Prevention and Treatment of Prostate Cancer with Natural Therapeutics

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. The main passage through the prostate is called the prostatic urethra, which can 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 2020, the National Cancer Institute (NCI) estimates that there will be 191,930 new cases of prostate cancer (10.6% of all new cancer cases) and the disease will kill 33,330 men (5.5% of all cancer deaths) in the United States. 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 main genes that seem to help predict prostate cancer are HOXB13, ATM, BRCA1 and BRCA2 the last two of which are also used for breast and ovarian cancer.[4,5] Importantly, simply having a mutation in any of these genes does not necessarily mean that a person will develop prostate cancer.

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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 can be felt during this 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.[6] Nevertheless, digital rectal examinations can double the chances of detecting prostate cancer, [7] 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 antigen.[8,9]

Prostate specific antigen (PSA)

Prostate specific antigen, better known as PSA, is an enzyme 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.[10] 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 (prostate infection). Even relatively minor events can raise PSA such as holding urine to the point of discomfort, a recent ejaculation, or even digital rectal examination itself.[11,12] 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 PSA 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 and 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).[13] 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.[14] Some organizations, such as the United States Preventive Services Task Force have recommended against using PSA for prostate cancer screening.[15] 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 men.[16]

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 men 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 (non-cancerous enlargement of the prostate) and bacterial prostatitis (infection of the prostate). 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 these 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.[17]

Prostate cancer appears to run in families, but scientists have just begun to identify the genes most often associated with the disease. Several candidates have been identified such as BRCA1, BRCA2, ATM, and HOXB13 along with other minor genetic polymorphisms, though more studies are needed.[18] In cases of hereditary prostate cancer, genetic tests for these mutations may be done, in part to determine which treatments are more likely to be effective.[19,20] To date, no genetic tests reliably predict the risk of developing prostate cancer.

However, genetic testing can help predict whether a tumor is likely to be more or less aggressive, and help to guide treatment decisions.[20,21] Research 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.[22] Compared to white men, black men with prostate cancer also have more aggressive tumors and higher mortality. [23] It is important to note that genetics may not entirely explain this difference—differences in diet between ethnicities may strongly affect prostate cancer incidence.[24]

Red meat and animal fats

Several studies have shown that a diet high in animal fat increases the risk for prostate cancer.[25,26,27] Red meat and processed meat, in particular, are associated with increased rates of prostate cancer,[25] and a lower intake of red meat is associated with lower risk of both advanced cancer and recurrence. [28] Higher dairy intake is associated with an increased risk of prostate cancer, while foods containing lycopene (found in cooked tomato products) are associated with a decreased risk of prostate cancer. [29] A diet containing few vegetables is also a risk factor for prostate cancer.[27] Men who consume less than 14 servings of vegetables each week have a 54% increased risk of prostate cancer than men who eat 28 or more servings of vegetables each week.[30]

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 to prevent prostate cancer,[31] but large, prospective clinical trials show high levels of omega-3 fatty acids can actually increase the risk of high-grade prostate cancer.[32,33] A 2020 systematic review and meta-analysis concluded that high intake of polyunsaturated fatty acids (PUFAs) may slightly intake cancer risk along with the expected cardiovascular benefits.[34] 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 that these studies may implicate high-fat diets as a risk factor for prostate cancer rather than corn oil itself. A 2019 study examined the effects of various cooking oils in rats, specifically the prostate weight to body weight (PW:BW) ratio. All of the cooking oils helped to reduce the weight (and therefore size) of the prostate in rats, thought this is perhaps more relevant to overall prostate health and management of benign prostatic hyperplasia as cancer risk was not examined.[37]

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 cancer,[38] but they do not seem to reduce the risk of developing prostate cancer.[39,40] In a 2018 randomized controlled trial, high total serum cholesterol was associated with increased risk of high-grade prostate cancer, though not with overall or low-grade prostate cancer risk. More studies are needed.[41]

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[42] and smoking cessation for those who smoke many help to decrease the risk of developing prostate cancer.[43]

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.[44] Likewise, in a prospective study, 10,660 men with low or modest alcohol intake (less than 50 g per day or three alcoholic beverages) had no increased risk for developing prostate cancer as compared to those with no alcohol intake. 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. [45] A later 2016 systematic review and meta-analysis, however, showed a dose-dependent increase in prostate cancer risk starting with even low-volume consumption.[46]

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,[47,48,49,50,51] but other studies failed to show the same effect.[52,53] Likewise, some studies have shown that low levels of Vitamin D may increase the risk of prostate cancer,[50,54] while others have indicated that both low and high levels of Vitamin D may increase the risk.[55,56] Based on current evidence, it seems that keeping vitamin D within the normal range (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, can cause prostate gland cells to become cancerous and

also to promote the growth of these cancerous prostate cells.[57] While a recent study showed a small but statistically significant association between 2% fat milk intake and advanced cancer, and between regular-fat dairy intake and risk for late stage prostate cancer, it did not show an association between dairy consumption and overall prostate cancer risk.[58] 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 (from both diet and supplements) to 1,500 mg to 2,500 mg per day.[59,60]

Vitamin E and selenium

Numerous laboratory studies showed that 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 blood samples drawn and frozen in the 1970s and were assessed for prostate cancer incidence 20 years later revealed that those with the highest selenium levels were only half as likely to have Prostate cancer as those with the lowest levels.[62]

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.[63,64,65] A longer followup with the men in the SELECT trial confirmed that vitamin E supplementation significantly increased the risk of developing prostate cancer.[67] 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.[66] 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).[68] Researchers have further proposed that genes involved with vitamin E and selenium metabolism may more specifically influence the risk of an individual developing prostate cancer from supplementation.[69] These results suggest that 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 that 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.[70] 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 have consumed 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 thhat regular dietary folic acid consumption was not closely monitored in this study, so it is possible men were consuming considerable amounts of dietary folic acid in addition to folic acid supplements. In a 2013 meta-analysis of previous trials, the researchers concluded that folic acid supplementation neither increased nor decreased risk of site-specific cancer, including prostate cancer, within the first 5 years of treatment.[71] However, as we have seen above, there may be more long-term risks. It would be important for future studies to quantify dietary levels in addition to supplement levels, and individual genetics may also play a part. For now, it seems safest to avoid folic acid supplementation, at least until there is more data.

Zinc

There are several reasons to believe that 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.[72] 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 that 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.[73]While more studies are needed, it may be safer to avoid supplemental zinc. The MCC-Spain study, a case control study, investigated the roles of dietary zinc and individual genetics in the development of prostate cancer. The researchers concluded that a higher intake of dietary zinc may increase the risk of low-grade prostate cancer, particularly in those with certain genetics.[74] Strangely enough, laboratory studies have shown that zinc, when coadministered with paclitaxel chemotherapy, may help to make the cancer cells more vulnerable to the drug.[75] More studies are needed to determine what relevance, if any, this may have in humans. An early 2016 systematic review and meta-analysis evaluated 14 studies that examined prostate disease in relation to zinc levels. They found that blood levels of zinc were considerably lower in patients with prostate cancer than in those with benign prostatic hyperplasia (BPH) or those with healthy prostates.[196] One hospital-based case-control study involved 127 African American men with newly diagnosed prostate cancer and 81 healthy controls. While zinc levels were higher in the healthy control group than in the men with prostate cancer, a meta-analysis of this and other studies showed no significant association between zinc intake and prostate cancer.[197] More studies are needed to determine whether supplemental zinc may be of benefit in prostate cancer prevention or progression.

Obesity and inactivity

Obesity increases the risk of prostate cancer.[76] It also increases the risk of high-grade tumors, possibly related to low androgen levels.[77] Moreover, being overweight and obese are risk factors for developing particularly aggressive prostate cancer.[78] High insulin levels resulting from insulin resistance may also play a part in the role of obesity in the development of prostate cancer.[79,80] The overall increased risk of prostate cancer resulting from obesity is relatively small, but the risk increases as the amount of excess weight increases.[81] Also, being obese as a child can increase the risk of prostate cancer later in life.[82,83] 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.[84] 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 resistance, and in those who eat excessive amounts of sugar.[59,79,80] One randomized controlled trial found a linear relationship between sugar-sweetened beverages and cases of prostate cancer; the higher the sweetened beverage consumption, the higher the risk of prostate cancer.[85] Unsweetened fruit juices were also found to increase prostate cancer risk, due to high amounts of natural sugars.[86] Conversely, reducing the amount of simple sugars can slow the growth of prostate cancer cells,[59] 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 reduce 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.[87] Nonetheless, in men who are taking metformin for diabetes and develop prostate cancer, metformin may be able to improve survival.[88] Further studies have shown metformin to have multiple anticancer effects, helping to reduce spread.[89]

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 cancers[90] and increases the risk of recurrence after prostate cancer surgery.[91] Dioxins, found in high concentrations in Agent Orange, are endocrine disruptors (disrupting reproductive hormones) and cancer-causing. Chlordecone is a pesticide used in the West Indies between 1973 and 1993. Chlordecone is also an endocrine disruptor, with estrogenis effects. Exposure to the substance increased the rate of developing prostate cancer in men[92] as well as the rate of recurrence.[93] Bisphenol A, widely known as BPA, has been and continues to be used in the manufacture of plastics. Evidence suggests that BPA exposure, especially early in life, increases the risk of developing prostate cancer later in life, though most work has been done in laboratory rather than clinical settings.[94,95] Other compounds that may increase the risk of prostate cancer include polyhalogenated biphenyls;[96] benzene, toluene, xylene and styrene;[97] cadmium and arsenic;[98,98] and diethylstilbestrol (DES).[96]

Tobacco Use

One study involving 73,668 veterans found that while smoking at the time of diagnosis is associated with a higher risk of dying from prostate cancer, a past history of smoking did not have this same association.[100] (Now is always a great time to quit!) A later systematic review and meta-analysis came to similar conclusions; tobacco smoking at the time of diagnosis was associated with increased risk of dying from prostate cancer, increased risk of dying from all causes, and increased risk of recurrence.[101]

Family History

In a 2019 systematic review and meta-analysis, having a first-degree relative (parents, children, or siblings) with prostate cancer increases the risk of developing prostate cancer by 68%, and having a first-degree relative with breast cancer increases the risk of developing prostate cancer by 21%,[102]

Vasectomy

While it has been proposed that vasectomy may contribute to an increased risk of prostate cancer,[103] most studies, including two systematic reviews and meta-analyses,[104,105] have found no association.[106,107,108]

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.[109] 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 (HIFU).

Radiation therapy can be administered by external beam radiation, brachytherapy, or both. 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 prostate removal, especially in patients with certain risk factors.[110,111] Stereotactic body radiosurgery (SBRT) (radiation during surgery that is applied to the prostate through an incision) is another option. The CyberKnife system allows a surgical oncologist to provide radiosurgery, which is closer to 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,[112] with fewer sexual or urinary side effects.[113] Men with low and intermediate risk prostate cancer may be candidates for CyberKnife treatment.

Newer procedures for prostate cancer treatment include helical tomotherapy (HT), cryotherapy, high-intensity focused ultrasound (HIFU), and others. Helical tomotherapy (HT) is a type of intensity-modulated radiotherapy (IMRT), in which the beam spirals around the patient. An image of the tumor is taken before the procedure, and the helical tomotherapy is used to target the therapy in such a way to cause less damage to nearby tissue, with low rates of urinary and gastrointestinal side effects.[114]

Both cryotherapy and high-intensity focused ultrasound (HIFU) 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.[115] Cryotherapy may cause pain and swelling in the treated region, incontinence (difficulty with urination), and impotence. 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 also be offered cryotherapy as a palliative therapy if other treatments for prostate cancer have failed.[116]

High-intensity focused ultrasound (HIFU) 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 asmall degree, which destroys the tissue. High-intensity focused ultrasound is not currently 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.[117]

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 (ADT), 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, enzalutamide, or others, or by surgically removing the testicles. Bicalutamide (Casodex) is an anti-androgen drug that 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.[118] Newer antiandrogen medications such as enzalutamide are more effective with fewer side effects.[119,120] Intermittent (vs. continuous) ADT may also be an option with fewer side effects.[121] Chemotherapy is not often used in prostate cancer, but if it is used, it may cause nausea, vomiting, hair loss, anemia, and immune system deficiencies.
Sipuleucel-T, a therapeutic vaccine, was approved by the FDA in 2010 for use in men with metastatic prostate cancer who are without symptoms or having mild symptoms only, and whose cancer is resistant to standard hormone treatment. In a double-blind placebo-controlled trial, participants were randomly assigned to either treatment or placebo. In the treatment group, there was a 22% decrease in the risk of death (representing a four-month increase in survival time) compared to placebo, though there were no differences in time-to-progression between treatment and placebo. The study authors concluded that this vaccine can prolong survival in men with metastatic, castration-resistant prostate cancer.[291]
Two new drugs showing promise in treating metastatic, castration-resistant prostate cancer are Ipatasertib and VERU-111. Ipatasertib interferes with cancer cell signaling, and is currently being studied in combination with abiraterone, a drug that inhibits androgens. In a Phase 2 study, the combination had better antitumor effects than abiraterone alone, with a longer period of time before cancer progression was detectable on imaging.[292] In a Phase 1b study, VERU-111 was tested in men with castration-resistant prostate cancer to determine a safe dose. Of the 39 patients recruited, 4 had at least a 30% decline in PSA and 2 had a 50% decline in PSA. The average length of progression-free time was 11 or more months, while the overall average of progression-free time with other treatments is only 3.4 months. Participants are currently being enrolled for a Phase 2 study with VERU-111 in prostate cancer.[293]

Protective factors

Coffee

Coffee, but not necessarily caffeine, protects against developing 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.[122] Most interestingly, decaffeinated coffee had the same effect, which means the protective ingredient is found within coffee, but is not caffeine. A laboratory study found that kahweol and cafestol, specific compounds within coffee, inhibit the growth and spread of prostate cancer.[123]

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, stigmasterol, 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.[124] Daidzein and genistein, two other substances in soy, have similar effects on urine flow through the prostate gland.[125] 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").[126] Laboratory studies also show that soy isoflavones such as genistein and daidzein control the cell cycle (by which cancer cells multiply) and apoptosis (when abnormal cells self-destruct as they should).[127] 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.[128]

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%.[129] In a survey of 1619 men of various ethnicities, those who ate soy products had reduced risk of prostate cancer.[130] 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.[131] Across various clinical studies, those who commonly ate soy and soy food products lowered their risk of prostate cancer by 30%.[132] A 2018 review and meta-analysis confirmed that soy (and its components genistein and daidzein) are associated with a lower risk of prostate cancer, though they acknowledge that additional factors such as family history of prostate cancer, body mass index (BMI) and smoking were not universally tracked.[133]

Typical Western diets provide only about 80 mg/day of phytosterols (some of the useful ingredients in soy) compared to a traditional Japanese diet, which contains about 400 mg/day.[134] 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.[125,128]

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 by causing cancerous prostate cells to commit suicide (apoptosis), stopping the replication of new cancer cells and preventing tumor cells from spreading through tissues to the rest of the body.[135] Men with the highest levels of lycopene in their blood were least likely to develop prostate cancer.[136,137] A prospective cohort study of 47,894 subjects found that lycopene intake from tomato products was inversely associated with the risk of prostate cancer.[138] Likewise, eating tomato sauce decreased the risk of prostate and other cancers.[139,140] 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.[141] 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 fatal prostate cancer.[142] 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.

One systematic review and meta-analysis confirmed that a higher level of lycopene in the blood was associated with a statistically significant lower risk of prostate cancer. The authors concluded that more studies are needed as to the mechanism of lycopene in reducing prostate cancer, and suggested there may be other anti-cancer components of tomato products in addition to lycopene.[143] A second systematic review and meta-analysis reached the same conclusion – the higher the dietary lycopene intake, the higher the blood levels of lycopene, and the lower the risk of prostate cancer. There was also a trend toward less aggressive prostate cancer when it did occur.[144] The ProDiet randomized, controlled trial investigated the effect of 3 cups of green tea daily; 600 mg of EGCG (from green tea) or placebo capsule daily; dietary lycopene daily; and 15 mg lycopene or placebo capsule daily. The trial involved 132 men with elevated PSA levels and negative prostate biopsies. Blood levels of lycopene and EGCG (from green tea) were higher in the dietary groups than in the capsule groups, though men preferred the capsules. This initial study was to establish safety and tolerability, and the interventions were both safe and tolerable.[145] In an additional subset of the same study, 159 metabolites (small molecules in the body that are a result of metabolism) were measured in the blood. Researchers proposed that the mechanism of lycopene's impact on prostate cancer risk may be due to lowering levels of pyruvate in the blood, though more studies are needed.[146] In another study, 79 patients with prostate cancer were randomized to one of three groups – tomato products containing 30 mg lycopene daily, tomato products plus other nutrients (soy isoflavones, omega-3 fatty acids, tea, grape juice, and pomegranate juice), or control diet, for three weeks. While there wasn't a statistically significant difference between treatment and control groups, the average PSA decreased in the tomato groups while it continued to increase in the control group. Researchers concluded that tomato or tomato combined with omega-3 fatty acids and selenium may help to lower PSA in patients with non-metastatic prostate cancer, due to elevated blood levels of lycopene and other nutrients.[147] A systematic review of laboratory and animal studies proposed that some of lycopene's benefits in prostate cancer prevention may be due to anti-androgenic effects.[148] An additional systematic review and meta-analysis showed that lycopene reduced the risk of prostate cancer overall, but did not reduce the risk of advanced prostate cancer.[149]

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, including sulforaphane and indole-3-carbinol, that are protective or potentially protective against prostate cancer. These molecules may block normal prostate cells from converting into cancer cells and also slow the rate of prostate cell growth and proliferation.[150] Interestingly, cruciferous vegetables disrupt intracellular signaling pathways in prostate cancer cells but not in healthy prostate gland cells.[150] 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.[151] 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.[152] In a randomized, controlled trial on the effects of sulforaphane, 49 men with prostate cancer were given a dietary intervention of 300 ml of broccoli soup, weekly, for 12 months. One group received soup made from standard broccoli, while the other two groups received soup from experimental broccoli designed to have 3 or 7 times the glucoraphanin of the regular (control) broccoli. (Glucoraphanin is converted to sulforaphane in the body.) The men who were given the experimental broccoli with higher amounts of glucoraphanin had decreased risk of cancer progression in addition to beneficial (anticancer) changes in gene expression.[153]

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).[154] 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.[155] Green tea catechins, including EGCG, suppressed the growth of human prostate cancer cells, and prompted them to "commit suicide" (apoptosis).[156] The polyphenolic fraction of green tea not only inhibited localized prostate cancer growth but also inhibited the metastasis of the cancer to distant sites.[157] Interestingly, green tea catechins tend to concentrate in the prostate gland after humans consume green tea, suggesting these molecules target the prostate.[158] Clinical trials in humans with green tea have been difficult because of differences in dosages and intake levels. As a result, many observational studies have not shown a strong connection between green tea consumption in the prevention of prostate cancer. In one randomized, placebo-controlled trial, 97 men were given a proprietary mixture of green tea catechins daily, containing 400 mg of EGCG, for one year. The participants had a diagnosis of either high-grade prostatic intraepithelial neoplasia (HGPIN), considered premalignant, or atypical small acinar proliferation (ASAP), abnormal cells that aren't clearly cancerous. Researchers concluded that EGCG did not reduce the risk of HGPIN or ASAP.[159] On the other hand, several phase 2 clinical trials have shown green tea extracts can inhibit prostate cancer progression from a precancerous state to a malignant state.[160] A 2017 systematic review and meta-analysis found that daily green tea was associated with a reduced risk of prostate cancer starting with only one cup per day, and that prostate cancer risk was significantly reduced with 7 cups per day.[161] 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.[162]

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.[163,164] A substance within garlic called diallyl disulfide may be a key factor that causes prostate cancer cells to enter apoptosis ("cell suicide").[165] The consumption of various Allium species and in particular garlic is associated with a reduced rate of developing prostate cancer.[166,167,168] Researchers combined the results of nine epidemiological studies which together included 132,192 participants. They found that garlic consumption reduced the risk of developing prostate cancer by 23% and onion consumption reduced that risk by 16%, through the onion result was not statistically significant.[169]

Ginger

Ginger *(Zingiber officinale)* 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.[170] Ginger has anti-inflammatory and antioxidant properties, which make it useful in the prevention of cancer initiation and development.[170,171] Various compounds extracted from ginger work together to block the proliferation of human prostate cancer cells in test tubes.[172] Extracts of ginger can block the cell cycle of prostate cancer cells and induce those cells to die through apoptosis ("cell suicide").[171] 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.[171] In laboratory studies, 6-Shogaol (a derivative of ginger) has been shown to have anti-cancer effects in both mouse and human prostate cancer cells. It was also found to induce apoptosis (cell suicide) of abnormal cancer cells.[173] Human trials of ginger root and/or ginger root extract in the treatment or prevention of prostate cancer have not yet been performed, but studies are warranted.

Curcumin

Curcumin, a compound found in turmeric *(Curcuma longa)* 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 effects in a variety of cancers.[174] Curcumin decreased the proliferation of both testosterone and prostate cancer cells in mice.[175] Curcumin also increased the tumor killing power of chemotherapeutic agents in test tubes.[176] Curcumin is known to have both radioprotective (protecting cells) and radiosensitizing (making cells more vulnerable to radiation) effects. In a double-blind, randomized, placebo-controlled trial, 40 men receiving radiation for prostate cancer were randomized to receive either curcumin (3 g/day) or placebo during external beam radiation. In the curcumin group,

while measurements of blood antioxidant status improved, there were no differences in outcome between treatment and placebo groups.[177]

In a parallel group study, 64 patients with prostate cancer were randomized to oral nanocurcumin (120 mg/day) or placebo, starting three days before radiotherapy and continuing through the radiation course. The curcumin did slightly decrease the incidence of radiation-induced proctitis, affecting 45.5% of the treatment group vs. 58.1% of the placebo group. No other differences were noted between groups, and curcumin did not seem to decrease other radiation side effects or improve tumor response.[178]

A phase 1 study used intravenous (IV) liposomal curcumin to establish safety and tolerability in patients with metastatic cancer of multiple types (including prostate), to establish a safe and tolerable dose for future clinical trials.[179]
A randomized, double-blind, placebo-controlled trial evaluated the effects of oral curcumin in prostate cancer. The 97 participants had finished a phase of intermittent androgen deprivation therapy (IADT) and were randomized to either curcumin or placebo for six months, then followed until their next IAD treatment. The progression of prostate cancer was considerably lower in the treatment group (10%) than in the placebo group (32%). PSA and testosterone levels remained the same in both groups.[180]
We know from other research that the bioavailability of curcumin is fairly low and absorption can be boosted in formulations by a variety of means, including the addition of piperine.[181] Absorption can also be enhanced through the use of liposomal formations and delivered as nanoparticles, as mentioned in a previous study.[182] More clinical trials for prostate cancer are needed.

Shiitake and Maitake mushrooms

Both Shiitake *(Lentinus edodes)* and Maitake *(Grifola frondosa)* mushrooms have been investigated as medicinal foods. Laboratory studies suggest that 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 hold the most promise are a beta glucan/glycan called lentinan and 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.[183] Dendritic cells create specific immunity and are very useful in fighting cancer.[184]

For Maitake mushrooms, the 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.[185] 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 PSA levels after six months of use.[186] 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.[187]
Laboratory studies continue to examine shiitake extract in human prostate cancer cells, striving to understand the mechanisms of its anti-cancer effects.[188,189] More clinical studies are needed.

Boron

Several lines of evidence suggest that 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%.[190] Interestingly, boron (in the form of boric acid) specifically inhibits the proliferation of prostate cancer cells without affecting normal prostate cells.[191] Boric acid appears to block the ability of prostate cancer cells to release calcium, which stunts their growth.[192]

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 had lower PSA levels and smaller prostate glands, suggesting that boron may be able to block abnormal prostate gland growth.[193] 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.[194] 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.[195]

Quercetin

Quercetin is a natural yellow pigment flavonoid found in fruits and vegetables. Quercetin commonly appears alongside other colored pigments, so quercetin-rich vegetables 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%,[198] 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.[198] 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.[199] The flavonoid can also interfere with prostate cancer cells as they try to invade other tissues and migrate through the body, blocks metastasis.[200] A double-blind crossover trial studied the effects of 500 mg quercetin or 100 mg of genistein vs. placebo, but unfortunately, results have not been published to reveal if either or both of these supplements helped to prevent the development of prostate cancer.[201] A clinical trial with 31 participants is currently in progress, using quercetin and green tea extract for 3-6 weeks before undergoing radical

prostatectomy. The hope is that quercetin will improve the absorption of green tea and augment its anticancer effects.[202]

Flaxseed

Flaxseed, also known as linseed, is from the *Linum usitatissimum* plant and 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 has been shown to reduce total cholesterol levels and PSA levels,[203] and also slowed the rate of prostate gland growth in people with benign prostatic hyperplasia (BPH).[203] 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.[204] In a group of 147 men with prostate cancer who were awaiting surgery, supplementation with lignans found in flaxseed (enterolactone and enterodiol) reduced tumor markers in the prostate cancer.[205] This suggested that flaxseed-derived lignans interfered with cancer cell proliferation.[205] More human clinical studies are needed.

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.[206] Similar effects were observed when grape seed extracts (particularly proanthocyanidins) were added to both testosterone-sensitive and testosterone-insensitive prostate cancer cells.[207] 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 developing prostate cancer by 41%.[208] 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%.[208] 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. Recent laboratory studies with human prostate cancer cells have shown that grape seed extract helps to keep cancer from spreading and causes abnormal cells to self-destruct. [209,210,211] More current human studies are needed.

Modified Citrus Pectin (MCP)

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 the pectin molecules are smaller and can pass into the blood stream. Modified citrus pectin inhibits the proliferation of prostate cancer cells and prompts the cancer cells to enter apoptosis ("cell suicide").[212,213] 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.[214] In other words, the supplement may be able to inhibit prostate cancer metastasis, which has been shown in animal studies.[215] 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.[216] The PSA doubling rate is a marker for prostate cancer growth,[217] hence, slowing the doubling rate indicates that modified citrus pectin may have slowed prostate cancer growth and progression. Laboratory studies have shown that MCP also helps to make cancerous cells more vulnerable to radiotherapy.[218]

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.[219] Saw palmetto has also demonstrated anti-estrogenic and receptor site-binding effects,[220] increased apoptosis (cell suicide) in prostate cells in the laboratory,[221] and blocked the stimulatory effects of the hormone prolactin on prostate cell proliferation.[222] A component of saw palmetto called myristoleic acid kills prostate cancer cells in test tubes.[222] Another study showed an extract of saw palmetto can inhibit the activity of an enzyme that is important in the development of prostate cancer.[223] A saw palmetto extract has been found to inhibit the enzyme 5alpha-reductase, which is the key factor in the development of prostate cancer.[224] A different study also found that saw palmetto inhibits 5alpha-reducase in human prostate cancer cell lines without affecting PSA levels.[221]

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, which was not statistically significant).[225] 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.[208]

European mistletoe

European mistletoe *(Viscum album)* 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 2002,[226] and was prescribed more often than tamoxifen. Most investigators believe that the lectins in mistletoe lectins are responsible for its positive effect on cancer. Mistletoe induce apoptosis ("cell suicide")[227] and can stimulate the immune system by increasing the number of neutrophils, lymphocytes, and natural killer cells.[228] The goal of supplementation with European mistletoe is fourfold: to improve quality of life, to boost the immune system, to improve the effects of conventional treatment, and to reduce its negative effects.[229] 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.[226] 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 that extracts of mistletoe may be able to extend the cancer-killing effects of traditional chemotherapy on prostate cancer cells.[230] In another laboratory study, human prostate cancer cells were treated with mistletoe in addition to chemotherapy. The chemotherapy (docetaxel and mitoxantrone), helped to decrease cancer growth, as anticipated, and increase apoptosis ("cell suicide") of the abnormal cancer cells. In low doses, the mistletoe did not interfere with the chemotherapy's anti-cancer effects; in higher doses, the mistletoe mildly increased the chemotherapy's anti-cancer effects.[231] It is important to note that all chemotherapy drugs are different, and that negative herb-drug interactions are possible unless proven otherwise.

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 identified as benign prostatic hyperplasia. Pygeum africanum is the most commonly used medicine in France for benign prostatic hyperplasia (BPH).[232] Pygeum has been shown to be effective in the treatment of BPH in several randomized, controlled trials.[233] Because of Pygeum's ability to reduce symptoms of prostate enlargement, Pygeum africanum may be useful for 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.[233,234] Circulating levels of testosterone-fueled prostate cancer cell growth and prostate tumors 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").[235] Moreover, the extract was able to reduce the incidence of prostate cancer in mice prone to develop the disease.[235] 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.[236] There have been many human studies using Pygeum for treating BPH. At this time, there are no human studies using Pygeum in prostate cancer.

Cernitin

Cernitin® is derived from rye pollen. Like Pygeum africanum, Cernitin 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. Cernitin can relax smooth muscle tone in the urethra while increasing bladder muscle contraction.[237] A study of 79 men given 63 mg of Cernitin pollen extract daily for 12 weeks experienced an increase in urinary flow rate and decreased amounts of residual urine in the bladder.[238] Men taking the pollen extract reported improvements in urgency, intermittency, delayed voiding, post-void dribbling, prolonged voiding, incomplete emptying, dysuria, and nocturia. Cernitin also blocks the effects of testosterone on the prostate gland,[239] 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.[240] Cernitin cut the growth rate of prostate cancer cells in half.[241] A recent laboratory study showed the Cernitin decreases androgen receptors and PSA scores.[242] In a recent clinical study, 61 men were given Cernitin (2 tablets, three times daily) for 30 days prior to having a prostate biopsy. PSA was measured before and after the Cernitin, and the changes were compared to the biopsy results. PSA decreased in 44 of the participants, and increased in 17. In those whose levels decreased, 36.4% had cancer on biopsy, and in those whose levels increased, 52.9% had cancer on biopsy. The study authors concluded that Cernitin treatment has the potential to reduce unnecessary prostate biopsies, as those whose PSA scores normalized would no longer qualify for a biopsy recommendation.[243] More studies are needed to evaluate the potential for Cernitin in patients with prostate cancer.

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, though it has been used in conditions as varied as hepatitis, chronic fatigue syndrome, and infertility. Extracts of licorice root are able to kill both testosterone-sensitive and testosterone-insensitive prostate cancer cells.[244] The extract does so by prompting the cancer cells to undergo apoptosis ("cell suicide"). A separate laboratory work suggests that an extract of licorice root, 18α-glycyrrhetinic acid, blocks the inflammation caused by prostate cancer cells.[245] Glycyrrhetinic acid also reduces the production of PSA by prostate cancer cells in test tubes.[246] Extracts of the root may also block prostate cancer cells from becoming metastatic and invading other tissues.[247] 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.[248] Recent laboratory studies have confirmed that several chemicals from licorice root have anti-cancer effects. The root extract itself is antiproliferative (inhibits cancer from spreading) and stimulates apoptosis ("cell suicide") of abnormal cells.[249] The alcohol extract was more effective than the water extract in inhibiting growth of prostate cancer cells, and the roasted root extract was more effective than the unroasted root extract. The roasted root is also a better choice in that it is less likely to raise blood pressure.[250] Isoliquiritigenin and lupiwighteone from licorice have anticancer effects and help to stimulate apoptosis ("cell suicide") of the cancer cells. It also affects the cell cycle, inhibiting proliferation.[251,252] Dibenzoylmethane (DBM) from licorice, in combination with Phenethyl isothiocyanate (PEITC) from cruciferous vegetables, helped to slow the growth of androgen-dependent prostate tumors in mice.[253] 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 *Ganoderma lucidum, 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.[254] 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.[254] Laboratory studies with human prostate cancer cells have shown that PC-SPES has antiproliferative effects (preventing the cancer from spreading) by affecting the cell cycle. It also inhibits androgen receptors and decreases PSA.[255] The multi-herb supplement also reduced PSA levels in men with prostate cancer.[255] A second clinical study in 16 men with hormone-refractory prostate cancer showed that PC-SPES improved quality of life and reduced pain and PSA levels.[256] 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.[257] 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.[257] The study authors report that 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 outperforming 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 estrogenic affects, which are likely responsible for its role in prostate cancer. This estrogenic effect also increases the risk for blood clots, which needs to be considered before starting treatment.

Unfortunately, it became known that some batches of PC-SPES were adulterated with pharmaceutical drugs, calling into question how much of the effects may have been from the herbs and how much from the drugs. The trials underway were shut down. It is unknown what functions the pure herbs may have on cancer cells, and the product was withdrawn from the U.S. market in 2002. The product is still being studied in China, and researchers report finding antiproliferative and antiandrogenic effects.[258]

Inositol Hexaphosphate

Inositol hexaphosphate (IP6) is a 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.[259,260] 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.[261] Moreover, tumors that grew in these IP6-treated groups were less advanced tumors, meaning they had lower Gleason scores.[261] The researchers found that IP6-treated groups had a lack of blood vessels supplying the tumor.[261] 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.[261] Clinical trials of IP6 in cancer patients are needed.

Vitamin A & carotenes

Vitamin A and its carotenoid precursors can help to decrease the risk of prostate cancer. Orange and yellow fruits and vegetables (ex. apricot, pumpkin, carrot, sweet potato, cantaloupe, and butternut squash) contain large amounts of beta carotene, which the body will then convert into vitamin A according to need. While green vegetables often have carotenes as well, the yellow-orange carotene is masked by the green chlorophyll. Animal sources with higher vitamin A levels include liver, eggs, and milk.

A 2013 laboratory study showed that Vitamin A together with vitamin D caused apoptosis ("cell suicide") of the prostate cancer cells.[262] In a lung cancer study, the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study, 29,133 white male smokers ages 50-69 were recruited from Finland. The study used vitamin E and beta carotene in an effort to prevent the development of lung cancer. The study initially found that vitamin E had no preventive effects, and beta carotene appeared to increase the risk of developing lung cancer. The authors concluded that while relevant to the population studied (smokers), it is not necessarily applicable to nonsmokers.[263] Within that study cohort, the risk of prostate cancer was also examined. Higher blood levels of vitamin A (in the form of retinol) were associated with a higher risk of developing prostate cancer. Again, all of the study participants were smokers, and it is unclear if this association exists in nonsmokers.[264] A 2015 systematic review and meta-analysis of 34 studies showed that while alpha carotene (dietary intake or blood levels) was associated with lower risk of prostate cancer overall, beta carotene (dietary intake or blood levels) was not. Neither carotene increased the risk of prostate cancer.[265] Given the dense micronutrients found in fruits and vegetables and their myriad of health benefits, it seems safest to supplement through dietary means.

Nettles

The *Urtica dioica* plant is commonly known as nettles or stinging nettles. It is mineral-rich and is commonly used in the treatment of BPH. In laboratory studies, the root extract has shown anti-cancer effects in human prostate cancer cells, including antiproliferative effects[266,267] and triggering apoptosis ("cell suicide").[268] It also showed anticancer effects in prostate tissue removed from patients with prostate cancer.[269] While there are mouse, rat, and human studies evaluating the use of nettles in treating BPH, animal and human studies of nettles in prostate cancer do not yet exist.

Bitterleaf

The *Vernonia amygdalina* plant, commonly known as bitterleaf, is eaten as a leaf vegetable in West and Central Africa. In laboratory studies, alcohol extracts of this have had antiproliferative effects and increased apoptosis ("cell suicide") of cancerous human prostate cells.[270] Another study showed that Paclitaxel-resistant prostate cancer cells were sensitive (responsive) to the bitterleaf extract.[271] Another laboratory study showed that the water extract of bitterleaf also had antiproliferative and apoptosis-inducing effects on human cancer cells.[272]

Reishi mushroom

There are several species of Ganoderma mushroom. *Ganoderma lucidum*, commonly known as reishi, has antiproliferative and apoptotic effects on human prostate cancer cells in laboratory studies.[273,274,275,276] *Ganoderma tsuga* extract also shows antiproliferative and apoptotic effects on human prostate cancer cells.[277,278] To date, there have been no human studies with either species of this mushroom.

Cranberry

Cranberry, from the *Vaccinium macrocarpon* plant, has been shown in laboratory studies to inhibit proliferation (spread) and to stimulate apoptosis ("cell death").[279,280] In one randomized, controlled human trial, prior to radical prostatectomy, 64 patients with prostate cancer were assigned to either the treatment group or control group. The treatment group received 1500 mg of cranberry powder daily for 30 days. The blood PSA decreased by 22.5% in the treatment group, though prostate tissue markers remained unchanged.[281] In another double-blind, randomized, placebo-controlled trial, 41 men with prostate cancer were assigned to either the treatment or placebo groups. Men in the treatment group took one capsule (standardized to 72 mg proanthocyanidins) once daily during radiation treatment and for 2 weeks after. Radiation-induced cystitis was considerably lower in the treatment group (65%) compared to the placebo group (90%), and severe cystitis occurred in 30% of the treatment group vs. 45% of the placebo group. Researchers concluded that cranberry treatment during and after may be helpful in preventing radiation-induced cystitis, particularly in those with baseline urinary symptoms or low-hydration requirements.[282] Another study, without placebo, compared the incidence of radiation-induced cystitis in cranberry vs. apple juice, 354 ml per day. There was no difference between the treatment groups, though it is important to note that the amount of proanthocyanidins in that amount of cranberry juice as less than the 72 mg used in the other study.[283]

Pomegranate

Pomegranate, from the *Punica granatum* plant, induces apoptosis and inhibits metastasis in human prostate cancer cells.[284] Both pomegranate juice and an extract from the peel have been used. Luteolin, ellagic acid and punicic acid are three of the compounds from pomegranate that inhibit proliferation and metastasis while stimulating apoptosis.[285] In a randomized, multi-center double-blind phase II study, 104 men with rising PSA and prostate cancer, without metastasis, were enrolled and treated for up to 18 months. The PSA doubling time (PSADT) lengthened from 11.9 at baseline to 18.8 months in the low dose group (1 g/day), and from 12.5 to 17.5 months in the high dose group (3 g/day). The PSADT more than doubled in 43% of patients. Pomegranate treatment was associated with increases in PSADT of 6 or more months, and in 13% of patients, PSA even decreased.[286] In a double-blind randomized study, 70 men with prostate cancer were given either two pomegranate pills daily or placebo, for up to 4 weeks before a radical prostatectomy. While there were no significant differences in PSA levels or cancer markers after the treatment, the authors concluded that more studies are needed.[287] In another randomized, double-blind, placebo-controlled study, researchers studied the relationship between pomegranate supplementation and PSADT in prostate cancer patients who had already undergone surgery or radiation. In this study, pomegranate did not prolong doubling time in those who had already undergone primary therapy of surgery and/or radiation. Both the treatment and the placebo groups had a prolonged PSADT, and the study authors concluded that more studies are needed with the consideration of individual genetics.[288]

ProstaCaid

ProstaCaid is a formula consisting of medicinal mushrooms, herbs, and nutrients, many of which we have already discussed – Ganoderma mushroom, green tea, saw palmetto, pumpkin seed, pomegranate, pygeum, turmeric, broccoli, and stinging nettle – among many others. In laboratory studies, this formula had antiproliferative effects in highly aggressive, hormone-resistant prostate cancer cells.[289] More specifically, it causes cell cycle arrest (stops cancer cells from dividing) and triggers apoptosis ("cell suicide") of the cancer cells in both mouse and human hormone-resistant prostate cancer cell lines.[290] At this time, there are not yet any studies in humans.

References

1. National Cancer Institute. Surveillance, Epidemiology, and End Results Program: Cancer of the Prostate - Cancer Stat Facts. SEER. https://seer.cancer.gov/statfacts/html/prost.html. Published 2020. Accessed October 25, 2020.

2. Siegel R, Ward E, Brawley O, Jemal A. Cancer statistics, 2011: the impact of eliminating socioeconomic and racial disparities on premature cancer deaths. CA Cancer J Clin. Jul-Aug 2011;61(4):212-236.

3. Hankey BF, Feuer EJ, Clegg LX, et al. Cancer surveillance series: interpreting trends in prostate cancer--part I: Evidence of the effects of screening in recent prostate cancer incidence, mortality, and survival rates. J Natl Cancer Inst. Jun 16 1999;91(12):1017-1024.

4. Liede A, Karlan BY, Narod SA. Cancer risks for male carriers of germline mutations in BRCA1 or BRCA2: a review of the literature. J Clin Oncol. Feb 15 2004;22(4):735-742. 5.

5. Brechka H, Bhanvadia RR, VanOpstall C, Vander Griend DJ. HOXB13 mutations and binding partners in prostate development and cancer: Function, clinical significance, and future directions. Genes Dis. 2017;4(2):75-87. doi:10.1016/j.gendis.2017.01.003

6. Chodak GW, Keller P, Schoenberg HW. Assessment of screening for prostate cancer using the digital rectal examination. J Urol. May 1989;141(5):1136-1138.

7. Coley CM, Barry MJ, Fleming C, Mulley AG. Early detection of prostate cancer. Part I: Prior probability and effectiveness of tests. The American College of Physicians. Ann Intern Med. Mar 1 1997;126(5):394-406.

8. Bretton PR. Prostate-specific antigen and digital rectal examination in screening for prostate cancer: a communitybased study. South Med J. Jul 1994;87(7):720-723.

9. Catalona WJ, Richie JP, Ahmann FR, et al. Comparison of digital rectal examination and serum prostate specific antigen in the early detection of prostate cancer: results of a multicenter clinical trial of 6,630 men. J Urol. May 1994;151(5):1283-1290.

10. Gann PH, Hennekens CH, Stampfer MJ. A prospective evaluation of plasma prostate-specific antigen for detection of prostatic cancer. JAMA. Jan 25 1995;273(4):289294.

11. Tchetgen MB, Oesterling JE. The effect of prostatitis, urinary retention, ejaculation, and ambulation on the serum prostate-specific antigen concentration. Urol Clin North Am. May 1997;24(2):283-291.

12. Yuan JJ, Coplen DE, Petros JA, et al. Effects of rectal examination, prostatic massage, ultrasonography and needle biopsy on serum prostate specific antigen levels. J Urol. Mar 1992;147(3 Pt 2):810-814.

13. Essink-Bot ML, de Koning HJ, Nijs HG, Kirkels WJ, van der Maas PJ, Schroder FH. Short-term effects of population-based screening for prostate cancer on health-related quality of life. J Natl Cancer Inst. Jun 17 1998;90(12):925-931.

14. Schroder FH, Hugosson J, Roobol MJ, et al. Prostatecancer mortality at 11 years of follow-up. N Engl J Med. Mar 15 2012;366(11):981-990.

15. Moyer VA. Screening for prostate cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. Jul 17 2012;157(2):120-134.

16. Smith RA, von Eschenbach AC, Wender R, et al. American Cancer Society guidelines for the early detection of cancer: update of early detection guidelines for prostate, colorectal, and endometrial cancers. Also: update 2001--testing for early lung cancer detection. CA Cancer J Clin. Jan-Feb 2001;51(1):38-75; quiz 77-80.

17. Delongchamps NB, Singh A, Haas GP. The role of prevalence in the diagnosis of prostate cancer. Cancer Control. Jul 2006;13(3):158-168.

18. Zhen JT, Syed J, Nguyen KA, et al. Genetic testing for hereditary prostate cancer: Current status and limitations [published correction appears in Cancer. 2019 Jul 1;125(13):2325]. Cancer. 2018;124(15):3105-3117. doi:10.1002/cncr.31316

19. Giri VN, Knudsen KE, Kelly WK, et al. Role of Genetic Testing for Inherited Prostate Cancer Risk: Philadelphia Prostate Cancer Consensus Conference 2017. J Clin Oncol. 2018;36(4):414-424. doi:10.1200/JCO.2017.74.1173

20. Heidegger I, Tsaur I, Borgmann H, et al. Hereditary prostate cancer - Primetime for genetic testing?. Cancer Treat Rev. 2019;81:101927. doi:10.1016/j.ctrv.2019.101927
21. Pilarski R. The Role of BRCA Testing in Hereditary Pancreatic and Prostate Cancer Families. Am Soc Clin Oncol Educ Book. 2019;39:79-86. doi:10.1200/EDBK_238977
22. Parker PM, Rice KR, Sterbis JR, et al. Prostate cancer in men less than the age of 50: a comparison of race and outcomes. Urology. Jul 2011;78(1):110-115.
23. King Thomas J, Mir H, Kapur N, Singh S. Racial Differences in Immunological Landscape Modifiers Contributing to Disparity in Prostate Cancer. Cancers (Basel). 2019;11(12):1857. Published 2019 Nov 25. doi:10.3390/cancers11121857
24. Baquet CR, Horm JW, Gibbs T, Greenwald P. Socioeconomic factors and cancer incidence among blacks and whites. J Natl Cancer Inst. Apr 17 1991;83(8):551-557.
25. Sinha R, Park Y, Graubard BI, et al. Meat and meat-related compounds and risk of prostate cancer in a large prospective cohort study in the United States. Am J Epidemiol. Nov 1 2009;170(9):1165-1177.
26. Kolonel LN, Nomura AM, Cooney RV. Dietary fat and prostate cancer: current status. J Natl Cancer Inst. Mar 3 1999;91(5):414-428.
27. Colli JL, Colli A. International comparisons of prostate cancer mortality rates with dietary practices and sunlight levels. Urol Oncol. May-Jun 2006;24(3):184-194. 22.
28. Wilson KM, Mucci LA, Drake BF, et al. Meat, Fish, Poultry, and Egg Intake at Diagnosis and Risk of Prostate Cancer Progression. Cancer Prev Res (Phila). 2016;9(12):933-941. doi:10.1158/1940-6207.CAPR-16-0070
29. Wilson KM, Mucci LA. Diet and Lifestyle in Prostate Cancer. Adv Exp Med Biol. 2019;1210:1-27. doi:10.1007/978-3-030-32656-21
30. Cohen JH, Kristal AR, Stanford JL. Fruit and vegetable intakes and prostate cancer risk. J Natl Cancer Inst. Jan 5 2000;92(1):61-68.
31. Gerber M. Omega-3 fatty acids and cancers: a systematic update review of epidemiological studies. Br J Nutr. Jun 2012;107 Suppl 2:S228-239.
32. Brasky TM, Till C, White E, et al. Serum phospholipid fatty acids and prostate cancer risk: results from the prostate cancer prevention trial. Am J Epidemiol. Jun 15 2011;173(12):1429-1439.
33. Brasky TM, Darke AK, Song X, et al. Plasma phospholipid fatty acids and prostate cancer risk in the SELECT trial. J Natl Cancer Inst. Aug 7 2013;105(15):11321141.
34. Hanson S, Thorpe G, Winstanley L, Abdelhamid AS, Hooper L; PUFAH group. Omega-3, omega-6 and total dietary polyunsaturated fat on cancer incidence: systematic review and meta-analysis of randomised trials. Br J Cancer. 2020;122(8):1260-1270.
35. Connolly JM, Coleman M, Rose DP. Effects of dietary fatty acids on DU145 human prostate cancer cell growth in athymic nude mice. Nutr Cancer. 1997;29(2):114119.
36. Lloyd JC, Masko EM, Wu C, et al. Fish oil slows prostate cancer xenograft growth relative to other dietary fats and is associated with decreased mitochondrial and insulin pathway gene expression. Prostate Cancer Prostatic Dis. Dec 2013;16(4):285-291.
37. Oyelowo O, Okafor C, Ajibare A, et al. Fatty Acids in Some Cooking Oils as Agents of Hormonal Manipulation in a Rat Model of Benign Prostate Cancer. Niger J Physiol Sci. 2019;34(1):69-75. Published 2019 Jun 30.
38. Yu O, Eberg M, Benayoun S, et al. Use of statins and the risk of death in patients with prostate cancer. J Clin Oncol. Jan 1 2014;32(1):5-11.
39. Platz EA, Leitzmann MF, Visvanathan K, et al. Statin drugs and risk of advanced prostate cancer. J Natl Cancer Inst. Dec 20 2006;98(24):1819-1825.
40. Bonovas S, Filioussi K, Sitaras NM. Statin use and the risk of prostate cancer: A metaanalysis of 6 randomized clinical trials and 13 observational studies. Int J Cancer. Aug 15 2008;123(4):899-904.
41. Jamnagerwalla J, Howard LE, Allott EH, et al. Serum cholesterol and risk of high-grade prostate cancer: results from the REDUCE study. Prostate Cancer Prostatic Dis. 2018;21(2):252-259. doi:10.1038/s41391-017-0030-9
42. Kenfield SA, Stampfer MJ, Chan JM, Giovannucci E. Smoking and prostate cancer survival and recurrence. JAMA. Jun 22 2011;305(24):2548-2555.
43. Cuzick J, Thorat MA, Andriole G, et al. Prevention and early detection of prostate cancer. Lancet Oncol. 2014;15(11):e484-e492. doi:10.1016/S1470-2045(14)70211-6
44. Bagnardi V, Blangiardo M, La Vecchia C, Corrao G. A meta-analysis of alcohol drinking and cancer risk. Br J Cancer. Nov 30 2001;85(11):1700-1705.
45. Gong Z, Kristal AR, Schenk JM, Tangen CM, Goodman PJ, Thompson IM. Alcohol consumption, finasteride, and prostate cancer risk: results from the Prostate Cancer Prevention Trial. Cancer. Aug 15 2009;115(16):36613669.
46. Zhao J, Stockwell T, Roemer A, Chikritzhs T. Is alcohol consumption a risk factor for prostate cancer? A systematic review and meta-analysis. BMC Cancer. 2016;16(1):845. Published 2016 Nov 15. doi:10.1186/s12885-016-2891-z
47. Chan JM, Giovannucci E, Andersson SO, Yuen J, Adami HO, Wolk A. Dairy products, calcium, phosphorous, vitamin D, and risk of prostate cancer (Sweden). Cancer Causes Control. Dec 1998;9(6):559-566.
48. Gao X, LaValley MP, Tucker KL. Prospective studies of dairy product and calcium intakes and prostate cancer risk: a meta-analysis. J Natl Cancer Inst. Dec 7 2005;97(23):17681777.
49. Giovannucci E, Liu Y, Stampfer MJ, Willett WC. A prospective study of calcium intake and incident and fatal prostate cancer. Cancer Epidemiol Biomarkers Prev. Feb 2006;15(2):203-210.
50. Ma J, Stampfer MJ, Gann PH, et al. Vitamin D receptor polymorphisms, circulating vitamin D metabolites, and risk of prostate cancer in United States physicians. Cancer Epidemiol Biomarkers Prev. May 1998;7(5):385-390.
51. Mitrou PN, Albanes D, Weinstein SJ, et al. A prospective study of dietary calcium, dairy products and prostate cancer risk (Finland). Int J Cancer. Jun 1 2007;120(11):2466-2473.
52. Severi G, English DR, Hopper JL, Giles GG. Re: Prospective studies of dairy product and calcium intakes and prostate cancer risk: a meta-analysis. J Natl Cancer Inst. Jun 7 2006;98(11):794-795; author reply 795.
53. Koh KA, Sesso HD, Paffenbarger RS, Jr., Lee IM. Dairy products, calcium and prostate cancer risk. Br J Cancer. Dec 4 2006;95(11):1582-1585.
54. Ingles SA, Coetzee GA, Ross RK, et al. Association of prostate cancer with vitamin D receptor haplotypes in African-Americans. Cancer Res. Apr 15 1998;58(8):16201623.
55. Ahonen MH, Tenkanen L, Teppo L, Hakama M, Tuohimaa P. Prostate cancer risk and prediagnostic serum 25-hydroxyvitamin D levels (Finland). Cancer Causes Control. Oct 2000;11(9):847-852.
56. Tuohimaa P, Tenkanen L, Ahonen M, et al. Both high and low levels of blood vitamin D are associated with a higher prostate cancer risk: a longitudinal, nested case-control study in the Nordic countries. Int J Cancer. Jan 1 2004;108(1):104-108.
57. Melnik BC, John SM, Carrera-Bastos P, Cordain L. The impact of cow's milk-mediated mTORC1-signaling in the initiation and progression of prostate cancer. Nutr Metab (Lond). 2012;9(1):74.
58. Preble I, Zhang Z, Kopp R, et al. Dairy Product Consumption and Prostate Cancer Risk in the United States. Nutrients. 2019;11(7):1615. Published 2019 Jul 16. doi:10.3390/nu11071615
59. Heber D, Freedland SJ, Jones LW, Nelson WG. Nutrition, Exercise and Prostate Cancer, Duke University; 2009.
60. Prostate Cancer Foundation. Understanding Prostate Cancer: Prevention. http://www.pcf.org/site/c.leJRIROrEpH/ b.5802029/k.31EA/Prevention.htm.
61. Weinstein SJ, Wright ME, Lawson KA, et al. Serum and dietary vitamin E in relation to prostate cancer risk. Cancer Epidemiol Biomarkers Prev. Jun 2007;16(6):1253-1259.
62. Nomura AM, Lee J, Stemmermann GN, Combs GF, Jr. Serum selenium and subsequent risk of prostate cancer. Cancer Epidemiol Biomarkers Prev. Sep 2000;9(9):883-887.
63. Lippman SM, Goodman PJ, Klein EA, et al. Designing the Selenium and Vitamin E Cancer Prevention Trial (SELECT). J Natl Cancer Inst. Jan 19 2005;97(2):94-102.
64. Dunn BK, Ryan A, Ford LG. Selenium and Vitamin E Cancer Prevention Trial: a nutrient approach to prostate cancer prevention. Recent Results Cancer Res. 2009;181:183193.
65. Lippman SM, Klein EA, Goodman PJ, et al. Effect of selenium and vitamin E on risk of prostate cancer and other cancers: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). JAMA. Jan 7 2009;301(1):39-51.
66. Klein EA, Thompson IM Jr, Tangen CM, et al. Vitamin E and the risk of prostate cancer: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). JAMA. 2011;306(14):1549-1556. doi:10.1001/jama.2011.1437
67. Kristal AR, Darke AK, Morris JS, et al. Baseline selenium status and effects of selenium and vitamin e supplementation on prostate cancer risk. J Natl Cancer Inst. Mar 2014;106(3):djt456.
68. Gaziano JM, Glynn RJ, Christen WG, et al. Vitamins E and C in the prevention of prostate and total cancer in men: the Physicians' Health Study II randomized controlled trial. JAMA. Jan 7 2009;301(1):52-62.

69. Chan JM, Darke AK, Penney KL, et al. Selenium- or Vitamin E-Related Gene Variants, Interaction with Supplementation, and Risk of High-Grade Prostate Cancer in SELECT. Cancer Epidemiol Biomarkers Prev. 2016;25(7):1050-1058. doi:10.1158/1055-9965.EPI-16-0104
70. Cole BF, Baron JA, Sandler RS, et al. Folic acid for the prevention of colorectal adenomas: a randomized clinical trial. JAMA. Jun 6 2007;297(21):2351-2359.
71. Vollset SE, Clarke R, Lewington S, et al. Effects of folic acid supplementation on overall and site-specific cancer incidence during the randomised trials: meta-analyses of data on 50,000 individuals. Lancet. 2013;381(9871):1029-1036. doi:10.1016/S0140-6736(12)62001-7
72. Kristal AR, Arnold KB, Schenk JM, et al. Dietary patterns, supplement use, and the risk of symptomatic benign prostatic hyperplasia: results from the prostate cancer prevention trial. Am J Epidemiol. Apr 15 2008;167(8):925-934. 56.
73. Leitzmann MF, Stampfer MJ, Wu K, Colditz GA, Willett WC, Giovannucci EL. Zinc supplement use and risk of prostate cancer. J Natl Cancer Inst. Jul 2 2003;95(13):10041007.
74. Gutiérrez-González E, Castelló A, Fernández-Navarro P, et al. Dietary Zinc and Risk of Prostate Cancer in Spain: MCC-Spain Study. Nutrients. 2018;11(1):18. Published 2018 Dec 20. doi:10.3390/nu11010018
75. Xue YN, Yu BB, Liu YN, et al. Zinc promotes prostate cancer cell chemosensitivity to paclitaxel by inhibiting epithelial-mesenchymal transition and inducing apoptosis. Prostate. 2019;79(6):647-656. doi:10.1002/pros.23772
76. MacInnis RJ, English DR. Body size and composition and prostate cancer risk: systematic review and meta-regression analysis. Cancer Causes Control. Oct 2006;17(8):989-1003. 58.
77. Ferro M, Terracciano D, Buonerba C, et al. The emerging role of obesity, diet and lipid metabolism in prostate cancer. Future Oncol. 2017;13(3):285-293. doi:10.2217/fon-2016-0217
78. Allott EH, Masko EM, Freedland SJ. Obesity and prostate cancer: weighing the evidence. Eur Urol. May 2013;63(5):800-809.
79. Bandini M, Gandaglia G, Briganti A. Obesity and prostate cancer. Curr Opin Urol. 2017;27(5):415-421. doi:10.1097/MOU.0000000000000424
80. Di Sebastiano KM, Pinthus JH, Duivenvoorden WCM, Mourtzakis M. Glucose impairments and insulin resistance in prostate cancer: the role of obesity, nutrition and exercise. Obes Rev. 2018;19(7):1008-1016. doi:10.1111/obr.12674
81. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. Lancet. Feb 16 2008;371(9612):569-578.
82. Moller E, Adami HO, Mucci LA, et al. Lifetime body size and prostate cancer risk in a population-based case-control study in Sweden. Cancer Causes Control. Dec 2013;24(12):2143-2155.
83. Giovannucci E, Rimm EB, Stampfer MJ, Colditz GA, Willett WC. Height, body weight, and risk of prostate cancer. Cancer Epidemiol Biomarkers Prev. Aug 1997;6(8):557-563.
84. Giovannucci EL, Liu Y, Leitzmann MF, Stampfer MJ, Willett WC. A prospective study of physical activity and incident and fatal prostate cancer. Arch Intern Med. May 9 2005;165(9):1005-1010.
85. Miles FL, Neuhouser ML, Zhang ZF. Concentrated sugars and incidence of prostate cancer in a prospective cohort. Br J Nutr. 2018 Sep;120(6):703-710. doi: 10.1017/S0007114518001812. Epub 2018 Jul 26. PMID: 30047347; PMCID: PMC6123266.
86. Chazelas E, Srour B, Desmetz E, et al. Sugary drink consumption and risk of cancer: results from NutriNet-Santé prospective cohort. BMJ. 2019;366:l2408. Published 2019 Jul 10. doi:10.1136/bmj.l2408
87. Margel D, Urbach D, Lipscombe LL, et al. Association between metformin use and risk of prostate cancer and its grade. J Natl Cancer Inst. Aug 7 2013;105(15):11231131.
88. Margel D, Urbach DR, Lipscombe LL, et al. Metformin use and all-cause and prostate cancer-specific mortality among men with diabetes. J Clin Oncol. Sep 1 2013;31(25):3069-3075.
89. Zaidi S, Gandhi J, Joshi G, Smith NL, Khan SA. The anticancer potential of metformin on prostate cancer. Prostate Cancer Prostatic Dis. 2019;22(3):351-361. doi:10.1038/s41391-018-0085-2
90. Zafar MB, Terris MK. Prostate cancer detection in veterans with a history of Agent Orange exposure. J Urol. Jul 2001;166(1):100-103.
91. Shah SR, Freedland SJ, Aronson WJ, et al. Exposure to Agent Orange is a significant predictor of prostate-specific antigen (PSA)-based recurrence and a rapid PSA doubling time after radical prostatectomy. BJU Int. May 2009;103(9):11681172.
92. Multigner L, Ndong JR, Giusti A, et al. Chlordecone exposure and risk of prostate cancer. J Clin Oncol. Jul 20 2010;28(21):3457-3462.
93. Brureau L, Emeville E, Helissey C, Thome JP, Multigner L, Blanchet P. Endocrine disrupting-chemicals and biochemical recurrence of prostate cancer after prostatectomy: A cohort study in Guadeloupe (French West Indies). Int J Cancer. 2020;146(3):657-663. doi:10.1002/ijc.32287
94. Prins GS, Hu WY, Shi GB, et al. Bisphenol A promotes human prostate stem-progenitor cell self-renewal and increases in vivo carcinogenesis in human prostate epithelium. Endocrinology. Mar 2014;155(3):805-817.
95. Prins GS, Hu WY, Xie L, et al. Evaluation of Bisphenol A (BPA) Exposures on Prostate Stem Cell Homeostasis and Prostate Cancer Risk in the NCTR-Sprague-Dawley Rat: An NIEHS/FDA CLARITY-BPA Consortium Study. Environ Health Perspect. 2018;126(11):117001. doi:10.1289/EHP3953
96. Kappas A, Anderson KE, Conney AH, Pantuck EJ, Fishman J, Bradlow HL. Nutrition-endocrine interactions: induction of reciprocal changes in the delta 4-5 alpha-reduction of testosterone and the cytochrome P-450-dependent oxidation of estradiol by dietary macronutrients in man. Proc Natl Acad Sci U S A. Dec 1983;80(24):7646-7649.
97. Blanc-Lapierre A, Sauvé JF, Parent ME. Occupational exposure to benzene, toluene, xylene and styrene and risk of prostate cancer in a population-based study. Occup Environ Med. 2018;75(8):562-572. doi:10.1136/oemed-2018-105058
98. Rapisarda V, Miozzi E, Loreto C, et al. Cadmium exposure and prostate cancer: insights, mechanisms and perspectives. Front Biosci (Landmark Ed). 2018;23:1687-1700. Published 2018 Mar 1. doi:10.2741/4667
99. Zimta AA, Schitcu V, Gurzau E, et al. Biological and molecular modifications induced by cadmium and arsenic during breast and prostate cancer development. Environ Res. 2019;178:108700. doi:10.1016/j.envres.2019.108700
100. Riviere P, Kumar A, Luterstein E, et al. Tobacco smoking and death from prostate cancer in US veterans. Prostate Cancer Prostatic Dis. 2020;23(2):252-259. doi:10.1038/s41391-019-0178-6
101. Darcey E, Boyle T. Tobacco smoking and survival after a prostate cancer diagnosis: A systematic review and meta-analysis. Cancer Treat Rev. 2018;70:30-40. doi:10.1016/j.ctrv.2018.07.001
102. Ren Z-J, Cao D-H, Zhang Q, et al. First-degree family history of breast cancer is associated with prostate cancer risk: a systematic review and meta-analysis. BMC cancer. 2019;19(1):871. doi:10.1186/s12885-019-6055-9
103. Siddiqui MM, Wilson KM, Epstein MM, et al. Vasectomy and risk of aggressive prostate cancer: a 24-year follow-up study. J Clin Oncol. 2014;32(27):3033-3038. doi:10.1200/JCO.2013.54.8446
104. Shang Y, Han G, Li J, et al. Vasectomy and prostate cancer risk: a meta-analysis of cohort studies. Sci Rep. 2015;5:9920. Published 2015 Apr 30. doi:10.1038/srep09920
105. Bhindi B, Wallis CJD, Nayan M, et al. The Association Between Vasectomy and Prostate Cancer: A Systematic Review and Meta-analysis. JAMA Intern Med. 2017;177(9):1273-1286. doi:10.1001/jamainternmed.2017.2791
106. Smith K, Byrne, Castaño JM, et al. Vasectomy and Prostate Cancer Risk in the European Prospective Investigation Into Cancer and Nutrition (EPIC). J Clin Oncol. 2017;35(12):1297-1303. doi:10.1200/JCO.2016.70.0062
107. Jacobs EJ, Anderson RL, Stevens VL, Newton CC, Gansler T, Gapstur SM. Vasectomy and Prostate Cancer Incidence and Mortality in a Large US Cohort. J Clin Oncol. 2016;34(32):3880-3885. doi:10.1200/JCO.2015.66.2361
108. Nayan M, Hamilton RJ, Macdonald EM, et al. Vasectomy and risk of prostate cancer: population based matched cohort study. BMJ. 2016;355:i5546. Published 2016 Nov 3. doi:10.1136/bmj.i5546
109. Mohler J, Bahnson RR, Boston B, et al. NCCN clinical practice guidelines in oncology: prostate cancer. J Natl Compr Canc Netw. Feb 2010;8(2):162-200.
110. Alemozaffar M, Regan MM, Cooperberg MR, et al. Prediction of erectile function following treatment for prostate cancer. JAMA. Sep 21 2011;306(11):1205-1214.
111. Capogrosso P, Vertosick EA, Benfante NE, et al. Are We Improving Erectile Function Recovery After Radical Prostatectomy? Analysis of Patients Treated over the Last Decade. Eur Urol. 2019;75(2):221-228. doi:10.1016/j.eururo.2018.08.039
112. King CR, Brooks JD, Gill H, Presti JC, Jr. Longterm outcomes from a prospective trial of stereotactic body radiotherapy for low-risk prostate cancer. Int J Radiat Oncol

Biol Phys. Feb 1 2012;82(2):877-882.
113. Katz A, Ferrer M, Suárez JF; Multicentric Spanish Group of Clinically Localized Prostate Cancer. Comparison of quality of life after stereotactic body radiotherapy and surgery for early-stage prostate cancer. Radiat Oncol. 2012;7:194. Published 2012 Nov 20. doi:10.1186/1748-717X-7-194
114. Cuccia F, Mazzola R, Arcangeli S, et al. Moderate hypofractionated helical tomotherapy for localized prostate cancer: preliminary report of an observational prospective study. Tumori. 2019;105(6):516-523. doi:10.1177/0300891619867846
115. Rodríguez SA, Arias Fúnez F, Bueno Bravo C, et al. Cryotherapy for primary treatment of prostate cancer: intermediate term results of a prospective study from a single institution. Prostate Cancer. 2014;2014:571576. doi:10.1155/2014/571576
116. Sesia G, Ferrando U, Fontana G, Laudi M, Cauda F. Palliative cryotherapy in inoperable prostate carcinoma. Recent Results Cancer Res. 1977(60):84-90.
117. Izadifar Z, Izadifar Z, Chapman D, Babyn P. An Introduction to High Intensity Focused Ultrasound: Systematic Review on Principles, Devices, and Clinical Applications. J Clin Med. 2020;9(2):460. Published 2020 Feb 7. doi:10.3390/jcm9020460
118. McLeod DG, Iversen P, See WA, Morris T, Armstrong J, Wirth MP. Bicalutamide 150 mg plus standard care vs standard care alone for early prostate cancer. BJU Int. Feb 2006;97(2):247-254.
119. Crawford ED, Schellhammer PF, McLeod DG, et al. Androgen Receptor Targeted Treatments of Prostate Cancer: 35 Years of Progress with Antiandrogens. J Urol. 2018;200(5):956-966. doi:10.1016/j.juro.2018.04.083
120. Ricci F, Buzzatti G, Rubagotti A, Boccardo F. Safety of antiandrogen therapy for treating prostate cancer. Expert Opin Drug Saf. 2014;13(11):1483-1499. doi:10.1517/14740338.2014.966686
121. Crawford ED, Heidenreich A, Lawrentschuk N, et al. Androgen-targeted therapy in men with prostate cancer: evolving practice and future considerations. Prostate Cancer Prostatic Dis. 2019;22(1):24-38. doi:10.1038/s41391-018-0079-0
122. Wilson KM, Kasperzyk JL, Rider JR, et al. Coffee consumption and prostate cancer risk and progression in the Health Professionals Follow-up Study. J Natl Cancer Inst. Jun 8 2011;103(11):876-884.
123. Iwamoto H, Izumi K, Natsagdorj A, et al. Coffee diterpenes kahweol acetate and cafestol synergistically inhibit the proliferation and migration of prostate cancer cells. Prostate. 2019;79(5):468-479. doi:10.1002/pros.23753
124. Berges RR, Windeler J, Trampisch HJ, Senge T. Randomised, placebo-controlled, double-blind clinical trial of beta-sitosterol in patients with benign prostatic hyperplasia. Beta-sitosterol Study Group. Lancet. Jun 17 1995;345(8964):1529-1532.
125. Messina M, Barnes S. The role of soy products in reducing risk of cancer. J Natl Cancer Inst. Apr 17 1991;83(8):541-546.
126. Kyle E, Neckers L, Takimoto C, Curt G, Bergan R. Genistein-induced apoptosis of prostate cancer cells is preceded by a specific decrease in focal adhesion kinase activity. Mol Pharmacol. Feb 1997;51(2):193-200.
127. Mahmoud AM, Yang W, Bosland MC. Soy isoflavones and prostate cancer: a review of molecular mechanisms. J Steroid Biochem Mol Biol. 2014;140:116-132. doi:10.1016/j.jsbmb.2013.12.010
128. Messina MJ, Persky V, Setchell KD, Barnes S. Soy intake and cancer risk: a review of the in vitro and in vivo data. Nutr Cancer. 1994;21(2):113-131.
129. Jacobsen BK, Knutsen SF, Fraser GE. Does high soy milk intake reduce prostate cancer incidence? The Adventist Health Study (United States). Cancer Causes Control. Dec 1998;9(6):553-557.
130. Kolonel LN, Hankin JH, Whittemore AS, et al. Vegetables, fruits, legumes and prostate cancer: a multiethnic case-control study. Cancer Epidemiol Biomarkers Prev. Aug 2000;9(8):795-804.
131. Kurahashi N, Iwasaki M, Inoue M, Sasazuki S, Tsugane S. Plasma isoflavones and subsequent risk of prostate cancer in a nested case-control study: the Japan Public Health Center. J Clin Oncol. Dec 20 2008;26(36):5923-5929.
132. Yan L, Spitznagel EL. Meta-analysis of soy food and risk of prostate cancer in men. Int J Cancer. Nov 20 2005;117(4):667-669.
133. Applegate CC, Rowles JL, Ranard KM, Jeon S, Erdman JW. Soy Consumption and the Risk of Prostate Cancer: An Updated Systematic Review and Meta-Analysis. Nutrients. 2018;10(1):40.
134. Adlercreutz H, Mazur W. Phyto-oestrogens and Western diseases. Ann Med. Apr 1997;29(2):95-120.
135. Holzapfel NP, Holzapfel BM, Champ S, Feldthusen J, Clements J, Hutmacher DW. The potential role of lycopene for the prevention and therapy of prostate cancer: from molecular mechanisms to clinical evidence. Int J Mol Sci. 2013;14(7):14620-14646.
136. Rao AV, Fleshner N, Agarwal S. Serum and tissue lycopene and biomarkers of oxidation in prostate cancer patients: a case-control study. Nutr Cancer. 1999;33(2):159164.
137. Putnam SD, Cerhan JR, Parker AS, et al. Lifestyle and anthropometric risk factors for prostate cancer in a cohort of Iowa men. Ann Epidemiol. Aug 2000;10(6):361-369.
138. Giovannucci E, Ascherio A, Rimm EB, Stampfer MJ, Colditz GA, Willett WC. Intake of carotenoids and retinol in relation to risk of prostate cancer. J Natl Cancer Inst. Dec 6 1995;87(23):1767-1776.
139. Guttenplan JB, Chen M, Kosinska W, Thompson S, Zhao Z, Cohen LA. Effects of a lycopene-rich diet on spontaneous and benzo[a]pyrene-induced mutagenesis in prostate, colon and lungs of the lacZ mouse. Cancer Lett. Mar 10 2001;164(1):1-6.
140. Agarwal S, Rao AV. Tomato lycopene and its role in human health and chronic diseases. CMAJ. Sep 19 2000;163(6):739-744.
141. Giovannucci E, Rimm EB, Liu Y, Stampfer MJ, Willett WC. A prospective study of tomato products, lycopene, and prostate cancer risk. J Natl Cancer Inst. Mar 6 2002;94(5):391-398.
142. Zu K, Mucci L, Rosner BA, et al. Dietary lycopene, angiogenesis, and prostate cancer: a prospective study in the prostate-specific antigen era. J Natl Cancer Inst. Feb 2014;106(2):djt430.
143. Chen P, Zhang W, Wang X, et al. Lycopene and Risk of Prostate Cancer: A Systematic Review and Meta-Analysis. Medicine (Baltimore). 2015;94(33):e1260. doi:10.1097/MD.0000000000001260
144. Rowles JL 3rd, Ranard KM, Smith JW, An R, Erdman JW Jr. Increased dietary and circulating lycopene are associated with reduced prostate cancer risk: a systematic review and meta-analysis. Prostate Cancer Prostatic Dis. 2017;20(4):361-377. doi:10.1038/pcan.2017.25
145. Lane JA, Er V, Avery KNL, et al. ProDiet: A Phase II Randomized Placebo-controlled Trial of Green Tea Catechins and Lycopene in Men at Increased Risk of Prostate Cancer. Cancer Prev Res (Phila). 2018;11(11):687-696. doi:10.1158/1940-6207.CAPR-18-0147
146. Beynon RA, Richmond RC, Santos Ferreira DL, et al. Investigating the effects of lycopene and green tea on the metabolome of men at risk of prostate cancer: The ProDiet randomised controlled trial. Int J Cancer. 2019;144(8):1918-1928. doi:10.1002/ijc.31929
147. Paur I, Lilleby W, Bøhn SK, et al. Tomato-based randomized controlled trial in prostate cancer patients: Effect on PSA. Clin Nutr. 2017;36(3):672-679. doi:10.1016/j.clnu.2016.06.014
148. Applegate CC, Rowles JL 3rd, Erdman JW Jr. Can Lycopene Impact the Androgen Axis in Prostate Cancer?: A Systematic Review of Cell Culture and Animal Studies. Nutrients. 2019;11(3):633. Published 2019 Mar 15. doi:10.3390/nu11030633
149. Wang Y, Cui R, Xiao Y, Fang J, Xu Q. Effect of Carotene and Lycopene on the Risk of Prostate Cancer: A Systematic Review and Dose-Response Meta-Analysis of Observational Studies [published correction appears in PLoS One. 2015;10(10):e0140415]. PLoS One. 2015;10(9):e0137427. Published 2015 Sep 15. doi:10.1371/journal.pone.0137427
150. Watson GW, Beaver LM, Williams DE, Dashwood RH, Ho E. Phytochemicals from cruciferous vegetables, epigenetics, and prostate cancer prevention. AAPS J. 2013;15(4):951-961.
151. Liu B, Mao Q, Cao M, Xie L. Cruciferous vegetables intake and risk of prostate cancer: a meta-analysis. Int J Urol. Feb 2012;19(2):134-141.
152. Richman EL, Carroll PR, Chan JM. Vegetable and fruit intake after diagnosis and risk of prostate cancer progression. Int J Cancer. Jul 1 2012;131(1):201-210. 96.
153. Traka MH, Melchini A, Coode-Bate J, et al. Transcriptional changes in prostate of men on active surveillance after a 12-mo glucoraphanin-rich broccoli intervention-results from the Effect of Sulforaphane on prostate CAncer PrEvention (ESCAPE) randomized controlled trial. Am J Clin Nutr. 2019;109(4):1133-1144. doi:10.1093/ajcn/nqz012
154. Liao S, Hiipakka RA. Selective inhibition of steroid 5 alpha-reductase isozymes by tea epicatechin-3-gallate and epigallocatechin-3-gallate. Biochem Biophys Res Commun. Sep 25 1995;214(3):833-838.
155. Satoh K, Sakamoto Y, Ogata A, et al. Inhibition of aromatase activity by green tea extract catechins and their endocrinological effects of oral administration in rats. Food

Chem Toxicol. Jul 2002;40(7):925-933.
156. Chung LY, Cheung TC, Kong SK, et al. Induction of apoptosis by green tea catechins in human prostate cancer DU145 cells. Life Sci. Jan 26 2001;68(10):1207-1214.
157. Gupta S, Hastak K, Ahmad N, Lewin JS, Mukhtar H. Inhibition of prostate carcinogenesis in TRAMP mice by oral infusion of green tea polyphenols. Proc Natl Acad Sci U S A. Aug 28 2001;98(18):10350-10355.
158. Henning SM, Aronson W, Niu Y, et al. Tea polyphenols and theaflavins are present in prostate tissue of humans and mice after green and black tea consumption. J Nutr. Jul 2006;136(7):1839-1843.
159. Kumar NB, Pow-Sang J, Egan KM, et al. Randomized, Placebo-Controlled Trial of Green Tea Catechins for Prostate Cancer Prevention. Cancer Prev Res (Phila). 2015;8(10):879-887. doi:10.1158/1940-6207.CAPR-14-0324
160. Yuan JM. Cancer prevention by green tea: evidence from epidemiologic studies. Am J Clin Nutr. Dec 2013;98(6 Suppl):1676S-1681S.
161. Guo Y, Zhi F, Chen P, et al. Green tea and the risk of prostate cancer: A systematic review and meta-analysis. Medicine (Baltimore). 2017;96(13):e6426. doi:10.1097/MD.0000000000006426
162. Boehm K, Borrelli F, Ernst E, et al. Green tea (Camellia sinensis) for the prevention of cancer. Cochrane Database Syst Rev. 2009(3):CD005004.
163. Guo Y, Zhi F, Chen P, et al. Green tea and the risk of prostate cancer: A systematic review and meta-analysis. Medicine (Baltimore). 2017;96(13):e6426. doi:10.1097/MD.0000000000006426
164. Raloff J. Radical prostates: Female hormones may play a pivotal role in a distinctly male epidemic. Science News. 1997;151(8):126-127.
165. Pinto JT, Qiao C, Xing J, et al. Alterations of prostate biomarker expression and testosterone utilization in human LNCaP prostatic carcinoma cells by garlic-derived S-allylmercaptocysteine. Prostate. Dec 1 2000;45(4):304-314.
166. Arunkumar A, Vijayababu MR, Kanagaraj P, Balasubramanian K, Aruldhas MM, Arunakaran J. Growth suppressing effect of garlic compound diallyl disulfide on prostate cancer cell line (PC-3) in vitro. Biol Pharm Bull. Apr 2005;28(4):740-743.
167. Zhou XF, Ding ZS, Liu NB. Allium vegetables and risk of prostate cancer: evidence from 132,192 subjects. Asian Pac J Cancer Prev. 2013;14(7):4131-4134.
168. Shukla Y, Singh M. Cancer preventive properties of ginger: a brief review. Food Chem Toxicol. May 2007;45(5):683-690.
169. Livingstone TL, Beasy G, Mills RD, et al. Plant Bioactives and the Prevention of Prostate Cancer: Evidence from Human Studies. Nutrients. 2019;11(9):2245. Published 2019 Sep 18. doi:10.3390/nu11092245
170. Yedjou CG, Mbemi AT, Noubissi F, et al. Prostate Cancer Disparity, Chemoprevention, and Treatment by Specific Medicinal Plants. Nutrients. 2019;11(2):336. Published 2019 Feb 4. doi:10.3390/nu11020336
171. Karna P, Chagani S, Gundala SR, et al. Benefits of whole ginger extract in prostate cancer. Br J Nutr. Feb 2012;107(4):473-484.
172. Brahmbhatt M, Gundala SR, Asif G, Shamsi SA, Aneja R. Ginger phytochemicals exhibit synergy to inhibit prostate cancer cell proliferation. Nutr Cancer. 2013;65(2):263272.
173. Rao CV, Rivenson A, Simi B, Reddy BS. Chemoprevention of colon carcinogenesis by dietary curcumin, a naturally occurring plant phenolic compound. Cancer Res. Jan 15 1995;55(2):259-266.
174. Huang MT, Newmark HL, Frenkel K. Inhibitory effects of curcumin on tumorigenesis in mice. J Cell Biochem Suppl. 1997;27:26-34.
175. Saha A, Blando J, Silver E, Beltran L, Sessler J, DiGiovanni J. 6-Shogaol from dried ginger inhibits growth of prostate cancer cells both in vitro and in vivo through inhibition of STAT3 and NF-κB signaling. Cancer Prev Res (Phila). 2014;7(6):627-638. doi:10.1158/1940-6207.CAPR-13-0420
176. Hour TC, Chen J, Huang CY, Guan JY, Lu SH, Pu YS. Curcumin enhances cytotoxicity of chemotherapeutic agents in prostate cancer cells by inducing p21(WAF1/CIP1) and C/EBPbeta expressions and suppressing NF-kappaB activation. Prostate. May 15 2002;51(3):211-218. 113.
177. Hejazi J, Rastmanesh R, Taleban FA, et al. Effect of Curcumin Supplementation During Radiotherapy on Oxidative Status of Patients with Prostate Cancer: A Double Blinded, Randomized, Placebo-Controlled Study. Nutr Cancer. 2016;68(1):77-85. doi:10.1080/01635581.2016.1115527
178. Saadipoor A, Razzaghdoust A, Simforoosh N, et al. Randomized, double-blind, placebo-controlled phase II trial of nanocurcumin in prostate cancer patients undergoing radiotherapy. Phytother Res. 2019;33(2):370-378. doi:10.1002/ptr.6230
179. Greil R, Greil-Ressler S, Weiss L, et al. A phase 1 dose-escalation study on the safety, tolerability and activity of liposomal curcumin (Lipocurc™) in patients with locally advanced or metastatic cancer. Cancer Chemother Pharmacol. 2018;82(4):695-706. doi:10.1007/s00280-018-3654-0
180. Choi YH, Han DH, Kim SW, et al. A randomized, double-blind, placebo-controlled trial to evaluate the role of curcumin in prostate cancer patients with intermittent androgen deprivation. Prostate. 2019;79(6):614-621. doi:10.1002/pros.23766
181. Shoba G, Joy D, Joseph T, Majeed M, Rajendran R, Srinivas PS. Influence of piperine on the pharmacokinetics of curcumin in animals and human volunteers. Planta Med. 1998;64(4):353-356. doi:10.1055/s-2006-957450
182. Anand P, Kunnumakkara AB, Newman RA, Aggarwal BB. Bioavailability of curcumin: problems and promises. Mol Pharm. 2007;4(6):807-818. doi:10.1021/mp700113r
183. Terakawa N, Matsui Y, Satoi S, et al. Immunological effect of active hexose correlated compound (AHCC) in healthy volunteers: a double-blind, placebo-controlled trial. Nutr Cancer. 2008;60(5):643-651.
184. Palucka K, Banchereau J. Cancer immunotherapy via dendritic cells. Nat Rev Cancer. 2012;12(4):265-277. 115.
185. Pyo P, Louie B, Rajamahanty S, Choudhury M, Konno S. Possible immunotherapeutic potentiation with D-fraction in prostate cancer cells. J Hematol Oncol. 2008;1:25.
186. deVere White RW, Hackman RM, Soares SE, Beckett LA, Sun B. Effects of a mushroom mycelium extract on the treatment of prostate cancer. Urology. Oct 2002;60(4):640-644. 117.
187. Tari K, Satake I, Nakagomi K, et al. [Effect of lentinan for advanced prostate carcinoma]. Hinyokika Kiyo. Feb 1994;40(2):119-123.
188. French C, Lc C, Clarke SL, et al. The Inhibitory Properties of Ethanol Extracts of Some Culinary-Medicinal Mushrooms on the Secretion of Interleukin-8 and Vascular Endothelial Growth Factor by PC3 Cancer Cells. Int J Med Mushrooms. 2019;21(7):645-656.
189. Xu Y, Ma J, Zheng Q, et al. MPSSS impairs the immunosuppressive function of cancer-associated fibroblasts via the TLR4-NF-κB pathway. Biosci Rep. 2019;39(5):BSR20182171. Published 2019 May 10. doi:10.1042/BSR20182171
190. Gallardo-Williams MT, Chapin RE, King PE, et al. Boron supplementation inhibits the growth and local expression of IGF-1 in human prostate adenocarcinoma (LNCaP) tumors in nude mice. Toxicol Pathol. Jan-Feb 2004;32(1):73-78. 119.
191. Barranco WT, Eckhert CD. Boric acid inhibits human prostate cancer cell proliferation. Cancer Lett. Dec 8 2004;216(1):21-29.
192. Barranco WT, Kim DH, Stella SL, Jr., Eckhert CD. Boric acid inhibits stored Ca2+ release in DU-145 prostate cancer cells. Cell Biol Toxicol. Aug 2009;25(4):309-320. 121.
193. Muezzinoglu T, Korkmaz M, Nese N, et al. Prevalence of prostate cancer in high boron-exposed population: a community-based study. Biol Trace Elem Res. Dec 2011;144(1-3):49-57.
194. Cui Y, Winton MI, Zhang ZF, et al. Dietary boron intake and prostate cancer risk. Oncol Rep. Apr 2004;11(4):887-892.
195. Barranco WT, Hudak PF, Eckhert CD. Evaluation of ecological and in vitro effects of boron on prostate cancer risk (United States). Cancer Causes Control. Feb 2007;18(1):71-77.
196. Zhao J, Wu Q, Hu X, et al. Comparative study of serum zinc concentrations in benign and malignant prostate disease: A Systematic Review and Meta-Analysis [published correction appears in Sci Rep. 2016 Jul 20;6:28606]. Sci Rep. 2016;6:25778. Published 2016 May 12. doi:10.1038/srep25778
197. Mahmoud AM, Al-Alem U, Dabbous F, et al. Zinc Intake and Risk of Prostate Cancer: Case-Control Study and Meta-Analysis. PLoS One. 2016;11(11):e0165956. Published 2016 Nov 8. doi:10.1371/journal.pone.0165956
198. Nair HK, Rao KV, Aalinkeel R, Mahajan S, Chawda R, Schwartz SA. Inhibition of prostate cancer cell colony formation by the flavonoid quercetin correlates with modulation of specific regulatory genes. Clin Diagn Lab Immunol. Jan 2004;11(1):63-69.
199. Yuan H, Young CY, Tian Y, Liu Z, Zhang M, Lou H. Suppression of the androgen receptor function by quercetin through protein-protein interactions of Sp1, c-Jun, and the androgen receptor in human prostate cancer cells. Mol Cell Biochem.

Jun 2010;339(1-2):253-262.
200. Senthilkumar K, Arunkumar R, Elumalai P, et al. Quercetin inhibits invasion, migration and signalling molecules involved in cell survival and proliferation of prostate cancer cell line (PC-3). Cell Biochem Funct. Mar 2011;29(2):87-95. 127.
201. Prostate Cancer Prevention Trial With Quercetin and Genistein - Full Text View - ClinicalTrials.gov. Clinicaltrials.gov. https://clinicaltrials.gov/ct2/show/NCT01538316?term=quercetin&cond=prostate+cancer&draw=2&rank=1. Published 2020. Accessed October 30, 2020.
202. Effect of Quercetin on Green Tea Polyphenol Uptake in Prostate Tissue From Patients With Prostate Cancer Undergoing Surgery - Full Text View - ClinicalTrials.gov. Clinicaltrials.gov. https://clinicaltrials.gov/ct2/show/NCT01912820?term=quercetin&cond=prostate+cancer&draw=2&rank=2. Published 2020. Accessed October 30, 2020.
203. Demark-Wahnefried W, Robertson CN, Walther PJ, Polascik TJ, Paulson DF, Vollmer RT. Pilot study to explore effects of low-fat, flaxseed-supplemented diet on proliferation of benign prostatic epithelium and prostate-specific antigen. Urology. May 2004;63(5):900-904.
204. Demark-Wahnefried W, Polascik TJ, George SL, et al. Flaxseed supplementation (not dietary fat restriction) reduces prostate cancer proliferation rates in men presurgery. Cancer Epidemiol Biomarkers Prev. Dec 2008;17(12):3577-3587. 129.
205. Azrad M, Vollmer RT, Madden J, et al. Flaxseedderived enterolactone is inversely associated with tumor cell proliferation in men with localized prostate cancer. J Med Food. Apr 2013;16(4):357-360.
206. Raina K, Singh RP, Agarwal R, Agarwal C. Oral grape seed extract inhibits prostate tumor growth and progression in TRAMP mice. Cancer Res. Jun 15 2007;67(12):5976-5982.
207. Vayalil PK, Mittal A, Katiyar SK. Proanthocyanidins from grape seeds inhibit expression of matrix metalloproteinases in human prostate carcinoma cells, which is associated with the inhibition of activation of MAPK and NF kappa B. Carcinogenesis. Jun 2004;25(6):987-995.
208. Brasky TM, Kristal AR, Navarro SL, et al. Specialty supplements and prostate cancer risk in the VITamins and Lifestyle (VITAL) cohort. Nutr Cancer. 2011;63(4):573-582. 133.
209. Chen M, Yu S. Lipophilic Grape Seed Proanthocyanidin Exerts Anti-Proliferative and Pro-Apoptotic Effects on PC3 Human Prostate Cancer Cells and Suppresses PC3 Xenograft Tumor Growth in Vivo. J Agric Food Chem. 2019;67(1):229-235. doi:10.1021/acs.jafc.8b05936
210. Tyagi A, Raina K, Shrestha SP, et al. Procyanidin B2 3,3(ϑ)-di-O-gallate, a biologically active constituent of grape seed extract, induces apoptosis in human prostate cancer cells via targeting NF-ϑB, Stat3, and AP1 transcription factors. Nutr Cancer. 2014;66(4):736-746. doi:10.1080/01635581.2013.783602
211. Kumar R, Deep G, Wempe MF, Agarwal R, Agarwal C. Procyanidin B2 3,3κdi-O-gallate inhibits endothelial cells growth and motility by targeting VEGFR2 and integrin signaling pathways. Curr Cancer Drug Targets. 2015;15(1):14-26. doi:10.2174/1568009614666141229102254
212. Yan J, Katz A. PectaSol-C modified citrus pectin induces apoptosis and inhibition of proliferation in human and mouse androgen-dependent and- independent prostate cancer cells. Integr Cancer Ther. Jun 2010;9(2):197-203. 134.
213. Yan J, Katz A. PectaSol-C modified citrus pectin induces apoptosis and inhibition of proliferation in human and mouse androgen-dependent and- independent prostate cancer cells. Integr Cancer Ther. 2010;9(2):197-203. doi:10.1177/1534735410369672
214. Glinsky VV, Raz A. Modified citrus pectin antimetastatic properties: one bullet, multiple targets. Carbohydr Res. Sep 28 2009;344(14):1788-1791.
215. Pienta KJ, Naik H, Akhtar A, et al. Inhibition of spontaneous metastasis in a rat prostate cancer model by oral administration of modified citrus pectin. J Natl Cancer Inst. Mar 1 1995;87(5):348-353.
216. Guess BW, Scholz MC, Strum SB, Lam RY, Johnson HJ, Jennrich RI. Modified citrus pectin (MCP) increases the prostate-specific antigen doubling time in men with prostate cancer: a phase II pilot study. Prostate Cancer Prostatic Dis. 2003;6(4):301-304.
217. Denham JW, Steigler A, Wilcox C, et al. Time to biochemical failure and prostate-specific antigen doubling time as surrogates for prostate cancer-specific mortality: evidence from the TROG 96.01 randomised controlled trial. Lancet Oncol. Nov 2008;9(11):1058-1068.
218. Conti S, Vexler A, Hagoel L, et al. Modified Citrus Pectin as a Potential Sensitizer for Radiotherapy in Prostate Cancer. Integr Cancer Ther. 2018;17(4):1225-1234. doi:10.1177/1534735418790382
219. Sultan C, Terraza A, Devillier C, et al. Inhibition of androgen metabolism and binding by a liposterolic extract of "Serenoa repens B" in human foreskin fibroblasts. J Steroid Biochem. Jan 1984;20(1):515-519.
220. Carilla E, Briley M, Fauran F, Sultan C, Duvilliers C. Binding of Permixon, a new treatment for prostatic benign hyperplasia, to the cytosolic androgen receptor in the rat prostate. J Steroid Biochem. Jan 1984;20(1):521-523. 140.
221. Ishii K, Usui S, Sugimura Y, Yamamoto H, Yoshikawa K, Hiran K. Extract from Serenoa repens suppresses the invasion activity of human urological cancer cells by inhibiting urokinase-type plasminogen activator. Biol Pharm Bull. Feb 2001;24(2):188-190.
222. Iguchi K, Okumura N, Usui S, Sajiki H, Hirota K, Hirano K. Myristoleic acid, a cytotoxic component in the extract from Serenoa repens, induces apoptosis and necrosis in human prostatic LNCaP cells. Prostate. Apr 2001;47(1):59-65.
223. Vacher P, Prevarskaya N, Skryma R, et al. The Lipidosterolic Extract from Serenoa repens Interferes with Prolactin Receptor Signal Transduction. J Biomed Sci. Oct 1995;2(4):357-365.
224. Anderson ML. A preliminary investigation of the enzymatic inhibition of 5alpha-reduction and growth of prostatic carcinoma cell line LNCap-FGC by natural astaxanthin and Saw Palmetto lipid extract in vitro. J Herb Pharmacother. 2005;5(1):17-26.
225. Bonnar-Pizzorno RM, Littman AJ, Kestin M, White E. Saw palmetto supplement use and prostate cancer risk. Nutr Cancer. 2006;55(1):21-27.
226. Horneber MA, Bueschel G, Huber R, Linde K, Rostock M. Mistletoe therapy in oncology. Cochrane Database Syst Rev. 2008(2):CD003297.
227. Bussing A, Schietzel M. Apoptosis-inducing properties of Viscum album L. extracts from different host trees, correlate with their content of toxic mistletoe lectins. Anticancer Res. Jan-Feb 1999;19(1A):23-28.
228. Hajto T, Hostanska K, Gabius HJ. Modulatory potency of the beta-galactoside-specific lectin from mistletoe extract (Iscador) on the host defense system in vivo in rabbits and patients. Cancer Res. Sep 1 1989;49(17):4803-4808.
229. Kienle GS, Berrino F, Bussing A, Portalupi E, Rosenzweig S, Kiene H. Mistletoe in cancer - a systematic review on controlled clinical trials. Eur J Med Res. Mar 27 2003;8(3):109-119.
230. Weissenstein U, Kunz M, Urech K, Baumgartner S. Interaction of standardized mistletoe (Viscum album) extracts with chemotherapeutic drugs regarding cytostatic and cytotoxic effects in vitro. BMC Complement Altern Med. 2014;14:6.
231. Pygeum africanum (Prunus africanus) (African plum tree). Monograph. Altern Med Rev. Feb 2002;7(1):71-74.
232. Weissenstein U, Kunz M, Urech K, Baumgartner S. Interaction of standardized mistletoe (Viscum album) extracts with chemotherapeutic drugs regarding cytostatic and cytotoxic effects in vitro. BMC Complement Altern Med. 2014;14:6. Published 2014 Jan 8. doi:10.1186/1472-6882-14-6
233. Wilt T, Ishani A, Mac Donald R, Rutks I, Stark G. Pygeum africanum for benign prostatic hyperplasia. Cochrane Database Syst Rev. 2002(1):CD001044.
234. Schleich S, Papaioannou M, Baniahmad A, Matusch R. Extracts from Pygeum africanum and other ethnobotanical species with antiandrogenic activity. Planta Med. Jul 2006;72(9):807-813.
235. Shenouda NS, Sakla MS, Newton LG, et al. Phytosterol Pygeum africanum regulates prostate cancer in vitro and in vivo. Endocrine. Feb 2007;31(1):72-81.
236. Papaioannou M, Schleich S, Roell D, et al. NBBS isolated from Pygeum africanum bark exhibits androgen antagonistic activity, inhibits AR nuclear translocation and prostate cancer cell growth. Invest New Drugs. Dec 2010;28(6):729-743.
237. Wilt T, Mac Donald R, Ishani A, Rutks I, Stark G. Cernitin for benign prostatic hyperplasia. Cochrane Database Syst Rev. 2000(2):CD001042.
238. Yasumoto R, Kawanishi H, Tsujino T, et al. Clinical evaluation of long-term treatment using cernitin pollen extract in patients with benign prostatic hyperplasia. Clin Ther. JanFeb 1995;17(1):82-87.
239. Talpur N, Echard B, Bagchi D, Bagchi M, Preuss HG. Comparison of Saw Palmetto (extract and whole berry) and Cernitin on prostate growth in rats. Mol Cell Biochem. Aug 2003;250(1-2):21-26.
240. Habib FK, Ross M, Buck AC, Ebeling L, Lewenstein A. In vitro evaluation of the pollen extract, cernitin T-60, in the regulation of prostate cell growth. Br J Urol. Oct

1990;66(4):393-397.
241. Habib FK, Ross M, Lewenstein A, Zhang X, Jaton JC. Identification of a prostate inhibitory substance in a pollen extract. Prostate. Mar 1995;26(3):133-139.
242. Dizeyi N, Mattisson IY, Ramnemark L, Grabe M, Abrahamsson PA. The effects of Cernitin® on inflammatory parameters and benign prostatic hyperplasia: An in vitro study. Phytother Res. 2019;33(9):2457-2464. doi:10.1002/ptr.6438
243. Togo Y, Ichioka D, Miyazaki J, et al. Oral administration of cernitin pollen extract (Cernilton®) for 30 days might be useful to avoid unnecessary biopsy in prostate biopsy candidates: A preliminary study. Int J Urol. 2018;25(5):479-485. doi:10.1111/iju.13549
244. Thirugnanam S, Xu L, Ramaswamy K, Gnanasekar M. Glycyrrhizin induces apoptosis in prostate cancer cell line DU-145 and LNCaP. Oncol Rep. Dec 2008;20(6):1387-1392.
245. Shetty AV, Thirugnanam S, Dakshinamoorthy G, et al. 18alpha-glycyrrhetinic acid targets prostate cancer cells by down-regulating inflammation-related genes. Int J Oncol. Sep 2011;39(3):635-640.
246. Hawthorne S, Gallagher S. Effects of glycyrrhetinic acid and liquorice extract on cell proliferation and prostatespecific antigen secretion in LNCaP prostate cancer cells. J Pharm Pharmacol. May 2008;60(5):661-666.
247. Park SY, Lim SS, Kim JK, et al. Hexane-ethanol extract of Glycyrrhiza uralensis containing licoricidin inhibits the metastatic capacity of DU145 human prostate cancer cells. Br J Nutr. Nov 2010;104(9):1272-1282.
248. Khor TO, Yu S, Barve A, et al. Dietary feeding of dibenzoylmethane inhibits prostate cancer in transgenic adenocarcinoma of the mouse prostate model. Cancer Res. Sep 1 2009;69(17):7096-7102.
249. Gioti K, Papachristodoulou A, Benaki D, et al. Glycyrrhiza glabra-Enhanced Extract and Adriamycin Antiproliferative Effect on PC-3 Prostate Cancer Cells. Nutr Cancer. 2020;72(2):320-332. doi:10.1080/01635581.2019.1632357
250. Park SY, Kim EJ, Choi HJ, et al. Anti-carcinogenic effects of non-polar components containing licochalcone A in roasted licorice root. Nutr Res Pract. 2014;8(3):257-266. doi:10.4162/nrp.2014.8.3.257
251. Zhang B, Lai Y, Li Y, et al. Antineoplastic activity of isoliquiritigenin, a chalcone compound, in androgen-independent human prostate cancer cells linked to G2/M cell cycle arrest and cell apoptosis. Eur J Pharmacol. 2018;821:57-67. doi:10.1016/j.ejphar.2017.12.053
252. Ren J, Huang Q, Xu Y, Yang M, Yang J, Hu K. Isoflavone lupiwighteone induces cytotoxic, apoptotic, and antiangiogenic activities in DU-145 prostate cancer cells. Anticancer Drugs. 2015;26(6):599-611. doi:10.1097/CAD.0000000000000224
253. Huang H , He Y , Zhang L , et al. Phenethyl isothiocyanate in combination with dibenzoylmethane inhibits the androgen-independent growth of prostate cancer cells. Food Funct. 2018;9(4):2398-2408. doi:10.1039/c7fo01983a
254. Tiwari RK, Geliebter J, Garikapaty VP, Yedavelli SP, Chen S, Mittelman A. Anti-tumor effects of PC-SPES, an herbal formulation in prostate cancer. Int J Oncol. Apr 1999;14(4):713-719.
255. Geliebter J, Tiwari R, Wu JM. PC-SPES in prostate cancer. N Engl J Med. Feb 18 1999;340(7):567-568. 167.
256. Pfeifer BL, Pirani JF, Hamann SR, Klippel KF. PC-SPES, a dietary supplement for the treatment of hormonerefractory prostate cancer. BJU Int. Mar 2000;85(4):481-485.
257. Small EJ, Frohlich MW, Bok R, et al. Prospective trial of the herbal supplement PC-SPES in patients with progressive prostate cancer. J Clin Oncol. Nov 12000;18(21):3595-3603.
258. Zhang BY, Li YF, Lai Y, Li YS, Chen ZJ. Zhongguo Zhong Yao Za Zhi. 2015;40(5):950-956.
259. Shamsuddin AM, Yang GY. Inositol hexaphosphate inhibits growth and induces differentiation of PC-3 human prostate cancer cells. Carcinogenesis. Aug 1995;16(8):19751979.
260. Liu G, Song Y, Cui L, Wen Z, Lu X. Inositol hexaphosphate suppresses growth and induces apoptosis in HT-29 colorectal cancer cells in culture: PI3K/Akt pathway as a potential target. Int J Clin Exp Pathol. 2015;8(2):1402-1410. Published 2015 Feb 1.
261. Raina K, Ravichandran K, Rajamanickam S, Huber KM, Serkova NJ, Agarwal R. Inositol hexaphosphate inhibits tumor growth, vascularity, and metabolism in TRAMP mice: a multiparametric magnetic resonance study. Cancer Prev Res (Phila). Jan 2013;6(1):40-50.
262. Sha J, Pan J, Ping P, et al. Synergistic effect and mechanism of vitamin A and vitamin D on inducing apoptosis of prostate cancer cells [published correction appears in Mol Biol Rep. 2013 May;40(5):3875]. Mol Biol Rep. 2013;40(4):2763-2768. doi:10.1007/s11033-012-1925-0
263. Blumberg J, Block G. The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study in Finland. Nutr Rev. 1994;52(7):242-245. doi:10.1111/j.1753-4887.1994.tb01430.x
264. Mondul AM, Watters JL, Männistö S, et al. Serum retinol and risk of prostate cancer. Am J Epidemiol. 2011;173(7):813-821. doi:10.1093/aje/kwq429
265. Wang Y, Cui R, Xiao Y, Fang J, Xu Q. Effect of Carotene and Lycopene on the Risk of Prostate Cancer: A Systematic Review and Dose-Response Meta-Analysis of Observational Studies [published correction appears in PLoS One. 2015;10(10):e0140415]. PLoS One. 2015;10(9):e0137427. Published 2015 Sep 15. doi:10.1371/journal.pone.0137427
266. Asadi-Samani M, Rafieian-Kopaei M, Lorigooini Z, Shirzad H. A screening of growth inhibitory activity of Iranian medicinal plants on prostate cancer cell lines. Biomedicine (Taipei). 2018;8(2):8. doi:10.1051/bmdcn/2018080208
267. Mohammadi A, Mansoori B, Aghapour M, Baradaran B. Urtica dioica dichloromethane extract induce apoptosis from intrinsic pathway on human prostate cancer cells (PC3). Cell Mol Biol (Noisy-le-grand). 2016;62(3):78-83. Published 2016 Mar 31.
268. Konrad L, Müller HH, Lenz C, Laubinger H, Aumüller G, Lichius JJ. Antiproliferative effect on human prostate cancer cells by a stinging nettle root (Urtica dioica) extract. Planta Med. 2000;66(1):44-47. doi:10.1055/s-2000-11117
269. Durak I, Biri H, Devrim E, Sözen S, Avci A. Aqueous extract of Urtica dioica makes significant inhibition on adenosine deaminase activity in prostate tissue from patients with prostate cancer. Cancer Biol Ther. 2004;3(9):855-857. doi:10.4161/cbt.3.9.1038
270. Johnson W, Tchounwou PB, Yedjou CG. Therapeutic Mechanisms of Vernonia amygdalina Delile in the Treatment of Prostate Cancer. Molecules. 2017;22(10):1594. Published 2017 Sep 22. doi:10.3390/molecules22101594
271. Cameron KS, Howard CB, Izevbigie EB, Hill BJ, Tchounwou PB. Sensitivity and mechanisms of taxol-resistant prostate adenocarcinoma cells to Vernonia amygdalina extract. Exp Toxicol Pathol. 2013;65(6):759-765. doi:10.1016/j.etp.2012.11.002
272. Howard CB, Johnson WK, Pervin S, Izevbigie EB. Recent perspectives on the anticancer properties of aqueous extracts of Nigerian Vernonia amygdalina. Botanics. 2015;5:65-76. doi: 10.2147/BTAT.S62984. Epub 2015 Nov 30. PMID: 27226742; PMCID: PMC4876981.
273. Qu L, Li S, Zhuo Y, Chen J, Qin X, Guo G. Anticancer effect of triterpenes from Ganoderma lucidum in human prostate cancer cells. Oncol Lett. 2017;14(6):7467-7472. doi:10.3892/ol.2017.7153
274. Wu K, Na K, Chen D, Wang Y, Pan H, Wang X. Effects of non-steroidal anti-inflammatory drug-activated gene-1 on Ganoderma lucidum polysaccharides-induced apoptosis of human prostate cancer PC-3 cells. Int J Oncol. 2018;53(6):2356-2368. doi:10.3892/ijo.2018.4578
275. Zhao X, Zhou D, Liu Y, et al. Ganoderma lucidum polysaccharide inhibits prostate cancer cell migration via the protein arginine methyltransferase 6 signaling pathway. Mol Med Rep. 2018;17(1):147-157. doi:10.3892/mmr.2017.7904
276. Jiang J, Slivova V, Valachovicova T, Harvey K, Sliva D. Ganoderma lucidum inhibits proliferation and induces apoptosis in human prostate cancer cells PC-3. Int J Oncol. 2004;24(5):1093-1099.
277. Huang SY, Huang GJ, Wu HC, Kao MC, Huang WC. Ganoderma tsugae Inhibits the SREBP-1/AR Axis Leading to Suppression of Cell Growth and Activation of Apoptosis in Prostate Cancer Cells. Molecules. 2018;23(10):2539. Published 2018 Oct 5. doi:10.3390/molecules23102539
278. Huang WC, Chang MS, Huang SY, et al. Chinese Herbal Medicine Ganoderma tsugae Displays Potential Anti-Cancer Efficacy on Metastatic Prostate Cancer Cells. Int J Mol Sci. 2019;20(18):4418. Published 2019 Sep 8. doi:10.3390/ijms20184418
279. MacLean MA, Scott BE, Deziel BA, et al. North American cranberry (Vaccinium macrocarpon) stimulates apoptotic pathways in DU145 human prostate cancer cells in vitro. Nutr Cancer. 2011;63(1):109-120. doi:10.1080/01635581.2010.516876
280. Déziel B, MacPhee J, Patel K, et al. American cranberry (Vaccinium macrocarpon) extract affects human prostate cancer cell growth via cell cycle arrest by modulating expression of cell cycle regulators. Food Funct. 2012;3(5):556-564. doi:10.1039/c2fo10145a
281. Student V, Vidlar A, Bouchal J, et al. Cranberry intervention in patients

with prostate cancer prior to radical prostatectomy. Clinical, pathological and laboratory findings. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2016;160(4):559-565. doi:10.5507/bp.2016.056
282. Hamilton K, Bennett NC, Purdie G, Herst PM. Standardized cranberry capsules for radiation cystitis in prostate cancer patients in New Zealand: a randomized double blinded, placebo controlled pilot study. Support Care Cancer. 2015;23(1):95-102. doi:10.1007/s00520-014-2335-8
283. Campbell G, Pickles T, D'yachkova Y. A randomised trial of cranberry versus apple juice in the management of urinary symptoms during external beam radiation therapy for prostate cancer. Clin Oncol (R Coll Radiol). 2003;15(6):322-328. doi:10.1016/s0936-6555(03)00161-4
284. Deng Y, Li Y, Yang F, et al. The extract from Punica granatum (pomegranate) peel induces apoptosis and impairs metastasis in prostate cancer cells. Biomed Pharmacother. 2017;93:976-984. doi:10.1016/j.biopha.2017.07.008
285. Wang L, Martins-Green M. Pomegranate and its components as alternative treatment for prostate cancer. Int J Mol Sci. 2014;15(9):14949-14966. Published 2014 Aug 25. doi:10.3390/ijms150914949
286. Paller CJ, Ye X, Wozniak PJ, et al. A randomized phase II study of pomegranate extract for men with rising PSA following initial therapy for localized prostate cancer. Prostate Cancer Prostatic Dis. 2013;16(1):50-55. doi:10.1038/pcan.2012.20
287. Freedland SJ, Carducci M, Kroeger N, et al. A double-blind, randomized, neoadjuvant study of the tissue effects of POMx pills in men with prostate cancer before radical prostatectomy. Cancer Prev Res (Phila). 2013;6(10):1120-1127. doi:10.1158/1940-6207.CAPR-12-0423
288. Pantuck AJ, Pettaway CA, Dreicer R, et al. A randomized, double-blind, placebo-controlled study of the effects of pomegranate extract on rising PSA levels in men following primary therapy for prostate cancer. Prostate Cancer Prostatic Dis. 2015;18(3):242-248. doi:10.1038/pcan.2015.32
289. Jiang J, Eliaz I, Sliva D. Suppression of growth and invasive behavior of human prostate cancer cells by ProstaCaid™: mechanism of activity. Int J Oncol. 2011;38(6):1675-1682. doi:10.3892/ijo.2011.996
290. Yan J, Katz AE. ProstaCaid induces G2/M cell cycle arrest and apoptosis in human and mouse androgen-dependent and-independent prostate cancer cells. Integr Cancer Ther. 2010;9(2):186-196. doi:10.1177/1534735410371478
291. Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med. 2010;363(5):411-422. doi:10.1056/NEJMoa1001294
292. de Bono JS, De Giorgi U, Rodrigues DN, et al. Randomized Phase II Study Evaluating Akt Blockade with Ipatasertib, in Combination with Abiraterone, in Patients with Metastatic Prostate Cancer with and without PTEN Loss. Clin Cancer Res. 2019;25(3):928-936. doi:10.1158/1078-0432.CCR-18-0981
293. New Drug Shows Promise in Metastatic Prostate Cancer. Medscape. https://www.medscape.com/viewarticle/938096. Published 2020. Accessed November 4, 2020.
294. To Evaluate Safety and Tolerability of VERU-111 in Men With Advanced Metastatic Castration Resistant Prostate Cancer - Full Text View - ClinicalTrials.gov. Clinicaltrials.gov. https://www.clinicaltrials.gov/ct2/show/NCT03752099?term=VERU&cond=prostate+cancer&draw=2&rank=2. Published 2020. Accessed November 4, 2020.

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