BJU Int 2022 doi:10.1111/bju.15683

BJUI
BJU International

Original Article

Population-based randomized trial of screening for clinically significant prostate cancer ProScreen: a pilot study

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Objectives

To evaluate the feasibility of a population-based screening trial using prostate-specific antigen (PSA), a kallikrein panel and multiparametric magnetic resonance imaging (MRI) aimed at minimizing overdiagnosis, while retaining mortality benefit.

Patients and Methods

Feasibility of the screening algorithm was evaluated in terms of participation, screening test results and cancer detection. A random sample of 400 men aged 65 years was identified from the population registry and invited for screening with three stepwise tests (PSA, kallikrein panel and MRI). Men with PSA levels ≥3 ng/mL were further tested with the kallikrein panel, and those with positive findings (risk >7.5%) were referred for prostate MRI. Men with positive MRI (Prostate Imaging Reporting and Data System [PI-RADS] score 3–5) had targeted biopsies only. Men with negative MRI, but PSA density ≥0.15 underwent systematic biopsies.

Results

Of the 399 men invited, 158 (40%) participated and 27 had PSA levels ≥3 ng/mL (7% of the invited and 17% of the participants). Of these, 22 had a positive kallikrein panel (6% of the invited and 81% of the PSA-positive men). Finally, 10 men (3% of the invited and 45% of 4Kscore [kallikrein panel]-positive) had a suspicious MRI finding (PI-RADS score ≥3) and five were diagnosed with a clinically significant prostate cancer (Gleason Grade Group [GG] ≥2) at fusion biopsy (3% of the participants), with two GG 1 cases (1%). Additional testing (kallikrein panel and MRI) after PSA reduced biopsies by 56%.

Conclusion

The findings constitute proof of principle for our screening protocol, as we achieved a substantial detection rate for clinically significant cancer with few clinically insignificant cases. Participation, however, was suboptimal.

Keywords

prostate cancer, screening, randomized trial, multiparametric MRI, prostate-specific antigen, 4-kallikrein panel, targeted biopsy, #ProstateCancer, #PCSM, #uroonc

Introduction

The general principles of cancer screening include detection of clinically significant disease with known natural progression in an asymptomatic population, with early diagnosis and treatment leading to improved outcomes and reduced mortality. In addition, the benefit derived from screening must outweigh the adverse effects, and screening must be cost-effective.

Prostate-specific antigen testing was first introduced in the mid-1980s [1]. The European Randomized Study of Screening for Prostate Cancer (ERSPC) trial has shown a consistent 20% relative reduction in prostate cancer mortality at 9–16 years with organized PSA screening every 2 or 4 years [2]. In absolute terms, this means that 570 men had to be invited for screening to prevent one prostate cancer death at 16 years, which is comparable to the effect of the established breast and colorectal cancer screening programmes [3]. After differences in contamination and biopsy compliance were accounted for, consistent results were found in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) trial in the USA [4]. However, the major problem associated with PSA-based screening is substantial overdiagnosis [5], with estimates varying from 1.7% to as high as 67% of screen-detected cases [6].

Potential new screening methods have been developed for identifying high-risk cancers, including multi-kallikrein panels, RNA-based urine tests and multiparametric MRI (mpMRI). The novel tests offer opportunities for improving screening outcomes, particularly with regard to reducing overdiagnosis and increasing specificity [7,8].

ProScreen is a population-based randomized screening trial using a three-step screening strategy combining PSA, a four-kallikrein panel and prostate MRI. The main trial will involve 67 000 men aged 50–63 years at baseline, with a quarter of these randomized to the intervention arm and the rest forming the control arm [9]. The screening interval is 2 years for men who are initially screen-positive (those referred to MRI), 4 years for screen-negative men with baseline PSA >1 ng/mL, and 6 years for men with initial PSA <1 ng/mL. The main endpoint supported by power calculations is prostate cancer mortality at 15 years, with the target of 22% reduction.

Here, we report the results of a pilot study aimed at evaluating the feasibility and acceptability of the three-step screening procedure.

Patients and Methods

The pilot study was conducted between October 2018 and June 2019 in Helsinki and Tampere, Finland. A sample of 400 men (200 from each city) was identified from the Finnish Population Registry. The men born in 1955, i.e., aged 64–65 years at screening, were invited by mail to participate in the pilot study and provided written information about prostate cancer, screening and study procedures. No reminders were used. All men were asked to sign an informed consent form and fill in a questionnaire (on paper or on the web) about general health, prostate cancer family history, previous PSA and previous prostate biopsies. After obtaining informed consent, a referral for drawing a blood sample for PSA determination was made. For collecting the blood samples (30 mL blood was drawn in a vacutainer EDTA tube with heparin), the Fimlab laboratories network was used in Tampere and HUSLAB in Helsinki. Total PSA levels were analysed using an electrochemiluminescence immunoassay with a Cobras 6000 analyser. If the serum PSA concentration was 3 ng/mL or higher, the frozen blood sample was sent for reflex testing of the four kallikrein markers in blood (total PSA, free PSA, intact PSA and human kallikrein-related peptidase-2) at the clinical chemistry laboratory at Lund University in Malmö, Sweden (Prof. H. Lilja). A panel of four kallikrein marker levels in blood has been developed and commercialized as the '4Kscore®' [10] combining biomarkers and clinical information to predict the risk of Gleason 7 or higher cancer in biopsy [11].

For the kallikrein panel, total and free PSA levels were measured using the AutoDelfia 1235 automatic immunoassay system using the dual-label DELFIA Prostatus total/free PSA assay (Perkin-Elmer, Turku, Finland) calibrated against the WHO 96/670 (PSA-WHO) and WHO 68/668 (free PSA-WHO) standards. Intact PSA and human kallikrein 2 were measured with F(ab')2 fragments of the monoclonal capture antibodies to reduce the frequency of nonspecific assay interference, as reported previously [8]. The prespecified 4Kscore algorithm was used to obtain the probability of clinically significant prostate cancer (Gleason score 7 or higher at biopsy), although previous biopsies were not included in the algorithm.

Participants with both PSA level ≥3 ng/mL and kallikrein panel ≥7.5% were regarded as screening-positive and referred to mpMRI of the prostate using a 3-T scanner with external coil including T2-weighted, diffusion-weighted and dynamic contrast-enhanced imaging sequences in both Helsinki and Tampere. The mean time from the 4K result to the MRI was 37.5 days. The MRI scans were evaluated by experienced uroradiologists (seven in Helsinki and three in Tampere), who have attended the European Society of Uroradiology 2-day prostate MRI course, who have read more than 1000 cases, and who reads at least 200–300 cases annually. MRI data were processed in DynaCad software. The lesions were assessed and reported according to the Prostate Imaging Reporting and Data System (PI-RADS) v2. Men with a malignancy-suspect finding in MRI (at least one region of interest with PI-RADS score 3–5) were referred to targeted

MRI/TRUS fusion biopsies combining a real-time ultrasound image with an earlier MRI scan using the UroNav system. If the MRI was negative, but PSA density was ≥0.15 ng/mL^2, the patient was referred to systematic biopsy.

Philips Achieva 3.0-T scanners were used for prostate MRI scans in both Helsinki and Tampere. The protocol consists of the following sequences: T2-weighted imaging, diffusion-weighted imaging with apparent diffusion coefficient mapping, and dynamic contrast-enhanced imaging. Details of the MRI are presented in Table S1. The imaging protocol was consistent with the PI-RADS recommendations. The MRI scans were reported according to the PI-RADS v2 recommendation using a structured form including number of lesions (up to 4), location and size (volume, maximum diameter) of each lesion, capsule contact length, extraprostatic extension, seminal vesicle invasion and lymph node metastasis.

Each biopsy core was placed on a separate container to allow location of the lesions. Biopsies were processed in pathology laboratories in Helsinki (HUSLAB) and Tampere (Fimlab Laboratories). The biopsies were evaluated by uropathologists at both hospitals using standardized pathology reports. All biopsy cores were evaluated separately. If a cancer was found, the length of the core and cancer was reported. Gleason grading was performed separately for each core. A clinically significant cancer was defined as Gleason ≥7 (WHO/International Society of Urological Pathology Gleason Grade Group [GG] ≥2).

SPSS (version 25) and Stata (version 15) were used for calculating the descriptive statistics, as well as the detection rate and predictive values. Exact 95% CIs for detection rates were calculated based on the binomial distribution. ProScreen power calculation and statistical analysis plan is available as Appendix S1.

The study protocol was reviewed by the Helsinki University Hospital Ethics committee (tracking number – 2910/2017). The trial is registered in the ClinicalTrials.gov registry: NCT03423303.

Results

Of the 400 invited men (aged 64–65 years), 170 (42%) agreed to participate and 158 (40%) gave a blood sample (Table 1). Altogether 13 men (8% of the participants) had a positive family history with an affected first-degree relative (10 fathers and three brothers). A previous PSA test at any time was reported by 112 (66%) of the men including 36 (21%) during the last year. Previous prostate biopsies were reported by seven men (4%).

The median PSA was 1.08 ng/mL and 27 men (16% of the participants) had a PSA level ≥3 ng/mL.

Of these 27 men, the four-kallikrein panel was positive (≥7.5% risk of clinically significant cancer) in 22 men (13% of the participants, 81% of the men with PSA ≥3 ng/mL). The positive kallikrein panel results were in the range 10%–98% (median 21%), seven were 7.5%–20%, 10 were 20%–40% and five were > 40%.

The mean time from consent to drawing the blood for PSA was 14.7 days, and kallikrein panel results were obtained on average in 16.5 days.

All the 22 men referred to MRI were examined, with 12 (55%) negative results. Six lesions with PI-RADS score 3 were

Table 1 A summary of the ProScreen pilot study results.

	Trial centre		Total
	Tampere	Helsinki	
Invited, *N*	200	199*	399
Consented, *N* (%)†	85 (43)	85 (43)	170 (43)
Previous PSA, *N* (%)‡	61 (72)	51 (61)	112 (66)
Previous prostate biopsy, *N*‡	2 (2)	5 (6)	7 (4)
Blood sample obtained, *N* (%)†	81 (41)	77 (39)	158 (40)
PSA ≥3 ng/mL, *N* (%)‡	13 (16)	14 (18)	27 (17)
Median PSA in men with PSA ≥3 ng/mL, ng/mL	4.4	5.5	5.0
Kallikrein panel ≥7.5%, *N* (%)‡	9 (69)	13 (93)	22 (81)
mpMRI negative/PI-RADS v2 score <3, *N* (%)‡	6 (67)	6 (46)	12 (55)
mpMRI suspect			
PI-RADS v2 score 3, *N* (%)	2 (22)	2 (15)	4 (18)
PI-RADS v2 score 4/5	1 (11)	5 (38)	6 (27)
Prostate cancer cases detected, *N* (%)	2 (67)	5 (71)	7 (70)
Prostate cancer, Gleason sum 6	2 (67)	0 (0)	2 (20)
Prostate cancer, Gleason sum 7+	0 (0)	5 (100)	5 (50)

*mpMRI, multiparametric MRI; PI-RADS, Prostate Imaging Reporting and Data System. *1 person was excluded from the invitation list because of sex change. †Proportion out of invited men. ‡Proportion out of men with information available, i.e. those who were included that stage of the screening protocol from PSA to kallikrein panel to MRI to biopsy.*

Table 2 Prostate Imaging Reporting and Data System v2 score and Gleason grade in the pilot study of the ProScreen trial.

Gleason score	PI-RADS v2 score		
	3	4	5
Negative biopsy	2		
3 + 3 = 6	1	1	
3 + 4 = 7		1	
4 + 3 = 7		1	1
4 + 4 = 8			2

found in four men and seven lesions with PI-RADS score 4–5 were found in six men.

The 10 MRI-positive men (6% of the participants) were referred to MRI/TRUS fusion biopsies at Tampere or Helsinki University hospitals. The mean time from MRI to biopsy was 34.1 days.

In addition, two men with a negative MRI had a PSA density ≥0.15 ng/mL^2 and were also referred for systematic prostate biopsies.

Five men had negative biopsy results: three fusion biopsies (MRI-positive men) and both systematic biopsies (MRI-negative men with PSA density ≥0.15) were negative. Altogether, seven prostate cancers were identified among 158 participating men (cancer detection rate 4%, 95% CI 2–9; Tables 2 and 3). Seven cases out of 12 men referred to biopsy corresponds to a positive predictive value of 58% (95% CI 28–85) or 1.7 men biopsied per cancer found for the three-step screening regimen, translating to a number needed to screen of 23 for any prostate cancer.

Of the men with cancer, five had PSA levels 3.0–10.0 ng/mL and two had a PSA level above 10 ng/mL. All cases had kallikrein panel scores >20%. Two cases were Gleason 6, three Gleason 7 (one 3 + 4 and two 4 + 3) and two Gleason 8. Hence, the detection rate of clinically significant cancer was 3% (95% CI 1–9), translating to 2.4 men biopsied for a clinically significant prostate cancer and a number need to screen of 32. In MRI staging, four cancers were stage T2, two T3a and one T4 (sphincter involvement). No major complications from biopsy were reported.

Two men with PI-RADS score 3 lesions, but negative biopsy findings, were followed up according to the treating clinician's decision.

When kallikrein panel scores were re-calculated taking into account previous negative biopsies, the score was reduced on average by 23 percentage points. The score would have been <7.5% for five of the 11 screen-positive men and they would have been screen-negative. Interestingly, three out of the five men were among those who were diagnosed with cancer. These three cases were graded as Gleason 3 + 3, Gleason 4 + 3 and Gleason 4 + 4.

Of the 112 men who reported a previous PSA value, 12 (11%) were referred to MRI and four biopsied, with three cancers (3%) detected, versus 10 (19%) with four cancers (8%) in seven biopsied men among the 52 PSA-naïve participants.

Discussion

Our pilot study is the first step toward the full-scale randomized screening trial and a proof of concept for logistic feasibility of the ProScreen protocol. The findings show that out of the 16% of men who had a PSA level ≥3 ng/mL, an additional 3% were eliminated by the four-kallikrein panel and, finally, 7% (including those with normal MRI but elevated PSA density) remained screen-positive after MRI as the final component of the three tiers of testing. Biopsies of the screen-positive men yielded a detection rate of 4% (95% CI 2–9) and a positive predictive value of 58% (95% CI 28–85) or 1.7 biopsies needed to detect a cancer. These findings demonstrate that the ProScreen approach can identify a small subgroup of men with a high risk of clinically significant prostate cancer as five out of seven cancers were Gleason

Table 3 Prostate-specific antigen, kallikrein panel, MRI and biopsy pathology results among men with cancer detected in the ProScreen pilot study.

Gleason score	PSA categorized*, ng/mL	Kallikrein panel*,†, %	PI-RADS score	Number of cores positive	Max cancer length per core, mm	Percent Gleason pattern 4 or 5
3 + 3	5–10	40–60	3	1	3	0
3 + 3	3–5	20–40	4	1	9	0
3 + 4	5–10	20–40	4	1	6	30
4 + 3	10–15	>60	4	3	10/4/4	90/80/60
4 + 3	3–5	20–40	5	1	8	80
4 + 4	5–10	>60	5	1	5	48
4 + 4	10–15	20–40	5	3	5/1/6	80/100/60

*PI-RADS, Prostate Imaging Reporting and Data System. *PSA results are categorized (scale: 3–5, 5–10, 10–15 ng/mL) for privacy protection. †Result of the kallikrein panel expressed as probability of clinically significant prostate cancer (%), calculated from the proprietary formula of the 4Kscore and categorized (scale: <20%, 20–40%, 40–60%, >60%) for privacy protection.*

score 7 (GG 2) or higher, of which four were Gleason 4 + 3 (GG 3) or higher. These results are in concordance with assumptions underlying the ProScreen trial design.

For comparison, the results in the first round of the FinRSPC trial showed that 11% of the men aged 63 years had a PSA level >4 ng/mL, with a detection rate of 3% for Gleason 7+ cases and a positive predictive value of 28% based on PSA (with a threshold of 4 ng/mL) and DRE as reflex testing in men with PSA 3.0–3.9 ng/mL. This suggests that the aim of decreasing biopsies without major loss in sensitivity, that is, detection of clinically relevant cancer, remains a feasible objective for the ProScreen trial. These findings are consistent with a re-analysis of the FinRSPC trial, where incorporating the kallikrein panel improved the area under the curve by 10–15%, although the analysis was limited to men with PSA levels >4 ng/mL [12].

Our approach using three levels of testing aims to achieve a pragmatic screening procedure that is manageable both logistically and economically. A single blood sample is used for both PSA and the kallikrein panel. Roughly one out of seven participants was referred to prostate MRI, which reduces the resources required and improves the economic viability of the protocol compared with MRI-based screening [13].

A major challenge in the ProScreen trial will be achieving a high participation rate. The participation in the pilot was suboptimal (41%), but this was based on a single contact with both consent and questionnaire required prior to laboratory visit. For the main study, commenced in 2018, the procedures were modified to improve this by adding a preliminary notice, a reminder and an opportunity to give a blood sample without having to fill in the baseline questionnaire beforehand.

In the previous Finnish prostate cancer screening trial (FinRSPC), participation was 69% in the first year [14]. A similar attendance was expected in the ProScreen trial. Contamination (prior PSA testing) was far more common in the ProScreen pilot (68%) compared with the first round of the FinRSPC (10%) [15], which very likely decreased participation. The target age group in the pilot, however, was older than in the ProScreen main study (64–65 years vs 50–63 years), and hence a lower contamination is expected in the full trial. This may also increase participation in the main study. A dilution effect of prior PSA testing was observed, with fewer screen-positive results and lower cancer detection among participants reporting a previous PSA test.

Previous studies have suggested that adding a kallikrein panel in men with modestly elevated PSA can not only reduce the number of biopsies by 30%–58% [8,9,11,15,16], but also predict 20-year risk of death from prostate cancer [17,18]. Comparable results have also been reported for another kallikrein panel, the Prostate Health Index [19–21].

In the PRECISION trial, MRI, with or without targeted biopsy, outperformed standard biopsy, and the 95% CI indicated the superiority of this strategy over standard biopsy [22]. In the PROMIS study, with confirmatory template prostate mapping biopsy, the mpMRI showed a 93% sensitivity, a high negative predictive value and 27% of patients could avoid a primary biopsy [23]. Similar results are shown in multiple studies [24–27].

The novel concept of the three-test combination has the benefit of reducing the need for prostate biopsies, with a higher positive predictive value. The desired improvement in sensitivity for aggressive cancer and reduction in overdiagnosis will need to be evaluated in the full study. Assessing the mortality effect will require 10–15 years of follow-up, as indicated by our power calculations [9].

Our pilot study has some limitations. One should be cautious in drawing conclusions based on the small number of participants in our feasibility study. Also, we did not use information on prior biopsies for calculation of the 4Kscore, which lowers the threshold for MRI referrals. This was chosen to minimize the risk of missing clinically relevant cases. A re-analysis showed that taking into account previous negative biopsies would have reduced the number of screen-positive men referred to MRI by five and the number of detected cancers by three cases, including two clinically significant tumours.

The pilot trial investigation shows that a three-tiered screening and risk stratification using a combination of PSA, a four-kallikrein panel and mpMRI is feasible in a population-based study.

Acknowledgements

The ProScreen study group includes also: Tuomas Saarinen, Juha Oksala, Jarno Riikonen, Tomi Pakarainen, Juha Koskimäki, Henrikki Santti, Niku Oksala, Kim Pettersson.

Disclosure of Interest

A. Rannikko is a member of the board of the Ida Montin Foundation and Orion Research Foundation, an advisory board member for medical companies Bayer, Orion Pharma and Janssen, a clinical advisor for Aqsens company in which he has stock, and an investigator in clinical trials by Rho-Vac, Orion Pharma, Bayer, Astellas, Pfizer and Janssen. A. Auvinen received a lecture fee from Amgen/Janssen. M. Leht received congress support from Janssen-Cilag and Swan Medical, and holds stocks in several pharmaceutical companies and funds. H. Lilja holds patents on assays for intact PSA and is named on a patent for a statistical method to detect prostate cancer (the 4Kscore test) commercialized by OPKO Health. H. Lilja receives royalties from sales of the test

and has stock in OPKO Health. The other authors declare no interests.

Funding

This work was supported in part by a grant from the Academy of Finland (Grant No 311336 to Prof. Auvinen and Prof. Taari), and Finnish Cancer Organisations (to Prof. Auvinen), Competitive State Research Funding (VTR) administered by Pirkanmaa Hospital District (Project No.9X003), Finnish Cancer Organizations (to Prof. Rannikko), Jane and Aatos Erkko Foundation (to Prof. Rannikko), the National Institutes of Health/National Cancer Institute with a Cancer Centre Support Grant to the Memorial Sloan Kettering Cancer Centre (P30 CA008748), a SPORE grant in Prostate Cancer to Dr H. Scher [P50 CA092629]. This work was also supported in part by the Swedish Cancer Society (CAN 2017/559), the Swedish Research Council (VR-MH project no. 2016-02974), and General Hospital in Malmö Foundation for Combating Cancer.

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Abbreviations: ERSPC, European Randomized Study of Screening for Prostate Cancer; GG, Gleason grade group; mpMRI, multiparametric MRI; PI-RADS, Prostate Imaging Reporting and Data System.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Details of the MRI protocols used for both sites and all the scanners.

Appendix S1. ProScreen power calculation and statistical analysis plan.