PSA Testing: Is There an Answer?

William Catalona, MD

I. Introduction

I am for prostate cancer screening, and I will present the other side of the issue. Most men with prostate cancer are detected through PSA screening, and the objectives of prostate cancer screening are to detect cancer earlier than it would be detected if you waited for symptoms and to allow for improved outcomes because the cancer was detected earlier.

II. First Large PSA Screening Study

The first large PSA screening study was published by my research group in 1991 in the *New England Journal of Medicine,* and it showed that PSA and the digital rectal exam together make up the optimal combination for screening detection. PSA is the better of the two tests and detects more prostate cancer than the digital rectal exam. As a man's PSA level increases, his risk of having prostate cancer increases, and men who are diagnosed with prostate cancer at lower PSA levels have more favorable tumor features than men with higher PSA levels and better treatment outcomes.

III. Importance of PSA at Diagnosis

These studies have also shown that most prostate cancers that are detected with a PSA of less than 10 are curable, and prostate cancers that are detected with a PSA of higher than 10 are more likely to have advanced disease at the time of diagnosis.

When we did the screening study, we enrolled 36,000 men, and the study went on for 12 years. When the study ended, we looked at the median PSA value for each age group. If we looked at the probably of being diagnosed with prostate cancer as a function of a man's PSA in relation to the median for his age group, if his PSA was lower than the median, his risk was not zero but it was very, very low. If it was higher than the median value, his risk was higher than the general population of his age group. The higher the PSA was in relation to the median, the greater the likelihood that he would be diagnosed with prostate cancer and the greater the likelihood that the prostate cancer detected would be an aggressive prostate cancer.

IV. PSA Derivatives Improve Accuracy

The PSA is not a perfect test and it does need improvement, but it's the best thing that we currently have. There are ways to improve the accuracy of PSA, which include measuring how rapidly it rises over time, which is called PSA velocity, measuring how big the prostate is in relation to the PSA level in the blood, which is called PSA density, and measuring the percentage of PSA that is free floating in the blood stream, which is called percent free PSA. There is also a new test that is under review by the U.S. FDA called the Pro-PSA that is approved in Europe and is commercially available there. It is more

accurate than PSA and preferentially detects the more aggressive forms of prostate cancer.

A PSA velocity of greater than 0.35 mg/ml/year is associated with a five-fold increased risk of prostate cancer death 15 or more years later. The PSA velocity test has long-term predictive value for life-threatening prostate cancer.

V. Overview

No screening test is perfect. There are false positives. Men who have inflammation in their prostates or a benignly enlarged prostate can have high PSAs, and these can cause false alarms that are sometimes very upsetting. False negatives also occur, and there are some very aggressive cancers that do not produce much PSA. In screening for cancer and trying to detect cancer earlier, you are going to diagnose and treat some tumors that would not have caused harm during the patient's lifetime. That goes with the territory.

VI. ERSPC

At a median follow up of nine years in the randomized European study (ERSPC), the prostate cancer mortality was 27% lower for men who were actually screened. The calculations of number needed to treat and number needed to screen, which were that 1,410 men needed to be screened and 48 cases treated to prevent one prostate cancer death are very dependent on the follow up. With greater follow up and greater differences in survival, the numbers have come down dramatically. Based on this European trial, screening reduces the prostate cancer death rate but carries with it a high risk for over diagnosis.

VII. PLCO

Another study, PLCO, is stated to be a study that found no difference, but the study was so flawed that it is impossible to interpret. Part of the reason is that 85% of the men in the screening arm were screened, but 40% of the men were screened before they even got into the study. In addition, during the study 40 to 50% of the men were screened. They weren't really comparing screening with non-screening. They were comparing screening in 85% versus screening in 52%.

Not only that, but of the men who had an abnormal PSA or an abnormal rectal exam, less than half of them underwent a biopsy within a year. The median follow up for the whole study was 9 years, but for the men with prostate cancer, the median follow up was only 6.3 to 5.2 years. The curves don't begin to separate until nine years. There is no way one can expect to see a mortality difference.

VIII. Goteborg Randomized Population-Based Screening Trial

The Goteborg study was a population-based study, and the men tended to be younger. They were screened more frequently, and they used lower PSA cut-offs. When the men had an abnormal screening test, 93% complied with an immediate biopsy.

The patients were treated according to the discretion of their physicians, and they had death certificates on the great majority of patients. Their outcomes were also linked to the

Swedish cancer registries, which are more accurate than the registries in the United States.

They found that the life-saving mortality benefit was not 20%, but it was 44%. If you looked at the men who were actually screened, the mortality benefit was 66%. The prostate cancer death rate was cut in half. The study had 14 years of follow up, and by 14 years you see a tremendous life-saving benefit associated with prostate cancer screening. The curves are still diverging. At 14 years of follow up, the number needed to screen came down from 1,400 to 293, and the number needed to treat came down from 48 to 12. The PSA is as effective as mammography for breast cancer screening.

IX. Decreased Prostate Cancer Mortality During the PSA Era

In the United States in the PSA era, since 1991, there has been a 75% decrease in the percentage of men who present with advanced metastatic prostate cancer at the time of diagnosis. There has also been a 40% reduction in the prostate cancer death rate in the United States, which is the same thing that was seen in the Swedish population. There are similar trends in the World Health Organization data.

The five-year survival rate for men who present with localized prostate cancer is 100%. For those who present with regional prostate cancer, it is 100%, and for those who present with metastases from prostate cancer, it is 31%. The clear issue is detecting prostate cancer before it metastasizes. From 1992 to 2007 the prostate cancer death rate in the U.S. decreased from less than 40 down to 22 deaths per 100,000, which is greater than a 40% reduction.

X. Quantifying PSA Screening's Effect on Prostate Cancer Mortality Rate

Does PSA screening explain the greater than 40% prostate cancer mortality decline in the U.S. SEER database? Two independent groups used their respective mathematical models to look at this, and both of them suggested that from 45% to 70% of the reduction in the prostate cancer death rates was due to PSA screening.

XI. Informed Use of PSA

Screening should begin at age 40 (age 35 in men with a family history of early-onset disease) for initial risk assessment. Screening should be repeated annually, and if the PSA is higher than the age-specific median, immediate repeat testing should be performed to verify the PSA level. To evaluate possible confounding from benign prostatic hypertrophy, PSA density should be estimated and the percent of free PSA should be measured. To help rule out prostatitis, a repeat PSA should be performed within a few weeks. If the PSA elevation is confirmed, a biopsy should be performed, or PSA should be monitored at three to six-month intervals to monitor the PSA velocity. If the PSA velocity is convincingly greater than approximately 0.35 ng/ml/year, a biopsy should be performed. Finally, a biopsy should be performed or strongly considered for all men with a PSA greater than 2.5 ng/ml. If you are a healthy man aged 40 to 69 who does not want to die of prostate cancer, there is conclusive evidence that PSA testing can save your life.