Prostate Cancer and Natural Medicine

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Benign Prostatic Hyperplasia and Prostate Cancer

The symptoms associated with benign prostatic hyperplasia can also be caused by prostatic cancer, though they are far more likely to be due to benign overgrowth. Men with BPH do not have a higher incidence of prostate cancer (Coley 1997). The relatively high rate of prostate cancer in the general population, however, requires that an accurate diagnosis be made.

One in 5 men (20%) has a *lifetime* probability of being diagnosed with this cancer. Over 40,000 men die of prostate cancer each year, making it the second leading cause of cancer death in the U. S. for men (Wingo, 1995). Ironically, at least 1/3 of these cancers might be avoided if men made some healthy dietary choices, especially eliminating red meat and most animal fat from the diet and increasing fruit and vegetable intake (Willett, 1995). A published review study of existing data on prostate cancer patients showed that for those with metastatic prostate cancer (stage D2), a statistically-relevant association occurred with a healthier diet, longer survival and improved quality of life (Carter et al, 1993).

To PSA or not to PSA

The importance of a good screening test for the early detection of prostate cancer is apparent. PSA, or *prostate specific antigen*, is a controversial test for the presence of prostate cancer (Luttge 1996). It is used along with digital rectal examination and transrectal ultrasonography (an image is made with ultrasound) in the diagnosis of prostate cancer. Anyone being evaluated for symptoms of prostatism will be faced with the decision of whether to have a PSA test done. PSA is a glycoprotein enzyme that performs the function of reliquefying the clot formed by the semen shortly after ejaculation. It is normally produced in quantity only in the prostate, hence its designation as prostate specific. Prostate cancer often creates a rise in PSA levels in the blood. Benign prostatic hypertrophy also leads to an increase, though the increase per unit volume of cancer is greater than per unit volume of benign growth (Stamey, 1987). Prostate cancer is the most common cancer diagnosed in the United States, and the advent of PSA testing has greatly increased the number of cases being diagnosed. Prostate cancer was on the rise before PSA testing became widespread, however (Lu-Yao 1994), with such notables as Linus Pauling dying from the disease.

PSA testing has been controversial for a number of reasons. There is currently not sufficient proof that PSA-based screening results in a reduction in prostate cancer-related mortality, and the sensitivity and specificity of PSA testing are not high enough to eliminate all uncertainty about the interpretation of the test.

Sensitivity measures the percentage of time a test will be positive when the disease being tested for is present in a patient. It is, therefore, also a measure of how often a test gives a negative result when the disease is actually present. This is called a *false negative*. The more false negative results given by a test, the lower the sensitivity. The fewer the false negatives, the higher the sensitivity. If cancer is present and the test fails to detect it, it is not sensitive enough. PSA is not uniformly elevated in the presence of prostate cancer. It is not unusual for someone with prostate cancer to have a normal (false negative) PSA level. PSA as a screening test has a fairly high but less than ideal sensitivity.

Specificity measures how often a positive test provides an accurate diagnosis of the disease. In other words, it takes into consideration how often someone who doesn't actually have cancer might still test positive.

It is a measure of the rate of *false positives*. Studies of the specificity of PSA testing have demonstrated varying results. One study revealed a specificity of about 60%

(Catalona 1991). A more recent prospective study showed a specificity of over 90% with only 96 of 1098 men who remained free of cancer having a false positive result (Gann 1995). When used as a screening test, PSA will be positive in some men who do not have cancer or have non-aggressive cancers. Many of these men will undergo unnecessary biopsy and sometimes unnecessary invasive treatment. The positive predictive value, which is the percentage of men who test positive who actually have the disease is less than 25%. In screening a large population, there will be many false positives. Two to four biopsies are performed for every cancer detected. A number of benign situations can raise PSA levels. Two thirds of men with a PSA value greater than 4, the usual cut-off value, will not have cancer. PSA levels are often elevated in benign prostatic hyperplasia, prostatitis, and other non-cancerous conditions, as well as when cancer is present. A digital rectal exam can also raise blood levels of PSA.

Despite its uncertainties, PSA can detect many prostate cancers at an earlier and potentially more treatable stage. As many as 1/3 of men over 50 have prostate cancer (Holund, 1980). However only 20 to 25% of them will ever develop clinically apparent cancer and only 1 out of 8 men diagnosed with prostate cancer will die of it (McConnell, 1994). A cost effectiveness study determined that a one time PSA test and digital rectal exam would only increase the life span of the average man between the ages of 50 and 69 by 2 weeks. Men over 69 would gain at best only a few days (Coley, 1997). These statistics along with the side effects of cancer treatment need to be considered. Screening with the PSA test may do more harm than good. As many as 40% of men treated for prostate cancer will have incontinence short-term, some longer, and as many as 90% will become sexually inactive. There is not yet strong evidence that PSA screening and treatment of prostate cancer lead to a decrease in the deaths or disease associated with the cancer. Many men who would have gone through life with no likelihood of developing prostate cancer will have to live with the concern generated by a false positive test. The need is threefold.

Clearly a test is needed that will detect cancer with greater sensitivity and specificity. Related to this is the need to develop tests for distinguishing which cancers are likely to become aggressive and life-threatening from those that will never develop into a problem. The third need is for better treatments for prostate cancer, ones that are effective with fewer harmful side effects (Garnick, 1996). Detecting a disease for which optimal treatment approaches have not been achieved is of limited value. Several approaches are being followed to refine screening for prostate cancer. One possibility is to determine the ratio of free to total PSA in the blood (Catalona, 1995; Partin, 1996). Much of the PSA in the blood is bound to other proteins. Some is free or unbound. The ratio of free to total PSA may help determine if a cancer is likely to grow rapidly and aggressively, or be slow growing and unlikely to be a significant health threat (Metter, 1997; Carter, 1997). In these studies, men with aggressive cancers were found to have more of their PSA bound. This test did not detect aggressive cancers with 100% specificity. Some men with slower growing cancers still have a low free to bound PSA ratio. If further testing confirms these results, the free to unbound ratio may help to identify more men who can be followed by watchful waiting rather than with unnecessary harmful treatment. It is not likely to identify all such men, however. In men with PSA values less than 10 ng/ml, the free to unbound ratio may be helpful in distinguishing prostate cancer from benign prostatic hypertrophy (Van Cangh, 1996). However, the lower revalence of cancer compared to BPH will still lead to harmful diagnoses because of false positive results. The specificity is still far from ideal. PSA density, which is determined by dividing the total prostate concentration by the prostate volume measured by ultrasound, has also been used to improve the specificity of the PSA test. It is questionable if the added expense and discomfort of the transrectal ultrasound that is used to determine the prostate volume is worth any small increase in specificity.

Another attempt to refine the usefulness of PSA testing is to measure what is called PSA velocity which is the change over time. Serial measurements increase the sensitivity of the test. The rate of change helps to

distinguish BPH from cancer (Carter, 1992). A greater than 20% rise in one year is considered suspicious.

There are other tests that may be beneficial as adjuncts to PSA testing.

Using DNA from biopsied specimens, researchers were able to distinguish cancerous from non-cancerous prostate tissue 100% of the time (Malins 1997). This form of testing does require taking biopsy specimens. Work is underway to determine if a protein called kallikrein which tests positive in the blood stream of men known to have prostate cancer might be helpful when used in conjunction with PSA, to identify cancers not detected by PSA (Tindall, 1997).

The *digital rectal examination* of the prostate should always be done as part of the evaluation of a patient for prostate cancer. Though it is a subjective test and not highly specific or sensitive for prostate cancer, cancers that will be missed by PSA are sometimes detected. Nodularity, induration, or asymmetry may warrant biopsy even if the PSA test is negative. PSA testing, of course, will indicate the presence of cancers not detected by the digital rectal exam.

In the future, there is promise that tests with higher sensitivity and specificity will allow an unequivocal answer to the question of whether to use them to test for prostate cancer. Tests will hopefully be developed that will distinguish aggressive from indolent cancers, and treatments for prostate cancer will with any luck become more effective and carry a lower cost in associated morbidity and mortality. Currently the National Cancer Institute does not endorse mass screening for prostate cancer using PSA. The American Cancer Society and the American Urological Association support screening beginning at age 50. The American College of Physicians recommends against screening (Sox, 1997). Screening is not recommended by any group for anyone with a life expectancy of less than 10 years. Screening has not reduced mortality. About 2/3 of people with PSA's of greater than 10 have cancer, and the recommendation is to biopsy these men.

Prevention of Prostate Cancer

Besides benign prostatic hyperplasia, prostate cancer of men is the most frequent disease of the prostate gland. It is the most common cancer in men and the second most common cause of death due to cancer in the United States as well as many European countries. If a man reaches the age of 50, one in ten will go on to develop prostate cancer, and up to 4% will die from the disease. During 1995 in the United States, almost 244,000 cases of prostate cancer were diagnosed and about 40,400 men died.

Although all the causative factors of prostate cancer have not been identified, it is likely that diet, exercise, and exposure to environmental toxins like herbicides all play a role (Hubbard, et al, 1994). A dietary link that has been often discussed is that of Japanese men with a distinctly lower prostate cancer incidence than Americans who, at least in the last generation, ate less animal fat and more vegetables and legumes like tofu. Prostate cancer is almost non-existent in Chinese men living in China. Chinese and Japanese men that come to the United States and begin eating a standard American diet showed a much higher incidence.

The following chart summarizes characteristic studies on the possible influence on prostate cancer from diet, dietary supplements, and environmental factors.

Table: The Influence of Diet and Environment on Prostate Cancer

Protective Food or Nutrient	Notes	Ref
Lycopene; tomatoes	Lycopene is a carotenoid found in tomatoes and other fruits and vegetables; researchers who have found biologically-active concentrations in the prostates of men with prostate cancer theorize it may help protect against cancer	Clinton et al, 1996
Reduction of dietary intake of animal fats	Especially foods high in saturated fats such as red meat.	Steinmetz, K.A. et al, 1996
Reduction of dietary fat intake	Up to 81% of prostate cancers are potentially preventable with a reduction of dietary fat.	Miller et all, 1994; Marchand et al, 1994
Selenium in brewer's yeast	Decrease of the incidence of prostate cancer over a 8-year period with the addition of 200 ug of selenium in brewer's yeast	Wynder & Fair, 1996
Vitamin E	A Finnish study of men receiving 800 I.U. of vitamin E for 5 years suggested a decrease in prostate cancer	Wynder & Fair, 1996
Genistein (an isoflavone from soy)	Asian men consistently have lower incidences of prostate cancer than blacks, Europeans, and Jews. A high consumption of soy products has been suggested as an important factor. In a study with Japanese men, lower prostate cancer rates were correlated with increased urinary excretion of genistein. Genistein is a specific inhibitor of tyrosine protein kinase, a key celll growth regulator, as well as a phytoestrogen that interacts with estrogen binding sites.	Wynder & Fair, 1996; Herman et al, 1993
Soy products	Soy products are a central part of the macrobiotic diet which is often recommended for people with cancer by holistic practitioners. In one study, pancreatic cancer patients eating a macrobiotic diet had a higher 1-year survival rate than a group who did not (Carter et al, 1993). Soy contains the sterol β-sitosterol, isoflavones, soybean trypsin inhibitor, saponins and genistein. There is both "observational and clinical evidence" that consuming a diet high in soy products can reduce the incidence of prostate cancer.	Kennedy et al, 1995; Clarkson et al, 1995
Vitamin C and β-carotene supplementation	No positive effect on incidence of prostate cancer was seen in a 30-year follow-up with 132 middle-aged men	Daviglus, 1996
Essential fatty acids (linoleic and linolenic acid)	We need a minimum amount of essential fatty acids (EFAs) in our diet), but levels	American Health

	above 15% of total daily caloric intake may lead to an increased risk of prostate cancer. Intake ratio of the two essential fatty acids should be balanced; best sources are whole seeds (such as freshly-ground flax seeds). Omega-3 fatty acids, which are rich in fish and fish oils, suppressed growth of cancer cells in human prostate cancer cells. A high fat diet increased prostate cancer cell growth in mice.	Foundation, 1996; Gann et al, 1994
High fat, low fiber diet	May change testosterone and estrogen metabolism in men, increasing the risk for prostate cancers. Daily urinary excretion of testosterone was 13% higher, and of estradiol and estrone were 12-28% lower with high fat diet.	Dorgan et al, 1996
Vitamin D	Vitamin D [1,25(OH)2D3] inhibited the growth of malignant prostate cancer cells *in vitro*; vitamin D is a complex mixture of compounds found in fish and fish oils. There is a clear inverse relationship between circulating levels of 1,25-dihydroxyvitamin D and prostate cancer development.	Peehle et al, 1994; Ross & Henderson, 1994
Estrogen levels, Estrogenic pesticides	Some researchers conclude that estrogen levels in men plays an important role in the development of BPH; the ratio of estrogen to testosterone were "significantly correlated with prostate size." Common pesticides such as alachlor, atrazine, endosulfan, DDT, PCBs, dioxin, and others may have an estrogenic effect in the human body. They have been implicated in reducing the quality of semen and increasing prostate cancer risk in men over the last few decades. An epidemiological study following 145,000 male Canadian farmers found that the risk of dying from prostate cancer was increased 2.23 times for every 250 acres that were sprayed with herbicides (locally).	Suzuki et al, 1995; *The Nutrition Week*, Nov. 12, 1993, pp. 2-3; Laino, 1993
Milk products	An Italian study compared the dietary habits of 271 prostate cancer patients and 685 hospital patient controls in Northern Italy. There was a strong correlation between milk consumption and prostate cancer.	Talamini et al, 1992
Red meat	A study following more than 51,000 U.S. men, 40 to 75 years old, determined that total red meat consumption had the strongest direct relationship to the risk of advanced prostate cancers and not necessarily due to its fat content. Fish or vegetable fats did not correlate with prostate cancer.	Giovannucci et al, 1993