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Prostate-Specific Antigen Screening and Overdiagnosis in Prostate Cancer: A Systematic Review and Meta-Analysis

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Abstract

Background: *Prostate cancer is the most frequently diagnosed malignancy among men. Screening strategies aimed at reducing prostate cancer–related mortality have raised concerns about overdiagnosis—defined as the detection of cancers that would not cause symptoms or death during a patient's lifetime—and subsequent overtreatment. This review systematically evaluates whether PSA-based screening primarily enables early detection or contributes to clinically relevant overdiagnosis.*

Methods: *Following PRISMA guidelines, randomized controlled trials and cohort studies enrolling men aged $\geq$ 40 years without prior prostate cancer were included. Studies compared PSA-based screening with no screening or alternative strategies. PubMed, Web of Science, and Scopus were searched from 2015 onward. Risk of bias was assessed using RoB2 for randomized trials and the Newcastle–Ottawa Scale for cohort studies. Primary outcomes included prostate cancer diagnosis, overdiagnosis, prostate cancer–specific mortality, and overall mortality.*

Results: *Thirteen studies enrolling men aged 45–74 years, with follow-up ranging from 2 to 22 years and sample sizes from 4,276 to 415,357, were included. Biopsy-related complications were infrequent ($\leq$2%), and MRI-guided biopsy was associated with fewer infectious complications compared with standard transrectal biopsy. Overdiagnosis estimates varied widely across studies; however, the pooled estimate was not statistically significant (RR 1.56 [95% CI 0.65–3.79]). PSA screening did not reduce overall mortality (RR 0.99 [95% CI 0.88–1.11]). Prostate cancer–specific mortality was modestly reduced, with pooled results borderline significant (IRR 0.87 [95% CI 0.76–1.00]). Substantial heterogeneity and risk of bias across studies limited the certainty and generalizability of pooled estimates.*

Conclusion: *PSA-based screening is associated with a modest reduction in prostate cancer–specific mortality without an improvement in overall survival. Lower overdiagnosis rates observed in more recent, risk-adapted screening strategies highlight the importance of shared decision-making and support the integration of modern diagnostic tools to minimize harms. Further well-designed, representative trials are needed to define optimal screening pathways across diverse populations.*

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Introduction

Prostate cancer is the most frequently diagnosed solid tumor amongst men and remains the second leading cause of male cancer mortality worldwide (Zhang et al., 2023). The introduction of prostate-specific antigen (PSA) testing in the late 1980s revolutionized early detection strategies (Kuriyama et al.,

1980). However, over time, concerns have emerged regarding the unintended consequences of widespread screening. Although PSA testing offers the possibility of identifying prostate cancer at a potentially curable stage, it is also associated with significant disadvantages, including overdiagnosis of indolent tumors and treatment-related morbidity, such as urinary incontinence, erectile dysfunction, decline in quality of life, and psychological distress (Donovan et al., 2016; Gulati et al., 2019). These consequences pose substantial challenges to both clinicians and patients in balancing the potential benefits and risks of screening.

Initial randomized controlled trials suggested that PSA-based screening could reduce prostate cancer-specific mortality (Schröder et al., 2014), but at the cost of increased overdiagnosis and overtreatment. In response to these concerns, more recent studies have aimed to refine the screening process. Strategies such as multivariable risk calculators, blood-based biomarkers, and pre-biopsy multiparametric magnetic resonance imaging (mpMRI) have been incorporated into risk-adapted screening pathways. Early evidence suggests these approaches may reduce unnecessary biopsies and improve the detection of clinically significant disease while minimizing harm. Despite these advancements, the interpretation of the evidence remains complex due to heterogeneity in study designs, screening protocols, populations, and outcomes.

While individual studies have demonstrated promising results, there is still no comprehensive synthesis of long-term outcomes associated with PSA screening, particularly when embedded within modern, risk-adapted diagnostic strategies. The generalizability of these findings to diverse populations and healthcare systems also remains uncertain, as most trials have been conducted in high-income countries with homogeneous demographics. Furthermore, the magnitude of benefit in terms of overall mortality remains limited, raising questions about the net clinical value of current screening practices. These gaps in evidence highlight the need for a systematic review to evaluate whether modern PSA-based screening approaches meaningfully reduce overdiagnosis and improve prostate cancer outcomes.

This systematic review aims to evaluate whether PSA-based screening for prostate cancer, especially when compared to risk-adapted strategies (e.g., mpMRI, biomarkers, risk calculators) or no screening, reduces overdiagnosis and improves clinically relevant outcomes. By consolidating current evidence, this review intends to inform clinical practice and public health policy, promote shared decision making, and guide future screening strategies in diverse settings.

Materials and Methods

Information Sources and Search Strategy

This systematic review followed the Preferred Reporting Items for Systematic Reviews (PRISMA) and Meta-Analysis for the design and reporting (Page et al., 2021). We systematically searched the following electronic databases: PubMed, Web of Science, and Scopus, including articles from January 2015 up to April 2025. The article's search included published randomized clinical trials (RCTs) and observational studies (cohort) in English for the diagnosis of prostate cancer using PSA screening compared to no screening (placebo or standard care). Details of the search strategy are outlined in Table S1.

Eligibility Criteria

The selected inclusion criteria were as follows: Studies conducted with men aged 40 years and above, with PSA screening. The studies needed to report PSA measurement($\geq 3\,\mathrm{ng/ml}$), biopsy, or any surgical procedure or surveillance after the PSA screening. Surgical procedures, biopsy, digital rectal examination, family history, and imaging studies of other obstructive symptoms in the comparison group were reported. The primary outcome was overdiagnosis of prostate cancer. Secondary outcomes included complications following diagnostic procedures (such as infections, hematuria, rectal bleeding, discomfort), biopsy or treatment-related adverse effects (including urinary incontinence and sexual dysfunction), false-positive results, and overall or prostate cancer–specific mortality. The review included randomized controlled trials (RCTs) and observational studies.

The analysis excluded several study types, such as case reports, editorials, preclinical studies, abstracts, posters, systematic reviews, meta-analyses, experts' opinions, narrative reviews, and guidelines. Trials involving a previous prostate biopsy before the original trial enrollment, previous prostate cancer before the original trial enrollment, previous prostate surgery or procedure before the original trial enrollment were excluded. Additionally, Studies focusing on unrelated conditions, such as prostatitis or alternative screening modalities, were excluded.

Selection of Studies, Outcome, and Data Extraction

The selection of the studies was done first by screening the title and abstract, followed by full-text screening. Each phase was performed by two

No.	First Author and year	Country	Study design and duration	Sample size (N: total)	Patients who underwent prostate biopsy/ results of the biopsies	Population	Intervention/ Exposure	Comparator	Outcomes Measured	Results
1	Krilaviciute, A. et al. 2023	Germany	Randomized screening trial	N: 46,495 (4.04%) Intervention group - 45 years old immediate screening arm n= 23,301 Control group -50 years old deferred PSA screening arm n=23,194 of those n: 6,537 had DRE.	Intervention group PSA screening group n:1, this biopsy was negative for prostate cancer Control group DRE group n: 36 of those patients n:3 prostate cancer	Men aged 45	PSA screening	Digital rectal examination	Cancer detection rate	A prospective analysis of 57 men with suspicious DRE at age 45 revealed three PCa. Detection rate by DRE was 0.05% (3/ 6537) as compared with a four-fold higher rate by PSA screening (48/ 23 301, 0.21%). The true-positive detection rate by DRE relative to screening by PSA was 0.22 (95% [CI] = [0.07–0.72]). alse-positive detection rate by DRE was 2.2 (95% CI = 1.50–3.17]). (2) Among PSA-screen–detected PCa cases, 86% had unsuspicious DRE (sensitivity relative to PSA was 14%) The majority of these tumors (86%) were located in potentially accessible zones of the prostate as seen by MRI.
2	Martin, R.M. et al. 2024	United Kingdom of Great Britain and Northern Ireland; United States of America	Cluster randomized controlled trial 15 years follow-up	N: 415,357 (36.12%) Intervention group n: 189,326 n: 75,694 underwent PSA screening Control group n: 219,395	Intervention group Underwent prostate biopsy n: 5,848 Developed prostate cancer n: 12,013 Control group Developed prostate cancer n: 12,958	Men aged 50 to 69 years	PSA screening	Standard practice (no invitation for a PSA screening)	15 years Prostate cancer mortality	Of 415 357 eligible men (mean [SD] age, 59.0 [5.6] years), 98% were included in these analyses. Overall, 12 013 and 12 958 men with a PCa diagnosis were in the intervention and control groups, respectively (15-year cumulative risk, 7.08% [95% CI, 6.95%-7.21%] and 6.94% [95% CI, 6.82%-7.06%]). At a median 15-year follow-up, 1199 men in the intervention group (0.69% [95% CI, 0.65%-0.73%]) and 1451 men in the control group (0.78% [95% CI, 0.73%-0.82%]) died of PCa (rate ratio [RR], 0.92 [95% CI, 0.85-0.99]; P = .03). PSA screening intervention increased detection of low-grade PCa (: 2.2% vs 1.6%; P < .001) and localized (T1/T2: 3.6% vs 3.1%; P < .001) disease but not intermediate, high-grade, locally advanced, or distally advanced) tumors. There were 45 084 all-cause deaths in the intervention group (23.2% [95% CI, 23.0%-23.4%]) and 50 336 deaths in the control group (23.3% [95% CI, 23.1%-23.5%]) (RR, 0.97 [95% CI, 0.94-1.01]; P = .11).
3	Nordström, T. et al. 2021	Sweden	Randomized controlled trial	Patients that were included had PSA ≥3 ng/mL or Stockholm3 of ≥0·11 N: 2,300 (0.2%) Intervention group n:1372 Control group n: 921	Intervention group n:921 Biopsies that were positive n:272 Control group n: 632 Biopsies that were positive n:308	Men aged 50-74 years living in Stockholm (Sweden)	Prostate cancer screening (PSA or Stockholm3 test)	No PSA screening	Overall mortality and prostate cancer detection rate	Out of 2293 men with elevated risk, n= 1372 were randomly assigned to the experimental group and n=921 to the control group. The AUC for detection of clinically significant PCa was 0·76 (95% CI 0·72–0·80) for Stockholm3 and 0·60 (0·54–0·65) for PSA. Stockholm3 ≥0·11 was non-inferior to a PSA of ≥3 ng/mL for detection of clinically significant prostate cancer (227 vs 192; [RP] 1·18 [95% CI 1·09–1·28], p<0·0001 for non-inferiority), and detected a similar number of low-grade PCa(50 vs 41; 1·22 [0·96–1·55], p=0·053 for superiority)s. Compared to a PSA of ≥ 3 ng/mL, a Stockholm3 of ≥0·15 provided identical sensitivity to detect clinically significant cancer, and led to fewer MRI procedures (545 vs 846; 0·64 [0·55–0·82]) and biopsies (311 vs 338; 0·92 (0·86–1·03). a Stockholm3 ≥ 0·11 combined with MRI-targeted and systematic biopsies was associated with higher detection of clinically significant cancers vs. PSA (227 [3·0%] men tested vs 106 [2·1%] men tested; RP 1·44 [95% CI (1·15–1·81]) and lower detection of low-grade cancers (50 [0·7%] vs 73 [1·4%]; 0·46 [0·32–0·66]), Patients in the experimental group had lower prescription of antibiotics (25 [1·8%] of 1372 vs 41 [4·4%] of 921; p=0·0002) and admission to the hospital (16 [1·2%] vs 31 [3·4%]; p=0·0003)
4	Hugosson, J. et al. 2018	Sweden	Randomized controlled trial 18 years follow-up	N: 20,000 (1.74%) Intervention group n: 9950 Control group n: 9,949	Intervention group n:4654 Diagnosis of prostate cancer n:1396 Control group n: *number of biopsies not mentioned* Diagnosis of prostate cancer n: 962	Men aged 50–64 years living in Göteborg	PSA screening	No PSA screening	Prostate cancer-specific mortality (Absolute and relative risk reduction in prostate cancer mortality)	Screening group, 77% (7647/9950) attended at least once. After 18 yr, 1396 men in the Interventiongroup and 962 in the control group had been diagnosed with PCa (hazard ratio [HR] 1.51, 95% CI[CI] 1.39–1.64). Cumulative PCa mortality was 0.98% (95% CI 0.78–1.22%) in the screening group versus 1.50% (95% CI 1.26–1.79%) amongst controls, an absolute reduction of 0.52% (95% CI 0.17–0.87%). The risk ratio (RR) for PCa death was 0.65 (95% CI 0.49–0.87). To prevent one death from PCa, the number needed to invite was 231 and the number needed to diagnose was 10. Systematic PSA screening demonstrated even greater benefit in PCa mortality for men who started screening at age 55–59 yr (RR 0.47, 95% CI 0.29–0.78) and men with low education (RR 0.49, 95% CI 0.31–0.78).
5	Fränlund, M. et al. 2022	Sweden	Randomized controlled trial 22 years follow-up	N: 20,000 (1.74%) Intervention group n: Control group n:	Intervention group diagnosis of prostate cancer n:1528 Control group diagnosis of prostate cancer n: 1,124 Number of patients that underwent prostate biopsy: Not mentioned	Men aged 50–64 years living in Göteborg	PSA screening every 2 years	No PSA screening	Overall mortality, prostate cancer detection rate, prostate cancer-specific mortality and biopsy rate	After 22 years, 1,528 men in the Intervention Group and 1,124 men in the CG had been diagnosed with PCa. In total, 112 PCa deaths occurred in the Intervention Group and 158 in the Controls. The intervention Group showed a PCa incidence rate ratio (RR) of 1.42 (95% CI, 1.31e1.53) and a PCa mortality RR of 0.71 (95% CI, 0.55e0.91). The 22-year cumulative PCa mortality rate was 1.55% (95% CI, 1.29e1.86) in tintervention group and 2.13% (95% CI, 1.83e2.49) in the Controls. Number needed to invite and number needed to diagnose was estimated to 221 and 9, respectively. PCa death risk was increased in nontesting men, men entering the program after age 60 and men with >10 years of follow-up after screening termination.

Table 1: *Characteristics of the included studies.*

6	Auvinen, A. et al. 2024	Finland; Sweden; United States of America	Randomized controlled trial 3.2 years follow-up	N: 60,745 (5.28%) Intervention group n: 15,201 Control group n: 45,544	Intervention group: n: 32 low-grade prostate cancer n:28 high-grade prostate cancer Control group n:65 low-grade prostate cancer n: 282 high-grade prostate cancer Number of patients that underwent prostate biopsy: Not mentioned	Men aged 50 to 63 years. Residents of Helsinki or Tampere, Finland at baseline in 2018	Prostate cancer screening (PSA and kallikrein risk score and PI-RADS)	No screening	Prostate cancer detection rate	Of 60 745 eligible men (mean [SD] age, 57.2 [4.0] years), 15 201 were randomized to undergo prostate cancer screening. Of 15 201 eligible males ig, 7744 (51%) participated. Among them, 32 low-grade PCa(cumulative incidence, 0.41%) and 128 high-grade PCa (cumulative incidence, 1.65%) were detected,. Among the 7457 invited men (49%) who refused participation, 7 low-grade PCa (cumulative incidence, 0.1%) and 44 high-grade cancers (cumulative incidence, 0.6%) were detected,. In the Screening group, 39 low-grade PCa (cumulative incidence, 0.26%) and 172 high-grade cancers (cumulative incidence, 1.13%) were detected. During a median follow-up of 3.2 years, in the Control group 65 low-grade PCa (cumulative incidence, 0.14%) and 282 high-grade cancers (cumulative incidence, 0.62%) were detected.
7	Godtman, R.A. et al. 2021	Sweden; Netherlands; Belgium; France; Switzerland; Germany; Italy; Spain; Finland	Randomized controlled trial 16 years follow-up	N: 241,234 (20.98%) Intervention group n:112,553 Control group n: 128,681	Number of patients that underwent prostate biopsy: Not mentioned	Men aged 55 to 69 years	PSA screening	No PSA screening	Intervention-related deaths: defined as deaths caused by complications during the screening procedure, treatment, or follow-up	In total, 34 deaths were determined to be intervention-related, of which 21 were in the screening arm and 13 in the control arm. The overall risk of intervention-related death was 1.41 (95% confidence interval 0.99-1.99) per 10 000 randomized men for both arms combined and varied among centers from 0 to 7.0 per 10 000 randomized men. A limitation of this study is that differences in procedures among centers decreased the comparability of the results.
8	Hugosson, J. et al. 2019	Sweden	Randomized controlled trial 16 years follow-up	N: 268,539 162 389 (14.12%) Intervention group n: 72,890 Control group n: 89,351	Intervention group: n: 4,761 low-grade prostate cancer n: 1,892 intermediate-grade prostate cancer n: 650 high-grade prostate cancer Control group n: 3,021low-grade prostate cancer n: 2,197 intermediate-grade prostate cancer n: 917 high-grade prostate cancer	Men aged 55 to 69 years	PSA screening	No PSA screening	Prostate cancer-specific mortality	The rate ratio of PCa mortality was 0.80 (95% confidence interval [CI] 0.72-0.89, p<0.001) at 16yr. The difference in absolute PCa mortality increased from 0.14% at 13yr to 0.18% at 16yr. The number of men needed to be invited for screening to prevent one PCa death was 570 at 16yr compared with 742 at 13yr. The number needed to diagnose was reduced to 18 from 26 at 13yr. Men with PCa detected during the first round had a higher prevalence of PSA >20ng/ml (9.9% compared with 4.1% in the second round, p<0.001) and higher PCa mortality (hazard ratio=1.86, p<0.001) than those detected subsequently.
9	Kilpeläinen, T. et al. 2015	Finland	Randomized controlled trial 15 years follow-up	N: 80,456 (7%) Intervention group n: 31,866 Control group n: 48,278	Number of patients that underwent prostate biopsy: Not mentioned Intervention group diagnosis of prostate cancer n: 2,725 Control group diagnosis of prostate cancer n: 4,082	Men aged 55 to 67 years	PSA screening	No PSA screening	Prostate cancer detection rate and Prostate cancer-specific mortality	Men in the Screening group were screened at four-year intervals and referred to biopsy if the PSA > 4.0 ng/ml, or 3.0–3.99 ng/ml with a free/total PSA ratio 16%. The median follow-up was 15.0 years. The absolute risk of PCa death was 0.76% in the Screening Arm and 0.85% in the Control Arm; the observed hazard ratio (HR) was 0.89 (95% confidence interval (CI) 0.76–1.04). After correcting for non-attendance, the HR was 0.78 (0.64–0.96); predicted effect for a hypothetical PSA threshold of 3.0 ng/ml the HR was 0.88 (0.74–1.04) and after eliminating the effect of interval cancers the HR was 0.88 (0.74–1.04). Non-participating men in the SA had a high risk of PCa death and a large impact on PCa mortality.
10	Carlsson, S. et al. 2017	Sweden	Prospective cohort study 17 years follow-up	N: 7,539 (0.66%) Intervention group - n: 3,479 men randomized to screening in the Göteborg cohort. Control group - n: 4,060 men unscreened in the Malmö cohort	Number of patients that underwent prostate biopsy: Not mentioned Intervention group diagnosis of prostate cancer n: 463 Control group diagnosis of prostate cancer n: 225	Men aged 55 to 64 years	PSA screening every 2 years	No PSA screening	Prostate cancer detection rate, Prostate cancer-specific mortality, Prostate cancer metastasis rate	PSA screening conveyed a two-fold higher risk of PCacompared with unscreened men in Malmo¨ (incidence rate ratio [IRR] 2.56, 95% confidence interval [CI] 2.18, 3.02) but resulted in a substantial decrease in the risk of metastases (IRR 0.43, 95% CI 0.22, 0.79) and PCa death (IRR 0.29, 95% CI 0.11, 0.67). There were 57 fewer PCadeaths per 10 000 men (95% CI 22, 92) in the screened group. At 17 yr, the number needed to invite to PSA-screening and the number needed to diagnose to prevent one prostate cancer death was 176 and 16, respectively.
11	Lujan. et al. 2015	Spain	Prospective cohort study 15.8 years follow-up	N: 4,276 (0.37%) Intervention group n: 2,415 Control group n: 1,861	Number of patients that underwent prostate biopsy: Not mentioned Intervention group diagnosis of prostate cancer n: 162	Men aged 45 to 70 years	PSA screening	No PSA screening	Overall mortality, cancer detection rate, Prostate cancer-specific mortality and Gleason score of detected cancers	4.276 men included (2.415 screening arm, 1.861 control arm). Mean age and serum-PSA were 57 years old and 0,90 ng/m. The mean follow-up time was 15,8 years. ¨ 242 PCa were diagnosed, 162 (6,7%) in the screening arm and 80 (4,3%) in control (p < 0,001). 214 (88,4%) of them did not present metastasis (91,4% screening arm vs 82,5% control, p = 0,024).
12	Remmers. et al. 2023	Dutch section of the ERSPC	Randomized controlled trial 20 years follow-up	N: 42,374 (3.69%) Intervention group n: 21,209 Control group n: 21,165		Men aged 55 to 70 years	PSA screening every 4 years	No PSA screening	Prostate cancer detection rate	
13	Arsov et al.	Germany	Cohort study 15 years follow-up	N: 46642 (4.06%) Intervention group: 23341 Control group: 23301	High risk patients 186 and 120 biopsies. Biopsies in the control group: 37	Men 45 and older.	Immediate PSA screening	Digital Rectal Examination and delayed PSA screening	Cumulative incidence of distant metastatic Prostate Cancer	Among 23,301 screened, 0.8% were high-risk; 48 cancers were found, mostly low grade. In the delayed arm, two low-grade cancers were detected by DRE. Participation was under 20%, due to low interest and skepticism about PSA testing.

PSA: Prostate Specific Antigen; DRE: Digital Rectal Examination; PCa: Prostate Cancer; AUC: Area Under the receiver-operating characteristic curve; CAP: The Cluster Randomized Trial of PSA Testing for Prostate Cancer; GS: Gleason score; TNM: Cancer Staging Score (Tumor, Nodules, Metastasis); MRI: Magnetic Resonance Imaging; PI-RADS: Prostate Imaging Reporting and Data System; ERSPC: European Randomized study of Screening for Prostate Cancer; HR: Hazard Ratio; RP: relative proportion

Table 1: *(continued) Characteristics of the included studies.*

independent reviewers, and conflicts were solved by a third independent reviewer. The data extraction was done by two independent reviewers. All the authors participated in the screening and data extraction process. Table S2a-c summarizes the reviewers involved in this process. The screening process and data extraction were executed using the COVIDENCE systematic review online tool.

Data Synthesis

The following variables were extracted from each of the included studies: title, first author, year of publication, country, study design and duration, sample size, patients that underwent prostate biopsy and results of the biopsies, population and setting, intervention and exposure, comparator, outcomes measured (overdiagnosis, specific disease mortality, overall mortality, complications), results (sensitivity, specificity, hazard ratio, false positives, Gleason Score, PSA measurement follow-up, Area Under the Curve, Relative Proportions, Odds Ratio). For this study, overdiagnosis was defined as non–clinically significant prostate cancer, characterized by a Gleason score < 7 or ISUP grade 1 at diagnosis, or as cancer unlikely to cause harm or be detected within the patient's lifetime. This definition aligns with those adopted by the included studies, when specified. This definition aligns with those adopted by the included studies, when specified.

Pooled effect estimates were derived via meta-analysis, performed using Stata version 19. Meta-analysis was conducted on the natural logarithms of risk ratios, implemented with the meta suite of commands. To account for potential heterogeneity across studies, a random-effects model was employed. Forest plots were generated to visually represent the risk ratios and their corresponding confidence intervals, with the exponentiated natural logarithm values used for plotting the summary estimates and the individual estimates.

Risk of Bias Assessment

The risk of bias assessment in the present study was performed using the ROB2 tool (Sterne et al., 2019) for all randomized controlled trials included in this review, and the Newcastle-Ottawa scale for the Cohort Studies included (Wells et al., n.d.). A designated group of three reviewers independently assessed every article using the domains included in the ROB2 tool and NOS. No conflicts were found at the time of the bias assessment.

Certainty of Evidence

This was measured using a funnel plot to assess publication bias.

Protocol Registration

We contacted the journal to clarify whether PROSPERO registration was required for this type of review. The editorial team informed us that preregistration in PROSPERO was not necessary for submission to this journal.

Results

The aim of this systematic review was to determine if PSA screening was associated with prostate cancer overdiagnosis and led to more complications. The comparisons made in the trials were between screened and unscreened men; the latter group included men who were screened with any other method that was not PSA or were not screened at all. We retrieved information regarding Prostate cancer-specific mortality, overall mortality, and complications from 10 randomized prospective trials and one cohort study. Table 1 shows the characteristics of the populations included in this review, with ages ranging between 45 and 74 years, and follow-up periods varying between 2 and 22 years.

Characteristics of the Studies

The initial search identified 576 studies, which were imported into Covidence for screening. After the removal of 8 duplicates manually and an additional 161 duplicates automatically identified by the software, 407 unique records remained for title and abstract screening. Following this stage, 215 studies were excluded as irrelevant, leaving 192 studies for full-text assessment. Of these, 179 were excluded for the following main reasons: wrong patient population (n=47), inappropriate study design (n=34), irrelevant outcomes (n=32), wrong intervention (n=28), and unsuitable comparator (n=18). Ultimately, 13 studies met the inclusion criteria and were included in the final synthesis. However, the study by Krilaviciute et al. (2023), although included in the systematic review, was excluded from the quantitative analysis, as no other study compared digital rectal examination (DRE) to prostate-specific antigen (PSA) testing. Figure 1 summarizes the Prisma flow diagram.

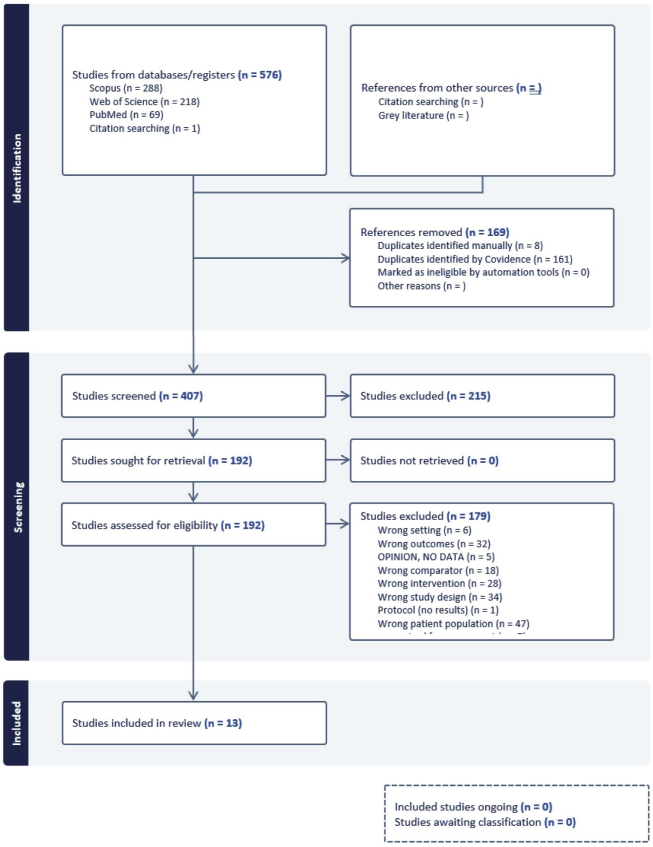

Figure 1: *PRISMA Flow diagram for the systematic review.*

Population

Sample sizes ranged from 4,276 to over 400,000 participants, with most trials using randomized controlled designs. Of the 13 studies included, 12 were Randomized Controlled Trials, with a total number of participants N: 1149808, median follow-up time: 16 years, and two of the papers included, due to their set outcome, did not follow up the patients. Out of this, the one by Martin et al. (2024) was the largest one, accounting for 36.12% of the total population. All studies were conducted in Europe; only one included data from the United States of America.

Intervention Characteristics and Effects/Exposure/Control

Intervention groups were typically invited for regular PSA screening (often every 2–4 years), with subsequent biopsies performed based on PSA thresholds or additional risk stratification (e.g., use of the Stockholm3 test or MRI guidance in Nordström et al., 2021). Studies like Martin et al. 2024 and the European Randomized Study of Screening for Prostate Cancer (ERSPC) included multi-country cohorts, enhancing generalizability but also introducing heterogeneity.

Outcomes

Table 2 summarizes the 13 studies outcomes and complications included in the main results.

Main Results

Complications were reported by Nordström et al. (2021; the infection and hospitalization rates 30 days after prostate biopsy were compared between transrectal standard biopsy (performed in the control group) and biopsy guided by Magnetic Resonance Imaging (MRI) (screening group). The Odds Ratio was 0.4 [0.2 to 0.7] for the former and 0.3 [0.2 to 0.7] for the latter. Godtman et al. (2021) reported intervention-related deaths. Thirty-four deaths occurred in the screening and control group combined, and one of them occurred during the diagnostic pathway, but was not directly associated with the biopsy or treatment. In total, the cumulative incidence of complications was$\leq$ 2%. Figure 2 summarizes the forest plot of this part.

The overdiagnosis ratio differed among the studies included. It was high in the study by Arsov et al., 2022: Risk Ratio 7.5 [1.7 to 32.6], and in the trial by

Study	Setting	Age (y) (At beginning of follow-up)	Follow-up (years)	Results
Nordström 2021	Population	50-74	-	Complications: MRI-guided Biopsy vs Standard Biopsy -Infection: OR=0.4 [0.2-0.7] -Hospitalization: OR=0.3 [0.2-0.7]
Kilpeläinen 2015	Population	55-67	15	Survival: HR=0.89 [0.76-1.04]
Hugossön 2018	Population	55-69	16	Overdiagnosis: RR=3.4 [2.9-3.9] Overall mortality: RR= 1.23 [1.18-1.29]
Franlund 2022	Population	50-64	22	Overdiagnosis: RR=0.39 [0.33- 0.44] Overall mortality: RR=1.02 [0.97-1.08] PCa specific mortality: RR: 0.7 [0.6-0.9]
Auvinen 2024	Population	50-63	3.2	Overdiagnosis: RD= 0.27 [0.12-0.42]
Martin 2024	Primary care practice	50-69	15	PCa mortality RR: 0.9 [0.85-0.99] Overall mortality OR: 0.97 [0.94-1.01]
Lujan 2015	Population	45-70	15.8	Overdiagnosis: RR=1.7 [1.3-2.3] PCa specific mortality: RR=0.3 [0.1-0.9] Overall mortality: RR=0.95 [0.82-1.01]
Arsov 2021	Population	45 yr. only	15	Overdiagnosis: RR=7.5 [1.7-32.6]
Godtman 2021	Population	55-69	16	Complications: 0.9x100.000 screened. Overall mortality: RR=0.79 [0.71-0.88]
Carlsson 2017	Population	50-54	17	Overdiagnosis: RR= 6.5 [5.0-8.5] PCa specific mortality: IRR=0.29 [0.1-0.7] Overall mortality: IRR= 0.99 [0.89-1.10]
Remmers 2023	Population	55-74	20	Overdiagnosis: RR=1.09 [1.04-1.15] Overall mortality: RR= 0.92 [0.91-0.94]

Table 2: *Outcomes and complications of the studies included in the main results.*

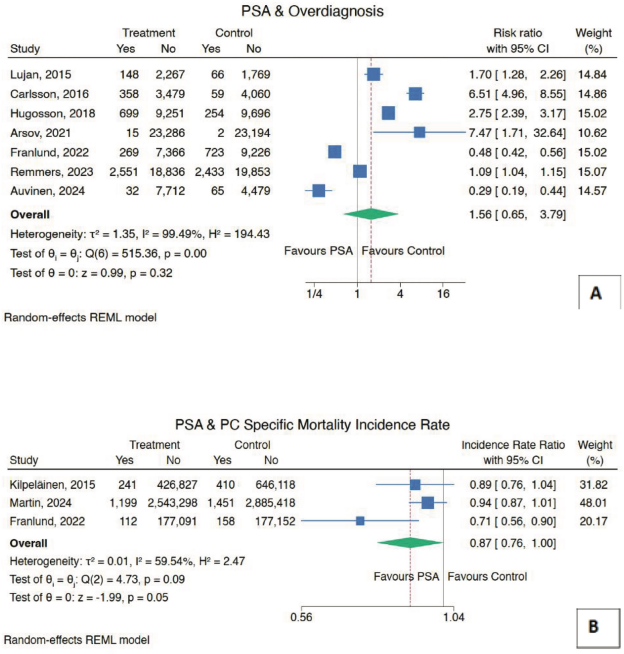

Figure 2:

Figure 2: *Forest plots from random-effects meta-analyses evaluating the impact of PSA screening: (A) overdiagnosis risk ratios (RRs), (B) prostate cancer-specific mortality incidence rate ratios (IRRs), and (C) overdiagnosis subgroup analysis of articles published after 2020.*

S. Carlsson et al. (2017): Risk Ratio 6.5 [5 to 8.5]. On the contrary, it was very low or non-significant in the rest of the articles, especially in those published after 2021. The pooled effect demonstrated that the overdiagnosis was non-significant: Risk Ratio 1.56 [0.65 to 3.79].

Across the studies, a consistent trend was observed: PSA screening significantly increased the detection of localized and low-grade prostate cancers. For example, Martin et al. (2024), Hugosson et al. (2018, 2019), and Frånlund et al. (2022) all reported increased incidence of early-stage cancers in screened groups compared to controls. PSA screening did not influence overall mortality; the common effect was near null: Risk Ratio 0.99 [0.88 to 1.11].

In terms of prostate-specific mortality, two of the long-term randomized trials, by Hugosson et al. (2018, 2019) and Kilpeläinen et al. (2015), demonstrated a reduction in prostate cancer mortality with screening, particularly with longer follow-up ($\geq$15 years). Hugosson et al. (2018) reported that Cumulative PCa mortality was 0.98% (95% CI 0.78–1.22%) in the screening group versus 1.50% (95% CI 1.26–1.79%) among controls, an absolute reduction of 0.52% (95% CI 0.17–0.87%). The rate ratio (RR) for PCa death was 0.65 (95% CI 0.49–0.87). To prevent one death from PC, the number needed to invite was 231, and the number needed to diagnose was 10. Kilpeläinen et al. (2015) reported that the absolute risk of PCa death was 0.76% in the SA and 0.85% in the CA; the observed hazard ratio (HR) was 0.89 (95% confidence interval (CI) 0.76–1.04). After correcting for non-attendance, the HR was 0.78 (0.64–0.96). The combined effect of the included studies showed a marginal decrease in this outcome: Risk Ratio: Incidence Rate Ratio 0.87 [0.76 to 1.0]. Figure 3 summarizes the forest plot of this part.

Assessment of Risk of Bias in Individual Studies

No discrepancies occurred among the designated group of three reviewers, who independently assessed every article; consensus was met when two out of the three were in agreement.

Among the intention-to-treat analyses, several studies, like Arsov et al. (2022), Auvinen et al. (2024), and Remmers et al. (2023), were judged to have an overall low risk of bias. However, others, including Godtman et al. (2021), Hugosson et al. (2018, 2019), and Martin et al. (2024), demonstrated high risk, particularly due to missing outcome data and deviations from intended interventions. The two studies evaluated under per-protocol analysis (Kilpeläinen et al., 2015; Krilaviciute et al., 2023) showed an overall high risk of bias, largely related to incomplete data and selective reporting. The only observational study assessed using the Newcastle-Ottawa Scale (S. Carlsson et al., 2017) received a moderate quality rating. Overall, the predominant concerns across studies were related to missing data and reporting bias, which may influence the certainty of evidence in pooled analyses. Figure 4 summarizes the assessment of risk of bias using Rob2 and the Newcastle-Ottawa Scale.

Certainty of Evidence:

Publication bias was significant for prostate cancer-specific mortality (p=0.0447) and especially for complications (p=0.000), which means that for those outcomes, there was a lack of small studies or negative results (see Figure 5, the funnel plots).

Discussion

Prostate cancer screening is complex, as it involves balancing mortality reduction with the risks of overdiagnosis and treatment complications. Large randomized clinical trials in Europe, such as those by Hugosson et al. (2018) and Frånlund et al. (2022), show that PSA screening can reduce prostate cancer-specific mortality, especially in younger populations undergoing repeated testing. The Göteborg study (Hugosson et al., 2018) shows a significant mortality reduction after 18 years, and Frånlund et al. (2022)'s report improved detection and reduced mortality with biennial screening in men aged 50 to 64 over 22 years, although with increased diagnoses.

Overdiagnosis and Overtreatment

Overdiagnosis and overtreatment continue to be a main concern. Data obtained from autopsy reviews (Bell et al., 2015), with screening studies from Germany and the UK, show the prevalence of clinically insignificant or incidental cancers, this being more important with increasing age. This supports data from the USPSTF and The Advanced Prostate Cancer: AUA/SUO guidelines, both providing information that 20-50% of prostate cancers detected via PSA screening may never be clinically significant (symptomatic or life-threatening). This increases the importance of accurate risk stratification, as overtreatment can often result in complications such as urinary incontinence and erectile dysfunction, among others (US Preventive Services Task Force et al., 2018). Suggestion: Studies from Latin America (Tourinho-Barbosa et al., 2016) reflect barriers to prostate cancer screening, reflecting global disparities. Similarly, the UK trial by Martin et al. (2024), with over 400,000 participants exceeding the cohorts of Hugosson et al.

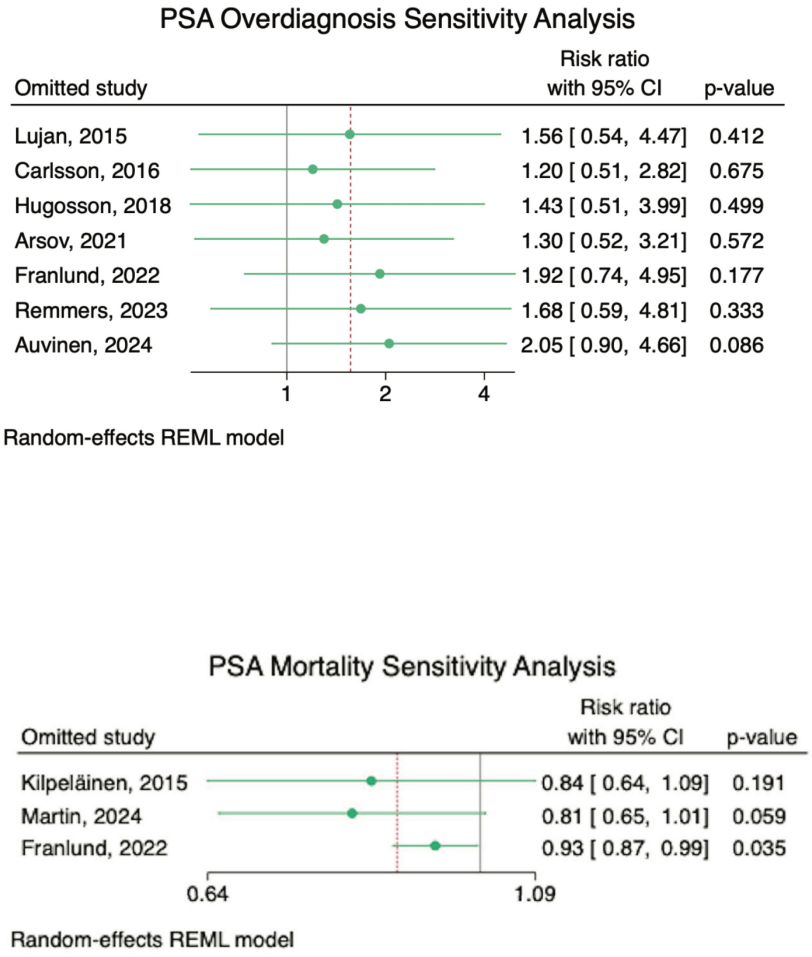

Figure 3: *Forest plots summarizing the effect of PSA screening on (A) overall mortality and (B) diagnostic pathway complications.*

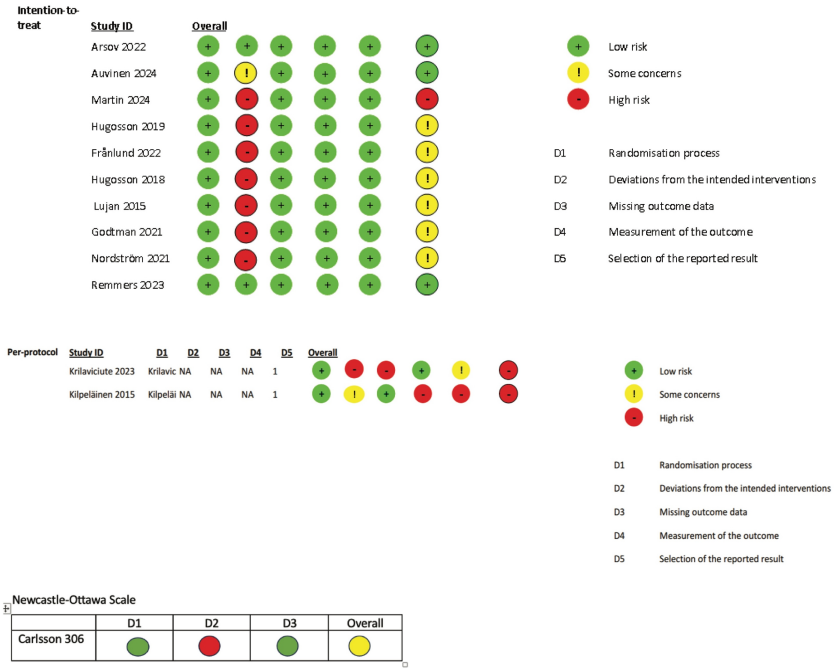

Figure 4: *Risk of bias assessment performed using the RoB2 tool and the Newcastle-Ottawa Scale.*

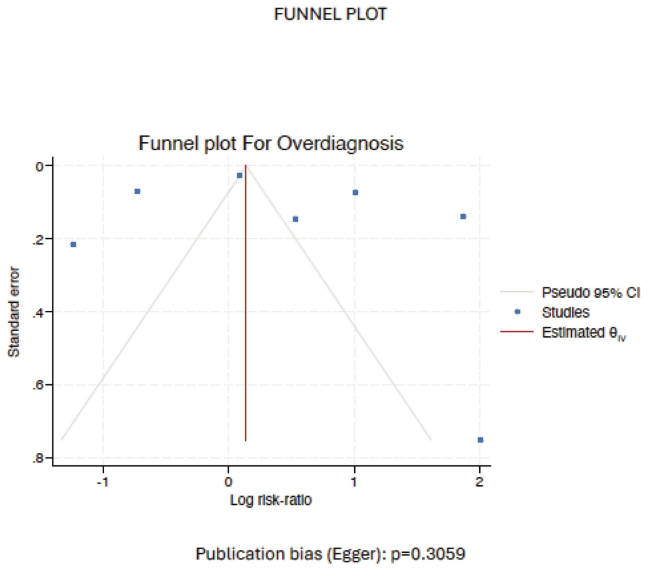

Figure 5: *Funnel plot assessing publication bias for overdiagnosis outcomes in PSA screening studies.*

(2018) and Frånlund et al. (2022), found no mortality difference after 15 years, reinforcing the discussion on the long-term effectiveness of population-wide PSA screening.

Divergent evidence has impacted PSA screening. Following the USPSTF recommendation against routine screening, a decline in screening rates was observed among American men aged 50 and older (Jemal et al., 2015). Simulation models estimate a 13–20% increase in mortality if screening is completely discontinued.

High-quality clinical trials show that PSA screening can reduce prostate cancer-specific mortality (Hugosson et al., 2010; Schröder et al., 2009, 2012), but the balance between risks and benefits is delicate. A personalized, risk-adapted approach is necessary to minimize overdiagnosis and treatment complications, considering healthcare system infrastructure and available diagnostic advances.

This review aims to provide an insight into PSA screening strategies that might reduce mortality while minimizing harms related to PSA screening. Due to the high heterogeneity observed across studies and sensitivity analysis, findings should be interpreted with caution.

Overdiagnosis is not inevitable: multiparametric MRI with targeted biopsy can halve the detection of insignificant tumors without missing aggressive cases (Hugosson et al., 2022; Wallström et al., 2025). Biomarkers like the 4Kscore can avoid up to 82% of unnecessary biopsies, enabling personalized screening (Lenfant et al., 2023).

Successful implementation depends on equitable access to these technologies and surveillance programs, which remain unevenly distributed in the region.

Heterogeneity and Generalizability

Across the studies included, several sources of heterogeneity were observed that may influence the interpretation of results. The most notable differences are related to the intervention, protocols, population demographics, and study setting. While all studies employed PSA- based screening, the specific implementation varied: some used traditional PSA testing alone, others, such as Nordström et al. 2021, incorporated additional algorithms like the Stockholm3 test. The screening intervals and follow-up durations also differed, ranging from single-time screening events to repeated biennial screenings over 15 to 22 years.

There was considerable variation in the comparator arms. Martin et al. (2024) compared PSA screening with standard care, while Krilaviciute et al. (2023) included digital rectal examination in the control group. This difference could impact both the detection rate and the subsequent management of prostate cancer across studies.

Demographically, the included populations ranged in age from 45 to 74 years, with geographical settings across Europe, like Sweden, the UK, and Germany, which may influence generalizability. Some studies enrolled men from specific cities, Göteborg and Stockholm, while others included broader na-

tional cohorts. Differences in healthcare infrastructure, baseline risks, and comorbidity profiles across these settings likely contributed to variability in outcomes such as biopsy rates, cancer detection, and mortality.

Moreover, the outcomes measured were not uniform. While cancer-specific mortality and overall mortality were commonly assessed, other studies focused more on detection rates or biopsy outcomes. Only a subset of trials comprehensively reported complications of diagnostic procedures, overdiagnosis, or false positives. Lastly, study design quality was largely robust, although the inclusion of one observational cohort study introduced further methodological heterogeneity.

Policy Implications

Furthermore, the articles cited previously reveal considerable heterogeneity in their methodologies, populations, and exposures, offering essential context for interpreting PSA screening in diverse settings. Tourinho-Barbosa et al. (2016) reported observational data from Latin America, where limited infrastructure and inconsistent adherence to clinical guidelines influence screening uptake and outcomes. In contrast, Jemal et al. (2015) used national registry data to evaluate PSA screening trends in the United States following the USPSTF's recommendation against routine testing, highlighting policy-driven variability in exposure to PSA. Methodologically, these studies ranged from ecological analyses to retrospective cohort designs and national surveys, and their populations varied in age, race, healthcare access, and baseline prostate cancer risk. Additionally, exposures differed: Jemal et al. (2015) evaluated the impact of public policy on screening behavior, while Tourinho-Barbosa et al. (2016) examined outcomes in under-screened or underserved populations. This heterogeneity limits its comparability but underscores the necessity of tailoring PSA screening strategies to diverse health systems and demographic realities.

These findings support the use of PSA only as an initial step in a stepwise diagnostic approach. After an elevated result, using risk calculators, MRI, or biomarkers reduces unnecessary biopsies while maintaining detection of aggressive cases (Arsov et al., 2022; Nordström et al., 2021). Biopsies and curative treatments should be reserved for men with clear signs of clinically significant cancer (S. V. Carlsson & Vickers, 2020; Hugosson et al., 2018). Healthcare systems, especially those with limited resources, need to prioritize access to these tools and active surveillance programs to minimize harms from overdiagnosis (Frånlund et al., 2022; Godtman et al., 2021). Public policies can support this by funding decision aids and reimbursement models that encourage risk-adapted screening instead of reflex PSA testing (Martin et al., 2024). Future research should standardize definitions of insignificant cancer, evaluate patient-centered outcomes, and assess the cost-effectiveness of MRI- or biomarker-first strategies in diverse populations, including regions with high mortality but limited infrastructure (Kilpeläinen et al., 2015; Krilaviciute et al., 2023).

Limitations and Strengths

The findings are relevant but have limited external validity. The studies mainly included white, asymptomatic middle-aged to older men from high-income countries with strong healthcare infrastructure. This limits applicability to diverse populations, such as Black men and low- or middle-income countries. Methodological heterogeneity across studies, such as differences in screening intervals, follow-up, and outcome definitions, hampers comparisons. Some used traditional PSA testing, while others, like Nordström et al. (2021), adopted advanced tools like the Stockholm3 algorithm, leading to inconsistencies with other healthcare settings. Although the review supports the long-term effectiveness of PSA-based screening within structured settings, its findings may not fully translate to regions with different infrastructure, healthcare delivery models, or evolving screening strategies like MRI or risk-adapted approaches. As such, caution is warranted when extrapolating these results to more heterogeneous or resource-limited populations.

A key limitation of this review is the use of a restricted search strategy with the combination of MESH terms and Titles and abstract phrases, which could have limited the number of studies included in this review. Embase and Cochrane CENTRAL were not included due to the lack of institutional access, and only open-access databases were used. Our search was limited to major databases to prioritize high quality articles. We acknowledge that this could lead to publication bias and explain the low numbers of complications reported in this review. On the other hand, the strengths of this review are the large sample size, which adds strength to the generalizability of the results.

Key Points

• Screening has not been shown to prolong men's lifespan. Looking at eleven solid studies that followed men for up to two decades, routine PSA testing

does not change overall life expectancy.
• Screening confers a minor reduction in prostate cancer-specific mortality. Estimates suggest that approximately one additional life is saved for every few hundred men who adhere to regular screening schedules. A key concern is the overdiagnosis of indolent tumors. Many tumors would not have affected patients' health during their lifetime; combined data suggest that PSA testing is more likely to identify clinically insignificant cancers rather than aggressive tumors. Current biopsy techniques offer improved safety methods. Serious infection or a hospital stay after biopsy is now rare (under 2%), and MRI-guided procedures make those complications even less likely.
• PSA screening should follow a personalized, stepwise pathway, escalating to imaging or biopsy when risk justifies it and the patient accepts the trade-offs. This approach may prevent a few clinically significant deaths while limiting unnecessary intervention, though high heterogeneity calls for caution in evaluating these findings.

Conclusions

Our findings indicate that the careful implementation of PSA screening may not result in a substantial increase in overdiagnosis. A modest reduction in prostate cancer–specific mortality was observed, with no relevant change in overall mortality and no significant rise in diagnostic pathway–related complications. We suggest that future investigations focus on optimizing risk-stratification strategies to more precisely identify individuals most likely to benefit from PSA screening while minimizing associated harms patient values.

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Supplementary Materials

Summary of the search strategy; screen title, abstract, and text; screen text.

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Conflicts of Interest

The authors declare no conflict of interest.

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