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PSA Screening: Pro

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Abstract

Purpose of review—Prostate cancer is the most common noncutaneous malignancy in US men, and is most frequently diagnosed through prostate-specific antigen (PSA)-based screening. Nevertheless, PSA testing has become increasingly controversial. In this review, we will present the evidence supporting the role of PSA in prostate cancer screening.

Recent findings—Numerous studies have shown that the risk of current and future prostate cancer is directly related to the serum PSA level. Moreover, increasing PSA levels predict a greater risk of adverse pathologic features and worse disease-specific survival. Substantial epidemiologic evidence has suggested a reduction in advanced disease and improvements in prostate cancer survival rates since the introduction of PSA-based screening. Recently, evidence from a randomized trial further validated that PSA testing reduces both metastatic disease and prostate cancer-specific mortality.

Summary—PSA is a valid marker for prostate cancer and its aggressiveness. Level 1 evidence is now available that PSA-based screening reduces both the rate of metastatic disease and prostate cancer-specific mortality.

Keywords

prostate cancer; screening; prostate-specific antigen; detection

Introduction

Screening is defined as the attempt at early disease identification in an asymptomatic population. First, there must be a valid marker for the disease of interest. In addition, for screening to be successful, it should reduce the proportion of advanced disease at diagnosis. Furthermore, there must be evidence that early diagnosis improves outcomes. In this review, we will summarize the evidence showing that PSA-based screening for prostate cancer fulfills these criteria.

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PSA is a Valid Marker for Prostate Cancer

First described as a marker for human semen in forensics, PSA was subsequently demonstrated in the serum of men with prostate disease.¹ Although PSA is prostate-specific, it is not prostate cancer-specific. Serum PSA levels may also be increased with urinary tract infection, instrumentation, or other benign conditions.²

That notwithstanding, the total PSA level is a strong predictor of future prostate cancer risk. In a hallmark 1995 study, Gann et al. showed that the baseline PSA level was significantly associated with subsequent prostate cancer risk.³ Specifically, compared to men with a baseline PSA <1 ng/ml, those with a PSA of 2 to 3 ng/ml had a 5.5-fold increased relative risk.

Our group has similarly demonstrated the strong predictive value of the baseline PSA level in a screening population. Men in their 40s and 50s with baseline PSA levels above the age-specific median were at substantially higher risk of prostate cancer, even if PSA remained below the biopsy threshold of 2.5 ng/ml.⁴ Additionally, among men in the Malmö Preventive Medicine Study, Lilja et al. reported that a baseline PSA level at age 50 predicted future prostate cancer diagnosis for >20 years after a single venipuncture.⁵

Finally, in the Baltimore Longitudinal Study of Aging, baseline PSA levels were associated with future prostate cancer risk.⁶ Moreover, in the same population, baseline PSA velocity (i.e., changes in PSA over time) predicted the future presence of life-threatening prostate cancer.⁷

Based on the aforementioned studies, there is substantial evidence that PSA is a valid marker for future prostate cancer risk. In addition, PSA is also a useful marker for the current presence of prostate cancer on biopsy. This was clearly demonstrated in the Prostate Cancer Prevention Trial, where the likelihood of cancer detection on empiric biopsy showed a significant direct relationship with PSA levels.⁸

PSA is a Valid Marker for Prostate Cancer Aggressiveness

Not only is PSA a valid biomarker for overall prostate cancer, but it is also correlated with disease aggressiveness. In our longitudinal screening study, cancers diagnosed at lower PSA levels were more likely to be organ-confined.⁹ We have also demonstrated a direct relationship between PSA derivatives- including PSA density and PSA velocity- with Gleason score and other adverse pathologic tumor features.^{10, 11}

Moreover, both the total PSA levels and PSA derivatives predict fatal prostate cancer. For example, Stephenson et al. showed a direct relationship between PSA and prostate cancer-specific mortality after radical prostatectomy.¹²

PSA-based adjunctive measures have also been used as markers for prostate cancer aggressiveness. For example, a PSA velocity >2 ng/ml/year during the year prior to prostate cancer diagnosis predicts prostate cancer-specific mortality after radical prostatectomy and radiation therapy.^{13, 14}

Overall, due to the strong relationship between PSA with pathologic tumor features and treatment outcomes, it is included in virtually all major risk classification schemes. In the Partin Tables, PSA is combined with clinical stage and biopsy Gleason score to predict pathologic stage.¹⁵ Both the CAPRA score and Kattan nomogram use PSA and other variables to predict biochemical progression.^{16, 17} Other nomograms to predict prostate cancer-specific mortality also include PSA.¹²

PSA-Based Screening Reduces Advanced Disease at Diagnosis

Having established that PSA is a valid marker for prostate cancer and its aggressiveness, our next objective is to present the evidence that PSA-based screening has led to a lower proportion of advanced stage disease at diagnosis. First, there is substantial epidemiologic evidence demonstrating a stage migration during the PSA era.

Additionally, Level 1 evidence from the European Randomized Study of Screening for Prostate Cancer (ERSPC) clearly demonstrated a decrease in advanced stage disease at diagnosis with PSA screening. Comparing the screening and control arms from the ERSPC, Schroder et al. reported a 41% reduction in advanced disease.¹⁸

A subsequent study compared the rates of metastatic disease between screened men from the ERSPC to a population from Northern Ireland where screening is rare.¹⁹ The proportion of metastatic disease at diagnosis was 0.1% and 0.6% in the two groups, respectively, corresponding to a 53% reduction in metastatic disease associated with screening.

Although a reduction in advanced stage disease is *necessary* to prove the utility of PSA screening, it is not *sufficient* proof in isolation. Therefore, in the next section we will review the evidence that PSA screening also reduces prostate cancer mortality.

PSA-Based Screening Saves Lives

Epidemiologic studies have demonstrated significant declines in prostate cancer mortality rates coincident with the introduction of widespread PSA-based screening. For example, Jemal et al. reported an annual 4.1% reduction in U.S. prostate cancer mortality from 1994 to 2005.²⁰ Mathematical models have suggested that PSA screening has accounted for approximately 80% of the reduction in advanced stage prostate cancer, and 40 to 75% of the decline in prostate cancer-specific mortality.^{21, 22} In European countries where screening is practiced, reductions in prostate cancer mortality have similarly been reported compared to other regions where screening is not routinely performed.^{23, 24}

To date, the most definitive evidence that screening saves lives was reported by Schroder et al. in the ERSPC.¹⁸ In the intent-to-treat analysis, the authors reported a rate ratio of 0.80 for prostate cancer mortality (i.e. a 20% reduction) in the screening arm compared to the control arm. That notwithstanding, some men randomized to screening did not receive screening (noncompliance) and some men randomized to the control arm underwent opportunistic screening (contamination). Factoring in the approximate frequency of noncompliance and contamination, Roobol et al. estimated a risk reduction of up to 33%.²⁵ Furthermore, van Leeuwen et al. reported a relative risk of 0.63 for prostate cancer-specific mortality in the Rotterdam ERSPC group compared to similarly aged men from Northern Ireland.¹⁹ It is possible that the mortality reduction in the ERSPC will increase with additional follow-up.

It is noteworthy that a second randomized trial- the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO)- did not demonstrate a survival difference between the screening and control arms.²⁶ There are many underlying reasons to explain these divergent results. In contrast to the European population, PSA screening had already become common in the United States at the time PLCO was initiated. As such, much of the “prevalent pool” of prostate cancer had already been diagnosed with prostate cancer. Beyond this issue of “prescreening,” contamination of the control arm was a much greater issue in the PLCO. Because more than 50% of controls underwent screening during the study period, Cooperberg and Carroll suggested that it be more aptly considered a trial of more versus less screening.²⁷ In addition, compliance with prompt prostate biopsy was poor among those

with abnormal screening results.²⁸ Clearly, greater similarity in the screening practices between the two arms of the trial would reduce the mortality risk difference between groups.

A final issue related to prostate cancer screening is the possibility for the diagnosis and treatment of some tumors that would not cause harm. This can be reduced through the use of more judicious screening practices (ex: performing baseline PSA measurements in the 40s for risk stratification, use of PSA velocity, discontinuing screening for elderly men with limited life expectancy), by reserving definitive treatment for patients who are most likely to benefit, and by further reducing treatment-related morbidity.

Conclusion

PSA is a valid marker for prostate cancer, reflecting the spectrum of future and current risk. PSA and its derivatives are also valid markers for prostate cancer tumor features and treatment outcomes. Finally, PSA screening has been shown in a randomized trial to reduce both metastatic disease and prostate cancer-specific mortality.

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