testing and 75% of men with abnormal PSA did not have prostate cancer even though they underwent prostate biopsy.¹³ Some organizations, such as the United States Preventive Services Task Force have recommended against using PSA for prostate cancer screening.¹⁴ Other groups such as the American Cancer Society and the American Urological Association suggest that prostate screening should be tailored to those individuals that have particular risk such as black men or older man.¹⁵

Signs and Symptoms

As mentioned, a man can have prostate cancer for quite some time before any symptoms are noticeable. However, if symptoms do occur they are usually the result of a prostate that has grown in size because of the cancer. Since the prostate gland rests just below the bladder and urine flows through the gland, swelling in the prostate can interfere with urination. This means that man may need to urinate more frequently than normal, particularly during the night. Moreover, men with prostate cancer may have difficulty starting urination and stopping urination. In severe cases, a tumor in the prostate gland will block urine flow entirely making urination impossible. Other symptoms of prostate cancer include blood in the urine, blood in the semen, pain during ejaculation, pain or burning during urination, and discomfort or pain in the pelvis, lower back, and/or upper legs.

Some of these symptoms may occur in diseases other than prostate cancer, such as benign prostatic hyperplasia and

bacterial prostatitis. Benign prostatic hyperplasia or BPH is very common and causes problems with urination, bacterial prostatitis, on the other hand, is an infection and inflammation of the prostate that causes generalized pain in the pelvis and lower back and may also interfere with urination. Therefore, a man that experiences the symptoms should seek medical attention as soon as possible but the symptoms do not necessarily mean that he has prostate cancer.

Risk factors and protective factors

Research over the past several decades has revealed a number of factors that either increase or decrease the risk of developing prostate cancer. There are four main risk factor groups: age, ethnicity, genetic predisposition, and diet/environment. Obviously little can be done about the first three risk groups, but overall risk for prostate cancer can be substantially lessened by avoiding certain dietary and environmental risk factors while augmenting and supplementing the diet with potentially beneficial foods and natural products.

Age and genetics

Advancing age is the most potent risk factor for prostate cancer. In fact, prostate cancer is more strongly associated with advancing age than any other human cancer.³ Diagnosed prostate cancer is very uncommon before the age of 40, though the prevalence of prostate cancer that is not clinically detectable ranges from 2 to 30% in men under the age of 40. The prevalence of prostate cancer peaks between the ages of 70 and 80 with as many as 83% of men in that age range having prostate cancer that may or may not be clinically detectable.¹⁶

Prostate cancer appears to run in families, but scientists have been unable to identify the gene or genes most often associated with the disease. Several candidates have been identified such as BRCA1, BRCA2, and HOXB13 along with other minor genetic polymorphisms. There are no genetic tests for the diagnosis of prostate cancer. Moreover, no genetic tests reliably predict the risk of developing prostate cancer. Nevertheless, research in this field is ongoing.

Ethnicity

African American men had the highest rates of prostate cancer out of any ethnic group in United States. In a sample of men in their 70s, African American men developed prostate cancer 60% more often than white men. Asian men, on the other hand, develop prostate cancer 30% less often than white men. Another important finding is that African American men generally develop prostate cancer earlier in life than other ethnicities. In a research study of over 12,000 participants under the age of 50, roughly 8% of black men had prostate cancer compared to 3% of white men.¹⁷ It is important to note that genetics may not entirely explain this difference—differences in diet between ethnicities may strongly affect prostate cancer incidence.¹⁸

Red meat and animal fats

Several studies have shown a diet high in animal fat increases the risk for prostate cancer.^{19,20,21} Red meat and processed meat, in particular, are associated with increased rates of prostate cancer.¹⁹ A diet containing few vegetables is a risk factor for prostate cancer²¹ and men who consume less than 14 servings of vegetables each week at a 54% increased risk of prostate cancer than men who eat 28 or more servings of vegetables each week.²²

Omega-3 fatty acids

While omega-3 fatty acids confer a number of health benefits, especially in heart disease, there is evidence to suggest that very high levels of omega-3 fatty acids may actually increase the risk of prostate cancer. Early studies seem to suggest omega-3 fatty acids helped prevent prostate cancer²³, but large, prospective clinical trials show high levels of omega-3 fatty acids can actually increase the risk of high-grade prostate cancer.^{24,25} Thus, it seems, that omega-3 fatty acid intake should be modest; it should be high enough to be helpful in heart disease and other forms of cancer but not so high as to increase the risk of prostate cancer.

Corn Oil

Evidence is emerging that the ingestion of large quantities of corn oil may increase the risk of developing prostate cancer and may stimulate the growth of cancer cells once prostate cancer starts. Studies in mice showed corn oil and linoleic acid stimulated the growth of prostate cancer cells.^{26,27} It is important to note these studies may implicate high-fat diets as a risk factor for prostate cancer rather than corn oil itself.

Cholesterol

Cholesterol is an important factor in the formation of testosterone, estrogen, and other 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. Likewise, cholesterol lowering drugs called statins may reduce the risk of dying from prostate cancer²⁸, but they do not seem to reduce the risk of developing prostate cancer.^{29,30}

Cigarette smoking

Smoking cigarettes appears to be a risk factor for the development of prostate cancer but it also worsens the prognosis once prostate cancer is diagnosed. The risk is especially strong in African-Americans. In a study of 1085 men with prostate cancer, those who were heavy smokers had an increased risk of advanced or aggressive prostate cancer than those who were light smokers or never smoked it all. Moreover, the risk was especially strong in African-Americans in this study. Those who smoke at the time of diagnosis are much more likely to have their prostate cancer recur or to die from the cancer than non-smokers.³¹

Alcohol

One large meta-analysis and one large clinical trial showed there is no association between modest alcohol consumption and prostate cancer. The meta-analysis combined the results of 235 studies with a total of 117,000 cases of prostate cancer. The researchers found there was no consistent relationship between alcohol intake and prostate cancer.³² Likewise, in a prospective study, 10,660 men with no or modest alcohol intake (less than 50 g per day or three alcoholic beverages) had no increased risk for developing prostate cancer. On the other hand, 260 men in the study who consumed four or more alcoholic beverages each day doubled their rate of aggressive (high-grade) prostate cancer.³³

Vitamin D, calcium, milk and casein

There is a complex association between vitamin D and calcium, milk and the risk of prostate cancer. Several studies have suggested that people who consumed higher levels of dairy products have a greater risk of prostate cancer^{34,35,36,37,38},

but other studies failed to show the same effect.^{39,40} Likewise, some studies have shown that vitamin D deficiency may increase as the risk of prostate cancer,^{37,41} while others have indicated high and very low levels of vitamin D increase the risk.^{42,43} Based on current evidence, it seems keeping normal levels of vitamin D (not too high or too low) is the best way to minimize risk. One factor that may partially explain the discrepancy and findings is the difference between vitamin D and calcium that comes from milk and vitamin D which comes from supplements. Laboratory evidence suggests casein, a major protein found in cow's milk cause prostate gland cells to become cancerous and also to promote the growth of these cancerous prostate cells.⁴⁴ While there is still more to learn about these substances and prostate cancer it seems the vitamin D and calcium from milk, especially cow's milk, may be a potential risk factor for prostate cancer. Some sources suggest limiting total calcium (diet and supplements) to 1,500 mg to 2,500 mg per day.^{45,46}

Vitamin E and selenium

Numerous laboratory studies showed that the vitamin E was able to inhibit the growth of various types of cancer cells, especially prostate cancer. Moreover, a study of 29,133 men found 1,732 developed prostate cancer during 19 years of follow-up and those who received vitamin E supplementation had a significantly reduced risk of developing prostate cancer.⁴⁷ Similar results have been shown for selenium supplementation. A study of 9,345 Japanese-American men who had serum samples drawn and frozen in the 1970s and were assessed for prostate cancer incidence 20 years later revealed those with the highest selenium levels only half as likely to have disease as those with the lowest levels.⁴⁸

Because of these and other studies, researchers performed large, prospective, clinical trials to study the effects of vitamin E and the risk of prostate cancer. The SELECT trial included 35,533 men who were randomly assigned to daily supplementation with 200 mcg of selenium, 400 IU of vitamin E, both, or neither (appropriate placebo). Not only did vitamin E or selenium not prevent prostate cancer, but the trial was stopped early because safety advisers found that people who were supplementing with vitamin E had a significantly increased incidence of prostate cancer.^{49,50,51} In the same trial (SELECT), vitamin E supplementation did not benefit men with low selenium levels but it did increase the risk of aggressive prostate cancer among men with high selenium levels in the blood.⁵² In the Physicians' Health Study II, a double-blind, placebo-controlled trial in which 14,641 male healthcare providers supplemented their diet with one or more vitamins, vitamin E supplementation had no effect on the incidence of prostate cancer (though in this study, vitamin E supplementation did not increase the risk).⁵³ These results suggest men who are interested in minimizing their risk of prostate cancer should maintain normal levels of vitamin E and selenium but should not exceed normal levels.

Folic acid

Limited evidence suggests folic acid supplementation increases the risk of prostate cancer. This data primarily comes from a large study designed to assess the role of aspirin and folic acid in the prevention of polyps in the large intestine.⁵⁴ A group of 1021 men was divided into two groups and randomly assigned to receive either 1 mg of folic acid each day or placebo. The folic acid was in addition to the amount they may take in through their diet. After 10 years of follow-up, 9.7% of the

men who consumed folic acid supplements developed prostate cancer compared to 3.3% in those who took placebo. In other words, folic acid supplements nearly tripled the risk of prostate cancer. It is important to note regular dietary folic acid consumption was not closely monitored in this study and so it is possible men were consuming considerable amounts of folic acid in their diet in addition to folic acid supplements.

Zinc

There are several reasons to believe zinc might be beneficial in preventing prostate cancer, but recent large clinical trials suggest just the opposite. Zinc can reduce the size of the prostate and can decrease symptoms of benign prostatic hyperplasia.⁵⁵ In laboratory studies, zinc was able to block the spread of prostate cancer cells and prompted the cells to "commit suicide" (i.e., a process known as apoptosis). On the other hand, the very large Health Professionals Follow-Up Study that followed 46,974 American men found those who consumed over 100 mg of zinc supplements each day for 10 years or more had a 2.29 fold increase in the incidence of prostate cancer.⁵⁶

Obesity and inactivity

Obesity increases the risk of prostate cancer.⁵⁷ Moreover, being overweight and obese are risk factors for developing particularly aggressive prostate cancer.⁵⁸ The overall increased risk of prostate cancer that results from obesity is relatively small, but the risk increases as the amount of excess weight increases.⁵⁹ Also, being obese as a child can increase the risk of prostate cancer later in life.^{60,61} A lack of physical activity is a risk factor for prostate cancer, but perhaps surprisingly, the effect only emerges after the age of 65. In other words, the amount of physical activity a man performs does not seem to be related to prostate cancer risk until that man reaches the age of 65. Afterwards, strenuous physical activity for more than three hours per week significantly reduces the risk of advanced or fatal prostate cancer.⁶² However, given the benefits of regular exercise throughout life and the fact it might be difficult to start a strenuous exercise regimen at the age of 65, a lifelong dedication to exercise is probably the better health decision.

Diabetes and excess sugar

Diabetes is a disease in which blood sugar levels become abnormally high because the cells of the body are not able to absorb glucose from the blood. Blood sugar or glucose is a key nutrient for all types of cancer cells, including prostate cancer. Normal, healthy cells can survive and even thrive on relatively low levels of sugar in the blood. Cancer cells, on the other hand, are highly metabolically active and need a lot of sugar to grow and reproduce. Evidence suggests cancer growth may be faster in people with diabetes, insulin insensitivity, and in those who eat excessive amounts of sugar.⁴⁵ Conversely, reducing the amount of simple sugars can slow the growth of prostate cancer cells⁴⁵, which may also explain, at least in part, why obesity is a risk factor for prostate cancer. Some studies suggested metformin, a treatment for type II diabetes, might have reduced the risk of prostate cancer. However, in a large study of nearly 120,000 men taking metformin it did not change the incidence of prostate cancer.⁶³ Nonetheless, in men who have diabetes, are taking metformin, and develop prostate cancer, metformin may be able to improve survival.⁶⁴

Environmental toxins

Certain environmental toxins have been shown to increase the risk of prostate cancer. Exposure to Agent Orange, a chemical

that was sprayed in the jungles of Vietnam between 1965 and 1971, increases the rate of aggressive prostate cancers⁶⁵ and increases the risk of recurrence after surgery for prostate cancer.⁶⁶ Dioxins, found in high concentrations in Agent Orange, are apparently cancer-causing ingredient. Chlordecone is a pesticide used in the West Indies between 1973 and 1993. Exposure to the substance increased the rate of prostate cancer in men.⁶⁷ Bisphenol A, widely known as BPA, has been and continues to be used in the manufacture of plastics. Evidence suggests BPA exposure, especially early in life, increase the risk of developing prostate cancer later in life, though most work has been done in laboratory rather than clinical settings.⁶⁸ Other compounds that may increase the risk of prostate cancer include polyhalogenated biphenyls, hexachlorobenzene, and diethylstilbestrol (DES).⁶⁹

Diagnosis and conventional treatment

The diagnosis of prostate cancer relies heavily on the results of a prostate biopsy. A pathologist will analyze the biopsy and assign a Gleason score or grade. Gleason scores reflect how likely it is that the tumor will spread. The score can vary between 2 and 10 where 2 indicates a small likelihood of spread and 10 indicates a high likelihood of spread. The oncologist will also determine the size of the tumor, if there are cancer cells in nearby lymph nodes or if there is any cancer present in distant tissues (metastasis). The choice of conventional treatment is based on PSA level, Gleason scores, and other information about the prostate tumor. Unfortunately, a negative biopsy (no disease seen) does not exclude the diagnosis of prostate cancer (i.e., a false negative result).

Patients are divided into one of several categories: very low risk, low risk, intermediate risk, high risk, locally advanced, and metastatic prostate cancer. In older patients with very low risk disease, conventional treatment may not be used; instead, doctors provide active surveillance or simply watch for signs of progression.⁷⁰ Depending on their individual risk, men with prostate cancer may be treated with active surveillance, radiation therapy, surgery, hormonal therapy, and chemotherapy. Some oncologists may offer other prostate cancer therapies including cryotherapy and high-intensity focused ultrasound or HIFU.

Radiation therapy is usually administered in one of two forms: external beam radiation or brachytherapy. External beam radiation involves a device placed on the outside of the body that projects a beam of ionizing radiation at the prostate gland. Brachytherapy involves the placement of small “seeds” or pellets in the prostate gland itself. These pellets emit low levels of radiation that affect the prostate tissue immediately surrounding each pellet. Since cancer cells grow and reproduce faster than healthy cells, the radiation disrupts prostate cancer more so than normal prostate cells. External beam radiation may cause inflammation of the bladder and the large intestine and it may also increase the risk for bladder and gastrointestinal cancers. While brachytherapy is less likely to cause adverse effects because the total dose of radiation is less and affects smaller areas of tissue, there are still side effects. Brachytherapy is also known to increase the risk of bladder cancer.

In men who have metastatic prostate cancer, a special form of radiation may be administered intravenously. Radium-223 moves from the bloodstream into bones, a common site for metastatic prostate cancer cells. The radium-223 is administered in a series of six injections, one per month.

Radium-223 emits radiation that kills prostate cancer cells that have migrated to bones.

The traditional surgery for prostate cancer is a radical prostatectomy, which is the complete removal of the prostate gland. Unfortunately, impotence is common after removal of the prostate gland, especially in patients with certain risk factors.⁷¹ The CyberKnife system allows a surgical oncologist to provide radiosurgery, which is closer radiation therapy than true surgery. The CyberKnife system was cleared by the FDA in 2001 for use on any target organ in which radiation therapy is appropriate and indicated. The physician uses advanced imaging technologies and robotics to selectively direct high doses of radiation at prostate cancer tissue. The radiation is delivered from outside the body, so it is noninvasive and no hospital stay is required. Effectiveness of CyberKnife is comparable to other primary treatments for prostate cancer.⁷² Men with low and intermediate risk prostate cancer may be candidates for CyberKnife treatment.

Other procedures for prostate cancer treatment—cryotherapy and high-intensity focused ultrasound—are still under clinical evaluation. Cryotherapy and high-intensity focused ultrasound are forms of ablation therapy which selectively destroy tissue either by freezing or by heating the tissue with ultrasound energy, respectively. Cryotherapy is performed under spinal/epidural anesthesia rather than general anesthesia and is less invasive than open surgery to remove the entire prostate gland. Cryotherapy is an option for men with localized disease or recurrent prostate cancer that remains near the prostate. Early use of cryotherapy was associated with very high complication rates and adverse events and was only offered by few surgical oncologists. However, the techniques associated with cryotherapy have improved, especially the addition of high precision transrectal ultrasound imaging, which allows the surgeon to view the prostate in real time and control the amount of tissue freezing. Because of these advancements, cryotherapy may be a reasonable choice for some men. Candidates for cryotherapy include men with early stage prostate cancer who have not yet had specific treatment such as radiation therapy or surgery. On the other hand, men may be offered cryotherapy as a palliative therapy if other treatments for prostate cancer have failed.⁷³ Cryotherapy may cause pain and swelling in the treated region, incontinence or difficulty with urination, and impotence.

High-intensity focused ultrasound is an outpatient procedure that takes about two hours. The ultrasound device is placed in the rectum near the prostate gland and ultrasound energy heats the cancerous tissue and surrounding tissues to small degree, which destroys the tissue. High-intensity focused ultrasound is not approved in the United States for the treatment of prostate cancer but clinical trials in the United States are ongoing. The technology has been approved for the treatment of prostate cancer in Europe and Asia.

Chemotherapy and hormone therapy are usually reserved for prostate cancer patients with high risk of disease. The hormone therapy for advanced prostate cancer is androgen deprivation therapy, which essentially means blocking or removing the effect of testosterone. Androgen deprivation therapy is accomplished by administering hormonal drugs such as leuprolide or goserelin plus flutamide or by surgically removing the testicles. Bicalutamide (Casodex) is an anti-androgen drug and is apparently ineffective in treating localized prostate cancer. The Early Prostate Cancer program was a

randomized, placebo-controlled, international trial with over 8,000 participants comparing bicalutamide or placebo added to standard prostate cancer treatment. After seven years of follow-up, bicalutamide provided no added benefit to men with localized prostate cancer, though men with locally advanced prostate cancer enjoyed significant clinical benefits.⁷⁴ Chemotherapy is not often used in prostate cancer, but if it is used, it may cause nausea, vomiting, hair loss, anemia, and deficiencies in the immune system.

Protective factors

Coffee

Coffee but not necessarily caffeine, protects against developing lethal (fatal or metastatic) prostate cancer. The Health Professionals Follow-up Study followed nearly 48,000 men over a period of 20 years and found just over 5000 men who developed prostate cancer. Of these, 642 men died or had metastatic prostate cancer. After controlling for other known prostate cancer risk factors, people who consumed more coffee per day were less likely to be in that group of 642.⁷⁵ Most interestingly, decaffeinated coffee had the same effect, which means the protective ingredient is found within coffee, but is not caffeine.

Soy

One of the reasons that Asian populations have far fewer cases of prostate cancer than Western cultures could be because many Asian nations have diets high in soy and soybean products. Soybeans are rich sources of healthful substances such as beta-sitosterol, stigmaterol, genistein, daidzein, and glycitein. In a group of 200 men with benign prostatic hyperplasia, those who consumed 20 mg of beta-sitosterol three times a day increased urine flow through the prostate gland and significantly reduced the amount of urine remaining in the bladder compared to those taking placebo.⁷⁶ Daidzein and genistein, two other substances in soy, have similar effects on urine flow through the prostate gland.⁷⁷ Genistein, in particular, has a number of anticancer properties: it has been shown to inhibit the growth of prostate cancer cells and cause abnormal cells to undergo apoptosis (“cell suicide”).⁷⁸ Animal studies have suggested a diet high in genistein and daidzein results in a lower incidence of prostate cancer and longer disease-free periods after exposure to cancer-causing agents.⁷⁹ Among a cohort of 12,395 California Seventh-Day Adventist men, 225 developed prostate cancer during the study period. Those men who frequently consumed soymilk reduced their rate of prostate cancer by 70%.⁸⁰ In a survey of 1619 men of various ethnicities, those who ate soy products had reduced risk of prostate cancer.⁸¹ Indeed, levels of genistein in the blood inversely correlated with risk of prostate cancer in 14,203 Japanese men, i.e., higher blood levels of genistein were associated with lower prostate cancer risk and vice versa.⁸² Across various clinical studies, those who commonly ate soy and soy food products lowered their risk of prostate cancer by 30%.⁸³

Typical Western diets provide only about 80 mg/day of phytosterols (the useful ingredients in soy) compared to a traditional Japanese diet, which contains about 400 mg/day.⁸⁴ A three-and-a-half ounce serving of soybeans or tofu contains about 90 mg of beta-sitosterol. Asian cultures are believed to consume about 20-80 mg/day of genistein, whereas Western populations consume about 2-3 mg/day.^{77,79}

Lycopene

Lycopene is a potent antioxidant found in high concentrations in tomatoes, tomato products, and certain other fruits and vegetables (e.g., watermelon, pink grapefruit, carrots, and green peppers). In addition to its antioxidant activity, lycopene has several anticancer effects. In laboratory studies, lycopene can slow the growth and proliferation of prostate cancer cells, can cause prostate cells to commit suicide (apoptosis), stop the cycle of new cancer cells from forming, and prevent tumor cells from spreading through tissues to the rest of the body.⁸⁵ Men with the highest levels of lycopene in their blood were least likely to develop prostate cancer.^{86,87} A prospective cohort study of 47,894 subjects found lycopene intake from tomato products was inversely associated with the risk of prostate cancer.⁸⁸ Likewise, eating tomato sauce decreased the risk of prostate and other forms of cancer.^{89,90} A prospective study showed two or more servings of tomato products or lycopene per week reduced the risk of developing prostate cancer by at least 23% compared to those who ate tomato products/lycopene less than once per month.⁹¹ In a study that examined 49,898 male health professionals over a period of 13 years, higher dietary intake of lycopene was associated with lower risk of deadly prostate cancer.⁹² Moreover, those that did develop prostate cancer had less angiogenesis (blood vessel connections) in the tumor. Tumors with fewer blood vessel connections do not grow as quickly and are less likely to spread.

Cruciferous vegetables

Cruciferous vegetables are vegetables such as cauliflower, cabbage, broccoli, bok choy, kale, brussels sprouts, collard greens, and various others. Cruciferous vegetables contain a number of molecules that are protective or potentially protective against prostate cancer, and block normal prostate cells from converting into cancer cells and also slow the rate of prostate cell growth and proliferation.⁹³ Interestingly, cruciferous vegetables disrupt intracellular signaling pathways in prostate cancer cells but not in healthy prostate gland cells.⁹³ Thus, these green vegetables are likely to be helpful in prostate cancer prevention but also may help slow the growth of prostate cancer once it exists. In a meta-analysis that included seven cohort and six population-based case-control studies, researchers found prostate cancer risk significantly decreased as intake of cruciferous vegetables increased.⁹⁴ On average, the reduced risk was between 10 and 20%. In men who have already developed prostate cancer, those who consumed the highest amounts of cruciferous vegetables decreased the risk of prostate cancer progression by 60% compared to those who consumed the fewest cruciferous vegetables.⁹⁵

Green Tea

Green tea inhibits prostate cancer cell growth. Studies in rats showed that compounds contained in green tea inhibit the activity of 5-alpha-reductase, the enzyme that converts testosterone to dihydrotestosterone (DHT).⁹⁶ DHT has carcinogenic effects on the prostate gland. Researchers have found the most potent of the green tea compounds is a catechin called epigallocatechin-3-gallate (EGCG). Aolyphenone-60, an extract of green tea that is rich in catechins, slowed the development of prostate cancer.⁹⁷ Green tea catechins, including EGCG, suppressed the growth of human prostate cancer cells, and prompted them to “commit suicide” (apoptosis).⁹⁸ The polyphenolic fraction of green tea not only inhibited localized prostate cancer growth but also inhibited the metastasis of the cancer to distant sites.⁹⁹ Interestingly, green tea

catechins tend to concentrate in the prostate gland after humans consume green tea suggesting these molecules target the prostate.¹⁰⁰ Clinical trials in humans with green tea have been difficult because of differences in dosages and intake levels. As a result, observational studies have not shown a strong connection between green tea consumption in the prevention of prostate cancer. On the other hand, several phase 2 clinical trials have shown green tea extracts can inhibit prostate cancers from progressing from a precancerous state to a malignant state.¹⁰¹ According to some reviews, the optimal amount of green tea intake in a day is between 3 to 5 cups, which should be sufficient to supply at least 250 mg of green tea catechins per day.¹⁰²

Garlic

Allium species include various forms of garlic, onion, leek, and chives. Allium vegetables are good source of molecules with cancer fighting properties, such as organic sulfur and flavonols. A compound in aged garlic significantly inhibited the growth of human prostate cancer cells in a laboratory setting.^{103,104} A substance within garlic called diallyl disulfide may be the key factor that causes prostate cancer cells to enter apoptosis (programmed cell death; “cell suicide”).¹⁰⁵ The consumption of various Allium species and in particular garlic is associated with a reduced rate of developing prostate cancer.¹⁰⁶ Researchers combined the results of nine epidemiological studies which together included 132,192 participants. They found garlic consumption reduced the risk of developing prostate cancer by 23% and onion consumption reduce that risk by 16% (the onion result was not statistically significant).¹⁰⁶

Ginger

Ginger is a root that is best known as a food substance; however, it possesses a number of interesting biological properties and has been used as a medicine for over two thousand years.¹⁰⁷ Ginger is an anti-inflammatory and antioxidant, which make it useful in the prevention of cancer initiation and development.^{107,108} Various compounds extracted from ginger work together to block the proliferation of human prostate cancer cells in test tubes.¹⁰⁹ Extracts of ginger can block the cell cycle of prostate cancer cells and induce those cells to die through apoptosis (“cell suicide”).¹⁰⁸ Animals with prostate cancer fed 100 mg per kilogram body weight of ginger extracts experienced a 56% slowing of their prostate tumor growth as measured by prostate size after eight weeks of treatment.¹⁰⁸ Human trials of ginger root and/or Ginger root extract in the treatment or prevention of prostate cancer have not yet been performed.

Curcumin

Curcumin, a compound found in turmeric and present in various curry preparations, is currently being evaluated in clinical trials for various forms of cancer, skin and joint disorders, and Alzheimer’s disease. In mice, curcumin has shown remarkable ability to block cancer affects in a variety of cancers.¹¹⁰ Curcumin decreased the proliferation of both testosterone and testosterone prostate cancer cells in mice.¹¹¹ Curcumin also increased the tumor killing power of chemotherapeutic agents in test tubes.¹¹² Clinical trials of curcumin treatment for prostate cancer have not yet been completed.

Shiitake and Maitake mushrooms

Both Shiitake and Maitake mushrooms have been investigated as medicinal foods. Laboratory investigation suggests Shiitake

and Maitake mushrooms may be able to boost the immune system and therefore could be helpful in treating conditions such as existing cancers and HIV/AIDS. Both forms of mushrooms have been used in Traditional Chinese Medicine for nearly 2000 years. In Western medicine, specific extracts of these mushrooms have been the focus of most studies. The two substances within shiitake mushrooms that holds the most promise is a beta glucan/glycan called lentinan or Active Hexose Correlated Compound (AHCC). AHCC is rich in alpha-glucans. In a double-blind, placebo-controlled trial, 21 healthy volunteers received either placebo or 3 g per day of AHCC for four weeks. The 10 volunteers in the AHCC group had a significant increase in the activity of dendritic cells.¹¹³ Dendritic cells create specific immunity and are very useful in fighting cancer.¹¹⁴

For Maitake mushrooms, the create key ingredient appears to be the D-fraction extract which is rich in beta 1,3 and 1,6 glucans. D-fraction was able to boost the immune system so that it attacked prostate cancer cells without attacking normal, healthy cells.¹¹⁵ Most work with these extracts has been done in breast cancer and some work in gastric cancer with relatively little attention paid to prostate cancer. However, since the mushrooms ask act as immune boosters there may be generalizable effects against all forms of cancer.

There have been few clinical trials using these mushrooms or their extracts in prostate cancer patients. One study of 62 men with active prostate cancer treated with a shiitake mushroom extract showed it was ineffective at lowering prostate specific antigen levels after six months of use.¹¹⁶ Conversely, a trial of 75 patients with metastatic prostate cancer showed that 2 mg per week of lentinan injected into a muscle, improved five year survival from the disease when combined with chemotherapy.¹¹⁷

Boron

Several lines of evidence suggest the element boron may protect against the development of prostate cancer. In animals with prostate cancer, those that consumed additional amounts of boron experienced nearly 90% reduction in PSA levels and tumor size shrunk by nearly 40%.¹¹⁸ Interestingly, boron (in the form of boric acid) specifically inhibits the proliferation of prostate cancer cells without affecting normal prostate cells.¹¹⁹ Boric acid appears to block the ability of prostate cancer cells to release calcium, which stunts their growth.¹²⁰

In a group of 456 men across 63 villages in Turkey, men were first divided by those who lived near and worked in boron mines and those who did not. Then the amount of boron in their urine was measured as an indication of boron exposure. While the rate of prostate cancer did not significantly differ between the high and low exposure groups (probably because of the small number of men in the study) those with high boron exposure at lower prostate specific antigen levels and smaller prostate glands, suggesting that boron may be able to block abnormal prostate gland growth.¹²¹ The National Health and Nutrition Examination Survey examined 8720 men and found that those who had the highest boron consumption in their diets were 54% less likely to develop prostate cancer than men with the lowest boron intake.¹²² Likewise, areas of Texas that have high amounts of boron in their groundwater have reduced prostate cancer rates and deaths from prostate cancer than areas with low boron concentrations.¹²³

Quercetin

Quercetin is a flavonoid is a natural yellow pigment that is a natural yellow pigment in fruits and vegetables, though it commonly appears alongside green pigments so that the vegetables that contain quercetin may not appear yellow. Foods that contain particularly high levels of quercetin include capers, dill, fennel, red onion, radicchio, and watercress. Quercetin exhibits a number of remarkable effects on prostate cancer cells in laboratory studies. Quercetin reduces the rate of growth of aggressive prostate cancer cells by nearly 70%.¹²⁴ This effect is likely due to the fact that quercetin can increase the expression of tumor suppression genes by more than 50% while almost completely suppressing genes that promote cancer.¹²⁴ Other evidence suggests that quercetin can block testosterone receptors on prostate cancer cells thus starving them of the hormone that they need to grow and proliferate.¹²⁵ The flavonoid can also interfere with prostate cancer cells as they tried to invade other tissues and migrate through the body (blocks metastasis).¹²⁶ A double-blind, placebo controlled trial of 500 mg per day of quercetin is nearing completion and results are expected by the end of 2014.

Flaxseed

Flaxseed, also known as linseed, is used in an enormous number of food products. It is also used to fortify the diets of livestock. For example, eggs with higher levels of omega-3 fatty acids come from hens who have been fed flaxseed. Various health benefits have been attributed to flaxseed including reduced risk of heart disease, cancer, stroke, diabetes, inflammation and inflammatory diseases, and menopausal hot flashes. A flaxseed-supplemented, fat-restricted diet for six months reduce total cholesterol levels and prostate specific antigen levels¹²⁷, and also slowed the rate of prostate gland growth in people with benign prostatic hyperplasia.¹²⁷ A later study by the same research group showed flaxseed supplementation without a fat restricted diet can reduce prostate cell proliferation after as little as 30 days.¹²⁸ In a group of 147 men with prostate cancer who were waiting surgery, supplementation with lignans found in flaxseed, enterolactone and enterodiol, reduced tumor markers in the prostate cancer.¹²⁹ This suggested that flaxseed-derived lignans interfered with cancer cell proliferation.¹²⁹

Grape seed

Grape seeds and extracts of whole grape seeds contain flavonoids, anthocyanins, phenolic procyanidins, and polyphenols such as resveratrol. Grape seeds are edible, but not palatable and so most people consume grape seed extracts. When 200 mg/kg grape seed extract was fed to mice with prostate cancer it significantly inhibited prostate cancer growth and progression.¹³⁰ Similar effects were observed when grape seed extracts (particularly proanthocyanidins) were added to testosterone-sensitive and testosterone-insensitive prostate cancer cells.¹³¹ In the VITAL cohort study that included 35,239 men, grape seed extract was by far the most successful supplement at reducing the risk of prostate cancer. Men who used any amount of grape seed supplements reduced their risk of acquiring prostate cancer by 41%.¹³² When the group was further divided into men who were “high users” (≥ 4 days/week and ≥ 3 years) the prostate cancer risk reduction was 62%.¹³² Unfortunately, the authors of the study did not list the amount of grape seed extract considered a standardized dose. Manufacturers recommend daily doses of grape seed extract between 50 mg and 600 mg, according to the study authors.

Modified Citrus Pectin

Pectin is a carbohydrate that is a collection of hundreds of individual carbohydrate molecules. In its natural state, pectin is a dietary fiber because the body cannot absorb it and it passes through the gastrointestinal system. However, modified citrus pectin has been chemically altered so each pectin molecule is smaller and can pass into the blood stream. Modified citrus pectin inhibits the proliferation of prostate cancer cells and prompted the cells to enter apoptosis (“cell suicide”).¹³³ Modified citrus pectin may also block prostate cancer cells’ ability to bind to blood vessels, move into other regions of the body, and develop their own blood supply.¹³⁴ In other words, the supplement may be able to inhibit prostate cancer metastasis, which has been shown in animal studies.¹³⁵ In a small clinical trial of 13 men with prostate cancer who had failed to respond to traditional treatment (i.e., prostate removal surgery, radiation, or ablation), modified citrus pectin slowed the rate at which prostate specific antigen levels doubled in 10 out of 13 men.¹³⁶ The PSA doubling rate is a marker for prostate cancer growth¹³⁷, hence, slowing the doubling rate indicates modified citrus pectin may have slowed prostate cancer growth and progression.

Saw Palmetto

Saw palmetto is obtained from the small palm tree called *Serenoa repens*, which grows in the West Indies and the southeast Atlantic coast of North America. Saw palmetto blocks the conversion of testosterone to DHT in the prostate, which may be helpful in reducing prostate cancer cell number and proliferation.¹³⁸ Saw palmetto has also demonstrated anti-estrogenic and receptor site-binding effects¹³⁹, increased apoptosis (cell suicide) in prostate cells in the laboratory¹⁴⁰, and also blocked the stimulatory effects of the hormone prolactin on prostate cell proliferation.¹⁴¹ A component of saw palmetto called myristoleic acid kills prostate cancer cells in test tubes.¹⁴¹ Another study showed an extract of saw palmetto can inhibit the activity of an enzyme that is important in the development of prostate cancer.¹⁴² A saw palmetto extract has been found to be inhibitor of the enzyme 5alpha-reductase, which is the key factor in the development of prostate cancer.¹⁴³ A different study also found saw palmetto inhibits 5alpha-reductase in human prostate cancer cell lines without affecting PSA levels.¹⁴⁰

Clinical studies of saw palmetto on the risk of prostate cancer have been disappointing thus far. Researchers followed a cohort of 35,171 men for a period of 10 years and found those who used saw palmetto at least once a week had no significant reduction in prostate cancer incidence (roughly 5% lower risk, not statistically significant).¹⁴⁴ However, this study was limited because it included many in the saw palmetto group that may have taken very little saw palmetto. Thus, an effect of the natural product would have been missed because of the study design. Other studies have shown similar results, however. In the VITAL study cohort of 35,239 men, saw palmetto use did not correlate with prostate cancer incidence.¹³²

European mistletoe

European mistletoe is a plant that grows on various trees in temperate regions and is not to be confused with American mistletoe, which is a holiday decoration. In Europe, European mistletoe is used as an adjunct or palliative therapy for cancer. In fact, mistletoe extract was the most commonly prescribed substance in outpatient oncology clinics in Germany in 2002¹⁴⁵, and was prescribed more often than tamoxifen. Most

investigators believe mistletoe lectins are responsible for its positive effect on cancer. Mistletoe lectins induce apoptosis¹⁴⁶ (“cell suicide”) and can stimulate the immune system by increasing the number of neutrophils, lymphocytes, and natural killer cells.¹⁴⁷ The goal of supplementation with European mistletoe is fourfold: to improve quality of life, to boost the immune system, to reduce the negative effects of traditional cancer therapy, and to improve the effects of conventional treatment.¹⁴⁸ A recent review of European mistletoe therapy in oncology identified 13 prospective trials examining survival duration in cancer and 16 prospective trials that examined quality of life, cancer symptom severity measures, and the ability of the supplement to reduce the negative effects of chemotherapy.¹⁴⁵ Six of the 13 survival trials showed European mistletoe extended survival in various cancers, but prostate cancer was not tested. Fourteen of the 16 trials showed European mistletoe extracts had a beneficial effect on quality-of-life and cancer symptoms. European mistletoe extracts are very well tolerated and cause few side effects. To date, clinical trials of European mistletoe in patients with prostate cancer have not been performed. However, laboratory studies show extracts of mistletoe may be able to extend the cancer-killing effects of traditional chemotherapy on prostate cancer cells.¹⁴⁹

Pygeum africanum

Pygeum africanum (*Prunus Africana*; African plum; Bitter Almond) is a large tree that grows in high elevations in Africa. South African tribes chewed the bark of this tree to improve symptoms of old man’s disease that was later realized to be benign prostatic hyperplasia. *Pygeum africanum* is the most commonly used medicine in France for benign prostatic hyperplasia.¹⁵⁰ *Pygeum* has been shown to be effective in the treatment of benign prostatic hyperplasia in several randomized, controlled trials.¹⁵¹ Because of the natural products ability to reduce symptoms of prostate enlargement, *Pygeum africanum* may be useful in symptomatic relief in patients with prostate cancer. Extracts from the bark of the plant improve bladder contractility, have anti-inflammatory activity, block testosterone’s effects on the prostate gland, and restore the prostate’s ability to create and pass secretions.^{151,152} Circulating levels of testosterone fueled prostate cancer cell growth and tumors of the prostate can interfere with the prostate gland’s ability to secrete substances. Extracts of *Pygeum africanum* inhibited growth of prostate cancer cells and prompted the cells to undergo apoptosis (“cell suicide”).¹⁵³ Moreover, the extract was able to reduce the incidence of prostate cancer in mice prone to develop the disease.¹⁵³ A molecule isolated from *Pygeum africanum* called N-butylbenzene-sulfonamide (NBBS) may be responsible for the beneficial effects of the tree bark on the prostate.¹⁵⁴

Cernilton

Cernilton is derived from flower pollen. Like *Pygeum africanum*, Cernilton has a long and successful history in the treatment of benign prostatic hyperplasia. It is a registered pharmaceutical agent well-known to men in Western Europe, Japan, Korea, and South America. Cernilton can relax smooth muscle tone in the urethra while increasing bladder muscle contraction.¹⁵⁵ A study of 79 men given 63 mg of Cernilton pollen extract daily for 12 weeks experienced an increase in urinary flow rate and decreased amounts of residual urine in the bladder.¹⁵⁶ Men taking the pollen extract reported improvements in urgency, intermittency, delayed voiding, post-void dribbling, prolonged voiding, incomplete emptying, dysuria, and nocturia. Cernilton also blocks the effects of

testosterone on the prostate gland¹⁵⁷, which may be helpful both in benign prostatic hyperplasia and prostate cancer. Cernitin is able to selectively block the growth of cancerous prostate cells while not interfering with normal prostate cells.¹⁵⁸ Cernitin cut the growth rate of prostate cancer cells in half.¹⁵⁹ Human trials testing the effect of Cernilton in prostate cancer patients have not yet been performed.

Licorice root

Licorice root (*Glycyrrhiza* spp.) has been used as a food and medicinal product in both Eastern and Western medicine. Robust scientific evidence supports the use of licorice root in the treatment of heartburn, but it has been used in conditions as varied as hepatitis to chronic fatigue syndrome to infertility. Extracts of licorice root are able to kill testosterone-sensitive and testosterone-insensitive prostate cancer cells.¹⁶⁰ The extract does so by prompting the cancer cells to undergo apoptosis (“natural cell suicide”). A separate laboratory work suggests that an extract of licorice root, 18 -glycyrrhetic acid, blocks the inflammation caused by prostate cancer cells.¹⁶¹ Glycyrrhetic acid also reduce the production of prostate specific antigen by prostate cancer cells in test tubes.¹⁶² Extracts of the root may also block prostate cancer cells from becoming metastatic and invading other tissues.¹⁶³ Mice with prostate cancer that were treated with an extract of licorice called dibenzoylmethane have slower growth and progression of their disease compared to control.¹⁶⁴ Unfortunately, human trials of licorice root have not yet been performed nor have prospective studies examining the effects of *Glycyrrhiza* on prostate cancer risk.

PC-SPES

PC-SPES is a dietary supplement that contains a number of different herbs (according to the manufacturer it contains *Ganoderma lucidium*, *Dendranthema morifolium*, *Glycyrrhiza glabra* L., *Isatis indigotica*, *Panax pseudoginseng*, *Rabdosia rubescens*, *Scutellaria baicalensis*, and *Serenoa repens*). The supplement can disrupt the growth cycle and proliferation of several types of prostate cancer cells.¹⁶⁵ the authors also report that rats with prostate cancer fed 0.025% and 0.05% diets of PC-SPES exhibited a dose-dependent reduction in the number of tumors and significantly slower tumor growth rate.¹⁶⁵ The multi-herb supplement reduced prostate specific antigen levels in men with prostate cancer.¹⁶⁶ A second clinical study in 16 men with hormone-refractory prostate cancer showed that PC-SPES improve quality of life and reduced pain and prostate specific antigen levels.¹⁶⁷ In a trial that included 33 men with testosterone-dependent and 37 men with testosterone-independent prostate cancer, nine capsules a day of PC-SPES reduced prostate specific antigen levels in the dependent group by 80% or more.¹⁶⁸ In this group, 97% of patients had reductions in testosterone equivalent to testicular removal surgery, which is the conventional treatment for prostate cancer in some men.¹⁶⁸ The study authors report severe toxicities occurred. There were three cases of serious blood clots and three other cases of allergic reactions to the compound. In a randomized, phase 2 clinical trial in men with testosterone-independent prostate cancer, men received three capsules of PC-SPES three times a day or the estrogen diethylstilbestrol. PC-SPES reduced prostate specific antigen levels by 50% or more in 40% of those treated and outperformed diethylstilbestrol. Unfortunately, even though men were on warfarin to thin the blood prophylactically, five people had clotting events (one in the PC-SPES group, and four in the DES group). The herbal supplement PC-SPES has strong pro-estrogen affects, which are likely responsible for its role

in prostate cancer. This estrogen effect also increases the risk for blood clots, which needs to be considered before starting treatment.

Inositol Hexaphosphate

Inositol hexaphosphate (IP6) is found in cereals, soy, and legumes. IP6 strongly inhibits growth of human prostate cancer cells in vitro and, quite interestingly, prompts differentiation of these cells.¹⁶⁹ Cell differentiation is important because it is a mark of less invasive, less aggressive cancer. In an in vivo study, mice with prostate cancer were fed water with varying concentrations of IP6 (0%, 1%, 2%, or 4%). These mice had been experimentally altered to grow prostate cancer from very early in life. While mice that did not receive any IP6 (0%) grew predictably large prostate tumors as they grew older, mice in the 2% and 4% groups developed much smaller tumors.¹⁷⁰ Moreover, tumors that grew in these IP6-treated groups were less advanced tumors, meaning they had lower Gleason scores.¹⁷⁰ The researchers found that IP6 treated groups had a lack of blood vessels supplying the tumor.¹⁷⁰ This means that IP6 likely has anti-angiogenic effects. IP6 also interfered with the prostate cancer cells ability to absorb glucose—essentially starving the cells of energy.¹⁷⁰ clinical trials of IP6 in cancer patients are needed.

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