Review Article

Prostate-Specific Antigen (PSA) Testing in Prostate Cancer Detection: A Systematic Review of Sensitivity, Specificity, and False Positive Influences

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Abstract

Background: Prostate-Specific Antigen (PSA) testing is a cornerstone in early prostate cancer detection. Despite its high sensitivity, low specificity remains a major clinical concern, often causing overdiagnosis and overtreatment of indolent tumors.

Objective: This systematic review evaluates the diagnostic accuracy of PSA testing, focusing on sensitivity and specificity, and investigates the biological, clinical, and methodological factors underlying its low specificity.

Methods: A comprehensive literature search was conducted across PubMed, Nature, and ScienceDirect for studies published between 2015 and 2025. From 26 screened articles, 12 met inclusion criteria, with six studies addressing diagnostic accuracy and six exploring causes of low specificity. All studies confirmed prostate cancer diagnosis via histopathological biopsy.

Results: PSA testing showed consistently high sensitivity (88.9%–94.5%) but low specificity (14.1%–26.6%) across most populations, except a Nigerian cohort reporting 60% specificity. Key factors contributing to low specificity included benign prostatic hyperplasia (BPH), prostatitis, physiological influences (e.g., ejaculation, infections), lack of cancer-specific PSA isoform detection, and uniform PSA thresholds that overlook individual variability (Kobayashi, 2023). Use of PSA density (PSAD) and population-specific adjustments improved specificity.

Conclusion: While PSA testing effectively detects prostate cancer, its low specificity limits its diagnostic value as a standalone test. Incorporating adjunct tools such as PSAD, age-adjusted cutoffs, and advanced imaging can enhance accuracy and reduce unnecessary interventions. Future research should focus on refining PSA-based models and identifying molecular biomarkers to better distinguish aggressive cancers from benign or indolent conditions.

Keywords: Prostate cancer, PSA testing, diagnostic accuracy, sensitivity, specificity, PSA density, BPH, overdiagnosis, biomarker, prostate biopsy, Cancer.

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Introduction

Prostate cancer is the second most diagnosed cancer and the fifth leading cause of cancer-related deaths among men worldwide, accounting for approximately 1.4 million new cases and over 375,000 deaths annually (Sung, 2021)[5]. Prostate-Specific Antigen (PSA) testing, introduced in the late 1980s, rapidly became the primary biomarker for early detection of prostate cancer and remains widely used in clinical practice due to its accessibility, cost-effectiveness, and ease of implementation (Schroder, 2009)[3].

Despite its widespread adoption, PSA testing has been the subject of considerable debate due to its suboptimal diagnostic specificity. While PSA is highly sensitive—detecting the majority of prostate cancer cases—it lacks specificity, resulting in high false positive rates and contributing to the overdiagnosis and overtreatment of clinically insignificant cancers (Vickers, 2009)[6]. For example, in the European Randomized Study of Screening for Prostate Cancer (ERSPC), PSA screening was associated with a 20% reduction in prostate cancer mortality but led to substantial overdiagnosis, with 50% of screen-detected cancers considered indolent (Schroder, 2014)[4].

Several biological and clinical factors contribute to this low specificity. PSA is not cancer-specific; its levels can be elevated due to benign prostatic hyperplasia (BPH), prostatitis, and other non-malignant conditions (Merriel, 2022)[2]. Furthermore, PSA levels naturally increase with age and may fluctuate due to physical activities, recent ejaculation, or digital rectal examinations (Kobayashi, 2023)[1]. This lack of specificity not only subject's men to unnecessary biopsies but also exposes them to potential harms such as bleeding, infection, anxiety, and the risk of overtreatment of indolent tumors.

The limitations of PSA testing underscore the urgent need for a more nuanced understanding of its diagnostic characteristics. This review aims to systematically evaluate the sensitivity and specificity of PSA in prostate cancer detection across diverse populations and clinical settings, while also exploring the biological, procedural, and technical reasons contributing to its low specificity.

Methodology

This systematic review was designed to evaluate the diagnostic performance of Prostate-Specific Antigen (PSA) testing in prostate cancer detection, with a particular emphasis on the causes of its low specificity.

Search Strategy

We searched PubMed, Science Direct, Scopus, and Google Scholar for studies from 2015 to 2025 using terms related to "PSA," "Prostate Cancer," "Sensitivity," "Specificity," and "PSA Density." Boolean operators (AND, OR) were used to refine the search strategy, ensuring comprehensive coverage of relevant studies. Filters were applied to include only English-language articles involving human subjects. Both original research articles and systematic reviews reporting PSA sensitivity and specificity with biopsy-confirmed prostate cancer were considered.

Three studies were removed because they were duplicates. Another three studies were excluded as they lacked complete data required for analysis. Two studies were excluded for not meeting the required methodological standards, as they did not have clear classifications of blood groups or failed to properly assess the relationship between blood groups and malaria outcomes. Two independent reviewers then assessed the remaining 21 studies for eligibility based on title, abstract, and full-text review. A total of 12 studies met the inclusion criteria and were selected for final analysis.

Inclusion criteria: required that studies: (1) reported PSA sensitivity and/or specificity; (2) used histologically confirmed prostate cancer via biopsy as the reference standard; and (3) involved human subjects across various populations.

Of the 12 selected studies, 6 specifically evaluated the diagnostic accuracy of PSA, reporting sensitivity and specificity values across different thresholds and clinical contexts. The remaining 6 studies were included to explore underlying causes of PSA's low specificity. These studies examined biological and clinical confounders such as benign prostatic hyperplasia (BPH), prostatitis, age-related PSA variation, PSA glycoform profiles, and test

standardization limitations (Gratacós-Mulleras, 2020)[12], (Teoh, 2017)[11,20], (Mabjeesh, 2020)[9]. Study designs included prospective and retrospective cohorts, as well as systematic reviews and meta-analyses, ensuring a comprehensive understanding of PSA's diagnostic strengths and limitations.

Risk of Bias

Most studies had low risk of bias in patient selection and reference standard (biopsy). Some studies had unclear risk in blinding and timing of tests, which may affect reliability. Overall, study quality was acceptable but limited by incomplete reporting.

Data Extraction

Two reviewers independently extracted data on study details, PSA cutoffs, sensitivity, specificity, and biopsy confirmation. Disagreements were resolved by discussion.

Protocol Registration

This systematic review was not registered in any public database such as PROSPERO. Although protocol registration is encouraged to enhance transparency and reduce risk of bias, this review was conducted following rigorous methodological standards to ensure validity and reliability of the findings.

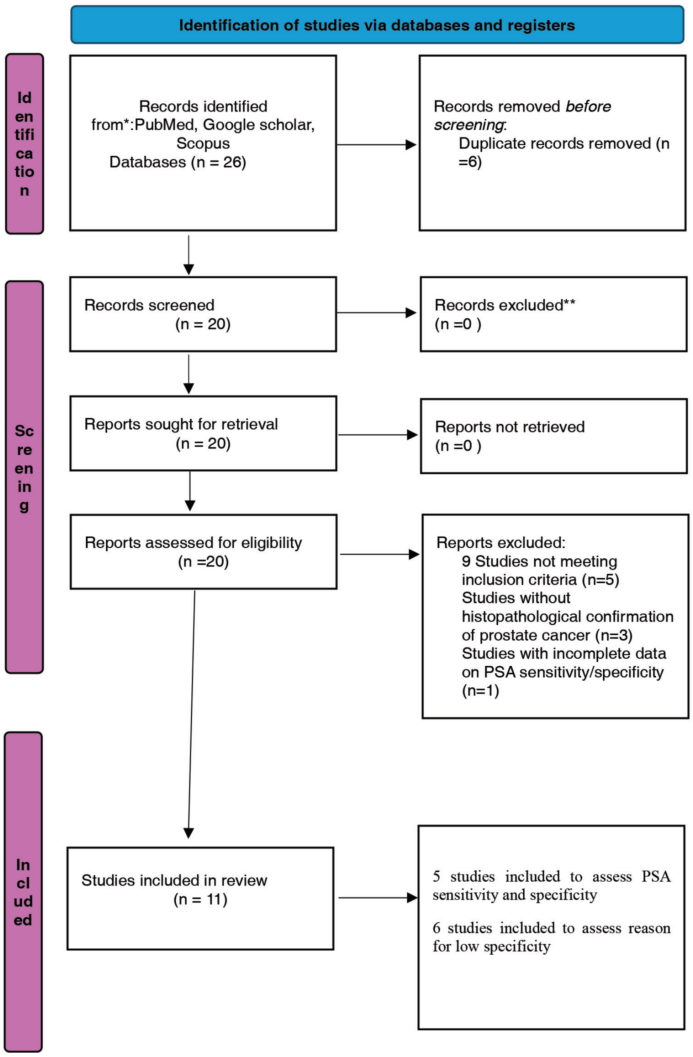

Image 1: PRISMA Flow Diagram for Systematic Review of PSA Testing in Prostate Cancer

Results

This systematic review synthesized evidence from six studies that assessed the diagnostic accuracy of Prostate-Specific Antigen (PSA) in detecting prostate cancer, focusing on sensitivity, specificity, and methodological rigor. The systematic review of Prostate-Specific Antigen (PSA) in detecting prostate cancer highlights its strengths and weaknesses across multiple studies, providing a comprehensive view of its diagnostic accuracy. PSA testing consistently demonstrates high sensitivity, but its specificity remains low, which results in an increased likelihood of false positives. This comparative analysis combines results from various studies to provide a broader perspective on PSA's performance and possible improvements. The included studies spanned various geographical regions and clinical contexts, with populations ranging from large-scale symptomatic cohorts in Europe and North America to targeted studies in Chinese and Nigerian men (Merriel, 2022)[2], (Imasogie, 2023)[7], (Teoh, 2017)[11,20]. All studies used histopathological confirmation via biopsy as the diagnostic gold standard (Jin, 2022)[8], (Schroder, 2014)[4], (Sii, 2024)[11]. As Studies noted allow specificity another 6 articles were access to know the reason of low specificity.

Merriel et al. (2022) conducted a **systematic review and meta-analysis** involving **14,489 symptomatic patients** drawn from 19 individual studies across **Europe and North America**. Participants presented with urinary or prostate-related symptoms. Diagnostic reference was based on prostate biopsy outcomes. The pooled sensitivity was 93%, while specificity was only 20%, emphasizing PSA's ability to detect cancer but also its tendency to trigger false positives. The study employed bivariate mixed-effects models to synthesize diagnostic accuracy metrics (Merriel et al., 2022)[2].

Jin et al. (2022) performed a **meta-analysis** of **11 hospital-based studies**, including both general and referred male patients who underwent PSA screening. The authors investigated the diagnostic value of PSA thresholds below 4 ng/mL, which are often used to detect cancer earlier. Using hierarchical summary ROC (HSROC) modelling, they reported a sensitivity of 92% and specificity of 16%. Their analysis highlighted the trade-off of increased sensitivity for further reduced specificity when applying lower thresholds (Jin et al., 2022)[8].

Teoh et al. (2017) conducted a **retrospective cohort study** in **2,606 Chinese men** undergoing prostate biopsy at a tertiary hospital. The men were asymptomatic or presented for health screening. At a PSA cutoff of 4.5 ng/mL, they found a sensitivity of 94.4% and specificity of 14.1%. The study also assessed **PSA density (PSAD)**, calculated by dividing PSA level by prostate volume, using transrectal ultrasound (TRUS) for measurement (Teoh et al., 2017)[11,20].

A **secondary analysis** by the same authors evaluated the **effectiveness of PSAD** using a cutoff of 0.12 ng/mL/cc in the same cohort. This adjustment improved specificity to 26.6% while preserving a high sensitivity of 94.5%, suggesting PSAD as a practical enhancement to PSA alone for biopsy decision-making (Teoh et al., 2017 – PSAD)[11,20].

Jin et al. (2022) also included a **subset analysis Jin et al. (2022)** also included a subset analysis of PSA values between 2 and 4 ng/mL within their meta-analysis. Even within the 2–4 ng/mL PSA range, sensitivity remains high (92–94%) but specificity stays low (16–17%), indicating limited utility for ruling out prostate cancer and supporting the need for adjunctive diagnostic tools. (jin et al.)[8]

In contrast, **Imasogie et al. (2023)** performed a **prospective observational study** involving **94 Nigerian men aged 50–85 years** who presented with lower urinary tract symptoms at a urology clinic. PSA was measured alongside digital rectal examination (DRE), and suspicious cases were referred for biopsy. They reported a lower sensitivity of 88.9% but a significantly higher specificity of 60%, possibly reflecting differences in genetic profiles, lower rates of benign prostate hyperplasia, or differing baseline PSA distributions in African men (Imasogie et al., 2023)[7].

Teoh et al. conducted a multicenter study of 5,220 Chinese men to assess prostate-specific antigen density (PSAD) for prostate cancer (PCa) detection. PSAD showed moderate diagnostic performance with an AUC of ~0.63 for both PCa and high-grade PCa. Using a cutoff of 0.10 ng/ml², sensitivity was about 89%, detecting most high-grade cases and potentially avoiding 20% of biopsies. Further validation is recommende.21

Overall, all studies confirmed PSA's strong sensitivity but highlighted its low specificity across different PSA thresholds and populations. The most methodologically robust improvements came from incorporating prostate volume (PSAD) or population-specific considerations, which modestly increased specificity while preserving cancer detection capabilities.

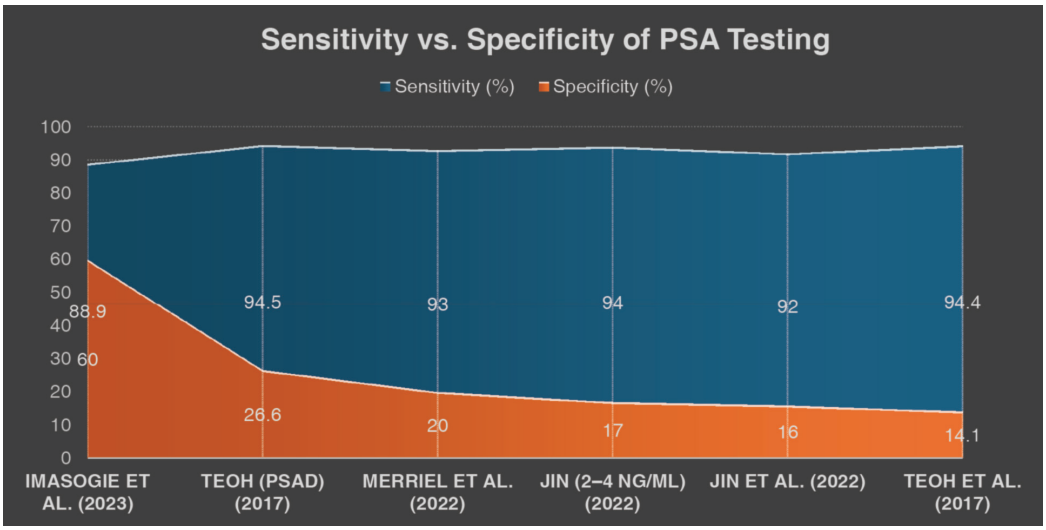

Image 2: PSA Test Accuracy Across Studies.

Table 1. Summary of Diagnostic Accuracy and Limitations of PSA Testing in Prostate Cancer Across Key Studies.

S. No	Study (Year)	Population (Country, Age)	PSA Cut off (ng/mL)	Sensitivity (%)	Specificity (%)	Methodology & Population Details	Conclusions	Problems & Limitations
1	Merriel et al., 2022	14,489 symptomatic men, Europe/N. Am, mixed adult ages	4	93	20	Systematic review and meta-analysis of 19 studies; histology from biopsy used as gold standard	High sensitivity (93%) but very low specificity (20%) in 14,489 symptomatic men. PSA detects cancer well but causes many false positives.	Very low specificity; leads to many false positives and unnecessary biopsies

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2	Jin et al., 2022	Meta-analysis of hospital patients worldwide, adult men	<4	92	16	Meta-analysis of 11 studies; used HSROC modelling for diagnostic accuracy; biopsy confirmation	PSA cutoff <4 ng/mL yields 92% sensitivity and 16% specificity. Lowering the threshold increases detection but worsens false positives.	Challenges balancing early detection with risk of overdiagnosis
3	Teoh et al., 2017	2,606 Chinese men, mean age ~65	4.5	94.4	14.1	Retrospective study: PSA and prostate volume measured; TRUS biopsy confirmation	In 2,606 Chinese men, PSA cutoff of 4.5 ng/mL gives 94.4% sensitivity and 14.1% specificity—good detection but poor accuracy.	Low specificity complicates biopsy decision-making
4	Teoh et al., 2017 (PSAD)	Same cohort as above	0.12 (PSAD cutoff)	94.5	26.6	PSA density (PSAD) calculated by dividing PSA by prostate volume; compared to PSA alone	Using PSA density (PSAD cutoff 0.12) improves specificity to 26.6% while maintaining high sensitivity (94.5%).	PSAD requires accurate prostate volume measurement; availability can be limited

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5	Jin et al., 2022 (PSA 2-4)	Subset of meta-analysis, adults	2.00 – 2.99 (ng/mL) 3.00 – 3.99 (ng/mL)	94 92	17 16	Focus on PSA cutoffs between 2 and 4 ng/mL; used biopsy as reference standard	PSA 2.00–3.99 ng/mL: Sensitivity 92–94%, Specificity 16–17%, Limited for Prostate Cancer Exclusion.	Lower cutoffs increase false positives and unnecessary biopsies
6	Imasogie et al., 2023	94 Nigerian men, age 50-85, mean 70	>4	88.9	60	Prospective study comparing PSA and DRE; biopsy confirmation	Among 94 Nigerian men, sensitivity was 88.9% and specificity much higher at 60%. Shows variation based on population/ genetic factors.	Small sample size: population differences may limit generalizability
7	Teoh et al. (2017) b	5220 Chinese men	0.10 (PSAD ng/ml²)	88.7	Not clearly reported	Multicenter, PSA ≥4 or PSA <4 + abnormal DRE; ROC and logistic regression	PSAD cutoff 0.10 detects PCa well, avoids 20% biopsies	Retrospective, limited specificity, single ethnicity

Across all studies reviewed, **Prostate-Specific Antigen (PSA)** demonstrated consistently high **sensitivity** ranging from **92% to 94.4%**, indicating its effectiveness in detecting prostate cancer, even at early stages. High sensitivity reflects PSA's ability to correctly identify most prostate cancer cases (Jin et al., 2022)[8]. However, the **specificity** of PSA remains notably low, ranging from **14.1% to 20%**, leading to a significant number of **false positives**. For example, **Merriel et al. (2022)** and **Teoh et al. (2017)** reported specificity values of **20%** and **14.1%**, respectively, at the commonly used PSA threshold of **4 ng/mL** (Merriel, 2022)(2; Teoh, 2017)[11,20]. Similarly, **Jin et al. (2022)** found that when PSA was evaluated below **4 ng/mL**, specificity dropped to **16%**, despite the high sensitivity (**92%**), highlighting the trade-off

between sensitivity and specificity in PSA testing (Jin et al., 2022)[8].

PSA Density (PSAD): Enhancing Specificity: One potential solution to improve PSA's specificity is the use of **PSA density (PSAD)**, which adjusts PSA levels based on prostate volume. In **Teoh et al. (2017)**, the incorporation of **PSAD** with a cutoff of **0.12 ng/mL/cc** improved specificity to **26.6%** while maintaining high sensitivity of **94.5%**. This suggests that accounting for prostate volume can help reduce false positives without compromising the ability to detect prostate cancer (Teoh et al., 2017 – PSAD)[11-20].

Lower PSA Thresholds: A Double-Edged Sword: While lowering the PSA threshold (e.g., **below 4 ng/mL**) increases **sensitivity**, it also significantly reduces **specificity**. In **Jin et al. (2022)**, a lower threshold resulted in a specificity of **16%** and a sensitivity of **92%**. This illustrates the challenge of balancing sensitivity and specificity, as the lower threshold leads to **false positives**, contributing to unnecessary procedures and overtreatment (Jin et al., 2022)[8]

Population-Specific Factors: Variations in PSA Performance: The performance of PSA also varies across different populations. **Imasogie et al. (2023)** reported a significantly higher specificity (**60%**) in a cohort of **94 Nigerian men** compared to other studies, possibly reflecting differences in genetic profiles, lower rates of benign prostate hyperplasia (BPH), or differing baseline PSA distributions in African men (Imasogie et al., 2023)[7]. These findings suggest that **population-specific factors** play a significant role in PSA's diagnostic accuracy and emphasize the need for **tailored screening strategies** based on regional, genetic, and age-related characteristics.

Overdiagnosis and Overtreatment: A critical issue with PSA screening is **overdiagnosis**, where **clinically insignificant prostate cancers** are detected that would not cause harm over the patient's lifetime. **Up to 50%** of PSA-detected cancers are indolent, leading to **unnecessary treatments** and procedures (Lophatananon, 2021)[13]. This overdiagnosis and subsequent overtreatment further emphasize the limitations of PSA testing as a diagnostic tool for prostate cancer.

Additional analysis of recent literature provides detailed insights into the underlying causes of PSA's low specificity. One of the most consistent findings is that PSA levels rise not only in the presence of prostate cancer but also due to benign conditions such as benign prostatic hyperplasia (BPH) and prostatitis. BPH affects approximately 30–50% of men over the age of 50, leading to elevated PSA levels that are not cancer-related (Vickers et al., 2009)[6]. Furthermore, transient PSA elevations can be caused by physiological and external factors such as recent ejaculation, urinary tract infections, and physical activity, with intra-individual variability in PSA reaching ±15–20% over short periods (Kobayashi et al., 2023)[1]. These factors significantly contribute to false positive results in PSA screening.

Moreover, technical limitations in standard PSA assays further reduce diagnostic specificity. Current tests measure total PSA, which includes various isoforms, without distinguishing cancer-specific glycoforms such as those with α2, 6-sialylation and core fucosylation—patterns more prevalent in aggressive tumors (Gratacós-Mulleras et al., 2020)[12]. Another critical issue is the significant overlap in PSA levels between healthy individuals and those with cancer, particularly within the diagnostic "gray zone" of 2–10 ng/mL. Jin et al. (2022) demonstrated that at PSA levels below 4 ng/mL, the sensitivity remained high (92%), but specificity dropped to only 16–17%. This is compounded using generalized static PSA cutoffs, which do not adjust for patient age or prostate size, as shown by Merriel et al. (2022)[2], who reported just 20% specificity at the 4 ng/mL threshold in symptomatic men. Additionally, PSA screening often leads to the overdiagnosis of indolent prostate cancers—tumors unlikely to cause harm—contributing to overtreatment. Up to 50% of PSA-detected cancers are clinically insignificant (Lophatananon et al., 2021), further reinforcing concerns about PSA's limited specificity.

Discussion

This review confirms that while PSA testing remains a cornerstone in the early detection of

prostate cancer, its diagnostic utility is hindered by consistently low specificity across diverse populations. The evaluated studies reported high sensitivity, typically between 88.9% and 94.5%, indicating that PSA is effective at identifying patients with prostate cancer, especially when combined with adjunctive markers such as PSA density (Teoh, 2017)[11,20]. However, specificity was strikingly low, ranging from 14.1% to 26.6% in most cohorts, with a notable exception in a Nigerian population where specificity reached 60% (Imasogie, 2023)[7]. These findings highlight the challenge of relying on PSA as a standalone screening tool, particularly given the significant overlap in PSA levels between malignant and benign conditions such as benign prostatic hyperplasia (BPH) and prostatitis (Merriel, 2022)[2], (Jin, 2022)[8].Recent literature provides additional mechanistic insights explaining this low specificity. PSA is not cancer-specific; it is secreted by both malignant and non-malignant prostate tissues, and its levels can be affected by a variety of benign physiological factors including urinary tract infections, recent ejaculation, and digital rectal exams (Kobayashi, 2023)[1], (Vickers, 2009)[6]. These factors contribute to intra-individual variability, potentially leading to transient false elevations in PSA that do not reflect malignancy. Moreover, standard PSA assays measure total PSA without distinguishing between benign and cancer-specific glycoforms. Studies have shown that aggressive tumors express distinct glycosylation profiles, yet these are not captured by conventional tests (Gratacós-Mulleras, 2020)[12]. The reliance on static PSA cutoffs (e.g., 4.0 ng/mL) without adjusting for age or prostate volume further exacerbates specificity issues, resulting in high rates of unnecessary biopsies and overtreatment. As Lophatananon et al. (2021) noted, up to 50% of cancers detected via PSA screening may be clinically insignificant (Lophatananon, 2021)[13].

Taken together, the evidence underscores the need for improved diagnostic strategies. While PSA remains a valuable initial test due to its accessibility and sensitivity, its limitations necessitate integration with additional parameters such as PSA density, free-to-total PSA ratio, multiparametric MRI, and novel molecular assays. These approaches can enhance specificity, reduce overdiagnosis, and support more personalized, risk-adapted prostate cancer screening pathways.

Conclusion

PSA testing continues to be a highly sensitive and widely accessible biomarker for the early detection of prostate cancer. However, its utility is significantly constrained by persistently low specificity, which leads to high false positive rates, unnecessary biopsies, and the overtreatment of clinically insignificant tumours. This limitation is rooted in several biological and methodological factors, including PSA elevation from benign prostatic conditions, physiological variability, the inability of standard assays to distinguish cancer-specific PSA isoforms, and the use of uniform PSA cutoffs without accounting for individual patient variability. A major limitation is that most studies included in the review were conducted in Western populations, particularly in Europe and North America, with limited representation from Asian or African cohorts. This restricts the generalizability of findings to non-Western populations like Chinese men. Also, Only English-language studies were included in the review, which may have led to language bias and the exclusion of relevant research published in other languages.

To address these challenges, there is a critical need to move beyond total PSA alone. Integrating PSA-based screening with adjunct tools—such as PSA density, age-adjusted thresholds, glycoform-specific assays, and imaging techniques like multiparametric MRI—offers a pathway to enhance diagnostic accuracy. These strategies can improve specificity, mitigate overdiagnosis, and support more tailored, risk-based approaches to prostate cancer screening. Future research should prioritize the development and validation of multifactorial diagnostic models that refine PSA interpretation, ultimately promoting better clinical outcomes and resource efficiency.

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