# PSA Controversy

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## I. Two Uses for PSA Test

There are two primary uses for the PSA test. One is screening for disease in both asymptomatic men and symptomatic men, and the other is surveillance in the follow up of patients previously diagnosed with prostate cancer.

## II. Screening Pros and Cons

In my opinion, the standard PSA blood test is not a very good screening test for prostate cancer, and it has limited sensitivity, specificity, and predictive value. I think what you have been hearing about the PSA and whether you should do it or not is actually wrong. Despite my view, however, the key issues really are can it save lives, and if it saves lives, is it cost-effective?

## III. What are the Data? How Should They be Interpreted

A ratio is simply one number divided by another, and that representation of data has a lot of biases associated with it, particularly if a denominator is small. You have to be careful. What is a difference? A difference is the subtraction of one number from another number, and with a small number, the trends that exist may not be apparent, again, because the numbers are tiny. The exact same data in different presentations can be misleading depending on what story I want to tell you if I haven't explained what the biases are.

## IV. Screening: Three Criteria

A good screening test must accurately identify persons with a condition, which is called sensitivity. It must also accurately identify those without the condition, which is specificity. In addition, it has to identify individuals early enough to make a difference in treatment outcomes, including survival and/or quality of life. Preferably, a screening test should have high sensitivity and high specificity, and it must be acceptable for the population screened, rapid, and ideally non-invasive. The PSA is not that good; we need better tests.

## V. Screening for Prostate Cancer:

The three testing approaches for detection of prostate cancer include the digital rectal exam, the prostate-specific antigen blood test, and the trans-rectal ultrasonography. The digital rectal exam is a mainstay of prostate cancer screening, but the examiner cannot feel the whole prostate or small lesions. The PSA is done with a small sample of blood and tests for the amount of a substance that is mainly produced by the prostate gland.

Trans-rectal ultrasonography has limited value for screening, but the patient's history, exam or lab findings may indicate a need for TRUS evaluation.

## VI. Risks & Benefits of Screening

The value of screening can be proven only by showing a reduction in the chance of dying of prostate cancer without an unacceptable reduction in quality of life from both the screening and increased use of treatments that can have negative side effects. Conclusive evidence for the value of prostate cancer screening has not yet accumulated, but some evidence does indicate that screening offers the possibility to diagnose early prostate cancer and to reduce deaths from this disease.

On the other hand, screening also detects cancers that do not threaten the patient's life. Finding such cases cannot be avoided at present, and when screening the general population for prostate cancer by PSA, over 50% of the prostate cancers detected will be minimal cancers. As immediate treatment of these has not been shown to be beneficial, detection and diagnosis of some tumors may be unnecessary and counter-productive, as in some patients there will be treatment-associated morbidity and rarely even mortality.

## VII. Prostate Specific Antigen

### 1. Issues in the Optimal Implementation of PSA Testing

PSA is a protein. It is almost exclusively produced by the epithelial cells of the prostate in normal and in pathologic conditions such as infection, urinary retention, enlargement of the prostate and prostate cancer. Approximately 40% of patients with organ-confined prostate cancer show no elevation of serum PSA. An unresolved issue is at what PSA value more invasive examinations should be done, such as prostate biopsies. Trials use different values. There are reasons why they chose them, but there are problems with setting them too high or too low. There are issues of whether it is age and/or race dependent. There is a question of whether clinical findings should be incorporated into testing algorithms such as PSA elevation associated with benign prostatic hypertrophy and acute prostatitis.

## VIII. Clinician-Patient Conversation

In order to have an evidence-based discussion of benefits, it is necessary to have data to support screening. In its absence of such data, clinicians have speculated loosely about the potential benefit and the potential harm of the PSA. The conversation needs to include a discussion of the morbidity and mortality associated with the screening since a positive test leads to additional diagnostic tests and possibly treatment, which also carries associated risks, not just benefits.

## IX. Early Treatment – The Controversies

A randomized trial has demonstrated that radical prostatectomy can decrease the chance of dying of prostate cancer as compared to delayed treatment. This benefit has been attributed in part to suppression of the male hormone, testosterone. However, even in the delayed treatment group, eight years later, only approximately 25% are at risk of

developing metastatic disease. Thus, a majority of those with prostate cancer die with, not from, the disease. It is still impossible to determine up front which cases will not progress, and it has not been shown that the same favorable results of surgery can be achieved when prostate cancer has been detected by screening. Uncertainty therefore remains.

## X. Benefits of Screening

Screening can find potentially lethal cancers at an early, still curable stage, as well as provide an opportunity for earlier, and possibly life-prolonging, treatment of additional tumors. Men who decide to be screened take a chance, and need to be informed about the potential risks and benefits of screening and subsequent treatment. The decision currently must be individualized, and men who choose to be screened should not be denied the early diagnostic tests. Given the current wave against prostate cancer screening, individuals will be denied the opportunity to be screened because it won't be reimbursed. That will be a disservice. Data concerning cost efficacy, an important determinant of public policy recommendations, are limited and controversial.

## XI. ERSPC—European Randomized Study of Screening for Prostate Cancer

The ERSPC was established over a decade ago, and it is the largest randomized study on screening for prostate cancer. Prostate cancer is the second leading cause of cancer death in men in Western Europe and in the U.S. The study provides some evidence-based advice about whether screening leads to an improvement in cancer-specific survival, and the initial results showed a 20% reduction in the rate of death from prostate cancer after the first ten years of follow up.

### 1. Caveats

The 20% reduction in rate of death due to prostate cancer, however, underestimates the true effect since some controls were also screened and some assigned to screening did not get screened, but the model-based adjustment, correcting for both contamination and noncompliance, indicates that screening reduces mortality by 31%.

The initial data analysis indicates that you need to screen over 1,400 men and actually treat 48 who were diagnosed with prostate cancer to save one life, but further modeling, which was published in 2011, indicates that the number needed to screen and the number needed to treat to prevent one prostate cancer death both decrease over time.

The ERSPC had a limited number of biopsy samples, fewer than are standard recommended practice today. There was an absence of African American subjects, and there was limited follow up.

## XII. PLCO—Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial

The objective of the PLCO was to provide some answers about the effectiveness of prostate cancer screening, and it was designed as a 17-year project of the National Cancer Institute. An initial report appeared in the *New England Journal of Medicine* March 18,

2009, coinciding with presentation of the ERSPC data at the European Association of Urology meeting in Stockholm, Sweden, but it was premature. The PLCO conducted six annual screenings for prostate cancer, and they found that more prostate cancer was diagnosed, but those diagnoses did not lead to fewer prostate cancer deaths.

### 1. Caveats

The limitations of this study include that they probably used the wrong PSA cutoff. Secondly, over 40% of the subjects were screened within three years of enrollment, meaning that you have already drawn out from the pool some of the individuals who would have been detected. Half of "non-screened controls" really got a PSA during the trial, and 15% assigned to screening did not get screened, which greatly reduced the power of the study. There was only a 33-percentage-point difference in intervention rates between the control and screening arms. That means that it would have to take them much longer to find a difference statistically if a true difference existed, which means you have to be extremely careful not to make premature determinations. Finally, the study incorporated a relatively short follow-up, and most men were not biopsied when they were advised to be biopsied, limiting the detection of early–stage prostate cancer. There were a limited and variable number of biopsies performed, and the patient care was variable. There were also very few African American men in the study.

Despite the above weaknesses, after ten years the number needed to screen in men with no or minimal comorbidities was 723 and the number needed to treat was 5 to prevent one prostate cancer death. Men with comorbidities who were diagnosed with prostate cancer, however, were less likely to receive curative treatment than men without comorbidities, and so they were perhaps more likely to progress to death due to prostate cancer, potentially reducing their benefit from screening and reducing the overall demonstrated value of screening in the PLCO.

At ten years, neither the ERSPC nor the PLCO showed much of a difference, and they have no data on what happens after ten years, but the curves do start to diverge in what looks like it might be a major way.

## XIII. Summary of Concerns

There are limitations to the protocols that may have reduced the efficacy of screening. Based on our knowledge of the epidemiology of prostate cancer, in each trial the follow-up period is too short to have expected to see the full potential benefits and much too short to calculate cost/benefit ratios, particularly if you expect most of the benefit to be later on, which is what I would expect given the epidemiology of the disease. Finally, the US PLCO trial was significantly underpowered to have been able to demonstrate a positive result due to PSA screening of controls.

## XIV. The Goteborg Trial

The Goteborg Trial is a smaller Swedish screening trial consisting of roughly 20,000 men, and it was designed with similar criteria to ERSPC. In fact, it is a sub-set of the European study data that was reported. The current data that they reported followed a total of 14 years of screenings and follow up. Their final results showed a roughly 50%

decrease in mortality from prostate cancer in the screening group versus the control group. The benefit was greatest over 10 years after the beginning of the trial. Half of the attendees who died of prostate cancer in the screening group were diagnosed in the first round of screening, and many of these men were 60+ years of age at entry. You would have to question whether it is the group that should be screened or not. The number of men from the control group who may have received independent screening was not known or was not included, which is a bias that may cause them to underestimate the benefits of screening. According to their published results, 293 men have to be screened and 12 diagnosed or treated to prevent one death from prostate cancer.

Looking at these trials, the data is still unclear, and in African American men there is even less data.

## XV. Current Screening Guidelines from Major U.S. Organizations

According to the American Urological Association, the use of the PSA is an individual decision for those with a ten-year life expectancy. A baseline PSA should be done at age 40, and there should be follow-up PSAs at subsequent intervals based on the PSA level and risk factors.

The American Cancer Society advises against routine screening, and their position is that the PSA should be offered as an option to patients who are age 45 with risk factors and patients who are age 40 who are at the highest risk.

The U.S. Preventive Services Task Force, on the other hand, states that patients over age 75 should not be screened routinely and there is inadequate evidence regarding younger ages. Their current draft recommendation is against PSA-based screening for any asymptomatic men. In my opinion, they have reached a definitive decision too early.

## XVI. Big Picture

The PSA is not for every patient. Clinicians have to look at the data and have a discussion to decide who really should be screened based on their best interpretation of the data. More evidence is needed to make good decisions. There are studies that are currently evolving for white males, but they need to be continued in order to provide enough information. There are not adequate studies for any other racial or ethnic groups.

Some of the benefit of PSA screening may have nothing to do with prostate cancer. It may be that it pulls men into the medical care system where they will be followed, watched and taken care of for different problems so that interventions can take place in a timely and effective manner.

Improved guidance is needed for clinicians as to what to do and in whom to do it. There is some evolving evidence of life-saving potential with PSA screening, and the costs in terms of the number needed to screen and the number needed to treat may be much less than the recently highly publicized estimates, which were focused on the ten-year point. It may be a cost-effective screening tool. Another issue to consider, however, is if clinicians are going to do the screening, they need to have a plan for how they will get patients into care, or doing the screening becomes a disservice.