Section: Urology

Systematic Review

EXPLORING PROSTATE SPECIFIC ANTIGEN AS A PREDICTOR OF HIGH-RISK PROSTATE CANCER: A SYSTEMATIC REVIEW

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Abstract

Background: Prostate-specific antigen (PSA) testing is widely used to detect prostate cancer. The use of PSA in asymptomatic patient screening has received considerable attention in cancer detection. The objective is to demonstrate the effectiveness of serum prostate-specific antigen (PSA) measurements in the diagnosis of prostate cancer in men. **Materials and Methods:** A systematic database search was conducted using PUBMED and Google Scholar databases. Studies reporting the diagnostic accuracy of PSA for prostate cancer in patients were included. The article's evaluation and data extraction were conducted according to PRISMA guidelines. The overall quality of evidence for each outcome was assessed using the GRADE methodology. **Result:** The literature search yielded 985 articles from the designated online databases for this study. After eliminating duplicate articles from the automation tools and for other reasons, such as improper citations and articles in other languages, 117 records were considered. After reviewing the titles and abstracts of these 62 articles, 12 were excluded because they were irrelevant. After a more detailed eligibility assessment, 10 articles were considered for qualitative and quantitative synthesis. These studies revealed a strong association between prostate-specific antigens and prostate cancer. **Conclusion:** Currently, the available evidence suggests that PSA is highly sensitive for prostate cancer detection. However, there is limited evidence regarding the performance of PSA in primary care.

INTRODUCTION

Globally, prostate cancer is the second most common cancer among men, followed by lung cancer. The primary risk factor for prostate cancer is age, with an average age of 66 years at the time of diagnosis, prostate cancer incidence and mortality are globally correlated with advancing age.[1] The primary risk factor for prostate cancer is age. According to IHME estimates, smoking is a contributing factor to 6% of all prostate deaths. Mutations in the BRCA1 and BRCA2 genes are linked to 1.5% to 3.5% of all prostate tumours.[2] Based on epidemiology, there are two types of prostate cancer: inherited and sporadic. While some families have identified genes that may be inherited in susceptibility to prostate cancer, such as CHEK2, RNASEL, MSR1, NSB1, and ELAC2, the percentage of cases of hereditary prostate cancer linked to germline mutations in these loci is small. Prostate cancer, which frequently occurs, has also been associated with mutations in these genes. Variations in alleles of the vitamin D receptor (VDR) gene lead to variations in VDR activity.

Prostate cancer and VDR alleles have an obvious correlation.[3] Early detection of prostate cancer (PCa) is aimed at minimising morbidity and mortality. Since the introduction of prostate-specific antigen (PSA) testing, the death rate from PCa has steadily decreased.[4] Unlike biomarkers found in solid tissues, circulating biomarkers comprise a wide range of substances found in the blood or urine. They act as prognostic and diagnostic tools and help to determine the most effective medications. These components include elements that are frequently measured in clinical peripheral blood analyses, such as electrolytes; proteins, such as albumin, alkaline phosphatase (ALP), and prostate cancer-specific antigen (PSA); and components of blood cells.[5] The microscopic assessment of prostate tissue obtained by needle biopsy is the basis for the diagnosis of prostate cancer. Traditionally, transrectal ultrasonography is used to perform a systematic prostate biopsy and obtain 10–12 tissue samples in a grid-like pattern.[6]

PSA testing in combination with a digital rectal exam (DRE) has been approved by the US FDA for the screening of prostate cancer. The upper limit of normal for PSA was 4 ng/ml. PSA is not specific to cancer, and conditions such as prostatitis, benign prostatic hyperplasia (BPH), prostate biopsies, and

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surgeries that damage the basal membrane epithelial cells of the prostate frequently cause hormone levels to increase in the bloodstream. Another test, the Prostate Health Index (PHI), was approved by the US FDA in 2012. It is based on three biomarkers and is calculated for each patient as [-2] proPSA/fPSA × PSA1/2. Compared to PSA and fPSA, this test improves the accuracy of established prostate cancer predictors at biopsy by determining whether a biopsy is necessary in cases where total PSA levels are between 4 and 10 ng/ml. This reduced the number of unnecessary biopsies.

PCA3, also known as DD3, is an antigen specific to prostate cancer that is encoded by a gene located on chromosome 9q21–22. Normal prostate tissue does not contain PCA3, prostate hyperplastic tissues have low expression levels of PCA3, and prostate cancer tissues have high expression levels of PCA3. PCA3 RNA is highly expressed in more than 95% of primary and metastatic cases of prostate cancer, making it a useful biomarker owing to its restricted expression profile.[7] This systematic review focuses on the efficiency of prostate-specific antigens in detecting prostate cancer.

MATERIALS AND METHODS

This systematic literature review and meta-analysis investigated the efficacy of prostate-specific antigens as a predictor of high-risk prostate cancer.

Adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, we followed the PRISMA 2009 guidelines for systematic literature review, data reporting, and discussion. The article's evaluation and data extraction were conducted according to the established guidelines.

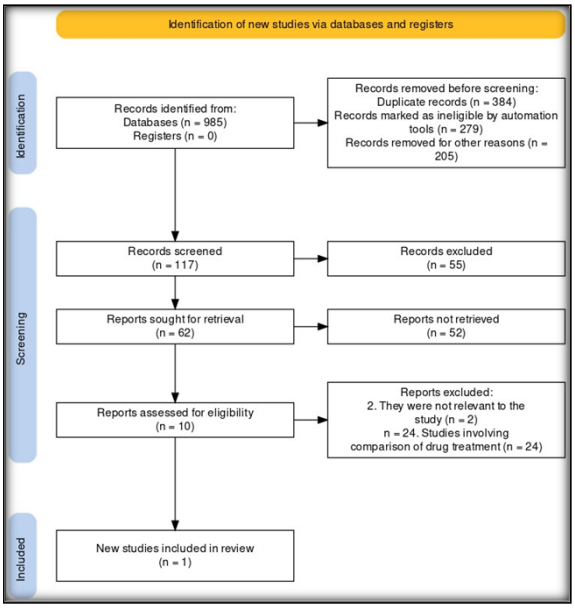
The overall quality of evidence for each outcome was assessed using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) methodology.

Search strategy: A systematic literature review was performed using PubMed (MedLine database). The search methodology was aligned with the PICOS strategy, integrating Medical Subject Headings (MeSH) as search terms whenever feasible. Filters were applied to include studies with designs such as randomised controlled trials (RCTs) and observational studies as well as articles encompassing systematic reviews and meta-analyses. The selected studies were limited to those conducted between 2014 and February, 2024. No additional filters were used and the search terms used in the literature review are outlined below.

We systematically searched two online databases, PubMed and Google Scholar, to identify all reviews and meta-analyses involving prostate cancer and prostate cancer-specific antigens to identify those with prostate cancer and prostate-specific antigens, both in the title.

Data extraction: The assessment of search results relied on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

Participants, interventions, comparators, and outcomes (PICO) criteria were used to determine the eligibility of articles for inclusion in the meta-analysis. Individuals who met the study enrolment criteria were included. Articles that met the following criteria were included: prostate cancer [MeSH Terms]) and prostate-specific antigen [MeSH Terms]).



PRISMA flow diagram

Study selection: The eligibility of all abstracts was assessed, and articles were incorporated into the qualitative synthesis if they fulfilled the following criteria.

Inclusion Criteria

We included studies that assessed the efficacy of prostate-specific antigens for diagnosing prostate cancer prognosis.

Exclusion Criteria

We excluded studies that lacked relevant outcome measures, had insufficient data, and were not published in English.

Data Analysis: Quantitative data synthesis, when applicable, was carried out using statistical software such as Review Manager and R. A meta-analysis was performed to compare the outcomes between studies. Heterogeneity was evaluated using the I2 statistic, and values exceeding 50% indicated substantial heterogeneity. Random-effect models were used in the presence of heterogeneity. Sensitivity analyses were performed to investigate the potential sources of heterogeneity and evaluate the robustness of the findings.

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RESULTS

The literature search outlined above yielded 985 articles from designated online databases for this study. After eliminating duplicate articles from the automation tools and for other reasons, such as improper citations and articles in other languages, 117 records were considered. After reviewing the titles and abstracts of these 62 articles, 12 were excluded because they were irrelevant. The excluded articles covered various topics, including review articles; studies involving medical conditions unrelated to prostate cancer; studies that did not report relevant outcomes related to the accuracy, comparison, or laboratory-based investigations that lack direct applicability to prostate cancer patients; studies with insufficient data quality, including those with missing or unreliable data necessary for accurate assessment of the efficacy of prostate-specific antigens to diagnose prostate cancer prognosis; and those that did not meet the inclusion criteria. After a more detailed eligibility assessment, 10 articles were considered for qualitative and quantitative synthesis.

Table 1: The outcome of various studies

Name of the author	Study type	Number of patients	Outcome
George Rodrigues et al.,	Cohort study	401	Significant changes in overall survival, distant metastasis, and biochemical failure are associated with abnormally high prostate-specific antigen levels at diagnosis.[8]
J. Hugosson et al.,	Cohort study	9973	Low-grade prostate cancer is detected in its early stages by PSA screening. A tPSA threshold of less than 4 ng/mL can be used to incorporate f/tPSA to increase both sensitivity and specificity.[9]
Fritz H. Schroder et al.,	Randomized control trial	32,270	The chance of developing metastatic prostate cancer is considerably decreased by PSA screening. There was an absolute 3.1 per cent reduction in the risk of metastatic disease per 1000 randomized men (0.31%).[10]
Gunnar Aus et al.,	Randomized control trial	10,000	The chance of developing metastatic prostate cancer was lowered by 48.9% following a ten-year follow-up period. The first step toward lowering the cancer death rate among younger men is PSA screening, which lowers the chance of receiving a diagnosis of metastatic prostate cancer. A 1.8-fold higher chance of being diagnosed with prostate cancer offsets this ostensible benefit.[11]
Idris Olasunmbo Ola et al.,	Randomized control trial	20,268	Rescreening intervals for developing prostate cancer could be as short as 3 years for men whose initial PSA was between 2.99 and 2.99 ng/mL, 6 years for men whose PSA was between 1.99 and 1.99 ng/mL, and 10 years for men whose PSA was less than 1 ng/mL, based on the cumulative incidence of clinically significant PCa (csPCa) rule.[12]
Mutlay Sayan et al.,	Randomized control trial	350	Following a median follow-up of 10.2 years, older age was linked to a lower risk of PSA failure after adjusting for other baseline clinical factors. PSA levels between 10 and 20 ng/mL and a Gleason score of 8 to 10 were associated with predicting the development of prostate cancer.[13]
Andrew J Vickers et al.,	Cohort study	115000	The risk of cancer-specific death and metastasis over the long term is lower at PSA levels below the age median (≤1ng/ml) and rises much more quickly at PSA levels above 1ng/ml than it does for screen- or clinically-detected cancer. More than ten times as many people die from the disease when PSA levels are between 1 and 4 ng/ml, whereas the risk of a positive biopsy rises by only roughly 1.5 times.[14]
Emeka I. Udeh et al.,	Prospective study	254	157 patients had benign prostatic hyperplasia (BPH), and ninety-seven patients had CAP. The serum PSA value of seventy-two patients fell between 4.0 and 10 ng/mL. The prostate-specific antigen density (PSAD) cutoff level of 0.04 (sensitivity 95.68%; specificity 287.7%) was used to identify prostate cancer.[15]
Donna Pauler Ankerst et al.,	Cohort study	1625	In 71.4% of cases, PSA detected cancer earlier. PSA testing ought to be done in conjunction with percent-free PSA to avoid needless biopsies and possibly identify cancer early.[16]
Kyung Tak Oh et al.,	Cohort study	1598	The diagnosis of PCa was thought to be significantly predicted by age and PSA. Among these, PSA is crucial in detecting PCa at an early stage.[17]

DISCUSSION

According to the evidence we collected, PSA screening appears to improve the detection of prostate cancer at any stage, increase the detection of prostate cancer in stages I and II, and marginally lower the detection of prostate cancer in stages III and IV. Simultaneously, it likely slightly lowers the mortality specific to prostate cancer but has no impact on overall mortality.

The process of developing disease biomarkers as clinical diagnostic tools that have been approved by the US Food and Drug Administration (FDA) is often complex, lengthy, and requires extensive validation.

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As a result, the US FDA has only recently approved a small number of prostate cancer biomarkers, including prostate-specific antigen, prostate health index, and prostate cancer antigen.[3,7]

A single PSA test performed before the age of 50 can risk stratifying men based on the likelihood of developing aggressive prostate cancer decades later, according to the American Urological Association's (AUA) guidelines on the detection of prostate cancer.18 A prostate biopsy should only be considered necessary if a PSA and/or suspicious digital rectal examination (DRE) are present, according to guidelines from the European Association of Urology and the National Comprehensive Cancer Network.[19]

The biopsy indication used by Hugosson et al. was tPSA level ≥3.0 ng/mL. Men with cancer at these tPSA levels may be more at risk of disease progression than those with lower tPSA levels, according to the finding that 47% of tumours spread outside the capsule at tPSA levels of 4–10 ng/mL. In one study, men with tPSAs between 3.0 and 4.0 ng/mL had a 15% cancer rate. Thus, tPSAs of 3.0–4.0 ng/mL were found in 36 of 145 (25%) of all men with cancer that was detected, but only five of the 36 (14%) had palpable cancer.[9]

According to Gunner Aus et al., 24 men (20 M1, 4 PSA>100ng/ml; 0.24%) in the screening arm and 47 men (37 M1, 10 PSA>100ng/ml; 0.47%) in the control arm were diagnosed with metastatic prostate cancer (p = 0.0084). For those who were randomly assigned to active screening, this difference indicates a 48.9% decrease in the chance of receiving an advanced prostate cancer diagnosis over 10 years.[11]

When estimating the risk of prostate biopsy-detectable cancer at the age of 60, Andrew J. Vickers et al. examined two distinct PSA-screened population-based cohorts and contrasted them with the risk of long-term metastasis and death from prostate cancer in an unscreened population. Researchers also discovered that men with PSA<1ng/ml, or about 50% of the population, can be informed that any prostate cancer thus discovered is unlikely to harm them and that, should they choose to proceed with treatment, they will probably be overtreating themselves.[14]

From the results obtained, it is evident that PSA can be used as a valid biomarker for detecting the prognosis of prostate cancer, even at earlier stages, which will be very useful in assessing and treating the disease.

CONCLUSION

In conclusion, this systematic review and meta-analysis provides insights into the assessment of the efficacy of prostate-specific antigens in the diagnosis of prostate cancer. This study revealed a strong association between prostate-specific levels and prostate cancer by showing references to various studies conducted at various sites. From the available data, it is evident that PSA levels of more than 4 ng/mL can be used as a definite biomarker for identifying prostate cancer; however, in some studies, even patients with PSA values of 1 ng/mL are likely to develop prostate cancer. This phenomenon should be evaluated accurately to fix standard values and ascertain intermediate and long-term outcomes; however, more research must be conducted in carefully planned and adequately powered trials.

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