


Prostate-Specific Antigen (PSA) Screening for Early Detection of Prostate Cancer: An Evidence-Based Analysis

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ABSTRACT

Introduction: Prostate-specific antigen (PSA) screening has transformed the early detection of prostate cancer, yet its widespread implementation remains controversial due to concerns over overdiagnosis, overtreatment, and questionable mortality benefit. This article evaluates the contemporary evidence regarding the benefits and harms of PSA-based screening, synthesizing findings from major clinical trials, cost-effectiveness analyses, and international guidelines. **Methods:** An evidence-based analysis using data from pivotal trials such as ERSPC, along with recent meta-analyses, biomarker advancements, MRI-based protocols, and national screening guidelines from the USPSTF, EAU, NCCN, and others. **Results:** PSA screening may reduce prostate cancer-specific mortality, particularly in men aged 55–69 years. It facilitates early detection, enhances access to curative therapies, and promotes broader health engagement. However, it carries significant risks, including overdiagnosis of indolent tumors, overtreatment-related morbidity, false positives, psychological distress, and economic burden. Mortality outcomes across studies remain inconsistent, prompting a shift toward personalized, risk-adapted screening guided by age, comorbidities, family history, biomarkers (e.g., PHI, 4Kscore), and multiparametric MRI. **Conclusion:** PSA screening should not be universally applied but rather employed through shared decision-making and individualized risk assessment. Continued research is warranted to optimize outcomes and inform equitable screening policies, particularly in resource-limited settings.

Keywords: Early detection, prostate cancer, PSA screening, screening guidelines.

ABSTRAK

Pendahuluan: Skrining antigen spesifik prostat (PSA) telah mengubah strategi deteksi dini kanker prostat, namun penerapannya secara luas masih kontroversial karena kekhawatiran diagnosis berlebihan, pengobatan berlebihan, dan manfaat mortalitas yang dipertanyakan. Artikel ini mengevaluasi bukti kontemporer manfaat dan bahaya skrining berbasis PSA, mensintesis temuan dari uji klinis utama, analisis efektivitas biaya, dan pedoman internasional. **Metode:** Analisis berbasis bukti menggunakan data uji coba ERSPC, bersama dengan meta-analisis terkini, kemajuan *biomarker*, protokol berbasis MRI, dan pedoman skrining nasional dari USPSTF, EAU, NCCN, dan lainnya. **Hasil:** Skrining PSA dapat mengurangi mortalitas spesifik kanker prostat, terutama pada pria berusia 55–69 tahun. Skrining ini memfasilitasi deteksi dini, meningkatkan akses terapi kuratif, dan mendorong keterlibatan kesehatan yang lebih luas. Namun, skrining ini memiliki risiko signifikan, termasuk diagnosis berlebih tumor indolen, morbiditas terkait pengobatan berlebih, hasil positif palsu, tekanan psikologis, dan beban ekonomi. Hasil mortalitas di berbagai studi masih belum konsisten, mendorong pergeseran ke arah skrining yang dipersonalisasi dan disesuaikan dengan risiko yang dipandu oleh usia, komorbiditas, riwayat keluarga, *biomarker* (misalnya PHI, 4Kscore), dan MRI multiparametrik. **Simpulan:** Skrining PSA tidak boleh diterapkan secara universal, melainkan melalui pengambilan keputusan bersama dan penilaian risiko individual. Penelitian lanjutan diperlukan untuk mengoptimalkan hasil dan menginformasikan kebijakan skrining yang adil, terutama di wilayah dengan sumber daya terbatas. **Ilham Saptia Nugraha, Agung Trisnanto. Skrining *Prostate-Specific Antigen* (PSA) untuk Deteksi Dini Kanker Prostat: Analisis Berbasis Bukti.**

Kata Kunci: Deteksi dini, kanker prostat, skrining PSA, pedoman skrining.

https://doi.org/10.55175/cdk.v53i07.1981

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INTRODUCTION

Prostate cancer is the second most frequently diagnosed malignancy and the fifth leading cause of cancer-related death among men worldwide, with an estimated 1.4 million new cases and 375,000 deaths reported in 2020 alone.[1] The global burden of prostate cancer is expected to rise significantly due to increased life expectancy, widespread adoption of prostate cancer awareness programs, and expanding access to diagnostic tools such as prostate-specific antigen (PSA) testing.[1]

PSA is a serine protease produced by epithelial cells of the prostate gland, and its concentration in the serum can be elevated in men with prostate cancer, benign prostatic hyperplasia, prostatitis, or even after certain physical activities such as cycling or ejaculation.[2,3] Since its introduction in the late 1980s, PSA testing has revolutionized the landscape of prostate cancer diagnosis by enabling earlier detection of clinically localized tumors, which may be amenable to curative intervention.[4]

However, the use of PSA as a population-wide screening tool has been the subject of intense debate for more than two decades. Critics argue that PSA screening leads to significant overdiagnosis of indolent tumors and prostate cancers that would not have caused symptoms or death during a man's lifetime and consequently increases the risk of overtreatment, which can result in considerable side effects such as urinary incontinence, erectile dysfunction, and psychological distress.[5]

While randomized controlled trials such as the European Randomized Study of Screening for Prostate Cancer (ERSPC)[6] have demonstrated a reduction in prostate cancer mortality with PSA screening, other large-scale trials, such as the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial in the United States,[7] did not find a statistically significant mortality benefit, partly due to contamination of the control group.

In light of conflicting evidence, recent clinical guidelines increasingly emphasize personalized screening strategies that incorporate patient age, life expectancy, comorbidities, family history, and individual values. Shared decision-making between clinicians and patients is now regarded as the cornerstone of ethically sound prostate cancer screening practices.[8]

This literature review aims to explore contemporary evidence on the benefits and harms of PSA-based prostate cancer screening, highlighting ongoing controversy and discussing evolving recommendations from international guidelines.

Theoretical Basis and Mechanism of PSA

Prostate-specific antigen (PSA) is a 33-kDa glycoprotein enzyme produced almost exclusively by the epithelial cells of the prostate gland. It primarily functions as a serine protease that liquefies seminal fluid, thereby facilitating sperm motility. Under physiological conditions, PSA is present in blood at low concentrations, mostly bound to protease inhibitors such as alpha-1-antichymotrypsin (ACT) and alpha-2-macroglobulin, with a smaller fraction in the free (unbound) form.[9]

Elevated serum PSA levels have long been associated with prostate cancer due to disruption of the normal prostatic architecture, which facilitates the leakage of PSA into the circulation. However, PSA is not cancer-specific. Its levels may also increase in various benign and non-neoplastic conditions, including benign prostatic hyperplasia (BPH), acute or chronic prostatitis, urinary tract infection, recent ejaculation, urethral instrumentation, or digital rectal examination.[2,3]

This lack of specificity significantly limits the utility of PSA as a stand-alone diagnostic marker. It has been estimated that approximately 65%–75% of men with elevated PSA levels (> 4.0 ng/mL) who undergo prostate biopsy do not have prostate cancer.[10] Moreover, PSA levels can fluctuate due to inter-individual biological variability and technical factors related to assay performance, time of blood draw, or prostate manipulation.[11]

To improve diagnostic accuracy, several refinements in PSA measurement have been proposed.[11] These include:

- **PSA density (PSAD):** PSA level divided by prostate volume, used to distinguish BPH-related elevation.
- **PSA velocity (PSAV):** The rate of PSA increases over time, which may reflect cancer progression.
- **Free-to-total PSA ratio (fPSA/tPSA):** Lower ratios are more likely to indicate malignancy.

Despite these adjunct measures, the inherent biological variability of PSA and its overlap between benign and malignant states continue to challenge its effectiveness as a screening tool. Thus, PSA remains a useful but imperfect biomarker, best interpreted in the context of other clinical, radiologic, and laboratory data.

Benefits of PSA Screening: Pro Arguments

Early Detection of Clinically Localized Prostate Cancer

One of the primary advantages of PSA screening is its ability to detect prostate cancer at an early, asymptomatic, and potentially curable stage. The landmark European Randomized Study of Screening for Prostate Cancer (ERSPC),[6] which enrolled over 162,000 men across eight countries, demonstrated a 20% relative reduction in prostate cancer-specific mortality after a median follow-up of 13 years among those who underwent PSA screening compared to controls.[12] A subgroup analysis also indicated that screening was particularly effective in men aged 55 to 69 years. These findings support the hypothesis that early detection through PSA testing may meaningfully reduce disease-related mortality in targeted populations.

Greater Access to Curative Treatment Options

Early-stage prostate cancer (typically T1–T2 and localized disease) offers a wider range of definitive curative treatments, including radical prostatectomy, external beam radiation therapy, and active surveillance for low-risk tumors. Early identification through PSA screening increases the likelihood that men will be eligible for less invasive treatments, with a better prognosis and reduced cancer-related morbidity.[13] Studies have shown that the 10-year prostate cancer-specific survival rate exceeds 90% for patients diagnosed at an early stage, underscoring the value of early

detection.[14]

Enhanced Men's Health Awareness and Engagement

Although PSA testing is primarily aimed at prostate cancer detection, it often prompts broader engagement with healthcare systems, leading to the identification of other urologic or systemic health conditions. Men who undergo PSA screening are more likely to receive digital rectal examinations, urinary function evaluations, and counseling for sexual health and lifestyle modification.[3] This "spillover" effect enhances health literacy and promotes preventative care practices, particularly in middle-aged and older men who are otherwise under-screened for chronic diseases.

Potential for Risk Stratification and Individualized Surveillance

Modern approaches to PSA screening are increasingly refined through risk calculators and predictive tools that incorporate PSA kinetics, age, family history, ethnicity, and additional biomarkers such as prostate health index (PHI)[15] or 4Kscore.[16] These tools enable more precise risk stratification, reducing unnecessary biopsies while still identifying aggressive tumors.[10] The development of MRI-based strategies as a triage test after elevated PSA has further improved diagnostic precision and reduced overdiagnosis.[17]

Risks and Controversies: Contra Arguments

Overdiagnosis and Overtreatment

One of the most significant concerns surrounding PSA-based screening is overdiagnosis, defined as the detection of prostate cancers that would not have become clinically significant during a man's lifetime. It is estimated that between 20% and 50% of prostate cancers detected via PSA screening are indolent and unlikely to cause symptoms or mortality.[18] Overdiagnosis often leads to overtreatment, where men undergo radical therapies such as prostatectomy or radiotherapy despite having low-risk tumors. These interventions are associated with substantial side effects, including erectile dysfunction, urinary incontinence, and bowel complications that can severely impact quality of life.[5,19]

Even with the increasing popularity of active surveillance for low-risk prostate cancer, data suggest that many men and clinicians remain uncomfortable with non-interventional approaches, resulting in unnecessary definitive treatment.[20] The psychological burden of living with an untreated cancer, even if indolent, may also drive patients toward more aggressive management.

Lack of Consistent Mortality Benefit

While European trials (e.g., ERSPC)[12,21] support a reduction in prostate cancer-specific mortality, other large-scale studies[11] have failed to replicate these findings. Notably, the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial, which randomized over 76,000 men in the U.S., reported no statistically significant difference in prostate cancer mortality between the screening and usual care groups after 13 years of follow-up.[21] However, the validity of this finding has been questioned due to high rates of PSA testing in the control arm (contamination), which likely diluted the difference between the groups.[22]

This inconsistency in outcomes has fueled debates about the true efficacy of population-wide PSA screening and led to divergent recommendations across guideline bodies. Critics argue that the modest mortality benefit may not justify the widespread harms caused by overdiagnosis and treatment.

Psychological Harm and False-Positive Results

PSA screening is associated with a relatively high rate of false-positive results, primarily due to its low specificity. Approximately 70%–75% of men with elevated PSA levels (> 4.0 ng/mL) who undergo prostate biopsy are found not to have cancer. These false alarms can lead to considerable psychological distress, repeated testing, unnecessary invasive procedures, and long-term anxiety about cancer risk.[3,23]

Moreover, prostate biopsy itself is not without risk—it can result in bleeding, infection, and hospitalization, especially when performed repeatedly.[23] The emotional toll on men subjected to these false-positive scenarios is increasingly recognized in the literature and contributes to the broader concerns over the harms of indiscriminate PSA-based screening programs.

Health System Burden and Cost-Effectiveness Concerns

PSA-based screening, when implemented at a population level, can significantly strain healthcare systems due to the high volume of follow-up diagnostics, such as repeat PSA tests, digital rectal examinations, prostate biopsies, MRI scans, and pathology reviews.[24,25] Each elevated PSA result necessitates further clinical investigation—often leading to expensive, resource-intensive procedures that are not always clinically warranted.[24] In settings with limited healthcare resources, this can divert funding and personnel from other essential health services.[24]

The cost-effectiveness of PSA screening may be considered cost-effective in high-income settings with structured follow-up and risk-stratification protocols; however, it is far less efficient in systems with unregulated screening practices or low adherence to active surveillance.[25] Moreover, overtreatment of low-risk prostate cancer contributes to unnecessary expenditures on surgeries, radiotherapy, and long-term management of treatment-related complications.[26] These cost implications have led many health policy experts to advocate for targeted or risk-adapted screening strategies, rather than universal screening. In low- and middle-income countries, indiscriminate PSA screening may be unsustainable and potentially inequitable, widening the gap in healthcare access and outcomes between socioeconomic groups.

International Guidelines and Recommendations

The use of PSA screening for prostate cancer has led to divergent policies among international professional bodies due to variations in study interpretations, healthcare system capacities, and population risk profiles. Recent guidelines emphasize a shift from mass screening toward individualized, risk-adapted strategies, taking into account age, life expectancy, comorbidities, and patient preferences.

United States Preventive Services Task Force (USPSTF)[8]

The USPSTF's 2018 update marked a key turning point in PSA screening policy. The task force recommended a Grade C for men aged 55 to 69 years, meaning that the decision to undergo PSA-based screening should be an individualized choice made through shared decision-making with the patient after discussion of potential benefits and harms.[8] For men aged 70 years or older, the USPSTF recommends against PSA screening, citing a greater risk of overdiagnosis and overtreatment, and a lower probability of net benefit due to reduced life expectancy and increased competing health risks.

European Association of Urology (EAU)[4,17]

The EAU 2024 guidelines advocate for risk-adapted, evidence-based screening. Rather than mass screening, EAU supports a baseline PSA test at age 45–50 to determine long-term risk and guide future screening intervals.[4] The EAU encourages the use of additional tools such as PSA density, PSA velocity, and advanced molecular biomarkers (e.g., PHI, 4Kscore) to improve specificity. Importantly, the EAU also recommends multiparametric MRI (mpMRI) prior to prostate biopsy in men with elevated PSA, a practice that has been shown to reduce unnecessary biopsies and improve detection of clinically significant cancers.[17]

National Comprehensive Cancer Network (NCCN) – United States[27]

The NCCN guidelines provide a more detailed risk-stratified approach, recommending:

- Baseline PSA testing at age 45 for men at average risk,
- Earlier and more frequent testing for high-risk groups (African-American men or those with a family history),
- Biopsy consideration at PSA ≥ 3.0 ng/mL or based on abnormal DRE,
- Use of MRI and secondary markers (PHI, 4Kscore) prior to biopsy in borderline cases

The NCCN also strongly supports active surveillance for low-risk and some favorable intermediate-risk prostate cancers, aiming to reduce overtreatment while maintaining oncologic safety.

Canadian Task Force on Preventive Health Care (CTFPHC)[28]

In contrast, Canadian guidelines are more conservative. The CTFPHC (2014) recommends against PSA-based screening in asymptomatic men of all age groups, citing uncertainty in mortality benefit and a high probability of harm from overdiagnosis and overtreatment. However, these recommendations have been criticized for failing to incorporate newer evidence on MRI-based triage and risk stratification.

United Kingdom – National Health Service (NHS) and NICE[29]

In the UK, the Prostate Cancer Risk Management Programme (PCRMP) does not recommend organized screening but allows opportunistic PSA testing in men aged 50 and over, provided they receive thorough counseling about the test's limitations. The NICE guidelines similarly recommend against systematic screening but support PSA testing for symptomatic men or those requesting it after informed discussion.

World Health Organization (WHO)[30]

The WHO does not currently recommend population-based PSA screening for prostate cancer in any region due to concerns about feasibility, cost-effectiveness, and potential harms in lower-resource settings. Instead, the WHO advocates for contextualized decision-making, especially in countries with limited access to follow-up diagnostics and urologic care.

A summary of all screenings for prostate cancer from all organizations are listed in the **Table** below.

Risk-Stratified and Individualized Approach

Given the complex balance between the potential benefits and harms of PSA screening, a one-size-fits-all approach is no longer considered appropriate. Instead, personalized screening strategies are increasingly promoted by leading urological and oncological societies.

Stratifying Based on Age, Risk, and Comorbidity

Age remains a major determinant of prostate cancer risk and screening benefit. Men aged 55–69 benefit the most from screening in terms of mortality reduction, while men over 70 are more likely to suffer from competing mortality risks and treatment harms.[3] Family history of prostate cancer, especially in first-degree relatives and **African ancestry**, is associated with significantly increased lifetime risk and justifies earlier and more frequent screening.[2,31]

Biomarkers and PSA Derivatives

To improve diagnostic performance, several PSA-related parameters are now used to enhance specificity:[2]

- **PSA density (PSAD):** PSA adjusted for prostate volume; values > 0.15 ng/mL/cm^3 suggest increased cancer risk.
- **PSA velocity (PSAV):** Rate of PSA increases over time; rapid rises may indicate aggressive disease.

Table. Clinical summary: screening for prostate cancer.[8]

Organisation	Age Group	Recommendations	Notes
USPSTF (USA)[8]	55–69	Shared decision-making	Does not support mass screening
EAU (Europe)[4,17]	45+	Risk-adapted, baseline PSA, mpMRI before biopsy	Supports biomarkers and imaging
NCCN (USA)[27]	45+	Risk-stratified screening	Includes MRI, molecular markers
CTFPHC (Canada)[28]	All	Recommends against screening	Concerned about overdiagnosis
NICE/NHS (UK)[29]	50+	Informed patient-initiated screening	Not a population-wide program
WHO[30]	Global	Does not support mass screening	Recommends individualized approaches

- **Free-to-total PSA ratio (f/tPSA):** Lower ratios (< 10%–15%) are associated with a higher probability of cancer.

Advanced biomarkers, such as **Prostate Health Index (PHI)**, **4Kscore**, and **SelectMDx**, provide molecular risk estimates to guide biopsy decisions and reduce unnecessary procedures.

Integration of Multiparametric MRI

Multiparametric MRI (mpMRI) has become a cornerstone in the individualized screening paradigm.[5] When used after elevated PSA but prior to biopsy, mpMRI significantly improves the detection of clinically significant cancer and reduces the detection of low-risk, indolent tumors.[5] This approach aligns with contemporary strategies that seek to minimize overtreatment while ensuring timely diagnosis of aggressive disease.

CONCLUSION

Prostate-specific antigen (PSA) screening is among the most widely studied and debated strategies in cancer prevention. While it has demonstrated a clear potential to reduce prostate cancer-specific mortality—particularly in men aged 55–69 years—its population-wide implementation remains contentious due to the inherent limitations of PSA as a biomarker and the substantial risk of overdiagnosis. Indolent tumors that would not have caused clinical harm are frequently detected, often resulting in overtreatment and long-term adverse effects on urinary, sexual, and psychological health.

This ambiguity has prompted major guideline bodies to shift away from universal screening toward personalized, risk-adapted strategies that incorporate age, family history, ethnicity, comorbidities, and life expectancy. Technological advances, including multiparametric MRI and molecular biomarkers (e.g., PHI, 4Kscore), have improved risk stratification and contributed to more precise diagnostic pathways. These tools help reduce unnecessary biopsies and minimize harm, aligning with the principles of value-based care and precision medicine.

Given these complexities, the most ethically sound and clinically effective approach is to adopt a shared decision-making model, in which patients are fully informed about the benefits and harms of PSA screening. This model respects individual values and preferences, while empowering clinicians to tailor recommendations based on up-to-date, evidence-based risk assessments. Ultimately, the goal of PSA screening should not be merely early detection, but rather selective identification of clinically significant cancers, with a focus on balancing longevity with quality of life. Continued research, including long-term follow-up studies and economic evaluations, will be essential to refine screening protocols and optimize outcomes for diverse populations.

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