Optimal use of prostate specific antigen for prostate cancer screening

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Introduction

Prostate cancer (PCa) and prostate specific antigen (PSA) screening have been the main focus of discussions among urologists and primary care physicians during the last few years. Ever since its introduction in the 1980s, PSA screening was implemented as standard of care in many developed countries, but without the supporting level I evidence to justify its initiation (mainly relating to reduction in cancer-specific mortality). Several retrospective reports, such as the Surveillance, Epidemiology, and End Results (SEER) database review suggested a significant decline in mortality rates of 32.5% from PCa due to screening; the Baltimore Longitudinal Study of Aging (BLSA) showed that PSA levels increased years before clinically detectable PCa and that this could lead to an effective early diagnosis and more effective therapy. Similar findings were observed in the study from Tyrol, Austria, where men from this particular region had a notable decrease in mortality after being screened with PSA in comparison to the rest of the country where PSA testing was not freely available. However, in 2009 two large, randomized, prospective studies attempted to answer this decade-long question: The Prostate, Lung, Colorectal and Ovarian Cancer screening trial (PLCO) from the United States which showed no benefit to screening and the European Randomized Trial of Screening for Prostate Cancer (ERSPC) which reported a 20% reduction in mortality from PCa, but at the expense of 1,410 men having to undergo screening and additional 48 men to undergo treatment in order to save 1 life. The rationale for screening after inconsistent results from these two large, randomized trials coupled with the inherent PCa treatment complications (including urinary, sexual, and bowel dysfunction) created a conflicting and confusing environment for the world-wide treating physicians and their patients. While many questions still remain unanswered, PSA (although an imperfect test) continues to be the only tool we currently have available to identify patients at higher risk of dying from PCa.

Adaption of new risk stratification strategies may be the solution to minimize patient harms and offset the risk/benefit ratio. In this report we provide evidence in support of early and targeted screening, earlier termination of screening, and prolongation of the screening interval to every 2–4 years.

Early “targeted” screening

Based on the observational data from Sweden, PSA screening when performed earlier in patient’s life seems to provide strong prognostic risks relating to future development of clinically important PCa. Lilja et al. reported that a single PSA test obtained in the middle-aged men (ages 45–50) had a highly predictive risk of developing subsequent PCa. Specifically, they found that men with total PSA ≥ 0.5...
ng/mL had a cumulative low (10.5%) risk of developing clinically meaningful cancer by age of 75, those with PSA between 0.51 ng/mL and 1.0 ng/mL had a 2.5-fold increased risk, and men with PSA between 2.0–3.0 ng/mL were associated with a 19-fold increased risk of developing cancer. Similarly, Vickers et al. reported that men with PSA ≤ 1.0 ng/mL at age 60 were highly unlikely to possess or develop life threatening PCa by age 85, and even lower risk (0.2%) of dying from disease.

These data are further supported by the findings observed by Stamey et al. regarding correlation between PSA level at radical prostatectomy and final pathology. After a careful evaluation of almost 1,300 specimens, they documented a strong association between the increasing PSA levels and prostate weight, or benign prostate hyperplasia (BPH), but not PCa. These observations imply that as men age and their prostates increase in size (mostly due to BPH), the PSA tends to lose its specificity for diagnosing PCa. As a result, in the current PSA era the main “driver” for PSA rise in older men seems to be mostly related to the amount of BPH. Therefore, “targeted” screening with focus on younger population where BPH represents a minimal confounder should improve the usefulness of PSA testing.

Based on these findings, early PSA elevation could identify a cohort of men who would benefit from early screening and/or preventive measures (pharmacological or lifestyle alterations). Similarly, in those men without early PSA elevation screening could be potentially deferred until age 50 and obtained less frequently. In cases with early PSA elevation, patients should only undergo biopsy if recognized indications for biopsy are present, such as PSA > 1.0 ng/mL, PSA velocity (v) > 0.75 ng/mL/year, free: total PSA < 10%, and those with strong family history of early PCa.

**Early “termination” of screening**

There is strong evidence from previous reports that screening men for PCa in the PSA era should be stopped earlier than current guidelines would suggest. According to a population-based study from the pre-PSA era by Albertsen et al., a significant number of PCa identified today in the population where BPH represents a minimal confounder should be considered only in highly select cases – those who are healthy and have a life expectancy of greater than 10–15 years.

**Risk stratification for prolonged screening interval**

The ERSPC study, which clearly showed a reduction in PCa-specific mortality due to screening, was based on a 2–4 year PSA screening interval. However, further analyses of the study seemed to support a potential for even further risk stratification and prolongation of screening time interval. For example, Roobol et al. evaluated a group of men with initially low PSA (< 1ng/mL) who underwent every 4–8 years screening interval and found only 0.23% risk of cancer diagnosis during the intervening visit. Another study showed a 0.5% risk of advanced disease and overall 2.5% risk of prostate cancer at 15 years follow-up. On the other hand, van Leeuwen et al. compared men from Gothenburg screening cohort (2-year screening interval) to Rotterdam cohort (4-year screening interval) and found that more frequent screening resulted in a higher proportion of screen-detected cancers (RR:1.18, p = 0.009). However, more frequent screening also led to increased incidence of clinically insignificant (low-risk) PCa (RR: 1.46, p < 0.001). Interestingly, the Gothenburg cohort also had a lower incidence of advanced cancer during the last follow-up (RR: 0.57, p = 0.048), which implied that more frequent screening resulted into more effective way of eliminating high-risk PCa from the population. Importantly, the effect on PCa-related mortality remained uncertain. This study implies that there is a certain population of men that may benefit from a more frequent screening program, but an individualized approach according to patient risks would be the most optimal way of screening. Currently, there is no data that supports annual PSA screening for PCa – the best evidence is based on screening every 4 years.

**Conclusion**

According to recent studies, PSA results obtained during an earlier age may be strongly predictive of long-term risk of clinically important PCa, and as a result a risk-stratification approach should be considered in order to minimize over-diagnosis and overtreatment of this disease. The focus of screening should become on tumors with greater malignant potential in the appropriate age population, instead of clinically insignificant tumors. Such an approach could also reduce associated economic burden of treating PCa in the present health-care system. Until new genomic-based markers are identified, PSA testing will continue to play an important role in identifying patients with high-risk PCa and should not be abandoned.
REFERENCES


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