TITLE

Magnetic Resonance Imaging in Prostate Cancer Screening: A Systematic Review and Meta-analysis

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KEY POINTS

Question: Do prostate cancer screening pathways that incorporate magnetic resonance imaging (MRI) and targeted biopsies outperform strategies relying solely on prostate-specific antigen (PSA) testing and systematic biopsy?

Findings: In this meta-analysis of 80,591 screened men from 12 studies, MRI-based screening was found to reduce the use of unnecessary prostate biopsy and the detection of clinically insignificant prostate cancer, while maintaining the detection of clinically significant prostate cancer, compared to PSA-only strategies.

Meaning: The findings of this meta-analysis support the integration of prostate MRI in prostate cancer screening to improve the balance of patient harms and benefits.

ABSTRACT

Importance: Prostate magnetic resonance imaging (MRI) is increasingly integrated within the prostate cancer (PCa) early detection pathway.

Objective: To systematically evaluate the existing evidence regarding screening pathways incorporating MRI with targeted biopsy and assess their diagnostic value compared to prostate-specific antigen-based (PSA) screening with systematic biopsy strategies.

Data Sources: PubMed/Medline, Embase, Cochrane/Central, Scopus, and Web of Science (through May 2023).

Study Selection: Randomized clinical trials and prospective cohort studies were eligible if they reported data on the diagnostic utility of prostate MRI in the setting of PCa screening.

Data Extraction: Number of screened individuals, biopsy indications, biopsies performed, clinically significant PCa (csPCa) defined as International Society of Urological Pathology (ISUP) grade≥2, and insignificant (ISUP1) PCa-s detected were extracted.

Main Outcomes, Measures and Data Synthesis: The primary outcome was csPCa detection rate, secondary outcomes included clinically insignificant PCa detection rate, biopsy indication rates, and positive predictive value for the detection of csPCa. The generalized mixed-effect approach with pooled odds ratios (OR) and random-effect models was used to compare the MRI-based and PSA-only screening strategies. Separate analyses were performed based on the timing of MRI (primary/sequential after PSA test) and cut-off (Prostate Imaging Reporting and Data System (PI-RADS) ≥3 or ≥4) for biopsy indication.

Results: We synthesized data from 80,114 men from 12 studies. Compared to standard PSA-based screening, the MRI pathway (sequential screening, PI-RADS≥3 cut-off for biopsy) was associated with higher odds of csPCa when tests results were positive (OR: 4.15, 95%-CI: 2.93-5.88, p≤0.001), decreased odds of biopsies (OR: 0.28, 95%-CI: 0.22-0.36, p≤0.001) and insignificant cancers detected (OR: 0.34, 95%-CI: 0.23-0.49, p=0.002), without significant differences in the detection of csPCa (OR: 1.02, 95%-CI: 0.75-1.37, p=0.86). Implementing a PI-RADS≥4 threshold for biopsy selection led to a further reduction in the odds of detecting insignificant PCa (OR: 0.23, 95%-CI: 0.05-0.97, p=0.048), and biopsies performed (OR: 0.19, 95%-CI: 0.09-0.38, p=0.01), without differences in csPCa detection (OR: 0.85, 95%-CI: 0.49-1.45, p=0.22).

Conclusion and relevance: Integrating MRI in PCa screening pathways reduces the number of unnecessary biopsies and the overdiagnosis of insignificant PCa, while maintaining csPCa detection as compared with PSA-only screening.

TEXT

I. Introduction

Prostate-specific antigen (PSA)-based prostate cancer (PCa) screening has been shown to reduce PCa-specific mortality, but is associated with unnecessary biopsies, overdiagnosis, overtreatment and an unclear impact on overall survival.[1,2] To balance these risks and benefits, clinical practice guidelines recommend shared decision making strategies to identify informed candidates most likely to benefit from PCa early detection.[3,4] This opportunistic approach has, however, led to widespread but untargeted testing accompanied by disparities in health care access and literacy.[3-5] Moreover, the inherent limitations of PSA-based PCa screening including unnecessary biopsies and overtreatment of low-grade disease have not been addressed.[5,6]

Pre-biopsy prostate magnetic resonance imaging (MRI) followed by targeted biopsies has been widely integrated in the diagnostic pathway for PCa, as it improves the detection of clinically significant PCa, while reducing the number of unnecessary biopsies and insignificant cancers in a clinical setting.[3,7,8] As a result, clinical practice guidelines recommend pre-biopsy MRI, however there is no consensus about the role of MRI as an integrated PCa screening tool.[3,4] Consequently, several ongoing clinical trials are investigating the value of incorporating pre-biopsy MRI with targeted biopsy into population-based PCa screening protocols, to overcome the limitations of conventional PSA-based screening.

In the setting of a large body of literature addressing the diagnostic role of prostate MRI and its growing global usage, there is a need to synthesize evidence to inform clinical practice, and help devise a screening strategy incorporating MRI information. To address this unmet need, in this systematic review and meta-analysis we summarised the currently available literature on the performance of PCa population-based screening strategies incorporating

MRI, and compared them to PSA-only-based screening approaches. We hypothesized, that PSA-MRI-based PCa screening strategies would outperform PSA-only-based screening, in terms of clinically relevant endpoints.

II. Methods

This systematic review and meta-analysis is reported according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guideline (eTable 1), and the Cochrane Handbook.[9,10] The study protocol was registered on PROSPERO (registration number: CRD42023423945).

Eligibility criteria, outcome measures

To evaluate the performance of MRI-based screening strategies, we utilized the PICO framework.[11] We included studies of men in the general population or those with elevated genetic risk for PCa screened for PCa (Population), who underwent MRI examination as part of the screening (Intervention) and were compared with men screened for PCa using PSA alone (Comparison). Studies were selected if they reported data in screening-like populations, while those addressing diagnostic test accuracy, or those enrolling preselected men for biopsy (men with lower urinary tract symptoms, elevated PSA, or suspect DRE) were excluded. The primary endpoint was the cancer detection rate (CDR) of clinically significant PCa, defined as International Society of Urological Pathology (ISUP) grade ≥2 (Outcome). Secondary endpoints included the CDR of insignificant PCa (defined as ISUP grade 1), positive-predictive values (PPV) for the detection of significant and insignificant PCa-s, MRI and biopsy indication, biopsy adherence, and complication rates. Moreover, we calculated CDR-s, using alternative definitions of significant (ISUP≥3) and insignificant (ISUP 1-2) PCa. This meta-analysis was restricted to prospective observational or randomized studies.

Search strategy, study selection, and data collection

The MEDLINE (via PubMed), Embase, Cochrane/Central, Scopus, and Web of Science databases were queried on the 5th of May 2023 to identify all available studies containing information on MRI-based screening strategies. After selection by two independent review authors the following data were extracted from the eligible studies: general information, study population characteristics, details of the intervention and comparator, including screening algorithm (MRI in first-line/sequential screening), sequence (biparametric/multiparametric) and type (1.5T/3T) of MRI, Prostate Imaging Reporting and Data System (PI-RADS) cut-off for the indication of biopsy (PI-RADS ≥3 or ≥4), type of biopsy approach (targeted+systematic/targeted-only, cognitive/image-fusion) PSA cut-off, additional novel biomarkers in the screening pathway, and outcomes of interest listed above.[12] In cases where studies did not provide information on our specified outcomes, two authors independently calculated them, using the data provided within the studies. Any disagreements on study selection and data extraction were resolved through consensus with a third author. Sensitivity, specificity, and negative predictive value could not be evaluated because prostate biopsies were not performed in cases of negative screening tests. To address inconsistencies or overlapping data among studies, we made adjustments to the study samples (eTable 2). More detailed descriptions of the inclusion criteria, search strategy, selection and data extraction process are presented in eAppendix 1 and eTables 2-3.

Statistical analyses

Quantitative data synthesis was carried out with the R statistical software (R Core Team, 2019, Vienna, Austria, R version 4.1) and adhered to the methods recommended by the working group of the Cochrane Collaboration.[10] Based on the likely heterogeneity of the studies included, we used random-effect models for our calculations.[13,14] To assess and compare CDR, PPV, MRI, biopsy indication rates, and adherence to biopsy of the different screening pathways, we calculated pooled event rates and odds ratios (OR) with 95%

confidence intervals (CI) using the generalized mixed effect approach.[15] To assess the optimal timing of MRI in the screening pathway, we conducted separate analyses based on different PI-RADS cut-offs for indicating biopsy (≥3,≥4) and MRI timing (primary/sequential). We utilized forest plots to visualize event rates and effect measures. To evaluate the moderator effect of different factors, type of MRI sequence, biopsy technique, and study design we performed subgroup analyses. Heterogeneity was assessed by calculating the I^2 measure and its CI. Publication bias could not be assessed due to the low number of articles for one outcome.[16] Full details of the statistical analysis are described in eAppendix 1. No ethical approval was required for this systematic review and meta-analysis, as already published, secondary data were used.

Risk of bias

For randomized and non-randomized studies, the risk of bias (RoB) was evaluated according to the Cochrane Collaboration's RoB assessment (RoB2), and the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tools, independently by two reviewers.[17,18] Disagreements were resolved via consensus with a third author.

III. Results

Study selection and baseline characteristics

Our search key identified 2037 studies of which 1464 were screened after removing duplicates. Finally, from the 28 full-text selected studies, 12 and eight were eligible for qualitative and quantitative evidence synthesis, respectively (Figure 1). Detailed explanation for the exclusion of the studies can be found in eAppendix 2. Table 1 shows the baseline characteristics of the included studies. Overall, we assessed 80,114 screened individuals from 12 studies. We identified four population-based randomized controlled trials, two prospective

cohort, and three prospective pilot studies.[19-28] Moreover, we included two studies that report on the efficacy of MRI in a pre-screened population.[29,30] We identified four studies that report data on the use of both novel molecular biomarkers and MRI in PCa screening.[23,26-28] Most publications included data on the use of MRI as a sequential screening tool (after PSA pre-screening), however, three studies were identified reporting on upfront MRI.[19,24,25] Five studies utilized biparametric MRI (bpMRI) and eight included multiparametric MRI (mpMRI) (Table 1). As for the method of biopsy, seven studies used MRI targeted-only, while six studies used additional systematic sampling (Table 1). For further details on the studies and interventions, please refer to eTables 4-5.

MRI as a sequential screening tool

We synthesized data from 57,081 men derived from six articles that applied MRI in a PSA-prescreened population (as part of sequential screening), with a PI-RADS≥3 cut-off as the biopsy indication.[19-22,29,30] A detailed overview of CDRs, PPVs, biopsy indication, and adherence rates can be found in Table 2 and eFigures 1-4. The number of men needed to screen to detect one significant PCa were 59 and 63 for PSA-only, and MRI-based strategies, respectively. Although we found no difference between MRI- and PSA-only screening methods in terms of clinically significant CDR (OR: 1.02, 95%-CI: 0.75-1.37, p=0.86) (eFigure 1), the MRI pathway was associated with lower odds of insignificant PCa detection (OR: 0.34, 95%-CI: 0.23-0.49, p=0.002) (Figure 2).[19,20,22,29,30] These trends in CDR remained similar, when alternative definitions were applied for significant (ISUP≥3, OR: 0.91, 95%-CI: 0.54-1.52, p=0.4), and insignificant PCa-s (ISUP1-2, OR: 0.54, 95%-CI: 0.23-1.29, p=0.09) (eFigure 5). Furthermore, screening strategies incorporating MRI, had a higher PPV for the detection of significant PCa (OR: 4.15, 95%-CI: 2.93-5.88, p=0.001), and a lower biopsy rate (OR: 0.28, 95%-CI: 0.22-0.36, p<0.001) than PSA-only-based ones (Figure 2, eFigures 2-3).[19,20,22,29,30] The pooled rate of MRI was 8.5% (95%-CI: 2.6-24.8%; I^2=100%) among the

screened individuals, and patients adhered more to the biopsy when MRI was used (OR: 4.61, 95%-CI: 2.39-8.89, p=0.01) (eFigure 4).[19-22,29,30] To identify the high rate of heterogeneity among the studies and to assess the role of possible confounders, we stratified studies based on the type of MRI sequence, biopsy method and study design (eFigures 6-7). We observed differences in terms of PPV, but not in CDR and biopsy rate. Compared to mpMRI, the use of bpMRI, led to a higher PPV for significant PCa (61.1% (95%-CI: 26.5-87.3%) vs 34.8% (95%-CI: 25.2-45.7%), p<0.001), and a lower PPV for insignificant PCa (11.5% (95%-CI: 1.3-55.1%) vs 19.5% (95%-CI: 12.3-29.6%), p=0.01), respectively, without heterogeneity across the subgroups (eFigures 7A,D). Notably, both targeted+systematic (vs targeted), and image fusion (vs cognitive) biopsies had a lower PPV for insignificant cancers (eFigures 7E,F).

Among 19,501 patients who underwent prostate MRI utilizing a PI-RADS cut-off of ≥4 as biopsy indication, we observed even lower odds of insignificant PCa detection (OR: 0.23, 95%-CI: 0.05-0.97, p=0.048) and lower odds of biopsy (OR: 0.19, 95%-CI: 0.09-0.38, p=0.01), with a higher PPV (OR: 7.01, 95%-CI: 1.76-27.98, p=0.03) and similar CDR (OR: 0.85, 95%-CI: 0.49-1.45, p=0.23) for significant disease, compared to standard PSA-only screening (Figure 3, eFigures 8-10).[19,20,29]

MRI as a first-line screening tool

To evaluate the performance of MRI (PI-RADS≥4) as a primary screening tool, we synthesized data from three articles involving 983 men.[19,24,25] Clinically significant and insignificant CDR-s were 6% (95%-CI: 0.6-39.4%, I^2: 92%), and 1.2% (95%-CI: 0.2-7.3%, I^2: 55%), respectively (eFigure 11A,B). Positive predictive value of upfront MRI to detect significant PCa was 41.9% (95%-CI: 16.1-73%, I^2: 57%) (eFigure 11C). Due to the limited availability of data, comparison of MRI-based screening with PSA-based approaches was

only feasible in terms of biopsy selection, which revealed no significant difference between the two strategies (OR: 0.81, 95%-CI: 0.23-2.87, p=0.5) (eFigure 12C).[19,24,25]

MRI- and novel biomarker-based screening strategies

We identified four articles reporting on the combination of MRI and novel biomarkers, however given the heterogeneity between populations and interventions within studies we did not perform quantitative data synthesis.[23,26-28] In this subset, the use of novel biomarkers was associated with fewer insignificant PCa-s, while maintaining significant disease detection.[23,26] Moreover, MRI has been shown to be an effective screening tool in patients, with a genetic predisposition for PCa.[28]

Risk of bias

The RoB 2 and ROBINS-I tools identified a low overall risk of bias in the majority of the included studies for our CDR, PPV, MRI, biopsy rates, and adherence to biopsy indication outcomes (eFigures 13,14). Among RCTs, the intervention in the PROBASE trial was found to be biased, as MRI examination was not part of the screening protocol, although, MRI data was available in 79% of participants, and 114 out of 120 men (95%) underwent MRI/ultrasound fusion targeted and systematic biopsy.[21] Despite some prospective cohort studies showing a moderate risk in categories mainly based on the population of the study, the majority of these articles displayed a low overall risk of bias.

IV. Discussion

We present the first systematic review and meta-analysis assessing the performance of MRI in the setting of PCa screening. There are several notable, and clinically relevant findings from our study. First, these analyses suggest that MRI as part of sequential screening performs similarly to conventional PSA-based strategies in the detection of clinically significant PCa, while reducing the number of detected insignificant cancers. Second, pre-biopsy MRI can

substantially reduce the number of unnecessary prostate biopsies performed, and enhances the PPV for significant PCa detection, compared to PSA-only screening with standard biopsies. Moreover, modifying the threshold of offering prostate biopsy to PI-RADS≥4, and the use of bpMRI may further reduce the rate of unnecessary biopsies, while not meaningfully compromising the detection of significant PCa. Finally, our results suggest that MRI as a first-line screening tool does not seem to exhibit the aforementioned benefits in reducing biopsy rates, and the detection of insignificant PCa.

Our findings support and strengthen the cumulative evidence suggesting that the use of MRI following initial PSA prescreen decreases the detection of insignificant PCa, compared to PSA-only approaches. Thus, MRI is a useful tool to mitigate the limitations of PSA-based screening, including overdiagnosis of indolent PCa, which can lead to overtreatment with unnecessary complications associated with any therapy.[31,32] On the other hand, the two screening strategies were similar in terms of CDR for clinically significant disease. Based on our analysis, the number needed to screen, to detect one significant PCa were 59 and 63 for PSA-only, and MRI-based strategies, respectively.

Moreover, use of MRI-based screening strategies was associated with higher PPV for the detection of clinically significant PCa, and reduced the number of biopsy indications. Based on our findings, the number of biopsies needed to detect one significant prostate cancer is 2 and 6 with MRI-based and PSA-only screening, respectively. These findings are particularly notable given the risks of bleeding, infection, discomfort, expense associated with prostate biopsy, as well as the psychological burden of screening triggered workup.[33,34] Moreover, avoiding biopsy and following up patients with negative MRI were shown to be a safe approach in screening.[35,36] According to our data, patients are more willing to undergo biopsy when the indication is underlined with MRI results, which is an important factor in achieving better outcomes, and a more equal distribution of health care resources.[5,37-39] In modelling

studies, MRI-based PCa screening is associated with an improvement in the benefit-harm profile, quality of life, cost-effectiveness, and environmental impact of screening for PCa, compared with standard PSA-based screening.[40-44] Accordingly, our results synthesizing high-quality prospective data suggest, that MRI is effective at identifying individuals most likely to require further evaluation and biopsy, potentially reducing the burden on healthcare resources, and sparing patients from unnecessary invasive procedures.

This study aggregates performance characteristics of MRI-based screening across PI-RADS cut-offs for biopsy selection, different sequences (multi- or biparametric), biopsy methods (targeted-only or targeted+systematic) and fusion types (cognitive or image fusion). Our analysis suggests, that implementing a PI-RADS≥4 cut-off can further reduce the number of insignificant cancers detected and biopsies performed. Additionally, the choice of MRI sequence, whether bi- or multiparametric, is an important aspect of screening, as shorter bpMRI protocols are faster, more cost-effective, and reduce exposure to contrast material, making them valuable in the screening process.[45,46] However, bpMRI interpretation may be more challenging, requiring a higher level of expertise.[47] Importantly, we found that bpMRI is associated with a higher PPV for the detection of significant PCa, which may be attributable to preferentially identifying larger, more conspicuous lesions in the absence of contrast.[45,48] Lastly, we examined the role of biopsy approach on MRI-based screening outcomes. These results revealed no significant differences in terms of CDR and PPV for significant disease between the targeted-only and targeted+systematic biopsy techniques, as well as between image fusion and cognitive biopsy methods. However, it is worth noting that both the targeted+systematic and image-fusion biopsies demonstrated a lower PPV for detecting clinically insignificant prostate cancer. These findings suggest that a screening pathway incorporating bpMRI following PSA pre-screening, coupled with a PI-RADS≥4 cut-off for biopsy indication, is a highly promising strategy for increasingly accessible, and cost-effective

screening. However, several key questions remain to be addressed in future investigations, including whether to employ targeted-only biopsy, the optimal method for fusion biopsy, a comprehensive analysis of screening costs, and an examination of long-term survival outcomes. Furthermore, it is worth noting that differences in oncologic risk profiles have been observed between PCa cases, diagnosed via MRI-based targeted biopsy, and those identified through standard biopsy methods.[49] These findings underscores the need for further research, to elucidate the behavior of PCa-s identified with MRI and targeted biopsy and their implications for patient management and treatment strategies.

Our study also highlights the importance of considering the timing and type of MRI, and biopsy in the screening process. While MRI, following PSA pre-screening (sequential pathway), demonstrated numerous advantages over PSA-only strategies, upfront MRI as a primary tool did not appear to exhibit the aforementioned benefits in terms of biopsy rates, and insignificant PCa detection, however it lead to a notable CDR for significant PCa. Although, these results are limited by the lack of data for formal statistical comparison, this suggests that while MRI is valuable for refining the selection of patients for biopsy, its utility as a primary screening tool needs to be further assessed in the future. Interestingly, among men under 55 years harboring breast cancer gene (*BRCA*) germline mutations, upfront MRI has been demonstrated to have the highest clinical benefit, highlighting its diagnostic value for patients with genetic predisposition for PCa.[28]

This study has several limitations. These include: (1) relatively low number of articles that could be included, and in line with this (2) subgroup evaluation, heterogeneity and publication bias assessment were limited. (3) As no biopsy was performed in case of negative MRI result, sensitivity, specificity and negative predictive values, therefore, could not be assessed. (4) The majority of the studies assessed a Scandinavian population, limiting the generalizability of our findings. (5) Safety and long-term survival data could not be synthesized, limiting the

full-scale interpretation of our results. (6) Finally, the optimal intensity and interval of MRI-based screening rounds have yet to be established, which require consideration of trade-offs regarding frequency of procedures, cancer detection, and associated costs.

V. Conclusions

The results of this systematic review and meta-analysis suggest that prostate MRI with targeted biopsies is an effective strategy for the early detection of prostate cancer. We found that MRI mitigates pitfalls of standard PSA-based strategies, as it can lead to fewer unnecessary biopsies and help to avoid the detection of insignificant cancers, while not comprising significant disease detection. Our results highlight the need to reassess our approach to population-based screening, however, the optimal setup of MRI and biopsy scheme in the screening process requires further evaluation.

FIGURE LEGENDS

Figure 1: Flow chart of the study selection process

Figure 2: Comparison of MRI- and standard PSA-based screening strategies in terms of prostate cancer detection, biopsy indication rate and PPV

Legends: Screening pathways incorporating MRI reduce the number of clinically insignificant disease (A), and biopsies (B), moreover they outperform PSA-only strategies in terms of PPV for clinically significant prostate cancer detection as well (C). MRI is applied as a sequential screening tool (after PSA-prescreen), with a PI-RADS≥3 cut off for biopsy indication. Abbreviations: CDR: cancer detection rate, MRI: magnetic resonance imaging, PSA: prostate-specific antigen, OR: odds ratio, CI: confidence interval, PPV: positive predictive value, PI-RADS: Prostate Imaging Reporting and Data System System.

Figure 3: The performance of MRI with a PI-RADS≥4 cut-off for biopsy indication.

Legends: Elevating the PI-RADS cut-off to four for the indication of biopsy leads to lower biopsy rates (B) and less insignificant prostate cancers found (A) compared to PSA. Moreover, it enhances PPV for significant disease detection (C). MRI is applied as a sequential screening tool (after PSA-prescreen) in this analysis. Abbreviations: CDR: cancer detection rate, MRI: magnetic resonance imaging, PSA: prostate-specific antigen, OR: odds ratio, CI: confidence interval, PPV: positive predictive value, PI-RADS: Prostate Imaging Reporting and Data System System.

eFigure 1: Clinically significant and insignificant prostate cancer detection rate in MRI-based (sequential, PI-RADS 3-5), and PSA-only screening strategies.

eFigure 2: Positive predictive value of MRI-based (sequential, PI-RADS 3-5) and PSA-only strategies for the detection of clinically significant and insignificant prostate cancer

TABLE LEGENDS

Table 1 – Baseline characteristics of the included studies

Table 2 – Diagnostic performance of screening stragies incorporating MRI

eTable 1 – PRISMA Checklist

eTable 2 – Data extraction

eTable 3 – Definitions of Outcomes

eTable 4 – Inclusion and exclusion criteria of the studies

eTable 5 – Details of MRI imaging and biopsy

First Author (Study name)	Year	Country	Study design	Age of the screened men (median, IQR)	Number of screened	Details of MRI-based strategy (Intervention)			Details of PSA-based strategy (Comparator)	
						Indication of MRI	MRI type	Method of biopsy	PSA cut-off	Type of biopsy
Eldred-Evans[19] (IP1-PROSTAGRAM)	2023	UK	Prospective cohort	57 (53-61)	All: 408 [a]	1st line screening and PSA ≥ 3ng/ml	bpMRI	Image fusion transperineal targeted	≥3ng/ml	Transperineal systematic
Hugosson[20] (Göteborg 2, 1st round)	2022	Sweden	RCT	56 (52-59)	Intervention: 11986 Comparator: 5994	PSA ≥ 3ng/ml	mpMRI	Cognitive transrectal targeted [b]	≥3ng/ml	Transrectal systematic [c]
Arsov[21] (PROBASE)	2022	Germany	RCT	45 (44-47) [d]	Intervention: 23341 Comparator: 23301	PSA ≥ 3ng/ml	mpMRI [e]	Image fusion transrectal targeted and systematic	NA	NA
Eklund[22] (STHLM3-MRI)	2021	Sweden	RCT	66 (61-71)	Intervention: 929 [f] Comparator: 603 [f]	PSA ≥ 3ng/ml	bpMRI	Image fusion transrectal targeted and systematic [g]	≥3ng/ml	Transrectal systematic
Nordström[23] (STHLM3-MRI)	2021	Sweden	RCT	66 (61-71)	Intervention: 1372 [h] Comparator: 921 [h]	PSA ≥ 3ng/ml or Stockholm 3 score ≥ 0.11	bpMRI	Image fusion transrectal targeted and systematic	≥3ng/ml	Transrectal systematic
Nam[25] (MVP – Pilot study)	2016	Canada	Prospective cohort	61 (55-68)	All: 47	1st line screening	mpMRI	Cognitive transrectal targeted and systematic	NA	NA
Nam[24] (MVP)	2022	Canada	RCT	68 (±7.3) [i]	Intervention: 259 Comparator: 266	1st line screening	bpMRI	Image fusion transrectal targeted and systematic	≥2.6ng/ml	Transrectal systematic

First Author (Study name)	Year	Country	Study design	Age of the screened men (median, IQR)	Number of screened	Details of MRI-based strategy (Intervention)			Details of PSA-based strategy (Comparator)	
						Indication of MRI	MRI type	Method of biopsy	PSA cut-off	Type of biopsy
Grenabo Bergdahl[30] (Göteborg, 10th round – Pilot study)	2016	Sweden	Prospective cohort	69 (69-70)	All: 384	PSA ≥ 3ng/ml	mpMRI	Cognitive transrectal targeted	≥3ng/ml	Transrectal systematic
Alberts[29] (ERSPC, 5th round – Pilot study)	2018	Netherlands	Prospective cohort	73 (72-73)	All: 713 [j]	PSA ≥ 3ng/ml	mpMRI	Image fusion transrectal targeted	≥3ng/ml	Transrectal systematic
Rannikko[26] (ProScreen – Pilot study)	2022	Finland	Prospective cohort	64-65 [k]	All: 170	PSA ≥ 3ng/ml and 4Kscore > 7.5%	mpMRI	Image fusion transrectal targeted	NA	NA
Benafif[27] (BARCODE1 – Pilot study)	2022	UK	Prospective cohort	61 (55-69) [l]	All: 307	Poligenic risk score ≥ 90th percentile	mpMRI	Image fusion transrectal targeted and systematic [m]	NA	NA
Segal[28] (NCT02053805)	2020	Israel	Prospective cohort	54 (±9.8) [n]	BRCA1: 108 BRCA2: 80	Elevated age-stratified PSA [o]	mpMRI	Image fusion transrectal targeted	Elevated age-stratified PSA [o]	Transrectal systematic

Table 1. Basic characteristics of the included studies

Footnotes:

[a] All patients underwent screening with both PSA and MRI, therefore both MRI as 1st line and 2nd line (after PSA) screening tool was assessed.

[b] In case of negative MRI and a PSA level >10ng/ml systematic biopsy was performed. In order to assess the performance of targeted biopsy only we excluded cancers detected with systematic biopsy and negative MRI in the experimental arm of the study from our analyses.

[c] In case of positive MRI in the reference arm, targeted biopsy was performed in addition to systematic. To assess the performance of systematic biopsy only we excluded cancers detected with targeted biopsy in the reference arm of the study from our analyses.

[d] Reported as mean and range.

[e] MRI examination was not part of the PROBASE screening protocol since the trial was started before mpMRI was recommended for primary diagnosis of PCa in the EAU guidelines in 2019. However, data on MRI are available in 79% of participants and 114 out of 120 men (95%)

underwent MRI/ultrasound fusion targeted and systematic biopsy. The Arm B of this study indicated prostate biopsy solely on the basis of rectal digital examination findings, therefore we did not include it in our analysis.

[f] The provided numbers represent patients with a PSA ≥ 3ng/ml, as randomization was performed after PSA pre-screening. Initially 12750 patients were screened with PSA.

[g] In case of negative MRI and a Stockholm 3 score ≥ 0.25 systematic biopsy was performed. To assess the performance of MRI-based biopsy only we excluded cancers detected with systematic biopsy on the basis of an elevated Stockholm 3 test.

[h] The provided numbers represent patients with a PSA ≥ 3ng/ml or a Stockholm 3 score ≥ 0.11, as randomization was performed after PSA and Stockholm 3 score-based pre-screening. Initially 12750 patients were screened.

[i] Reported as mean (±standard deviation). Number reported here represent the MRI arm of the study. The mean age of PSA arm was 68 (±7.8).

[j] Number of screened men was adjusted to "Arm 2" of the study.

[k] Only 64–65-year-old men were enrolled.

[l] Reported as mean and range.

[m] All patients with a polygenic risk score ≥ 90th percentile undergo MRI and systematic biopsy. In case of positive MRI (PI-RADS score ≥ 3) targeted biopsy is added.

[n] Reported as mean (±standard deviation). This study enrolled germline breast cancer gene 1 or 2 positive patients.

[o] Elevated age- stratified PSA is defined as: ≥ 1 ng/ml for ages 40-50 years, ≥ 2 ng/ml for ages 50-60 years, ≥ 2.5 ng/ml for ages 60-70 years.

Abbreviations: RCT: randomized controlled trial, IQR: interquartile range, UK: United Kingdom, MRI: magnetic resonance imaging, mpMRI: multiparametric MRI, bpMRI: biparametric MRI, PI-RADS: Prostate Imaging–Reporting and Data System. PSA: prostate-specific antigen, PSAD: PSA density, 4Kscore: kallikrein panel, BRCA1/2: Breast cancer gene 1/2, NA: not applicable.

		Cancer detection rate (95% CI)		Positive predictive value (95% CI)		Biopsy indication rate (95% CI)	Biopsy adherence rate (95% CI)
		Significant PCa	Insignificant PCa	Significant PCa	Insignificant PCa		
MRI sequential (PI-RADS 3-5)	**MRI**	1.1% (0.4-3.1%) I^2: 98%	0.4% (0.1-1.4%) I^2: 94%	41.9% (28.5-56.7%) I^2: 90%	16.3% (10.8-23.9%) I^2: 67%	2.9% (1.4-6.2%) I^2: 99%	95.9% (77.1-99.4%) I^2: 95%
	PSA	1.7% (1-2.8%) I^2: 86%	1.9% (0.7-4.6%) I^2: 96%	16.1% (10.4-24.2%) I^2: 76%	18.4% (11.9-27.3%) I^2: 74%	13.2% (7.3-22.8%) I^2: 98%	88% (75.1-94.6%) I^2: 93%
	MRI vs PSA (OR)	1.02 (0.75-1.37) p=0.86	0.34 (0.23-0.49) p=0.002	4.15 (2.93-5.88) p=0.001	1.0 (0.5-2.0) p=0.99	0.28 (0.22-0.36) p<0.001	4.61 (2.39-8.89) p=0.01
MRI sequential (PI-RADS 4-5)	**MRI**	1.2% (0.4-3.9%) I^2: 86%	0.4% (0.2-0.7%) I^2: 45%	48.9% (35.4-62.6%) I^2: 0%	21.1% (11.9-34.7%) I^2: 0%	2.4% (0.9-6.3%) I^2: 89%	98.7% (86.6-99.9%) I^2: 0%
	PSA	1.4% (0.4-4.7%) I^2: 87%	1.9% (0.2-17.5%) I^2: 98%	14.9% (9.5-22.7%) I^2: 15%	20.9% (7.7-45.5%) I^2: 74%	11.9% (2.9-38.2%) I^2: 99%	90.5% (72.2-97.2%) I^2: 76%
	MRI vs PSA (OR)	0.85 (0.49-1.45) p=0.23	0.23 (0.05-0.97) p=0.048	7.01 (1.76-27.98) p=0.03	0.99 (0.29-3.32) p=0.96	0.19 (0.09-0.38) p=0.01	4.68 (0.37-59.49) p=0.12
MRI primary (PI-RADS 4-5)	**MRI**	6.0% (0.6-39.4%) I^2: 92%	1.2% (0.2-7.3%) I^2: 55%	41.9% (16.1-73.0%) I^2: 57%	10.1% (2.2-35.9%) I^2: 0%	15.0% (3.1-49.7%) I^2: 91%	93.1% (48.1-99.5%) I^2: 0%
	PSA	NA	NA	NA	NA	18.1% (4.7-49.7%) I^2: 91%	NA
	MRI vs PSA (OR)	NA	NA	NA	NA	0.81 (0.23-2.87) p=0.53	NA

Table 2: Diagnostic performance of screening strategies incorporating MRI. We evaluated MRI as primary or sequential screening tool and PI-RADS cut-offs of three or four for the biopsy indication. Pooled rates are represented in percentages, with 95% CI-s. Between-study heterogeneity is expressed by I^2 values. For the comparison of MRI- and PSA-based screening we calculated odds ratios (OR) with 95% CI-s.
Abbreviations: MRI: magnetic resonance imaging. PCa: prostate cancer. PI-RADS: Prostate Imaging–Reporting and Data System. PSA: prostate-specific antigen. OR: odds ratio. CI: confidence interval. NA: not applicable.

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Ethical approval

No ethical approval was required for this systematic review with meta-analysis, as all data were already published in peer-reviewed journals. No patients were involved in the design, conduct or interpretation of our study.

Data sharing statement

The datasets used in this study can be found in the full-text articles included in the systematic review and meta-analysis. The statistical codes used in the analyses are available upon request.