

WHAT EVERY DOCTOR WHO TREATS MALE PATIENTS SHOULD KNOW

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“A Primer on Prostate Cancer, The Empowered Patient’s Guide”

Prostate cancer diagnosis clinical practice guidelines:

Every man should have an annual PSA and DRE starting at forty years of age. Men at risk due to a family history of prostate cancer (brothers, fathers),¹⁻³ men with a family history of breast cancer (mothers, sisters, aunts)^{1,4-6} and African-American men should begin annual screening at age 35.

A PSA of 2.0 and over at any age should be investigated to rule out prostate cancer (PC).

A first step in investigation of a PSA elevated at 2.0 or above should be a free PSA percentage test.

- A free PSA percentage of over 25% is associated with a low risk of prostate cancer.
- A free PSA percentage of under 15% is associated with a higher risk of prostate cancer.⁷
- A benign cause of an elevated PSA and a correspondingly low free PSA percentage could be prostatitis. Four to six weeks of Cipro or similar antibiotic should be prescribed prior to recommending a biopsy if prostatitis symptoms are noted and/or if expressed prostatic secretions (EPS) are consistent with prostatitis. At the end of the Cipro therapy, a repeat PSA determination should be made. If there is significant lowering of the PSA, an element of prostatitis is most likely present. The PSA value after antibiotic therapy will more aptly reflect the status of the patient in the situation where PC is subsequently established.
- BPH (benign prostate hyperplasia) does not cause a low free PSA percentage. It may cause an elevated PSA, however. Therefore, in the case of an elevated PSA but a high free PSA percentage ($\geq 25\%$), an estimate of gland volume by DRE or via transrectal ultrasound of the prostate may reveal findings consistent with a diagnosis of BPH. A general rule of thumb is that an accurate gland volume (best determined by transrectal ultrasound of the prostate) x 0.066 will equal the amount of benign-related PSA. Therefore, assuming only the presence of BPH, a 60-gram or 60 cubic centimeter prostate is entitled to secrete approximately 3.96 ng of PSA into the blood.

Blood sampling for PSA determinations, done at least three months apart, and by the same laboratory using the same testing procedure, are necessary to establish PSA velocity (PSAV) and PSA doubling time (PSADT). The validity of such determinations is increased if such testing involves at least three determinations over an 18-month span of time. However, a progressive and serial increase in PSA values should raise flags of concern that prostate cancer is present and a greater degree of vigilance is mandatory.

- A PSAV that exceeds 0.75 ng/ml/yr is associated with a higher probability of PC.⁸
- A PSADT of less than 12 years is associated with a higher probability of PC.

PSA's that bounce up and down are more indicative of a benign process than a malignant process.

A PSA that show a persistent rise over time, particularly three consecutive rises, three months apart is suspicious for PC regardless of the level of the PSA. As mentioned above, gland volume in cubic centimeters (cc) multiplied by 0.066 yields the amount of PSA produced by the benign-related epithelial cell population of prostate cells. Any amount of PSA in excess of this should be considered to be produced by a malignant process, until proven otherwise.

Recently, an additional new screening tool has become available. Bostwick Labs now offers the uPM3 test, the first urine-based genetic test for prostate cancer. uPM3 is based on PCA3, a specific gene that is profusely expressed in prostate cancer tissue. On average, the incidence is 34 times greater in malignant prostate tissue as opposed to benign prostate tissue. No other human tissues have ever been shown to produce PCA3. The uPM3 test predicts cancer as confirmed by prostate biopsy with 81% accuracy, compared to 47% accuracy for prostate specific antigen (PSA). Therefore, after an elevated PSA, further investigations are possible, which reasonably might include uPM3 testing to enhance the accuracy of diagnosis. Systematic biopsies of the prostate under ultrasound guidance, however, must be considered mandatory when clinical &/or laboratory findings suggest the possibility of prostate cancer.

An approach using biological detection techniques such as those described above would eliminate advanced presentations of PC. Annual screening in this manner presents us with an opportunity to detect localized PC in over 95% of men.⁹ Such statistics offer an outstanding chance for a curative approach to this disease.

An approach involving these profiling techniques allows the patient-physician team to discern the very slow growing (indolent) presentations of PC that may be monitored using watchful waiting as opposed to the standard PC cases for which local treatments typically result in long term biological non-evidence of disease. Most importantly, attention to PSA kinetics accomplished by monitoring the PSA and PSA derivatives such as free PSA percentage, PSADT, PSAV and other calculations, should result in an almost total disappearance of highly aggressive presentations of PC. It is the latter that is associated with rapidly progressive disease and fatalities.

These opposite extremes in the clinico-pathological nature of PC, i.e. the indolent "pussycats" variants versus the aggressive "tigers" ones, are important to differentiate

due to the highly different evaluation and management recommendations advised for each circumstance.

Indolent versus Aggressive PC (“Pussycats” versus “Tigers”)

Pussycats in general, have low PSA values (under 10) and long doubling times (greater than 24 months & often 48 months or longer), as well as low PSA velocities (0.75 ng/ml/yr \pm 10%). If a biopsy is done on a patient with a PSA that is under 10, the Gleason score often turns out to be (3,3). Depending on the calculated tumor volume, clinical stage, PSA doubling time, and other factors, these objectified biologic parameters may allow many such patients to be candidates for objectified observation (“watchful waiting”). Of course, these patients are also candidates for any of the currently FDA-approved local therapies. Patients who choose to monitor their illness rather than seek immediate local therapy must be cognizant of the significance of change over time, or trend. They need to be aware that if manifestations of disease progression become evident, reevaluation of their situation is warranted. In such circumstances, consideration must be made for some form of local treatment—before the window of opportunity for successful local therapy is lost.

Tigers in general, have high PSA’s (over 10), OR very low PSA’s associated with very aggressive, high Gleason score [(4,3), (4,4), (4,5), (5,4), (5,5)] cancers. These are very dangerous because they often escape investigation for long periods of time since the PSA’s appear to be in the so-called normal range. Investigating all PSA’s 2.0 and over will help to catch these prostate cancers while they are still organ-confined and treatable with local therapies. The probability of spotting these low PSA/high Gleason score cancers is enhanced if patients and doctors monitor PSA levels over time to note any persistent increases even if the PSA is very low. High Gleason score cancers often have reverted to such a primitive state that they no longer secrete PSA into the blood. Checking the serum for elevations in other markers such as CGA (Chromogranin A), NSE (Neuron Specific Enolase), CEA (Carcino-Embryonic Antigen) and PAP (Prostatic Acid Phosphatase) is important to discern PC activity secondary to de-differentiated tumor cell populations. Therefore, in cases such as this, the normal guidelines for PSA velocity and doubling time may not be applicable. However, the concept of slope or trend in a biomarker of disease activity remains valid, and any biomarker elevation should be tracked at regular intervals to determine the presence of abnormal growth of primitive tumor cell clones.

CONCLUSIONS:

If we scientifically observe the biological manifestations of prostate health or disease, we can detect PC at a time when currently available therapies are most likely to cure the most common malignancy facing man. If we ignore these biological communications that are red flags to alert us to the presence of a threat to our life, a vital opportunity to change the course of an illness is missed. The loss of life, productivity, and the extreme costs to the health care system—all of which result from a late-stage diagnosis of this disease—should provide impetus for all of us to be proactive when it comes to an early diagnosis of a malignant condition. This fundamental concept has been heralded for

many malignances, such as cancer of the cervix, lung cancer, colorectal malignancy and breast cancer. When will we make the same connection when it comes to men with PC?¹⁰ Aren't the almost 300,000 American lives lost each decade too great a price to pay?

RESOURCES FOR PHYSICIANS AND PATIENTS:

On the Web:

The Prostate Cancer Research Institute (PCRI) web site at <http://www.pcri.org>. This site has a wealth of information including the Prostate Cancer Address Book, which lists expert prostate cancer physicians, software tools, and articles and downloadable issues of the publication PCRI INSIGHTS.

The Phoenix5 web site at <http://www.phoenix5.org>

This is a vast resource for the prostate cancer student, with information on nearly every aspect of the disease as well as an excellent glossary, many first person stories and the prostate cancer journal of the webmaster who died of prostate cancer in June, 2003.

Us TOO! INTERNATIONAL at <http://www.ustoo.org/>. This is the world's largest independent, charitable network of education and support groups for men with prostate cancer and their families.

In print:

“A Primer on Prostate Cancer, The Empowered Patient's Guide” by Stephen B. Strum, MD, FACP and Donna Pogliano, copyright 2002. The Primer is available at web booksellers such as www.amazon.com, <http://www.barnesandnoble.com>, and www.lefprostate.org. It can also be ordered through the Life Extension Foundation (1-866-820-7457) and at Barnes & Noble, Borders, and other fine bookstores everywhere. This is an in-depth guide about prostate cancer that presents a comprehensive approach to the diagnosis, evaluation and selection of therapies currently available to the prostate cancer patient. It consists of 368 pages of fully indexed text with 168 full color graphics to enhance a clear understanding of prostate cancer. It is intended to bring the patient—partner—physician team involved with prostate cancer from a basic understanding of this disease to a highly sophisticated level of understanding.

Working together, we can achieve vast inroads into the diagnosis, evaluation and treatment of this illness.

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