

EVALUATION OF DETECTION METHODS FOR PROSTATE CANCER

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After decades of near indifference to prostate cancer, the population and physicians have geared up to detect this potentially fatal malignancy at a stage before it spreads. This is in marked contrast to the past when prostate cancer was found most commonly when it had traveled through the blood stream into the bones and was incurable. New technology produces new questions. These include not only how to interpret innovative tests but how to best treat localized disease.

In a recent editorial, Catalona and Smith in the American Cancer Society's sponsored journal, *Cancer*, reviewed the Prostatic Specific Antigen (P.S.A.) screening test for prostate, a blood test that is easily available and is highly useful - but not definitive in detecting prostate cancer.

The authors pointed out the importance of the blood test, P.S.A., saying "Measurement of serum prostate specific antigen (P.S.A.) concentration is the most accurate single test for early prostate cancer detection. Adding P.S.A. testing to digital rectal screening increases the prostate cancer detection rate by 78% and the percentage of cancers that are curable at the time of detection by 100%."

What more can one say? If one believes that it is important to detect cancers early then P.S.A. and rectal examination should be part of the medical armamentarium used in evaluating otherwise healthy men.

When a blood test exists, there is created the question of what is defined as normal and abnormal. This is somewhat arbitrary. Whatever level is recommended, there can be cancers hidden below that level and normal prostates above.

When the point of greater than 4 ng/ml (nanograms per milliliter of blood) is used - presently the upper limit of normal - approximately 35% of men will have prostate cancer detected while 65% have an elevated P.S.A. but no detectable cancer.

It might sound alarming that two-thirds of men with an elevated P.S.A. who undergo biopsy have no cancer detected. For purposes of comparison it should be noted that approximately 80% of women who undergo breast biopsies have no cancer found.

How can physicians better evaluate P.S.A. for prostate cancer? Authors have suggested one mechanism is "based on the fact that prostate cancer leaks ten times more P.S.A. in the blood stream than does benign hyperplastic tissue. Accordingly a high P.S.A. concentration is more likely to be caused by cancer in a man with a small prostate gland than in a man with a large gland." Based on this some have proposed dividing P.S.A. by prostate size.

Others have evaluated the change of P.S.A. over time. It is observed that the blood test increases more quickly in malignant than benign conditions. Others have recommended using different reference points for the blood test based upon age. There is increasing incidence of benign enlargement of the prostate gland with increasing age.

A study from Mettlin et al has proposed alternative methods of evaluating P.S.A. Evaluated were comparisons of "The relative sensitivities and specificities of P.S.A. level, P.S.A. density, age specific P.S.A. and P.S.A. change noted in the results of the American Cancer Society National Prostate Cancer Detection Project".

As the editorial well stated, "There is a reciprocal relationship between sensitivity and specificity. Any increase in specificity usually is accompanied by a decrease in sensitivity, and vice versa. Therefore, reducing the number of false positives by reducing the number of biopsies usually will result in a decrease in cancers detected, and the cancers missed are usually the most curable ones. The curable cancers that are missed have been shown to be clinically important."

The Mettlin study evaluated P.S.A. levels related to outcome using the most recent P.S.A. available. Age referenced P.S.A. suggested that a normal should be considered 2.5 in men aged 40-49; 3.5 in men aged 50-59; 4.5 in men aged 60-69; 6.5 in men aged 70-79.

Another method suggested "Prostate Specific Antigen density which was computed by dividing the most recently obtained P.S.A. level by the gland volume measured in cubic centimeters." A third method was performed using the change in P.S.A. level. That entailed "dividing the difference between the first P.S.A. assessment and the most recent by the intervening time interval."

It should be noted that in this study of 2,999 men seen annually for five years, 80% of the detected cancers were localized and considered candidates for curative therapy. Fifteen percent were felt to be so early that treatment was not necessary while only 5% were clinically advanced.

For the entire male population, the mean P.S.A. level was 2.92 ng/ml. For the 171 men with prostate cancer detected, the mean P.S.A. was 12.02. For the men with cancer detected, 71.9% had a P.S.A. greater than 4. This meant more than 28% with prostate cancer had a P.S.A. less than 4 - considered normal.

Evaluating the prostatic specific antigen density, the mean prostate gland volume was 33.5 cubic centimeters. For those with cancer, it was 38.9cc. Determining a P.S.A. density, it was 0.06 for men with normal prostate, 0.08 for the entire group and 0.35 for men with prostate cancer. This method, as well, did not detect all patients and in fact had a sensitivity of only 74.7%.

Similarly, the age-referenced P.S.A. had a sensitivity level of 67.3%. Similar evaluation was performed of the 1473 men who had two P.S.A. determinations and of 84 men in the series with P.S.A. for more than one year. If a rise of 0.75 ng-ml per year is used as a standard for monitoring P.S.A. in those considered healthy, specificity of P.S.A. change was 95.5%. In men with P.S.A.'s of less than 4 initially, the specificity was 96.4% while the sensitivity was only 45.7%.

The authors evaluated various age-related methods but found that reducing the cut-off rate for older men decreased the number of localized and potentially curable cancers found by up to 47%.

What are the limits of this study? As the authors well point out, the analysis may include men who do not have cancer detected at this time but will have it detected later.

After extensive evaluation of P.S.A. the authors concluded, "The goal of prostate cancer screening should be to detect potentially curable cancers and the use of a serum P.S.A. cut-off of 4 ng/ml appears to be the best way to achieve this goal. Although the alternative methods may reduce the number of false positives, the trade off is a failure to detect an appreciable number of organ-confined cancers. If a man is healthy enough to be screened for prostate cancer, a cut-off should be used that provides him with the best opportunity to detect a curable cancer. Men whose general health and life expectancy are not sufficient to warrant treatment would be served better by not being screened at all rather than by undergoing a screen that uses a cut-off that would detect less curable cancers."

Having a “normal” PSA does not make one immune from prostate cancer. It is estimated that about 20% have prostate cancer when the PSA is in the range of 2.5 to 4. I, personally, have experience treating men with prostate cancer whose PSA is even less than 1.0.

So an understanding doctor combined with a questioning patient will help decide on work-up. There are many factors that can fluctuate – each man must ultimately make up his own mind after hearing the pros and cons.