PSA Screening and Prostate Cancer Screening for Risk and Early Detection

Prostate cancer is the most common, non-cutaneous cancer affecting men. It will be diagnosed in approximately 190,000 men each year and kill 27,000-30,000 men each year. In its early stages, it is asymptomatic. Symptoms are almost always caused by metastases or advanced disease. If we are to have any meaningful impact upon the natural history of prostate cancer, we must find it in its early stages, which means we have to look for it. We look for it with a DRE and serum PSA.

PSA is a benign, harmless glycoprotein produced by the epithelial cells that line the acini and ducts of the prostate. It is concentrated in prostatic tissues and seminal fluid. Disruption of normal prostatic architecture by trauma, inflammation or cancer allow for greater amounts of PSA to enter the circulation. Elevated levels of serum PSA has therefore become an important marker for a variety of prostatic conditions…not just prostate cancer. It is a marker specific to the prostate, but it is not cancer specific. When we use PSA for screening, we are really screening for risk of prostate cancer with a goal of early detection.

The current American Urologic Association guidelines for use of PSA, emphasizes the point that PSA is one among many factors to be considered when estimating an individual’s risk for prostate cancer. The other factors to be considered are % free PSA, PSA velocity, DRE findings, family history, ethnicity, and prior biopsy history.

The AUA guidelines recommend that all of the factors be considered together and that we begin at the age of forty. They no longer recommend a PSA threshold cutoff value for biopsy as recommended in the past. The National Comprehensive Cancer Network [NCCN] also recommends that screening begin at age forty, but is more specific about interpreting PSA values. Their guidelines recommend a baseline PSA and DRE at age forty. Provided the DRE is normal, if the baseline PSA is <0.6, then annual screening may begin at age forty five. If the baseline PSA is > 0.6, then screening should begin annually at age forty. They recommend a biopsy if the PSA is > 2.5. If the PSA is < 2.5, they recommend a biopsy if the PSA velocity is > 0.5ng/ml/yr.

Clearly, interpreting PSA as a risk factor for prostate cancer can be tricky. The new normal is a moving target. The NCCN has continued to endorse cutoff values for biopsy, while the AUA has dropped the recommendation.

The AUA did so because of the findings of the 2004 Prostate Cancer Prevention Trial. This seven year trial was designed to determine if finasteride would reduce a man's risk of developing prostate cancer when compared to a placebo. All men were biopsied at the conclusion of the trial regardless of their PSA. No cutoff PSA value was used. Of the several thousand men in the trial, 2950 of them had a PSA of < 4 at the end of the trial and were biopsied. 6.6% of the men had prostate cancer with a PSA of <0.5ng/ml. 29.6% had prostate cancer with a PSA between 3.1 and 4. In other words, there is no PSA level below which a man can be reassured that he does not have prostate cancer. The AUA therefore discarded the notion of a threshold cutoff PSA value and instead, recommended individualized risk assessment. Risk assessment strategies use PSA in the context of other risk factors and place more emphasis on PSA kinetics such as PSA velocity.

PSA velocity is the change in PSA over time. In general, a man with prostate cancer will have a higher PSA velocity than a man without prostate cancer. How much change is suspicious for cancer varies from study to study. Most agree that if the PSA is between 4 and 10, it shouldn’t increase by more than 0.75ng/ml/yr. If the PSA is less than 4, it shouldn’t increase by more than 0.4ng/ml/yr. If the PSA were to change by more than these recommended amounts, the PSA should be repeated. PSA may vary for a variety of reasons and may vary by as much as 20-25% when different assays are used. It is therefore recommended that when following a man’s PSA, that the same lab and assay be used, abnormal values be repeated and that PSA velocity be calculated over an 18 month period of time using at least three PSA values. The goal of this strategy is to increase sensitivity [not miss cancers], and to increase specificity [avoid unnecessary biopsies].

The result of early detection and early intervention has been a steady decline in prostate cancer mortality of about 30% over the last 15-20 years. This decline is associated with a significant stage migration. According to the Center for Prostate Disease Research, in 1988, 19.2% of men with prostate cancer presented with radiographic evidence of metastatic disease. Of the 80% presenting with clinically localized disease, 35% actually had nodal metastases at the time of operative treatment, and 67% had evidence of locally advanced extraprostatic disease. Today, less that 4% present with metastases. This is consistent with clinical observation, in that, before PSA was introduced for screening in 1987, our urology wards were filled with men suffering the consequences of advanced disease. Those consequences were not trivial. They included intractable skeletal pain, spinal cord
Why then does controversy and debate about the value of early detection of prostate cancer persist? It persists because the successes achieved by early detection have come at the cost of over detection and over treatment. It persists because of the wide discrepancy between the prevalence of prostate cancer and the risk of dying from prostate cancer. A man’s lifetime risk of developing prostate cancer is about 17% while his risk of dying from prostate cancer is about 3.3%. The problem of over detection, that is finding a cancer that will most likely remain silent and cause no morbidity during that man’s lifetime, is that it leads to over treatment. Study after study has confirmed that most men will seek treatment due to their anxiety about the cancer and not because of the actual risk of disease progression. This is really a problem of managing prostate cancer, rather than a problem of screening and early detection. The difficulties with making good management decisions have affected and confused the issue of screening. The issue has been further complicated by two large studies published by the NEJM in 2009.

The studies, known as the European Randomized Study of Screening for Prostate Cancer (ERSPC) and the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO) both examined large numbers of men, screened and unscreened for prostate cancer with prostate cancer mortality as the endpoint, and arrived at different conclusions. The European study found a 20% reduction in prostate cancer deaths at 9 years for the screened population. The American study found no difference in prostate cancer deaths at 7 and 10 years. These are large studies with conflicting conclusions. Specifically, the ERSPC enrolled 162,387 men. It screened 72,952 men and followed 89,350 as controls and found a 20% reduction in prostate cancer deaths supporting the role of screening. The PCLO enrolled 76,693 men. It screened 38,343 men and followed 38,350 men as controls and found no difference in prostate cancer mortality. These studies are impressive for their numbers, for their sophisticated randomization which resulted in near perfect distribution of men and for their compliance. They are also impressive for their flaws. The European study included seven centers from different countries using different PSA cutoff values for biopsy and different follow up routines. For 87% of the screened group, screening occurred at 4 year intervals in a 9 year study. The American study included 10 centers in one country with annual screening for the screened group. However, 44% of the men were screened before entering the trial and 52% of the control group went off the reservation and had screening outside of the trial. This contamination of the control group would explain the absence of a difference in mortality since it was really a trial of regular, frequent screening compared to irregular, infrequent screening.

The problems of course, is that someone is dying. 27,000 men are expected to die from prostate cancer this year, emphasizing the importance of putting a diagnosis of prostate cancer in proper perspective. First, one has to make the diagnosis at a time when choices are still available for management. Only then can we characterize a particular cancers risk by noting the Gleason score, volume of disease in the biopsy and the PSA. Then risk categories can be assigned and evaluated in the context of a man’s life expectancy. Treatment or non-treatment decisions can then be made. The goal is to not let an important cancer go untreated, but not let an overdone concern about a trivial cancer lead to unnecessary treatment.

In summary, PSA screens for risk of prostate cancer and is just one of several factors to be considered. There is no threshold cutoff value for PSA. Screening allows early detection of prostate cancer, but carries the risk of over detection which can lead to over treatment. The AUA therefore recommends offering screening to informed men who would wish to pursue an early diagnosis. Treatment or non-treatment decisions are the real challenge and can only be made once the cancer is found in its early stages.

The lessons that we can take from these studies are that less frequent screening may be as beneficial as annual screening. This may be especially true for the man with a low baseline PSA and no other risk factors. Another important observation is the relatively small proportion of men who actually died from prostate cancer during these studies. In the European trial, 162,387 men were followed and only 214 died in the screened group and 326 in the control group over a 9 year period. This should support our awareness and acceptance of active surveillance for many men with a life expectancy of 10 years or so.

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