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AS WE SEE IT

Does PSA Promote Prostate Cancer?

Reviewed and critiqued by Stephen B. Strum, MD, FACP



Echogram, axial section: tumor of a patient with prostate cancer.

The acronym PSA stands for prostate-specific antigen, the most abundant protein synthesized in the prostate gland. Men have their blood tested for PSA in order to detect prostate cancer at an early stage when it is often curable. The PSA test can also help assess the efficacy of various prostate cancer treatments.

Until now, PSA has been viewed only as a blood indicator of prostate cancer, infection, or inflammation. Emerging evidence, however, reveals that PSA may be more than just a marker of prostate health. It appears that PSA itself may play a role in the progression and metastasis of prostate cancer,¹⁻³ thus opening up new therapeutic pathways for preventing and treating this epidemic disease.



by William Faloon

A significant amount of published data associates high intake of certain nutrients with reduced incidences of prostate cancer.⁴⁻¹² A few studies suggest that these same nutrients may even help control advanced stages of the disease.^{13,14}

Scientists are now finding that some of these nutrients function to reduce or interfere with PSA activity in the prostate gland. With new data suggesting that PSA itself may be involved in the progression and spread of prostate cancer, the anti-PSA activity of these nutrients becomes significant and helps explain why men who consume certain nutrients have lower incidences of the disease and a slower progression of disease when prostate cancer has been diagnosed.

STAGGERING STATISTICS ON PROSTATE CANCER

Cells in the prostate gland are very prone to gene mutation, while other tissues in the same anatomical region, such as the seminal vesicles, develop primary cancers at a significantly lower rate.¹⁵

Autopsy evidence indicates that prostate cancer is histologically evident in up to 34% of men aged 40-49 and up to 70% of men aged 80 and older.^{16,17} Most men, however, never progress to clinically diagnosed disease, indicating the presence of control mechanisms that keep prostate cancer cell colonies small and thus controlled.

It now appears possible to partially regulate some of the genes that ordinarily enable cells to divide out of control and eventually form a prostate tumor, which may then proliferate, invade, and metastasize. These new findings make it more important than ever for men to monitor their blood PSA levels to detect prostate cancer at its earliest stages.

TREATING ADVANCED PROSTATE CANCER WITH LYCOPENE

Cancer confined to the prostate gland is usually curable.¹⁸⁻²³ The medical literature indicates, however, that untreated prostate cancer leads to continued growth of the tumor cell population. This greater tumor burden is associated with genetic mutation that is likely responsible for the development of hormone-insensitive prostate cancer.²⁴⁻²⁷ Once prostate cells mutate into aggressive hormone-refractory forms that escape into the body, metastatic prostate cancer usually is diagnosed and the patient faces a grueling battle to survive.



In a study of 20 patients with metastatic hormone-refractory prostate cancer, each patient received 10 mg a day of lycopene for three months.¹⁴ No other treatment was given. One patient achieved a complete response, defined as a reduction of PSA (to under 4 ng/ml) and the absence of any sign of the disease for eight weeks. Six patients (30%) had a partial response, defined as a 50% reduction in PSA and alleviation of other symptoms such as bone pain if present. The disease remained stable in 10 patients (50%) and progressed in three (15%). A remarkable 63% (10 of 16) with bone pain were able to reduce their daily use of

pain-suppressing drugs. The study concluded, "Lycopene therapy appears to be effective and safe in the treatment of hormone-refractory prostate cancer."

In another study of 54 metastatic prostate cancer patients, half (27) were castrated, while the other half were castrated and given 2 mg of lycopene twice daily.¹³ Castration (removal of the testes) reduces testosterone levels and is a treatment for those with androgen-dependent prostate cancer. After six months, PSA declined significantly in both groups, but more so in the group receiving lycopene. After two years, 40% of the castrated group had a PSA reduction of less than 4 ng/ml, compared to 78% in the lycopene group. Bone scans showed that twice as many patients in the lycopene-plus-castration group attained a complete response compared to the castration-only men.

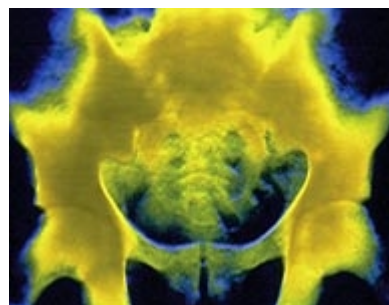
The author concluded, "Adding lycopene to orchidectomy (castration) produced a more reliable and consistent decrease in serum PSA level; it not only shrinks the primary tumor but also diminishes the secondary tumors, providing better relief from bone pain and lower urinary tract symptoms, and improving survival compared with orchidectomy alone." What is impressive about these two studies is that only small doses of lycopene (4-10 mg/day) were used. That low doses of lycopene produced such favorable results in these late-stage prostate cancer patients is quite remarkable and worthy of further study.

LYCOPENE REDUCES PROSTATE CELL DNA DAMAGE

Because cancer is initiated and promoted as the result of ongoing DNA damage, researchers conducted a study to evaluate the genomic effects of lycopene in men with localized disease. For three weeks, a group of 32 men consumed tomato sauce each day supplying 30 mg of lycopene. Prostate tissue was obtained initially at biopsy and then again after surgical removal of the prostate gland.²⁸ After three weeks, PSA levels declined by 17.5% and a blood marker of DNA damage fell by 21.3%. An analysis of the prostate tissues showed that the lycopene-supplemented patients had major reductions in many of the DNA factors that usually favor uncontrolled prostate cancer cell propagation. Moreover, in the lycopene-supplemented patients, prostate cancer cells as well as hyperplastic prostatic tissue showed an increase in apoptosis (programmed cell death). This study showed that prostate cells readily take up lycopene, with cellular lycopene levels increasing 2.92-fold after only three weeks. This increase in lycopene correlated with a significant reduction of DNA damage in prostate tissue.

BORON SHRINKS PROSTATE TUMORS, REDUCES PSA IN MICE

As noted earlier, most doctors regard PSA solely as a useful laboratory marker for diagnosing prostate cancer. At a cellular level, however, PSA functions as an active growth factor in the prostate gland. One such mechanism involves PSA's enzymatic ability to degrade extracellular matrix (structural support) proteins such as fibronectin and laminin.¹ This action of PSA may promote tumor growth and metastasis. Another potential tumor-promoting action of PSA involves freeing insulin-like growth factor 1 (IGF-1) from its binding protein (BP-3), providing increased local levels of IGF-1, leading to tumor growth.^{2,3} To understand the nature of our enemy—the cancer cell—we must realize that the tumor cell is functional and produces cell products that favor its growth, invasiveness, and spread!



X-ray of hip showing prostate cancer.

Studies by Gallardo-Williams and colleagues have shown that boric acid and boronic acid significantly inhibit the degradation of fibronectin by enzymatically active PSA.¹ In another study in mice, the same authors used immunohistochemistry staining of tissues to show that expression of IGF-1 in tumors was markedly reduced by boric acid. In response to both low- and high-dose boron supplementation, PSA levels plummeted by an average of 87%, while tumor size declined by 31.5% on average. Also noted was a significantly lower incidence of mitotic figures in the boron-supplemented groups. Mitotic figures reflect DNA synthesis and proliferative activity.²⁹

Consistent with these findings, a recent study showed that boron inhibited the proliferation of prostate cancer cell lines DU-145 (an androgen-independent line) and LNCaP (an androgen-dependent cell line) in a dose-dependent manner.³⁰ These animal and cell line studies appear to be relevant to humans, based on a report from UCLA in which Cui and colleagues showed that men with the highest dietary boron intake reduced their prostate cancer risk by 54% compared to men with the lowest boron intake! While the authors noted that the observed association should be interpreted with caution because of the small case sample size and the nature of the cross-sectional study design, clearly these findings deserve further investigation. If the above-cited animal studies can be replicated in human patients, boron at doses ranging from 6 to 15 mg a day may become an effective and very low-cost adjuvant therapy.¹²

HOW PSA MAY PROMOTE PROSTATE CANCER

Until now, PSA has been regarded by most physicians and the lay public as simply a blood test—a laboratory indicator of possible prostate problems such as benign prostatic hyperplasia (BPH), prostatitis, or prostate cancer. However, emerging evidence reveals that PSA may be more than just a marker of prostate health.

PSA itself is a cell product—a serine protease enzyme with several key functions. In the context of a healthy prostate gland, PSA production is primarily confined to the prostatic ducts and relatively little PSA escapes into the peripheral blood. This is why in a purely healthy prostate—unaffected by BPH or prostatitis—PSA levels are typically less than 1.0 nanogram (ng) per milliliter (ml). In this setting, the enzymatic nature of PSA serves a major function: to liquefy the male ejaculate to facilitate fertilization of the female egg or ovum.

By contrast, in the context of prostate cancer, the enzymatic activity of PSA functions to break down cell barriers. PSA's enzyme activity acts to digest the extracellular matrix, the tissue surrounding the cells. The digestion of extracellular tissue may accelerate the invasion and spread of cancer. Our understanding of the functional nature of many laboratory tests such as PSA opens up new therapeutic pathways for preventing and treating this epidemic disease.

Intelligently used, the PSA test is one of the most critical elements in our armamentarium to understanding men's health. PSA is also used to evaluate men with prostate cancer before and after any therapy used in treatment of the cancer. Such therapeutic interventions include active objectified surveillance (watchful waiting), surgery (radical prostatectomy), radiation (brachytherapy or external beam radiation therapy), cryosurgery, high-intensity focused ultrasound, and androgen-deprivation therapy, as well as other investigational approaches to controlling prostate cancer. PSA also can be used to evaluate men with BPH or prostatitis, as these conditions will affect PSA production.

HIDDEN DANGERS OF PSA

Because PSA may contribute not only to prostate cancer progression but also to the ability of these cells to escape the prostate and metastasize to distant sites within the body, we can no longer think of PSA as merely a blood marker reflecting prostate health.

In fact, many, if not all, of the biomarkers used in tracking a wide array of cancers may have specific cancer-facilitating properties. Therefore, in men with prostate cancer, and perhaps even in those trying to prevent the emergence of prostate cancer, taking steps to keep PSA levels low may reduce one's risk of developing this illness or having it progress to a clinically symptomatic condition.

The easiest way to reduce PSA levels by half is to inhibit the enzyme 5-alpha reductase, which transforms testosterone into the more androgenic dihydrotestosterone (DHT). DHT has a growth-promoting effect on prostate cells that is significantly greater than that of testosterone. In the peer-reviewed literature, this differential effect of DHT on prostate cell growth is 2.4-10 times greater.³¹⁻³³

The most effective DHT-lowering prescription drug is Avodart®. Unlike the more popular Proscar® that inhibits only type 2 5-alpha reductase, Avodart® blocks both type 1 and type 2 5-alpha reductase, thus reducing blood DHT levels by 93%. Using a 5-mg dose of Avodart®—10 times that routinely prescribed for BPH—Andriole and colleagues demonstrated a 97% reduction of intra-prostatic DHT.³⁴ Lazier and colleagues found that Avodart® inhibited DHT-induced secretion of PSA as well as cancer cell proliferation, and that at higher doses, Avodart® resulted in cancer cell death in both androgen-dependent (LNCaP) and androgen-independent (PC-3) cell lines.³⁵

Such findings are pertinent to human clinical trials of Avodart®. In a study of 4,325 men with benign prostate enlargement who were randomly selected to receive either Avodart® (0.5 mg/day) or placebo, those receiving Avodart® had a cumulative incidence of prostate cancer of 1.2% compared to 2.5% for the placebo group at 27 months of follow-up. This equates with a 52% reduction in prostate cancer in the Avodart® group.³⁶ In another study using Proscar®, 18,882 men aged 55 or older (with normal digital rectal examination results and a PSA level of 3.0 ng/ml or lower) were randomly assigned treatment with Proscar® (5 mg/day) or placebo for seven years. Prostate cancer was detected in 803 of the 4,368 men in the Proscar® group and 1,147 of the 4,692 men in the placebo group, for a 24.8% reduction in prevalence over seven years. High-grade cancers were noted in 6.4% of Proscar®-treated patients compared to 5.1% of men receiving placebo.³⁷ (As noted earlier, Proscar® suppresses only type 2 5-alpha reductase, whereas Avodart® blocks both type 1 and type 2 5-alpha reductase. Avodart® thus appears to be the better drug.)

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Aging men should consider having their blood tested for DHT. If DHT levels are elevated, Avodart® drug therapy appears to be safe and effective not only for improving urinary flow symptoms, but more importantly for potentially reducing prostate cancer risk. Avodart® appears to accomplish these effects by reducing the growth-promoting effects of DHT on prostatic tissue, while decreasing the cancer-inducing properties of PSA by reducing PSA synthesis in the prostate gland.

Avodart® does have several downsides. At more than \$3 per capsule, it is expensive. Moreover, a small percentage of men who use it have sexual dysfunction problems such as decreased libido (4%), impotence (7%), and a decreased volume of ejaculate (2%). The frequency of these side effects reportedly decline after six months of continued use of Avodart®.

BLOCKING PSA'S DETRIMENTAL EFFECTS NATURALLY

There may be another way to protect the prostate gland against its own PSA. Since consuming green tea has been reported to lower the risk of prostate cancer, scientists investigated the effects of the green tea flavonoid epigallocatechin gallate (EGCG) on the expression and activity of PSA by prostate cancer cells. In addition to restraining PSA expression, EGCG inhibited numerous cancer-promoting properties of PSA in a dose-dependent manner. EGCG inhibited tumor-promoting activities such as degradation of type IV collagen. EGCG's beneficial effects were at blood levels close to those measured in serum following ingestion of green tea.³⁸ The study authors proposed that green tea extract may be a natural inhibitor of prostate carcinoma aggressiveness.

EFFECTS OF SOY ON PSA LEVELS

Another potential way to lower PSA levels is to increase soy consumption. It has long been known that human populations that consume soy products have a lower risk of prostate cancer.^{9,39}

Scientists have evaluated soy's effects on PSA and other prostate cancer-related blood markers in men who had already developed prostate cancer.⁴⁰ A group of 29 men scheduled to undergo surgical removal of the prostate were put on a 50-gram soy bread supplement or a 50-gram wheat supplement. The soy group saw a 12.7% reduction in PSA levels, whereas the wheat group experienced a 40% increase in cancer-promoting PSA. The free/total PSA ratio increased by 27.4% in the soy-supplemented group, compared to a decrease of 15.6% in the wheat group. (A higher free/total PSA ratio is a favorable indicator.) The investigators concluded that men who consume diets high in soy might have a reduced risk of prostate cancer development and progression.

CURCUMIN INDUCES CANCER CELL SUICIDE

Cancer cells do not follow normal, healthy cell suicide programs. Old cells need to die and be discarded, but cancer cells proliferate and grow.

Numerous studies over the past two years have identified specific mechanisms by which curcumin inhibits the growth of prostate cancer cells and then activates genes that tell cancer cells to self-destruct (also referred to as apoptosis).^{41,42} One study showed that curcumin reprograms prostate cancer cells so as to make them less likely to metastasize to the bone, while another study demonstrated that curcumin has radiation-sensitizing effects, making cancer cells more vulnerable to destruction by conventional radiation therapy.^{43,44} The research on curcumin is so promising that pharmaceutical companies are currently developing curcumin analogs that can be patented as anti-

cancer therapies.^{45,46}

CRITICAL IMPORTANCE OF ANNUAL PSA TESTING

In 2004, the *New England Journal of Medicine* published an article indicating that the rate of increase in PSA is a more important predictor of mortality than the PSA reading itself. Men who showed a 2.0 ng/ml or greater increase in PSA from the previous year's level were 10 times more likely to die within seven years.⁴⁷ The researchers recommended that men over the age of 35 should have a baseline PSA reading and then retest each year to measure the rate of increase (PSA velocity). A sharp rise in PSA mandates the need for more comprehensive evaluation and treatment. Without previous PSA readings, it is impossible for



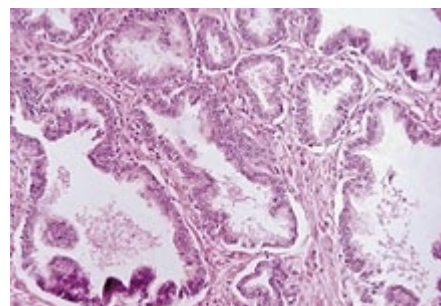
your doctor to calculate PSA velocity. Optimal measurement of PSA velocity requires at least three PSA readings, with each obtained at least six months apart and tested at the same laboratory using the same PSA laboratory procedure.

In summary, accumulating data suggest that PSA is no longer merely a laboratory test of prostate gland activity. Instead, PSA is recognized as a functional protein: an enzyme that may facilitate prostate cancer cell proliferation, invasion, and metastasis. Taking steps to suppress PSA may reduce prostate cancer risk and progression. Meaningful reductions in PSA, as demonstrated in many of the studies cited in this article, appear achievable by using natural supplements like lycopene, soy, green tea, and boron, as well as through prescription drugs such as Avodart® or Proscar®, which normally reduce serum PSA levels by 40-50%.⁴⁸⁻⁵⁰

LOW-COST BLOOD TESTING

A number of blood tests can identify correctable risk factors before clinically advanced disease becomes established. Most people test their blood to ascertain levels of cardiovascular disease markers such as homocysteine, C-reactive protein, LDL (low-density lipoprotein), and HDL (high-density lipoprotein).

While the PSA test has become well known, some men have been reluctant to have it done for fear that it will reveal a problem that cannot be easily corrected. Over the past few years, however, a significant number of publications have revealed safe methods of lowering PSA and potentially reducing prostate cancer risk.



Photomicrograph of a human prostate gland section, magnified 36 times (at 24 x 36 mm).

Until June 1, 2005, Life Extension members can obtain comprehensive blood test panels at extra-low discounted prices. The popular Male Panel includes the PSA test, along with homocysteine, DHEA sulfate, C-reactive protein, and numerous other tests. It does not, however, include the dihydrotestosterone (DHT) test that would be of significant importance if PSA levels were in any way elevated.

High DHT levels stimulate the androgen receptor to induce greater PSA production.⁵¹ DHT also interacts with extracellular tissues to increase prostate cancer cell mobility.⁵² These and other findings may well be the basis for the reduction in prostate cancer development seen in men treated with inhibitors of DHT. The normal retail price for the DHT test is \$60, but during the annual blood test sale, members pay only \$23 for this test.

If you have delayed ordering your annual blood test panel, please do not wait any longer, as the Blood Test Super Sale ends on June 1, 2005. Now more than ever before, determining your PSA (and DHT) levels may dramatically reduce your odds of becoming a prostate cancer victim.

For longer life,

A handwritten signature in black ink, appearing to read 'William Faloon'. The signature is fluid and cursive, written in a professional style.

William Faloon

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