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Screening Asymptomatic Men for Prostate Cancer Using Prostate-Specific Antigen as An Early Detection Tool: A Review of Existing Literature

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ABSTRACT

Prostate cancer remains the most common non-skin cancer in men. Prostate-specific antigen (PSA) is recognized as a biomarker for the diagnosis, monitoring, and risk prediction of prostate cancer. However, its role in prostate cancer screening has been controversial. While some authorities have recommended its use for screening, others have stated otherwise. Some clarity is required about its precise role in clinical practice. There need to be more consistent recommendations surrounding using PSA screening in clinical practice. Serum PSA measurements show variable reliability when screening for Prostate cancer, given the dynamics of PSA physiology and the conflicting results from two large, randomized control trials that sought to determine its role in prostate cancer screening and early detection. Hence surrogate measures like PSA density, PSA velocity, free-to-complexed PSA ratio, and percentage Pro-PSA among others, have been used to improve the predictive utility of this assay for Prostate cancer diagnosis. However, the debate on screening still lingers. The current review aims to highlight the controversies and objectively outline the current recommendations. This literature review examined scholarly papers and recommendations about the use of PSA for prostate cancer screening with the aim to rationalize the pros and cons of such approaches. We concluded that although more recent guidelines from the USPSTF recommend that screening be based on individual preference and professional judgment by the healthcare provider, differences in the specific details on how to best employ a PSA screening program still exist and require further review.

Keywords: prostate cancer; prostate-specific antigen (PSA); screening asymptomatic men

INTRODUCTION

Prostate cancer (PCa) is the most prevalent cancer in males in Western countries. In the United States, it is the most common male cancer and the second leading cause of male cancer deaths. Several factors have been found to increase the risk of prostate cancer, including age, race/ethnicity, and family history. Of these risk factors, age is the most critical risk factor, as over 99% of cases occur in males over 50 [1]. Family history and race/ethnicity are the following most significant risk factors. In the US, it is more common in African American men than in Whites. Consistent with the evidence that race/ethnicity is a significant risk factor, recent findings show that prostate cancer has a significant heritable component, as having a first-degree relative with the disease increases the risk by two to threefold. Specific germline mutations have been implicated, with BRCA1/2 being the most significant. Individuals at risk for hereditary prostate cancer have been shown to have earlier onset and a more aggressive course [2]. Other risk factors include a diet high in processed meat, red meat, or milk products or low in certain vegetables. Early PCa is asymptomatic, with lower urinary tract symptoms, hematuria, pelvic pain, and bony pain representing advanced disease. Accordingly, many men diagnosed with PCa never know they have the disease unless they are tested. The rising incidence of PCa has made it a significant health issue [3].

Most prostate cancers are slowly growing; however, some grow relatively quickly. The age-adjusted incidence rate has increased steadily since 1975, with particular dramatic increases associated with the inception of widespread use of prostate-specific antigen (PSA) screening in the late 1980s and early 1990s following the approval of PSA as a screening test by the US Food and Drug Administration (FDA) in 1986, followed by a fall in incidence [4]. A decline in the early-stage prostate cancer incidence rates from 2011 to 2012 (19%) in men aged 50 years and older persisted through 2013 (6%). Between 2013 and 2015, mortality rates stabilized. It has been suggested that the decline in mortality rates in certain jurisdictions reflects PSA's benefits. Nevertheless, others have noted that these observations may be explained by independent phenomena such as improved treatments.

Prostate-specific antigen (PSA) is recognized as a biomarker for the diagnosis, monitoring, and risk prediction of PCa [5-7]. PSA remains the most used biomarker in the detection of early PCa. PSA, also known as gamma-seminoprotein or Kallikrein-3 (KLK3), is a glycoprotein secreted by epithelial cells of the prostate gland. It is in small quantities in the serum of men with healthy prostates (0-4ug/l). Its elevation (>4ug/l) has been widely used as a screening modality for prostate cancer. However, approximately 1.5 million US men aged 40 to 69 have a PSA level greater than 4.0ug/l [8]. It is, therefore, not a unique indicator of prostate cancer, as elevated values may also be detected in other prostate disorders such as prostatitis, benign prostatic hyperplasia, and even from prostate massage during a digital rectal examination [9].

Screening is characterized as the systematic examination of asymptomatic men (at risk) and is initiated by health authorities to reduce mortality and maintain quality of life [10]. The use of PSA as a screening tool for prostate cancer has, however, been associated with controversies due to uncertainties as to whether the benefits of screening ultimately outweigh the risks of overdiagnosis and overtreatment, keeping in mind that a significant modality of management of the early-stage disease is watchful waiting and that overtreatment has complications that may worsen the state of the patient, increase morbidity and potentially result in patient's mortality rather than the disease itself. This has generated controversies among professionals (i.e., primary care providers and urologists), leading to some strongly recommending against PSA testing and some strongly advising in favor of the testing. This paper, therefore, reviews current and previous literature on the harms and benefits of using PSA as a screening tool for early detection of prostate cancer in asymptomatic men, looking at evidence and documentation favoring current guidelines.

DISCUSSION

Prostate cancer screening is an effort to find unsuspected cancers in those without symptoms. Options include the digital rectal examination (DRE) and the prostate-specific antigen (PSA) blood test. PSA blood test has remained a cheap, non-invasive, and widely used test in screening for prostate cancer over the years. It has helped in the early detection of numerous cases of prostate cancer. However, its use in prostate cancer detection has been controversial, especially regarding its role in improving outcomes. For many, it has led to unnecessary disruption and possibly harmful consequences. Harms of population-based screening, primarily due to over-diagnosis (the detection of latent cancers which would have gone symptomless and undiscovered), may outweigh the benefits.

For this reason, different authorities have developed guidelines for screening patients at different age ranges using PSA. United States Preventive Services Task Force (USPSTF) has suggested the decision-making between the patient and the physician for patients 55-69 years of age. They also have recommended against screening for asymptomatic males aged 70 or older [11]. The center for disease control and prevention (CDC) shared USPSTF's prior conclusion. The American Society of Clinical Oncology and the American College of Physicians discourage screening for those who are expected to live less than ten to fifteen years. In those with a greater life expectancy, a decision should be made by the person in question based on the potential risks and benefits. They concluded that "it is uncertain whether the benefits associated with PSA testing for prostate cancer screening are worth the harms associated with screening and subsequent unnecessary treatment."

What are the potential benefits of PSA screening?

Early detection of PCa through screening may allow for early disease stratification, prognosis, and treatment prior to disease progression. In a study conducted in Austria, freely available PSA testing in men aged 45-75 years conferred a notable shift to lower stages of PCa, as seen in one of the most extensive trials in this field to date [12]. Similarly, data from the European Randomized Study of Screening for PCa (ERSPC) Rotterdam section [13] revealed a statistically significant transition to improved histological grades and clinical stages on biopsy in the screening arm compared with the control arm. This evidence suggests that PSA screening strategies result in an earlier diagnosis of PCa. The earlier diagnosis and treatment of PCa may provide men with an oncological benefit. The ERSPC study spanning follow-up over 13 years demonstrated a significant 21% relative PCa mortality reduction in favor of screening, and the relative risk reduction in men screened was 27% after adjustment for selection effects [14]. Indeed, the benefit of early treatment for localized PCa was identified by the Scandinavian Prostate Cancer Group Trial 4 (SPCG-4).

The SPCG-4 trial, which followed up 700 men, showed that, at 15 years, the absolute risk reduction of dying from PCa was 6.1% following randomization to radical prostatectomy compared with watchful waiting [15]. These findings were maintained at extended follow-up [16]. These findings conflict with those of the Prostate Intervention Versus Observation Trial (PIVOT), which did not identify any statistically significant difference between the intervention and observation cohorts. However, subgroup analysis reduced all-cause mortality in men with PSA >10 ng/mL after radical prostatectomy [17]. Roehl et al. also demonstrated improved survival rates [18]; 7-year progression-free survival rates post-radical prostatectomy was higher in patients who underwent screening than physician-referred patients ($P < 0.002$). These benefits do not account for the psychological benefits of a normal PSA test, especially for those with a family history of PCa. Importantly and often not mentioned are the benefits of PSA screening in reducing presentations of men with metastatic disease by around 70% [19].

Is there harm in Prostate cancer screening other than overtreatment?

There is convincing evidence that PSA-based screening leads to substantial overdiagnosis of prostate tumors. Overdiagnosis occurs in men in whom PCa would not have been detected in their lifetime had it not been for screening, culminating in potentially unnecessary morbidity associated with invasive investigations, therapies, and the mental implications of the cancer diagnosis [20]. One study estimated that the mean lead time ranged from 5.4 to 6.9 years, and overdiagnosis ranged from 23% to 42% of all screening-detected cancers [21]. The findings from the Goteborg screening study similarly highlighted considerable overdiagnosis in PCa following organized screening compared to opportunistic PSA testing. This study concluded that opportunistic screening had minimal effect on the relative risk reduction in PCa mortality.

Furthermore, this group estimated that almost twice the number of men needed to be diagnosed to save one man from dying from PCa compared to men offered an organized 2-yearly PSA screening [22]. Katz DA, [23] did a cross-sectional study using men at university-affiliated primary care practices in Wisconsin, Iowa, and Indiana; 97% white, mostly college-educated, had PSA done two months prior to the study. It was an outcome study using the Short Form-36 Health Survey (SF-36) and State Anxiety Index (SAI-6). Questions about prostate cancer–related worry (using a 5-point scale), perception of cancer risk, and sexual function were asked. They had observed that although abnormal screening results did not affect summary measures of anxiety or health-related quality of life, men with false-positive PSA screening test results were more likely to worry specifically about prostate cancer, have a higher perceived risk for prostate cancer, and report problems with sexual function compared with control participants for up to 1 year after the test. In a prospective study by McNaughton-Collins and colleagues [24], whose participants were men aged 40 years at primary care practices of 3 Boston teaching hospitals, 88% were white and mostly college educated. McNaughton-Collins and colleagues compared 167 men with an abnormal screening result but a benign biopsy specimen with 233 men with a normal PSA level (defined as 2.5 g/L). After six weeks, 49% of men in the biopsy group reported thinking about prostate cancer "a lot" or "some of the time," compared with 18% of the control group. In addition, 40% of the biopsy group worried "a lot" or "some of the time" about developing prostate cancer compared with 8% of the control group. A total of 26% of men experienced moderate-to-severe pain from the biopsy.

For 25% of men, the most recent benign biopsy was their third biopsy or more. Statistically significant differences between the biopsy and control groups in anxiety related to prostate cancer and perceived prostate cancer risk persisted six months and one year later. After one year, more men in the biopsy group than in the control group had at least one additional PSA test (73% vs. 42%) and another biopsy (15% vs. 1%). Brindle and colleagues [25] administered standardized assessments of anxiety, depression, and mental health to 7344 men who received PSA testing. Of the 855 men with a PSA level greater than an age-specific or numerical threshold, 770 returned for a biopsy and then retook the questionnaires before receiving their biopsy results. Assessment scores did not change in patients with an elevated PSA level.

Because some elevated PSA levels were true positive, this study could not specifically assess the psychological effect of a false-positive PSA result. It was not clear whether the measures used were sensitive enough to detect changes in mental health related to anxiety specific to prostate cancer. In 2011 the United States Preventive Services Task Force (USPSTF) strongly advised against PSA screening based on a review of six well-done trials, underlying harms related to subsequent evaluation and treatments [26]. Nevertheless, several studies showed evidence that screening reduces the risk of metastasis at diagnosis and during follow-up [27-28]. Furthermore, [29] Gulati et al., suggested that discontinuing PSA screening for all men may generate many avoidable cancer deaths in the following years. On the other hand, [30] (Stephan C 2014) remarked on methodological limitations in the meta-analysis showing no evidence of a PCa-specific mortality reduction, suggesting the value of multivariable risk-prediction tools to select appropriate treatment or active surveillance. Additionally, in a recent review, Carlsson and Roobol (2016) [31] underlined data emerging in recent years that suggest a new approach to PCa screening according to PSA-based risk stratification at an early age. Similarly, [32] Eapen et al., postulated in favor of a more innovative screening approach based on relatively infrequent PSA testing, consistent use of multivariable risk stratification, and selective treatment focused on patients with high-grade PCa.

Findings from the ERSPC trial [33] Roobol MJ, showed that screening increased PCa incidence by ~80% through the effect of overdiagnosis. In addition to this, the risk of undergoing radical prostatectomy or radiation therapy was more than twice as high in the screened group than in the control group. Approximately 3% of men screened are diagnosed with aggressive PCa, [34]; given that the median age of PCa death is 80 years, often other causes of mortality ensue at this time regardless of the PCa detected [35].

Furthermore, the benefits of screening were affected by large-scale USA data suggesting that PCa screening provided no reduction in mortality during the first seven years of the trial, with similar results after ten years [36]. This trial was criticized as the control arm was contaminated with many patients having PSA testing (so comparing screened with partially screened unlikely to show a difference) and has been roundly condemned for being given the same weight as the ERSPC-a better-conducted trial lacking contamination.

Highlighting overdiagnosis, the newer practice of active surveillance for low-volume Gleason (3 + 3 = 6) in appropriate patients, has helped reduce the implications of overdiagnosis [37]. In addition, issues surrounding PSA levels are widely recognized.

They include other possible influences on PSA levels, which include prostatitis, urinary tract infection, history of transurethral resection, benign prostatic hyperplasia, and recent prostate biopsy. However, the degree to which these conditions affect PSA levels remains unclear [38]. It is, therefore, pertinent for the clinician and patient to discuss the clinical relevance of PSA levels in the context of the patient's clinical picture. Furthermore, variation among PSA measurements between laboratories has been identified as a limitation to its accuracy as a screening tool. However, efforts to achieve international standardization of PSA assays exist.

What is the natural history of PSA-detected, localized prostate cancer?

As part of studies on the natural history of PSA-detected localized prostate cancer, Hardie and colleagues [39] tested the feasibility of a surveillance protocol in 80 men (median age, 70.5 years) with localized prostate cancer (stage T1 to T2) who were referred to a single tertiary care center in the United Kingdom from 1993 to 2002. Delayed treatment was recommended based on serial PSA-level testing and life expectancy assessments. After a median of 42 months of follow-up, 64 men remained on surveillance, 11 had received delayed treatment, and five had died of causes other than prostate cancer. This study was limited by the self-selected nature of participants (representing only 10% of eligible patients during the study enrolment period) and the absence of a standardized PSA-based threshold (absolute value or rate of increase) for initiating treatment. Roemeling and colleagues [40] studied 64 men (mean age, 68.4 years) who chose watchful waiting and were part of a larger cohort of 293 men with stage T1c or T2 prostate cancer who met favorable risk criteria.

After a mean follow-up of 82.4 months (range 23.8 to 119.9 months), 37 men were living and untreated, 19 had chosen treatment, and eight had died of causes other than prostate cancer. There were no deaths from prostate cancer. The same authors examined health outcomes in 278 men (median age, 69.8 years) who chose an active surveillance protocol [41] (Roemeling S R. M., 2007). After a median follow-up of 3.4 years (range, 1.2 to 6 years), 170 men remained on surveillance, 26 had died of causes other than prostate cancer, and 82 had chosen treatment. There were also no deaths from prostate cancer itself. Both studies by Roemeling and colleagues were limited by having highly self-selected patient populations and high dropout rates.

Does screening for prostate cancer decrease morbidity and mortality?

Two mathematical modeling teams of the US national cancer Institute's Cancer intervention and surveillance modeling Network independently projected disease mortality in the absence and presence of PSA screening. Both teams relied on surveillance, epidemiology, and end-result registry data for disease incidence. The idea was to quantify the plausible contribution of PSA screening to the decline in the US prostate cancer mortality rate observed in the 1990s. The team projected similar mortality increases in the absence of screening and decreases in the presence of screening after 1895. By 2000, the model projected that 45% (Fred Hutchinson Cancer Research Centre) to 70% (University of Michigan) of the observed decline in prostate cancer mortality could be plausibly attributed to the stage shift induced by screening. They concluded that PSA screening may account for much, but not all, of the observed drop in prostate cancer mortality [42]. Labrie and colleagues [43] studied forty-six thousand four hundred and eighty-six (46,486) men aged 45-80 years registered in the electoral roll of the Quebec City area, randomizing them in 1988 between screening and no screening.

The screening included measurement of serum PSA using 3.0 ng/ml as an upper limit of normal and digital rectal examination (DRE) at the first visit. At follow-up visits, serum PSA only was used. Seventy-four (74) deaths from prostate cancer occurred in the 14,231 unscreened controls, while ten deaths were observed in the screened group of 7,348 men during the first 11 years following randomization. The Median follow-up of screened men was 7.93 years. A proportional hazard model of the age at death from prostate cancer shows a 62% reduction of cause-specific mortality in the screened men suggesting a continuous decrease in prostate cancer mortality observed in North America. However, on reanalysis of the data provided by Labrie et al., USPSTF in 2002 found no mortality benefits from screening.

Another study by Sandblom and colleagues [44] compared total mortality and prostate cancer-specific mortality in 1494 men who received DRE and PSA screening with those in 7532 control participants. They found no statistical difference in total or prostate cancer-specific mortality between the two groups [44].

The prostate, lung, colorectal, and ovarian cancer screening (PLCO) trial was designed to determine the effect of annual PSA testing and DRE on mortality from prostate cancer. The screening group was offered annual PSA testing for six years and DRE for four years. A follow-up report in 2009 (after 7-10 years of follow-up screening) demonstrated no reduction in prostate cancer mortality [45]. The author, however, gave several explanations as to why there was no significant change in the result obtained. One such was that having a short follow-up of roughly ten years was inadequate for a generally slowly growing cancer [46].

These reviews, as does many of the other pieces of literature on the risk-benefit assessment of prostate cancer screening using PSA, were thought to have been flawed with limitations such as selection bias, small sample size not sufficient for a generalizable conclusion, patients not being followed up long enough to determine the outcome. Overall, while some demonstrated evidence that supports that PSA screening reduced mortality to some extent, others demonstrated the harms involving screening for prostate cancer in asymptomatic patients with PSA. This has made the idea of whether the benefits outweigh the risk inconclusive, as there needs to be more evidence to surmount the opposing evidence.

The evidence clearly stating that PSA testing successfully reduces prostate cancer mortality is still lacking. The harms of screening-induced over-diagnosis and over-treatment being justified by the benefits of reduced prostate cancer mortality are open to debate. Therefore, the degree of benefit and harm of PSA screening remains a topic continuously being discussed among the public and medical community. However, PSA screening saves lives and reduces the burden of metastatic disease [47-53].

CONCLUSION

To conclude, diverging results of these large clinical trials have resulted in varying guidelines and recommendations by authorities for PSA screening for PCa. The primary goal of PCa screening is to reduce PCa-specific mortality with little or no harm to the individual. The issue of overdiagnosis and subsequent overtreatment is acknowledged, and these discussions are still ongoing.

Since the inception of prostate cancer screening using PSA, the incidence of prostate cancer has increased. It has, however, had both beneficial and non-beneficial effects.

While it has helped to reduce morbidity and mortality associated with the disease to some extent, it has also led to overdiagnosis and overtreatment. Other less beneficial effects include increased anxiety, potential adverse health effects associated with false positive and negative results, higher perceived risk of prostate cancer, increased chance of repeated PSA, and biopsies with its antecedent complications. These have made the debate about its efficacy a recurring dilemma among professionals. However, the PSA test remains the only biomarker for detecting and monitoring prostate cancer (despite its lack of sensitivity and specificity).

Over time the opinion on PSA-based screening has shifted towards the notion of informed choice as current evidence cannot thoroughly substantiate that the benefits outweigh the risks following the screening. Recently, it has been considered unethical to screen men without them being aware of the pros and cons of PSA testing. The current recommendation for men and their health professionals is that men who have a life expectancy of < 7 years should be informed that screening for PCa is not beneficial and has harm because many of the benefits from screening may take > 10 years to ensue. In keeping with this, the new guidelines state that because any mortality benefit from early diagnosis of PCa from PSA testing is not seen within < 6 years from testing, PSA testing is not recommended for men who are unlikely to live another seven years.

Conversely, men with favorable prognoses may be considered for surveillance screening protocols following adequate counseling. The PSA velocity (PSAV) risk count is of further relevance, defined as the number of serial PSAV measurements exceeding 0.4 ng/mL/yr. PSAV can significantly improve overall PCa and high-grade disease screening performance by reducing unnecessary biopsies and PCa overdiagnosis compared with PSA alone. Also, for individuals at increased risk for hereditary prostate cancer, National Comprehensive Cancer Network (NCCN) has recently expanded its guidelines to include a more aggressive screening and treatment approach for them, considering that these individuals are at risk of earlier onset disease with a more aggressive course (NCCN 2020). Lowering the PSA threshold from 4.0 ng/mL to 3.0 ng/mL has been advocated in previous years. Most recently, the NHMRC decided on a lower 3.0 ng/mL threshold. However, the high false-negative rate associated with this cutoff has real implications at a population level.

Hence, it is more appropriate to refer to age-adjusted and median levels provided on PSA tests to guide the most appropriate range for any patient. The necessity for a more flexible approach to threshold values has become apparent and is reflected in the various guidelines. The recent guidelines offer a sensible pathway for testing to the public and their GPs. As a screening tool, PSA should consider the age at which screening starts and use different thresholds and screening intervals to ensure that the lag time to diagnosis and over-testing" are both minimized.

CONFLICTS OF INTEREST

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