BJU Int 2024 doi:10.1111/bju.16394

BJUI
BJU International

Original Article

Which men benefit from prostate cancer screening? Prostate cancer mortality by subgroup in the European Randomised Study of Screening for Prostate Cancer

Niko Pasanen[1,2], Kirsi Talala[4], Sebastiaan Remmers[7], Teuvo L. J. Tammela[2,3], Jonas Hugosson[8,9], Monique J. Roobol[7], Kimmo Taari[5,6], Rebecka Arnsrud Godtman[8,9], Chris Bangma[7] and Anssi Auvinen[1]

[1]Faculty of Social Sciences, [2]Faculty of Medicine and Health Technology, Tampere University, [3]Department of Urology, Tampere University Hospital, Tampere, [4]Finnish Cancer Registry, [5]Department of Urology, Helsinki University Hospital, [6]Faculty of Medicine, University of Helsinki, Helsinki, Finland, [7]Department of Urology, Erasmus University Medical Centre, Cancer Institute, Rotterdam, The Netherlands, [8]Department of Urology, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, and [9]Department of Urology, Region Västra Götaland, Sahlgrenska University Hospital, Gothenburg, Sweden

Objective

To evaluate whether a subgroup of men can be identified that would benefit more from screening than others.

Materials and Methods

This retrospective cohort study was based on three European Randomised Study of Screening for Prostate Cancer (ERSPC) centres, Finland, the Netherlands and Sweden. We identified 126 827 men aged 55–69 years in the study who were followed for maximum of 16 years after randomisation. The primary outcome was prostate cancer (PCa) mortality. We analysed three age groups 55–59, 60–64 and 65–69 years and PCa cases within four European Association of Urology (EAU) risk groups: low, intermediate, high risk, and advanced disease.

Results

The hazard ratio (HR) for PCa mortality in the screening arm relative to the control arm for men aged 55–59 years was 0.96 (95% confidence interval [CI] 0.75–1.24) in Finland, 0.70 (95% CI 0.44–1.12) in the Netherlands and 0.42 (95% CI 0.24–0.73) in Sweden. The HR for men aged 60–64 years was 1.03 (95% CI 0.77–1.37) in Finland, 0.76 (95% CI 0.50–1.16) in the Netherlands and 0.97 (95% CI 0.64–1.48) in Sweden. The HR for men aged 65–69 years was 0.80 (95% CI 0.62–1.03) in Finland and 0.57 (95% CI 0.38–0.83) in the Netherlands, and this age group was absent in Sweden. In the EAU risk group analysis, PCa mortality rates were materially lower for men with advanced disease at diagnosis in all three countries: 0.67 (95% CI 0.56–0.82) in Finland, 0.28 (95% CI 0.18–0.44) in the Netherlands, and 0.48 (95% CI 0.30–0.78) in Sweden.

Conclusion

We were unable to unequivocally identify the optimal age group for screening, as mortality reduction differed among centres and age groups. Instead, the screening effect appears to depend on screening duration, and the number and frequency of screening rounds. PCa mortality reduction by screening is largely attributable to stage shift.

Keywords

prostate cancer, mortality, screening, randomised trials, Finland, the Netherlands, Sweden

Introduction

There is ongoing debate concerning the balance of benefits and harms of PSA-based prostate cancer (PCa) screening, and the need for improved screening strategies is clear. Several population-based studies have evaluated the impact of PSA screening on PCa mortality and overdiagnosis.

The available evidence for PCa mortality reduction from screening comes primarily from the European Randomised Study of Screening for Prostate Cancer (ERSPC), which showed a modest reduction in PCa mortality [1]. The rate ratio in the ERSPC remained statistically significant at 13 and 16 years of follow-up and the absolute effect increased from 13.5 to 17.6 per 10 000 men [2]. PCa (31 cases per 1000 men

at 16 years) indicates substantial overdiagnosis [1]. A Cochrane meta-analysis of the ERSPC, and the Prostate, Lung, Colorectal and Ovarian cancer screening (PLCO) trial showed no significant reduction in PCa mortality among men who were randomised to the screening arm (SA) [3]. This small effect in the PLCO trial was attributable to high contamination and low biopsy compliance [4]. However, a meta-analysis of data from five randomised PSA screening trials showed no reduction in PCa mortality [3].

In this study, we evaluated differences in PCa mortality within the ERSPC. Our aim was to identify whether a specific age group or groups clearly benefit from PCa screening. We compared PCa mortality between the trial arms in the three largest ERSPC centres: Finland, the Netherlands and Sweden. Firstly, we analysed differences between the trial arms by age group (55–59, 60–64 and 65–69 years at entry). Secondly, PCa deaths were stratified by prognostic risk group (low-, intermediate-, high-risk, and advanced or metastatic cancer) at diagnosis based on the European Association of Urology (EAU) guideline. Secondary analyses were also conducted limiting follow-up time to the ages of 67–77 years to enhance comparability and using Cancer of the Prostate Risk Assessment (CAPRA) classification instead of EAU risk group for prognostic subgroups.

Materials and Methods

The retrospective cohort analysis was conducted as a subgroup analysis of the trial by age group at randomisation and stratifying tumour characteristics (EAU risk group) at diagnosis, with PCa mortality in the SA vs the control arm (CA) within each subgroup as the outcome. This study included men from the three largest ERSPC centres: Finland, the Netherlands and Sweden.

A Zelen design was used in Finland and Sweden, with men randomised before consent. Men who were assigned to the SA were invited to screening, while men in the CA were not contacted. In the Netherlands, men were invited to participate and were randomised after consent. Eligible men were aged 55, 59, 63 or 67 years at baseline in Finland, 55–74 years in the Netherlands and 50–69 years in Sweden [5].

The analysis included 80 144 men in Finland, of whom 8000 were annually allocated randomly to the SA during 1996–1999, with the remainder forming the CA. This led to 31 867 men comprising the SA and 48 277 men in the CA representing, approximately a 1:1.5 allocation ratio (SA:CA). [6] We accounted for this allocation ratio in all our analyses.

The analysis included 34 832 men in the Netherlands after exclusions because of age or death prior to randomisation. The men were randomised to the SAs and CAs using a 1:1 allocation ratio, resulting in 17 442 men in the SA and 17 390 in the CA.

In Sweden, 20 000 men aged 50–64 years were randomised from the population register either to the SA or CA using a 1:1 allocation ratio [5]. We excluded 8071 men younger than 55 years for comparability with the other centres. Out of 11 851 men eligible for this analysis, 5900 men were in the SA and 5951 in the CA.

The primary screening test was serum PSA determination. The cut-off point used for diagnostic examination in Finland was 4.0 ng/mL, and men with PSA 3.0–3.9 ng/mL were referred to a secondary test (DRE in 1996–1998 and free/total PSA ratio <0.16 from 1999). In the Netherlands, DRE, TRUS and PSA (cut-off point 4.0 ng/mL) were used before 1997 and from 1997 PSA alone was used, with a cut-off of 3.0 ng/mL. In Sweden, only PSA was used, with cut-offs of 3.0 ng/mL in 1995–1998 and 2.5 ng/mL from 1999. The screening interval was 4 years in Finland and the Netherlands, and 2 years in Sweden. In Finland, men were invited to screening a maximum of three times until age 71 years, in the Netherlands a maximum of five times until age 55–74 years, and in Sweden a maximum of 10 times until age 67–71 years (until the end of 2014).

In each country, the men were followed for mortality from randomisation until death or end of follow-up (common closing date). Follow-up was truncated at 16 years to ensure comparability across countries. Because of this, the maximum number of screening rounds men could attend during the follow-up was three in Finland, four in the Netherlands and eight in Sweden (Table S1).

The diagnostic evaluation included DRE, TRUS and TRUS-guided systematic prostate biopsy in all countries [5]. In Finland, from 1996 until 2002 sextant biopsies were used, but in 2002, a shift was made to use 10–12 core biopsies. In Sweden, sextant biopsies were used from 1995 until 2009, when 10-core biopsies were adopted. In the Netherlands, sextant biopsies were used from 1993 until the end of follow-up [6].

Prostate cancer-specific mortality was defined based on International Classification of Diseases (ICD)-9 and ICD-10 codes in Finland and Sweden. The causes of death were determined by a Cause of Death Committee based on review of medical records (blinded to trial arm). Excellent agreement between official causes of death and the assignments of the Cause of Death Committee was demonstrated, hence the official causes of death were employed as the outcome after 2003 [7–10].

The main data analysis compared PCa mortality between the trial arms within subgroups of the population using Cox proportional hazard regression to estimate hazard ratios (HRs) and their 95% CIs. We also calculated absolute effect as mortality rate differences (RDs). Subgroup differences were evaluated using likelihood ratio tests as a measure of goodness of fit, comparing a model including the main effects

Table 1 Distribution of men in age and EAU risk groups by arm and their causes of death from the European Randomised Study of Screening for Prostate Cancer.

	Finland Trial arm		The Netherlands Trial arm		Sweden Trial arm	
	Screening	Control	Screening	Control	Screening	Control
Age at randomisation, *n* (%)						
55–59 years	18 841 (59.1)	28 632 (59.3)	6827 (39.1)	6663 (38.3)	3123 (52.9)	3162 (53.1)
60–64 years	6897 (21.6)	10 389 (21.5)	5603 (32.1)	5646 (32.5)	2777 (47.1)	2789 (46.9)
65–69 years	6129 (19.2)	9256 (19.2)	5012 (28.7)	5081 (29.2)	–	–
Total	31 867 (100)	48 277 (100)	17 442 (100)	17 390 (100)	5900 (100)	5951 (100)
EAU risk group of prostate cancer, *n* (%)						
Low	1485 (1.9)	1311 (1.6)	1652 (4.7)	612 (1.8)	566 (4.8)	277 (2.3)
Intermediate	1258 (1.6)	1871 (2.3)	577 (1.7)	391 (1.1)	200 (1.7)	227 (1.9)
High	513 (0.7)	846 (1.1)	171 (0.5)	200 (0.6)	57 (0.5)	67 (0.6)
Advanced and metastatic	743 (0.9)	1432 (1.8)	55 (0.2)	167 (0.5)	57 (0.5)	89 (0.8)
Missing	140 (0.2)	166 (0.2)	97 (0.3)	32 (0.1)	40 (0.3)	65 (0.5)
Total	31 867 (39.8)	48 277 (60.2)	17 442 (50.1)	17 390 (49.9)	5900 (49.8)	5951 (50.2)
Cause of death, *n* (%)						
Prostate cancer	263 (0.83)	433 (0.90)	110 (0.63)	166 (0.95)	61 (1.0)	87 (1.5)
Other causes	9407 (29.5)	14 118 (29.2)	5178 (29.7)	5272 (30.3)	1697 (28.8)	1717 (28.9)

EAU, European Association of Urology.

only with a nested model with an interaction term for trial arm and for either age or risk group. Harrell's C was used to describe the goodness of fit for CAPRA score.

We compared PCa mortality by age group (55–59, 60–64 and 65–69 years at baseline, i.e., randomisation) and analysed mortality by tumour prognostic features at diagnosis, i.e., EAU risk groups defined by Gleason grade, TNM stage and PSA level at diagnosis. Follow-up from randomisation was also used in the analyses by prognostic features to avoid lead-time bias. In addition, we performed secondary analyses where follow-up started at 67 years for all age groups and was truncated at 77 years, to improve comparability in analyses by age at randomisation. This limited the maximum follow-up time to 10 years. In addition, we used CAPRA points, which provide more granular prognostic classification, to create smaller groups and compared SAs and CAs within these groups [11]. CAPRA groups were combined to achieve sufficient sample sizes (minimum of 24 deaths). In Finland, men were classified into eight groups comprising each point separately, with the exception of men with CAPRA scores of 7 and 8, which were combined. In the Netherlands, CAPRA scores of 1 and 2 were merged, as well as scores of 8 and 9. In Sweden, scores were grouped into 1–3, 4–5 and 8–9 points. A per-protocol analysis of men who ever participated at screening was performed to assess the impact of excluding non-participating men from the SA.

Data analysis was performed using Stata statistical software (version 17; StataCorp LLC, College Station, TX, USA).

Results

As expected, the distribution of men by age group at baseline was similar in the two trial arms. During the 16-year follow-up, there were 696 PCa deaths in Finland, 276 in the Netherlands and 148 in Sweden (Table 1). In Finland, the cumulative PCa mortality at 16 years was 0.83% in the SA and 0.90% in the CA. In the Netherlands, the cumulative risks were 0.63% (SA) and 0.95% (CA), and in Sweden they were 1.0% (SA) and 1.5% (CA; Table 2). Risk group distribution was more favourable in younger ages in all three centres (Table S2).

Analyses by age at entry

We used an interaction term to evaluate differences between the trial arms by age group. The interaction term did not significantly improve the model fit in the combined dataset including all three centres ($P = 0.18$), nor in any of the centres ($P = 0.40$ in Finland, $P = 0.56$ in the Netherlands and $P = 0.16$ in Sweden). A three-way interaction term between age, SA and centre did not indicate significant differences in the screening effect between age groups by centre ($P = 0.25$).

In Finland, in the Cox regression analysis, the HR for PCa death in the SA relative to the CA was close to unity for the men aged 55–59 and 60–64 years (HR 0.96, 95% CI 0.75–1.24 and 1.03, 95% CI 0.77–1.37, respectively) and was slightly below one for men aged over 65 years at entry (HR 0.80, 95% CI 0.62–1.03). Furthermore, the RD was close to unity for men aged 55–64 years and slightly larger, although nonsignificant, for men aged 65–69 years (Table 2; Fig. 1).

In the Netherlands, the HR for the SA relative to the CA was slightly, although nonsignificantly, lower for the men aged 55–59 years (HR 0.70, 95% CI 0.44–1.12) and 60–64 years (HR 0.76, 95% CI 0.50–1.16), with a larger and significant reduction for men aged 65–69 years (HR 0.57, 95% CI 0.38–0.83). Moreover, the RD increased with age at entry, and was

Table 2 Prostate cancer deaths and mortality rates by European Randomised Study of Screening for Prostate Cancer arm and country.

	Prostate cancer deaths		PCa mortality rate (cases/10 000 person-years)		HR (95% CI)	Mortality rate difference per 10 000 person-years (95% CI)
	Screening	Control	Screening	Control		
Finland						
Age at randomisation						
55–59 years	98	155	3.65	3.79	0.96 (0.75–1.24)	−0.14 (−1.08, +0.79)
60–64 years	77	114	8.36	8.18	1.03 (0.77–1.37)	0.18 (−2.22, +2.57)
65–69 years	88	164	11.56	14.44	0.80 (0.62–1.03)	−2.88 (−6.15, +0.40)
Total	263	433	6.02	6.54	0.92 (0.79–1.07)	−0.52 (−1.48, +0.43)
PCa EAU risk group						
Low	20	15	0.46	0.23	2.02 (1.03–3.95)	0.23 (0.00, +0.46)
Intermediate	41	42	0.94	0.63	1.48 (0.96–2.27)	0.30 (−0.42, +0.65)
High	51	40	1.17	0.60	1.93 (1.28–2.92)	0.56 (0.19–0.93)
Advanced and metastatic	147	330	3.36	4.99	0.67 (0.56–0.82)	−1.62 (−2.39, −0.86)
Missing	4	5	0.09	0.08	1.21 (0.33–4.51)	−0.16 (−0.96, +0.13)
Total	263	432	6.02	6.53	0.92 (0.79–1.08)	−0.51 (−1.46, +0.44)
The Netherlands						
Age at randomisation						
55–59 years	31	43	3.08	4.37	0.70 (0.44–1.12)	−1.29 (−2.99, +0.41)
60–64 years	39	51	4.96	6.49	0.76 (0.50–1.16)	−1.53 (−3.89, +0.83)
65–69 years	40	72	6.29	11.14	0.57 (0.38–0.83)	−4.84 (−8.07, −1.61)
Totals	110	166	4.53	6.87	0.66 (0.52–0.84)	−2.34 (−3.68, −1.00)
PCa EAU risk group						
Low	11	2	0.45	0.08	5.46 (1.21–24.63)	0.37 (+0.08, +0.66)
Intermediate	41	33	1.69	1.37	1.23 (0.68–1.95)	0.32 (−0.37, +1.02)
High	23	44	0.95	1.82	0.52 (0.31–0.86)	−0.87 (−1.54, +0.21)
Advanced and metastatic	24	85	0.99	3.52	0.28 (0.18–0.44)	−2.53 (−3.37, −1.68)
Missing	8	2	0.33	0.08	3.98 (0.85–18.75)	0.25 (−0.09, +0.50)
Total	107	166	4.40	6.87	0.64 (0.50–0.82)	−2.46 (−3.80, −1.13)
Sweden						
Age at randomisation						
55–59 years	18	43	4.02	9.51	0.42 (0.24–0.73)	−5.49 (−8.89, −2.09)
60–64 years	43	44	11.47	11.76	0.97 (0.64–1.48)	−0.29 (−5.17, +4.59)
Total	61	87	7.42	10.53	0.70 (0.51–0.97)	−3.11 (−6.00, −0.22)
PCa EAU risk group						
Low	11	4	1.34	0.48	2.76 (0.88–8.66)	0.85 (−0.07, +1.78)
Intermediate	15	17	1.82	2.06	0.89 (0.44–1.77)	−0.23 (−1.58, +1.11)
High	9	11	1.09	1.33	0.82 (0.34–1.98)	−0.24 (−1.30, +0.83)
Advanced and metastatic	24	50	2.92	6.05	0.48 (0.30–0.78)	−3.13 (−5.18, −1.09)
Missing	2	5	0.24	0.61	0.40 (0.78–2.07)	−0.36 (−0.99, +0.27)
Total	61	87	7.42	10.53	0.70 (0.51–0.98)	−3.11 (−6.00, −0.22)

Hazard ratios and mortality rate differences for the screening arm compared to the control arm. EAU, European Association of Urology; HR, hazard ratio; PCa, prostate cancer.

largest and statistically significant for the age group 65–69 years (Table 2; Fig. 1).

In Sweden, the HR for the SA was materially lower for the men aged 55–59 years (HR 0.42, 95% CI 0.24–0.73) and close to unity for the age group 60–64 years (HR 0.97, 95% CI 0.64–1.48). The Swedish trial did not include men older than 65 years at randomisation. Additionally, the RD indicated a materially lower PCa-specific mortality for the men in the SA aged 55–59 years, while there was hardly any difference between the trial arms among men aged 60–64 years (Table 2; Fig. 1).

Analyses by EAU Risk Group

An interaction term for SA and EAU risk group contributed to the model fit in the combined dataset but did not quite reach statistical significance ($P = 0.07$). In Finland, the Cox regression analysis showed higher mortality in the SA for the low- and high-risk groups (HR 2.02, 95% CI 1.03–3.95 and HR 1.93, 95% CI 1.28–2.92, respectively), slightly higher mortality for the intermediate-risk cases (HR 1.48, 95% CI 0.96–2.27) and materially lower mortality only for advanced disease at diagnosis (HR 0.67, 95% CI 0.56–0.82). The RD favoured the CA for low-risk, intermediate-risk and high-risk PCa, and favoured the SA for advanced disease (Table 2; Fig. 2).

In the Netherlands, the HR was materially higher in the SA for low-risk PCa (HR 5.46, 95% CI 1.21–24.63), slightly and nonsignificantly higher for the intermediate-risk PCa (HR 1.23, 95% CI 0.68–1.95), somewhat lower for high-risk PCa (HR 0.52, 95% CI

Fig. 1 Hazard ratios (HRs) for the screening arm compared to the control arm within age groups by centre. FI, Finland; NL, the Netherlands; SE, Sweden.

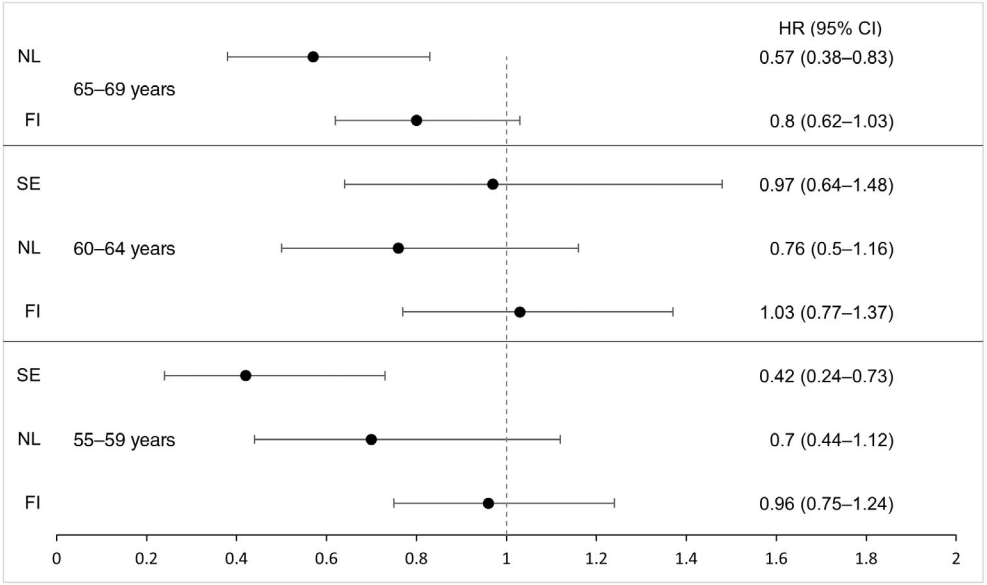
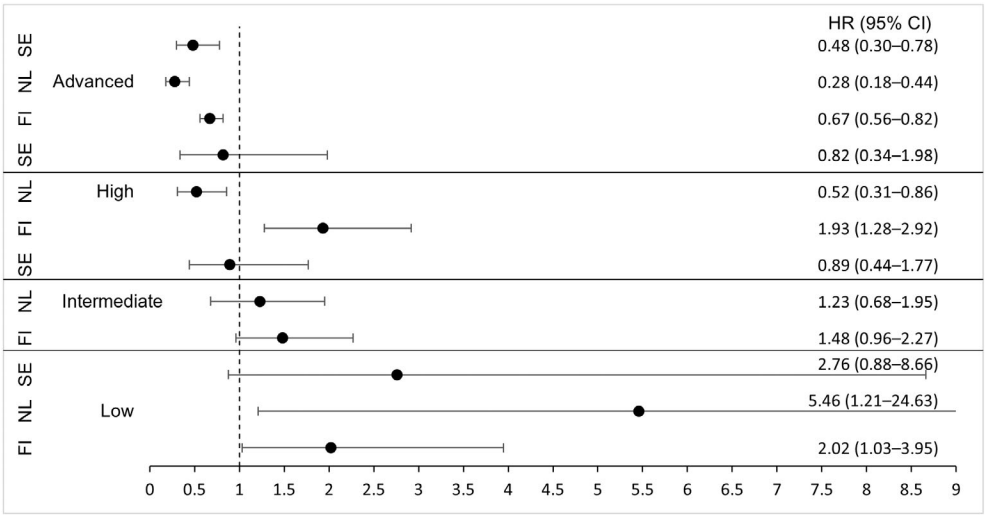


Fig. 2 Hazard ratios for the screening arm compared to the control arm within European Association of Urology risk groups (advanced group includes metastatic disease) by centre. FI, Finland; NL, the Netherlands; SE, Sweden.



0.31–0.86) and clearly reduced for advanced disease (HR 0.28, 95% CI 0.18–0.44). The RDs showed identical results to the HRs (Table 2; Fig. 2).

In Sweden, mortality from low-risk PCa was slightly and nonsignificantly higher in the SA than in the CA (HR 2.76, 95% CI 0.88–8.66), was slightly lower for the intermediate- and high-risk groups (HR 0.89, 95% CI 0.44–1.77 and HR 0.82, 95% CI 0.34–1.98, respectively), and was materially lower for advanced disease (HR 0.48, 95% CI 0.30–0.78). The RDs followed the same pattern as the HRs (Table 2; Fig. 2).

Secondary Analyses

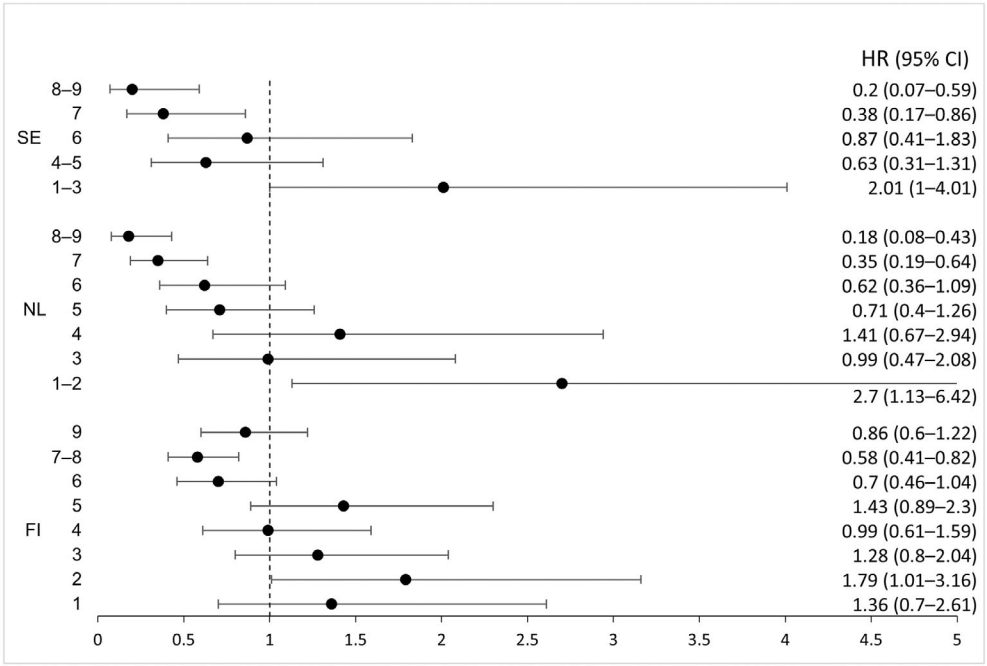
In the secondary analyses, the results for Finland did not differ from the main analysis when starting follow-up at age 67 years and truncating at 77 years, limiting follow-up to 10 years. In the Netherlands, the mortality reduction among screened men was clearer in the secondary analysis among men aged 60–64 years at entry (HR 0.56, 95% CI 0.34–0.91). In Sweden, the difference between the arms in the age group 55–59 years diminished in the restricted analysis (HR 0.56, 95% CI 0.28–1.10; Table 3). In a per-protocol analysis excluding men who never participated in screening from the

Table 3 Prostate cancer deaths and mortality rates by European Randomised Study of Screening for Prostate Cancer arm and country.

	PCa deaths		PCa mortality rate (cases/10 000 person-years)		HR (CI 95%)	Mortality rate difference per 10 000 person-years (CI 95%)
	Screening arm	Control arm	Screening arm	Control arm		
Finland						
Age at randomisation						
55–59 years	59	105	5.76	6.74	0.86 (0.62–1.18)	−0.98 (−2.93, +0.98)
60–64 years	51	76	8.34	8.19	1.02 (0.71–1.45)	0.14 (−2.79, +3.08)
65–69 years	41	84	7.71	10.54	0.73 (0.50–1.06)	−2.83 (−6.10, +0.43)
Total	151	266	6.96	8.07	0.86 (0.71–1.05)	−1.11 (−2.58, +0.37)
The Netherlands						
Age at randomisation						
55–59 years	16	20	4.17	5.35	0.78 (0.40–1.50)	−1.18 (−4.29, +1,93)
60–64 years	25	45	5.02	8.97	0.56 (0.34–0.91)	−3.96 (−7.23, −0.68)
65–69 years	19	40	4.50	9.33	0.48 (0.28–0.83)	−4.83 (−8.36, −1.30)
Totals	60	105	4.60	8.05	0.57 (0.42–0.78)	−3.45 (−5.38, −1.52)
Sweden						
Age at randomisation						
55–59 years	13	24	7.58	13.66	0.56 (0.28–1.10)	− 6.09 (−12.93, +0.76)
60–64 years	33	33	13.61	13.62	1.00 (0.62–1.62)	− 0.01 (−6.58, +6.57)
Total	46	57	11.11	13.64	0.82 (0.55–1.20)	−2.53 (−7.31, +2.25)

Hazard ratios and mortality rate differences for the screening arm compared to the control arm within follow-up time truncated by age (covering only ages 67–77 years). HR, hazard ratio; PCa, prostate cancer.

Fig. 3 Hazard ratios for the screening arm compared to the control arm within groups defined by Cancer of the Prostate Risk Assessment (CAPRA) score by centre. FI, Finland; NL, the Netherlands; SE, Sweden.



SA, the oldest age group in Finland and men aged 60 to 64 years in the Netherlands showed a statistically significant benefit from screening (Table S3).

In the analysis by CAPRA score, PCa mortality in cases with high scores was lower in the SA compared with the CA in all three centres (Harrell's C = 0.95 for Finland and the Netherlands, 0.85 in Sweden). Conversely, PCa mortality in cases with low CAPRA scores (1–3 points) was higher in the SA compared to the CA in all three centres (Fig. 3).

Discussion

This retrospective cohort analysis shows that PCa mortality reduction through screening differed by age group across the

three major ERSPC centres, except for the age group 60–64 years, where the screening effect was minimal. A paradoxical effect of screening was a stage shift resulting in excess mortality from early-stage cancer observed in all centres, contrasting with a significant reduction in late-stage PCa-specific mortality. The Netherlands and Sweden displayed a gradient toward a larger effect with higher EAU risk groups, unlike Finland, where benefits were mainly observed among men with advanced disease.

Screening had a smaller impact on mortality overall in Finland than in the other countries in all age and EAU risk groups, consistent with earlier analyses. Finnish men aged 65–69 years at randomisation in the SA had slightly, and nonsignificantly lower PCa mortality than those in the CA. Lower mortality was also found from advanced disease. In the Netherlands, screening lowered PCa mortality slightly for men in the age groups 55–59 and 60–64 years and materially for men older than 65 years at entry. Furthermore, in the Netherlands, PCa mortality from advanced cancer and to a lesser extent also from high-risk disease was lower in the SA than in the CA. In Sweden, the screening effect on PCa mortality was largest for men aged 55–59 years at baseline and those with advanced PCa. In all three centres, the SA showed excess mortality from low-risk cancer, although it was less pronounced and nonsignificant in Sweden. Despite differences in the overall PCa mortality level within the SA, PCa mortality was notably higher in the Swedish CA compared with the Finnish and Dutch CAs at ages 55–59 years.

A similar analysis has also been conducted in the PLCO trial. In the intervention arm, 44% and in the usual care arm 48% of men with Gleason scores of 8–10 died from PCa. Consistent with our results, PCa mortality with Gleason score <7 cancer was higher in the intervention arm than in the CA (26% vs 20%) [12].

The CAP trial [13] showed no significant screening effect on PCa mortality overall or within age groups. The rate difference between the SA and CA per 1000 person-years for men aged 55–59 years was 0, for men aged 60–64 years it was −0.07 and for men aged 65–69 years it was +0.07 [13].

A previous analysis of the Swedish arm of the ERSPC showed a substantially larger PCa mortality reduction in men aged 55 years at entry compared to those aged 60 years [14].

Study limitations include the fact that comparison of mortality by EAU risk group was not and could not be based on a randomised comparison. Also, we had no family history or genetic data. Screening protocols and treatment approaches varied among centres as these were not defined in the trial protocol. Our results are based on data from three European countries, limiting their generalisability. At randomisation only men older than 55 years were included, so we could not assess screening effectiveness for younger men. Our findings may not be directly applicable to the current diagnostic pathway for PCa with multiparametric MRI imaging and targeted biopsies [15].

There are several potential explanations for the differences in results among countries. Variations in screening protocols resulted in different screening patterns even within age groups between the three centres in terms of number of screening rounds, screening duration, and time since the last screen which may decrease comparability. The number of screening rounds during the 16 years of follow-up for the youngest ages ranged from three in Finland to eight in Sweden. Stopping age was 63–71 years in Finland, 71–74 years in the Netherlands and 67–70 years in Sweden. The last screen for the oldest age group was 4 years before the younger age groups in Finland, and 8 years before the youngest in the Netherlands, and therefore a declining trend in PCa mortality could also have affected the results. The larger mortality reduction in the age group 55–59 years in Sweden compared to Finland and the Netherlands is probably attributable to the larger number of screening rounds and longer screening duration. Possible differences in treatment may also play a role, although no clear differences have been shown between trial arms in the ERSPC [16].

The main analysis covered follow-up at different ages and various time periods since the last screen by age group, and to an extent also among the centres. A previous Swedish analysis suggested that mortality reduction is at its largest during the first 6 years since the last screen and diminishes to practically zero by 10 years [17]. To enhance comparability, a secondary analysis was conducted, truncating follow-up to ages 67–77 years (10 years). The secondary results closely mirrored the main findings. In the Netherlands, men aged 60–64 years had lower PCa mortality in the SA compared with the CA. In Sweden, the screening effect was consistent with the main analysis, although with a slightly smaller magnitude in the age group 55–59 years and with no effect in the age group 60–64 years.

To refine risk stratification, in a secondary analysis, we used CAPRA score as a more granular prognostic classification than EAU risk group. This showed similar results to the main analysis with EAU risk groups. Low-risk groups in the SAs appeared to have excess mortality, while high-risk groups had lower mortality across centres. The findings suggest prognostic misclassification and ineffective treatment for screen-detected low-risk disease.

Length bias can distort comparisons based on survival time in screening studies [18]. We minimised this by starting follow-up at randomisation rather than at diagnosis. However, our analysis of EAU risk groups indicated increased mortality in the SA for low-risk PCa, likely due to length bias. These cancers were detected early and would have been more advanced at diagnosis in the absence of screening. Therefore, similar cases in the CA were probably classified as

higher risk disease. Of course, if all early cancers could be cured, no such shift would have occurred, as there would be no mortality from screen-detected cases.

In addition to survival time, earlier detection by screening can also affect distribution by stage and prognostic risk group. Of the PCa deaths in the SA, 8%–18% were from cases that were initially classified as low-risk disease but that progressed after diagnosis and primary management. In the CA without screening, some of those cases are probably diagnosed at a later stage with more advanced presentation. This means that cases diagnosed at an early stage are not comparable between the trial arms, and our results suggest that those in the SA include more cases that are bound to progress. This is a likely explanation for the higher mortality in the SA for low-risk PCa, instead of poorer outcome due to screening. Another probable explanation for the observed difference is the later diagnosis date in the CA. With more precise prognostic categorisation, improved identification of higher risk cases results in a shift of cancers from the low-risk group to the higher risk group, which results in better outcomes in both low- and high-risk categories, even in the absence of real improvement of prognosis [19].

Sticky-diagnosis bias may falsely elevate PCa mortality [18] but analyses within the ERSPC have shown excellent concordance between official and adjudicated causes of death and no differences between the trial arms [7,8]. Also, intervention-related deaths could increase PCa mortality. However, there were only 34 intervention-related deaths in the entire ERSPC, so this is unlikely to have affected the results [20].

Strengths of our study include the high-quality data from the large, randomised ERSPC trial. The causes of death data have been validated, and the conclusion was that the risk of deaths from other causes incorrectly attributed to PCa in the screening group was minimal [7–9].

The European Commission recently published its draft screening recommendation including PSA screening for men up to 70 years, emphasising a risk-stratified approach [21]. This study offers pertinent evidence to identify men who are likely to benefit from screening. Although the optimal age group for a larger screening effect within ages 55–69 years could not be unequivocally identified, our findings suggest that sufficient duration of screening and number of screening rounds are important for screening effectiveness.

Further investigation is necessary to determine an optimal population-based screening regimen concerning age range, duration, and frequency, likely incorporating MRI and additional biomarkers alongside PSA. Our results are consistent with the notion that the PCa mortality reduction from PSA-based screening is attributable to finding advanced cancers early enough to be treatable. The addition of MRI might only increase overdiagnosis and stage migration, not actually finding advanced cancer earlier [22]. However, it is hard to draw inference to the current setting from the old setting of systematic biopsies based on PSA alone.

In conclusion, we were unable to identify unequivocally the optimal age group with the largest screening effect within the range 55–69 years, as the PCa mortality reduction differed among centres and age groups, with no clear pattern. However, our findings suggest that duration of screening, together with number and frequency of screening rounds, are important for screening effectiveness. PCa mortality reduction in the SA was mainly attributable to an effect of stage shift.

Acknowledgements

Niko Pasanen: data analyses and presentation, preparation of the initial draft manuscript, manuscript revision. Kirsi Talala and Sebastiaan Remmers: data curation, manuscript review and commenting. Teuvo Tammela, Jonas Hugosson, Monique Roobol, Kimmo Taari, Rebecka Arnsrud Godtman and Chris Bangma: research process, data collection, resource acquisition, project administration, coordination of study conduct, manuscript review and commenting. Anssi Auvinen: study conceptualisation, methodology, resource acquisition, project administration, supervision, manuscript review and commenting.

Disclosure of Interests

Niko Pasanen, Kirsi Talala, Sebastiaan Remmers, Monique Roobol and Anssi Auvinen have no competing interests to declare. Jonas Hugosson has received grants from the Swedish Cancer Society, the Swedish Research Council, agreement on medical education and research between the western Götaland region and the University of Gothenburg, the Swedish Prostate Cancer Society, and Karin and Christer Johanssons Fund, has received support from the EAU to attend European Multidisciplinary Congress on Urological Cancer 2023, and has stocks in C Medical Inc. and Carasent AB. Teuvo Tammela has received research funding from the Finnish Cancer Society, Sigrid Juselius Foundation, Astellas Pharma, Bayer, Janssen and Pfizer. Rebecka Arnsrud Godtman has received lecture fees and travel honoraria from IPSEN and Astellas. Chris bangma has participated on data safety monitoring board for the ERSPC, is on the Board Dutch Urologic Association as an unpaid member, and is a member on the Causes of Death Committee ERSPC. The Finnish randomised trial has been supported by the Academy of Finland (grant nos 123054 and 311336) and the Competitive Research Funding of the Pirkanmaa Hospital District (grant no. 9x032) and Cancer Foundation Finland. We thank Jani Raitanen, MSc, Tampere University for statistical advice, Neill Booth, Health Sciences, Tampere University for software assistance, and the Dutch Causes of Death Committee for data access.

References

1 **Hugosson J**, **Roobol MJ**, **Månsson M et al.** A 16-yr follow-up of the European randomized study of screening for prostate cancer. *Eur Urol* 2019; 76: 43–51

2 **Schröder FH**, **Hugosson J**, **Roobol MJ et al.** Screening and prostate cancer mortality: results of the European Randomised Study of Screening for Prostate Cancer (ERSPC) at 13 years of follow-up. *Lancet* 2014; 384: 2027–35

3 **Ilic D**, **Neuberger MM**, **Djulbegovic M**, **Dahm P**. Screening for prostate cancer. *Cochrane Database Syst Rev* 2013; 2013: CD004720

4 **de Koning HJ**, **Gulati R**, **Moss SM et al.** The efficacy of prostate-specific antigen screening: impact of key components in the ERSPC and PLCO trials. *Cancer* 2018; 124: 1197–206

5 **Lin K**, **Croswell JM**, **Koenig H et al.** Prostate-Specific Antigen-Based Screening for Prostate Cancer: An Evidence Update for the U.S. Preventive Services Task Force [Internet]. 2011. Available at: www.ahrq.gov

6 **Kilpeläinen TP**. Population-Based Screening for Prostate Cancer – Weighing Up the Beneficial and Adverse Effects of Screening. 2012. Available at: https://trepo.tuni.fi/handle/10024/66964. Accessed October 2023

7 **Walter SD**, **de Koning HJ**, **Hugosson J et al.** Impact of cause of death adjudication on the results of the European prostate cancer screening trial. *Br J Cancer* 2017; 116: 141–8

8 **Kilpeläinen TP**, **Mäkinen T**, **Karhunen PJ et al.** Estimating bias in causes of death ascertainment in the Finnish randomized study of screening for prostate cancer. *Cancer Epidemiol* 2016; 45: 1–5

9 **Godtman R**, **Holmberg E**, **Stranne J**, **Hugosson J**. High accuracy of Swedish death certificates in men participating in screening for prostate cancer: a comparative study of official death certificates with a cause of death committee using a standardized algorithm. *Scand J Urol Nephrol* 2011; 45: 226–32

10 **De Koning HJ**, **Blom J**, **Merkelbach JW et al.** Determining the cause of death in randomized screening trial(s) for prostate cancer. *BJU Int* 2003; 92: 71–8

11 **Cooperberg MR**, **Pasta DJ**, **Elkin EP et al.** The University of California, San Francisco Cancer of the Prostate Risk Assessment score: a straightforward and reliable preoperative predictor of disease recurrence after radical prostatectomy. *J Urol* 2005; 173: 1938–42

12 **Pinsky PF**, **Miller E**, **Prorok P**, **Grubb R**, **Crawford ED**, **Andriole G**. Extended follow-up for prostate cancer incidence and mortality among participants in the Prostate, Lung, Colorectal and Ovarian randomized cancer screening trial. *BJU Int* 2019; 123: 854–60

13 **Martin RM**, **Donovan JL**, **Turner EL et al.** Effect of a low-intensity PSA-based screening intervention on prostate cancer mortality the CAP randomized clinical trial. *JAMA* 2018; 319: 883–95

14 **Carlsson SV**, **Arnsrud Godtman R**, **Pihl CG et al.** Young age on starting prostate-specific antigen testing is associated with a greater reduction in prostate cancer mortality: 24-year follow-up of the Göteborg randomized population-based prostate cancer screening trial. *Eur Urol* 2023; 83: 103–9

15 **Mottet N**, **Van Den Bergh RCN**, **Briers E et al.** EAU-EANM-ESTRO-ESUR-SIOG guidelines on prostate cancer-2020 update. Part 1: screening, diagnosis, and local treatment with curative intent. *Eur Urol* 2021; 79: 243–62

16 **Carlsson SV**, **Månsson M**, **Moss S et al.** Could differences in treatment between trial arms explain the reduction in prostate cancer mortality in the European randomized study of screening for prostate cancer? *Eur Urol* 2019; 75: 1015–22

17 **Grenabo Bergdahl A**, **Holmberg E**, **Moss S**, **Hugosson J**. Incidence of prostate cancer after termination of screening in a population-based randomised screening trial. *Eur Urol* 2013; 64: 703–9

18 **Smith RA**, **Mettlin CJ**, **Eyre H**. Methodologic issues in the evaluation of early detection programs. [Internet]. In **Kufe DW**, **Pollock RE**, **Weichselbaum RR** et al. eds, *Holland-Frei Cancer Medicine*, 6th edn. Hamilton, ON: BC Decker, 2003. Available at: https://www.ncbi.nlm.nih.gov/books/NBK13473/. Accessed October 2023

19 **Feinstein AR**, **Sosin DM**, **Wells CK**. The Will Rogers phenomenon. *N Engl J Med* 1985; 312: 1604–8

20 **Godtman RA**, **Remmers S**, **Aus G et al.** Intervention-related deaths in the European randomized study of screening for prostate cancer. *Eur Urol Open Sci* 2021; 34: 27–32

21 **European Health Union**. A new EU Approach on Cancer Detection – Screening More and Screening Better [Internet]. 2022. Available from: https://ec.europa.eu/commission/presscorner/detail/en/ip_22_5562. Accessed October 2022

22 **Vickers AJ**. Effects of magnetic resonance imaging targeting on overdiagnosis and overtreatment of prostate cancer. *Eur Urol* 2021; 80: 567–72

Correspondence: Niko Pasanen, Arvo Ylpön katu 34, Tampere FI-33520, Finland.

e-mail: niko.pasanen@tuni.fi

Abbreviations: CA, control arm; CAPRA, Cancer of the Prostate Risk Assessment; ERSPC, European Randomised Study of Screening for Prostate Cancer; HR, hazard ratio; ICD, International Classification of Diseases; PCa, prostate cancer; PLCO, Prostate, Lung, Colorectal and Ovarian cancer screening; RD, rate difference; SA, screening arm.

Supporting Information

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

Table S1. Number of screening rounds during the 16 years of follow-up and stopping age for the Finnish, Dutch and Swedish ERSPC centers.

Table S2. Risk group distribution by age group at randomisation in all three centres.

Table S3. Per-protocol analysis of prostate cancer mortality by ERSPC trial arm and country. Men who never participated at screening were excluded from the screening arm. Hazard ratios for the screening arm compared to the control arm (per centre).