



European Association of Urology



Platinum Priority – Prostate Cancer

Editorial by Allison S. Glass, Matthew R. Cooperberg and Peter R. Carroll on pp. 753–755 of this issue

Screening for Prostate Cancer Decreases the Risk of Developing Metastatic Disease: Findings from the European Randomized Study of Screening for Prostate Cancer (ERSPC)

Fritz H. Schröder^{a,*}, Jonas Hugosson^b, Sigrid Carlsson^b, Teuvo Tammela^c, Liisa Määtänen^d, Anssi Auvinen^e, Maciej Kwiatkowski^f, Franz Recker^f, Monique J. Roobol^a

^aDepartment of Urology, Erasmus MC, Rotterdam, The Netherlands; ^bDepartment of Urology, Sahlgrenska University Hospital, Göteborg, Sweden; ^cDepartment of Urology, Tampere University Hospital and University of Tampere, Tampere, Finland; ^dFinnish Cancer Registry, Helsinki, Finland; ^eTampere School of Public Health, University of Tampere, Tampere, Finland; ^fDepartment of Urology, Kantonsspital Aarau, Aarau, Switzerland

Article info

Article history:

Accepted May 31, 2012
Published online ahead of print on June 7, 2012

Keywords:

Prostatic neoplasm
Neoplasm metastases
Mass screening



www.eu-acme.org/
[europeanurology](http://europeanurology.com)

Please visit

www.eu-acme.org/europeanurology to read and answer questions on-line. The EU-ACME credits will then be attributed automatically.

Abstract

Background: Metastatic disease is a major morbidity of prostate cancer (PCa). Its prevention is an important goal.

Objective: To assess the effect of screening for PCa on the incidence of metastatic disease in a randomized trial.

Design, setting, and participants: Data were available for 76 813 men aged 55–69 yr coming from four centers of the European Randomized Study of Screening for Prostate Cancer (ERSPC). The presence of metastatic disease was evaluated by imaging or by prostate-specific antigen (PSA) values >100 ng/ml at diagnosis and during follow-up.

Intervention: Regular screening based on serum PSA measurements was offered to 36 270 men randomized to the screening arm, while no screening was provided to the 40 543 men in the control arm.

Outcome measurements and statistical analysis: The Nelson-Aalen technique and Poisson regression were used to calculate cumulative incidence and rate ratios of M+ disease.

Results and limitations: After a median follow-up of 12 yr, 666 men with M+ PCa were detected, 256 in the screening arm and 410 in the control arm, resulting in cumulative incidence of 0.67% and 0.86% per 1000 men, respectively ($p < 0.001$). This finding translated into a relative reduction of 30% (hazard ratio [HR]: 0.70; 95% confidence interval [CI], 0.60–0.82; $p = 0.001$) in the intention-to-screen analysis and a 42% ($p = 0.0001$) reduction for men who were actually screened. An absolute risk reduction of metastatic disease of 3.1 per 1000 men randomized (0.31%) was found. A large discrepancy was seen when comparing the rates of M+ detected at diagnosis and all M+ cases that emerged during the total follow-up period, a 50% reduction (HR: 0.50; 95% CI, 0.41–0.62) versus the 30% reduction. The main limitation is incomplete explanation of the lack of an effect of screening during follow-up.

Conclusions: PSA screening significantly reduces the risk of developing metastatic PCa. However, despite earlier diagnosis with screening, certain men still progress and develop metastases.

The ERSPC trial is registered under number ISRCTN49127736.

© 2012 European Association of Urology. Published by Elsevier B.V. All rights reserved.

* Corresponding author. Erasmus MC, University Medical Center, PO Box 2040, 3000 CA Rotterdam, The Netherlands. Tel. +31 10 7030145; Fax: +31 10 7035315.
E-mail address: secr.schroder@erasmusmc.nl, f.h.schroder@hetnet.nl (F.H. Schröder).

1. Introduction

Screening for prostate cancer (PCa) remains controversial, even after the European Randomized Study of Screening for Prostate Cancer (ERSPC) [1,2] reported a 21% relative reduction of deaths from PCa at 11 yr of follow-up and the Gothenburg (Sweden) trial, one of the ERSPC centers, showed 44% reduction at 14 yr [3]. The main reason for controversy concerns the harms associated with PCa screening, such as the high risk of overdiagnosis and overtreatment [4].

The occurrence of metastatic disease is a very important contributor to the suffering caused by PCa. Its prevention or delay is a legitimate secondary end point of screening. Earlier studies have reported that early diagnosis by prostate-specific antigen (PSA) testing results in a reduction of the number of men with metastatic disease [5–7]. The ERSPC study has shown a 41% decrease of metastatic disease in the screening arm at the time of diagnosis [1]; however, progression to metastatic disease during follow-up after initial treatment that was not evaluated in the ERSPC study [1] should also be influenced by screening.

The goal of this paper is to compare the incidence of metastatic disease, not only at diagnosis but also during subsequent follow-up, in the screening and control arms of four major centers of the ERSPC study group.

2. Materials and methods

The ERSPC is a randomized trial comparing an intervention arm of men to whom regular PSA screening is offered with a control arm to which such screening is not offered. Details of the methodology have been described previously for all centers in the ERSPC study [1] and for the Gothenburg trial by Hugosson et al. [3]. In all centers, known cases of PCa were excluded before randomization. The Swedish center utilized a 2-yr screening interval, whereas a 4-yr interval was applied at the other centers. In Finland, randomization was carried out at a ratio of 1:1.5 between the screening group and the control group. In addition, men with PSA 3.0–3.9 ng/ml were not referred directly to further diagnostic examination but were offered an ancillary test, a digital rectal examination (in 1996–1998) or a free/total PSA ratio (with cut-off of 0.16), from 1999 onward.

As in the previous reports, the focus of the paper is on the core age group of 55–69 yr. Follow-up of cancer cases in the control arm was by 6-mo chart review. Diagnostic and treatment decisions were in the hands of the regional care providers.

The current evaluation is limited to those centers for which information on metastatic status is available in both the screening and control arms of the study and was collected during the entire period of postdiagnosis follow-up. No common follow-up scheme was established in the ERSPC protocol, but patients with progressive disease were typically checked every 3–6 mo for PSA and clinical status. Bone scans were generally performed in men with bone pain or suspicion of M1 as well as in men with PSA values of ≥ 20 ng/ml and/or high Gleason scores ≥ 7 . Similar procedures were followed for patients in both arms within all centers.

The M+ status was assigned in the presence of one of two findings. M1 disease status was defined in line with the TNM definition by an obviously positive bone scan or x-ray. In doubtful situations, computed tomography or magnetic resonance imaging studies were used to confirm or exclude metastatic disease. Patients with a PSA value >100 ng/ml were considered to have metastatic disease if imaging

studies were not reported. An analysis of the rate ratios (RRs) for M1 disease at imaging and for M+ disease overall, at diagnosis, and during follow-up was carried out to investigate the correctness of this assumption. We categorized men who were diagnosed with M+ disease in spite of screening as *missed at screen* (biopsied according to protocol, no PCa detected), *nonattendees, above the upper age cut-off* (age 69–74 yr), and *rapid progressors* (no biopsy indication at last screen).

For purpose of risk stratification, low, intermediate, and advanced clinical risk groups at the time of detection were defined, respectively, in line with definitions used by Schröder et al. [1,2]: (1) clinical stage T1, T2 and Gleason score ≤ 6 ; (2) clinical stage T1, T2 with Gleason score 7, or T3 with Gleason score ≤ 7 ; and (3) clinical stage T1, T2, or T3 with Gleason score 8–10 or clinical stage T4 with any Gleason score. To allow better comparison with current guidelines, we also analyzed the effect of the inclusion of PSA in line with the European Association of Urology guidelines [8].

2.1. Statistics

The study differentiated between M+ disease found *at diagnosis*, which was identified within 3 mo after the diagnosis of PCa, and M+ disease found *during follow-up*, that is, identified >3 mo after the diagnosis of PCa and after initial management.

Follow-up with evaluation of PSA and clinical parameters started at randomization. Last date of follow-up in men without PCa was the last date with cancer incidence data available from the cancer registry, the date of death, or the date of emigration. In men with PCa, last date of follow-up was either the date of established M+ or the date of last check-up.

Cumulative hazards of M+ disease in both study arms were calculated according to the Nelson-Aalen method [9]. Ratios between arms were assessed using Poisson regression analysis as rates per 1000 men. The number needed to invite (NNI) to prevent one M+ case was calculated as the inverse of the absolute risk reduction. The number needed to diagnose (NND) was calculated as the inverse absolute risk reduction multiplied by the overall excess incidence of PCa (any stage) in the screening arm (excess incidence indicates the PCa cases that were found by screening in addition to the control population). The analyses were conducted by the use of SPSS 17.0 and Stata v.12 software.

3. Results

The study population is shown in Figure 1, which also shows the part of the total ERSPC population that is included in the present report. In addition, absolute numbers of participants, cancers and M+ cases diagnosed, and deaths per arm are shown. The numbers of participants in the screening and control arms, the numbers of men with M+ disease per center and per study arm, and the relative risks of M+ at diagnosis and during follow-up are specified in Table 1. The follow-up periods differed slightly between centers with an overall median of 12.0 yr (Netherlands: 12.0 yr; Sweden: 14.9 yr; Finland: 12.9 yr; Switzerland: 9.1 yr). The RRs of screening versus control of M+ disease diagnosed solely by imaging (proven M1) were compared with the M+ data based on both imaging and PSA >100 . For M+ disease, overall RRs of 0.66 and 0.70 resulted for screening versus control, respectively; for M+ at diagnosis, RRs were 0.54 and 0.50; and for M+ during follow-up, RRs of 1.00 and 1.16 were found. The closeness of these RRs justifies the use of PSA >100 as a surrogate for M1 disease.

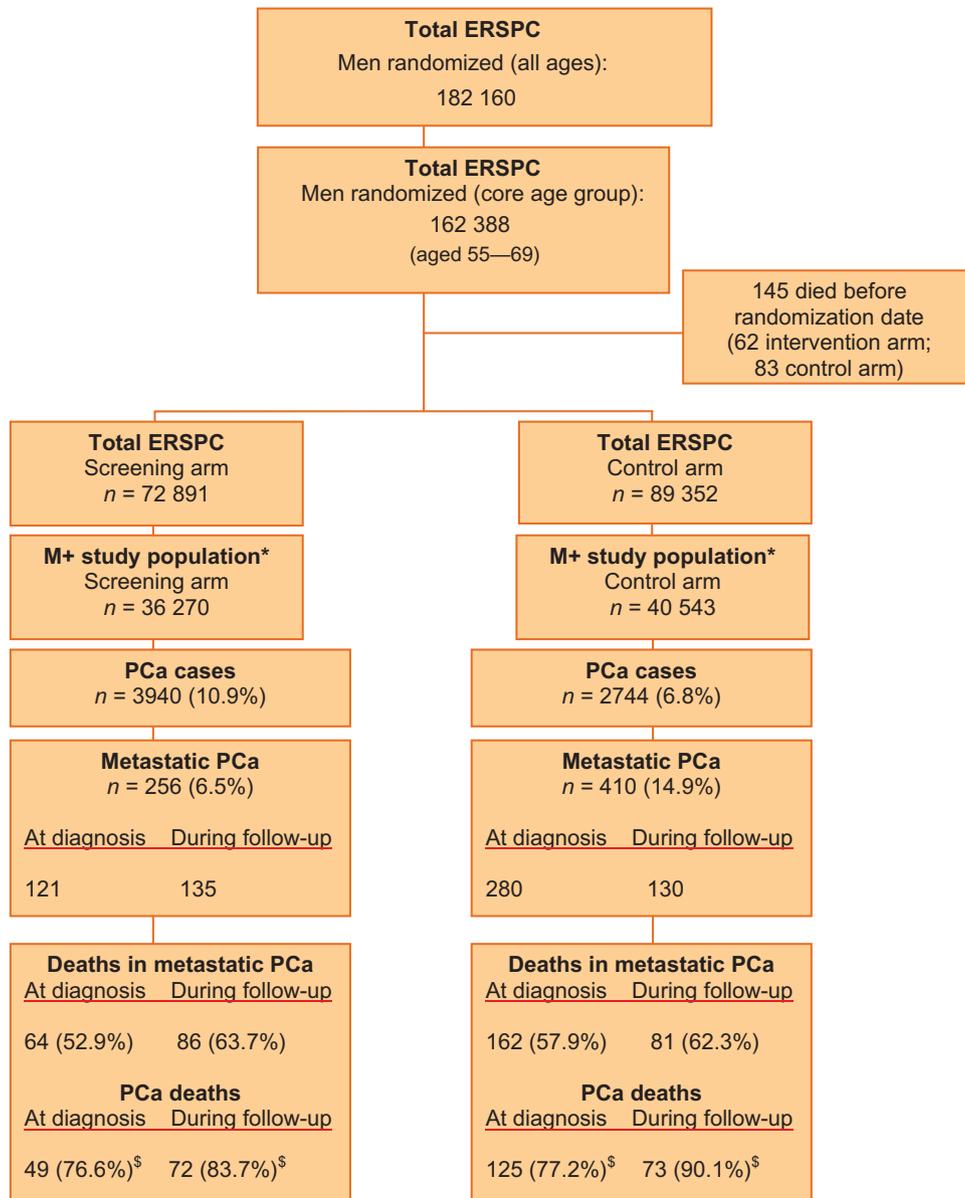


Fig. 1 – Flow diagram of the study.

ERSPC = European Randomized Study of Screening for Prostate Cancer; PCa = prostate cancer.

*Comprising data of four of the eight ERSPC centers: The Netherlands, Sweden, Finland (Tampere), and Switzerland.

§ Percentage of men with M+ PCa that died.

The Nelson-Aalen plot showed divergence of the cumulative hazard for M+ disease overall (ie, at time of diagnosis and during follow-up combined) starting at years 4 and 5, with a lower risk in the screening arm (Fig. 2a). At 12 yr of follow-up, the RR of M+ disease overall in the screening group compared with the control group was 0.70 (95% confidence interval [CI], 0.60–0.82; $p = 0.001$). The absolute risk reduction was 3.1 (95% CI, 1.8–4.4) metastatic PCa cases per 1000 in men randomized (0.31%). The excess incidence of PCa (all cases) in the screening arm amounted to 37.6 cases per 1000 men. This number translates into a 55.6% higher incidence rate in the screening arm compared with the control arm, indicating the potential amount of

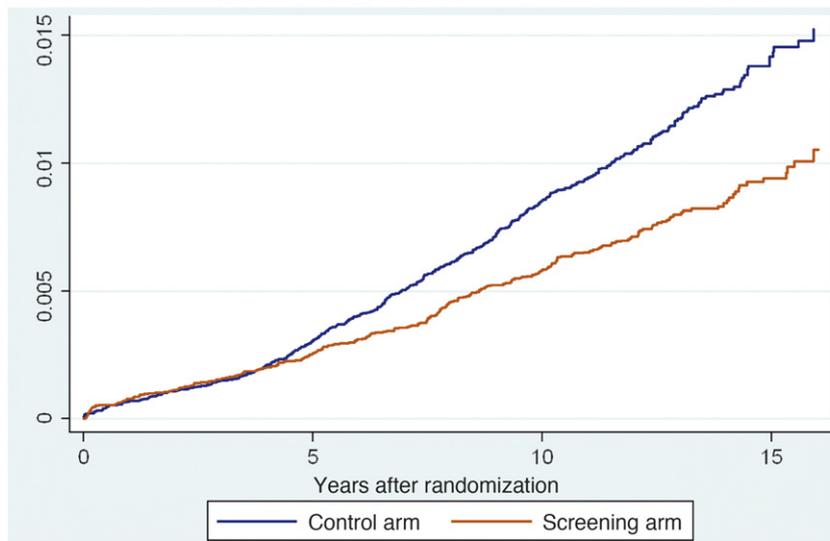
overdiagnosis. The resulting NNI for screening to avoid 1 case of metastatic disease was 328, and the NND was 12. If the analysis was restricted to attendees only, this resulted in a relative risk reduction of 42% compared with the control group (RR: 0.58; 95% CI, 0.45–0.74; $p < 0.001$). Figures 2b and 2c show the Nelson-Aalen curves for M+ PCa found at diagnosis and during follow-up. An analysis of the numbers of M+ cases detected at diagnosis per year after randomization is shown in Figure 3. The effect seen at diagnosis represents the main effect of screening in preventing M+ disease, but this effect decreases during the later years of follow-up due to increasing numbers of M+ starting with year 7 in the screening arm.

Table 1 – Rate ratios of M+ cases overall, at diagnosis, and during follow-up per center

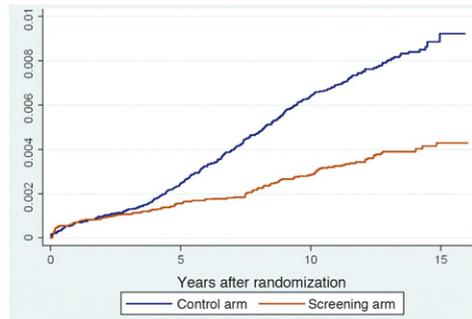
| | Men in screening arm, n | Men in control arm, n | M+ overall | | | | | |
|---------------------|-------------------------|-----------------------|------------------------|-----------------------------|----------------------|---------------------------|-------|---------|
| | | | M+ in screening arm, n | Rate of M+ in screening arm | M+ in control arm, n | Rate of M+ in control arm | RR | p value |
| NL | 17 443 | 17 390 | 132 | 0.71 (0.60–0.84) | 184 | 1.00 (0.86–1.15) | 0.713 | 0.003 |
| S | 5901 | 5951 | 71 | 0.97 (0.77–1.22) | 107 | 1.45 (1.20–1.75) | 0.666 | 0.008 |
| FIN | 7978 | 12 247 | 36 | 0.43 (0.31–0.60) | 96 | 0.75 (0.62–0.92) | 0.574 | 0.004 |
| SWI | 4948 | 4955 | 17 | 0.43 (0.27–0.70) | 23 | 0.59 (0.39–0.89) | 0.734 | 0.334 |
| Total | 36 270 | 40 543 | 256 | 0.67 (0.59–0.76) | 410 | 0.86 (0.88–1.06) | 0.695 | <0.001 |
| M+ at diagnosis | | | | | | | | |
| NL | | | 54 | 0.31 (0.24–0.41) | 114 | 0.63 (0.52–0.76) | 0.498 | <0.0001 |
| S | | | 35 | 0.51 (0.37–0.71) | 70 | 0.98 (0.78–1.24) | 0.523 | <0.0001 |
| FIN | | | 27 | 0.34 (0.23–0.50) | 83 | 0.67 (0.54–0.83) | 0.590 | <0.0001 |
| SWI | | | 5 | 0.14 (0.06–0.33) | 13 | 0.34 (0.20–0.59) | 0.396 | <0.079 |
| Total | | | 121 | 0.34 (0.28–0.41) | 280 | 0.68 (0.60–0.76) | 0.503 | <0.0001 |
| M+ during follow-up | | | | | | | | |
| NL | | | 78 | 0.42 (0.34–0.52) | 70 | 0.38 (0.30–0.48) | 1.107 | 0.534 |
| S | | | 36 | 0.49 (0.35–0.68) | 37 | 0.50 (0.36–0.69) | 0.977 | 0.921 |
| FIN | | | 9 | 0.11 (0.06–0.20) | 13 | 0.10 (0.06–0.18) | 1.059 | 0.895 |
| SWI | | | 12 | 0.30 (0.17–0.54) | 10 | 0.26 (0.14–0.48) | 1.191 | 0.682 |
| Total | | | 135 | 0.35 (0.30–0.42) | 130 | 0.31 (0.26–0.36) | 1.156 | 0.238 |

NL = The Netherlands; S = Sweden; FIN = Finland; SWI = Switzerland; RR = rate ratio.

(a) Risk ratio: 0.695 (0.595–0.815)



(b) Risk ratio 0.503 (0.406–0.622)



(c) Risk ratio 1.156 (0.909–1.471)

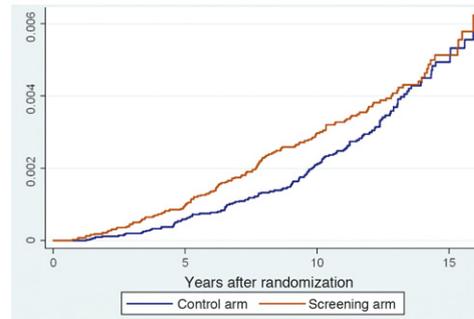


Fig. 2 – Nelson-Aalen cumulative hazard estimates of M+ prostate cancer (a) overall, (b) at time of diagnosis, and (c) during follow-up. PCa = prostate cancer.

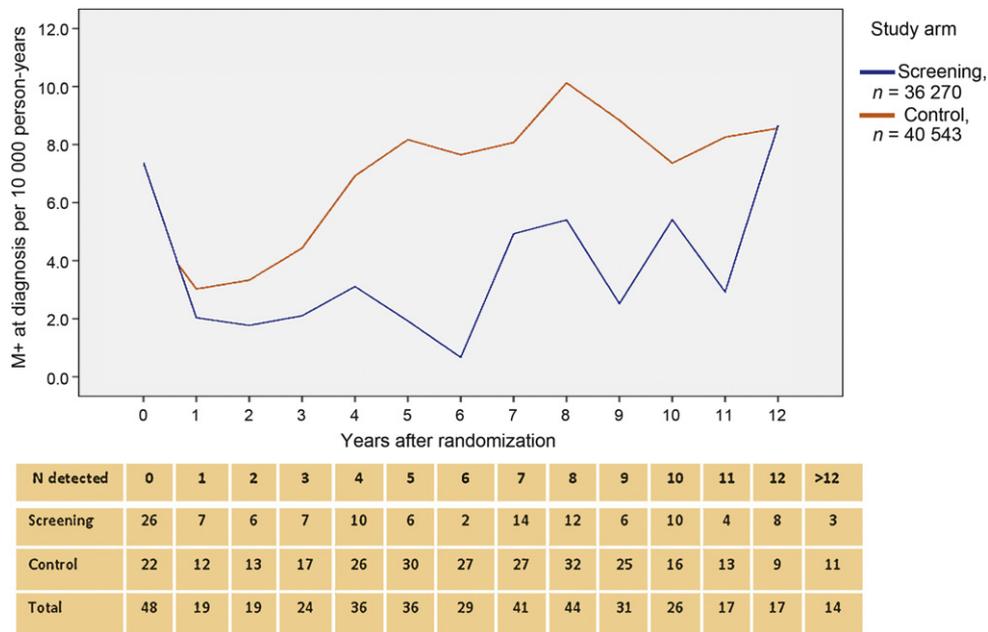


Fig. 3 – Rate per 10 000 person-years of M+ at diagnosis per study arm and by years after randomization.

Table 2 – M+ at diagnosis >6 yr after randomization, core age group (all centers)

| Years after randomization | Missed at screen | Rapid progressor | No show | | Too old | Screen detected | Total |
|---------------------------------------|------------------|------------------|---------|--------------|---------|-----------------|-------|
| | | | Never | Later rounds | | | |
| 7–8 | 1 | 4 | 9 | 6 | 3 | 5 | 28 |
| 9–10 | 2 | 1 | 5 | 4 | 3 | – | 15 |
| ≥11 | 1 | 3 | 5 | 1 | 6 | – | 16 |
| All | 4 | 8 | 19 | 11 | 12 | 5 | 59 |
| Death | – | 2 | 13 | 6 | 2 | 3 | 26 |
| PCa death | – | 2 | 7 | 5 | 2 | 2 | 18 |
| Time diagnosed to PCa death, yr, mean | – | 2.3 | 1.4 | 2.0 | 1.4 | 3.0 | 2.0 |

PCa = prostate cancer.
 Missed at screen: attended last visit, had biopsy indication and was biopsied.
 Rapid progressor: attended last visit, had no biopsy indication (ie, PSA below cutoff).
 No show, never: did not attend any of the screening visits.
 No show, later rounds: Attended initial screening but declined any repeat screening round.
 Too old: Attended screening but was diagnosed at an age 2–4 yr above the upper age cut-off (differs per center).
 Screen detected: was detected at a screening visit.

3.1. Detailed analysis of M+ disease at diagnosis in the screening arm

Table 2 shows the data for periods after randomization starting at year 7 classified by mechanism of detection and includes numbers of deaths and times to deaths for the subgroups in the screening arm only. The 7-yr cut-off was chosen to address the observation of the increase of M+ as of year 7 in the screening arm seen in Figure 3. Only 4 of 59 M+ cases were considered to have been missed at screening, and 5 of 59 were screen detected.

3.2. Detailed analysis of M+ occurring during follow-up

In Table 3, the total numbers of PCa and M+ cases per screening round, per screening interval (4 yr), and for

nonattendees are given. These data are potentially biased by differences in available follow-up. This problem is circumvented by applying a fixed follow-up period for all subgroups, as is done in columns 5 and 6, where a follow-up period of 5 yr is used. The comparison of the screening rounds shows that the largest proportion of cases that progress to M+ comes from the first round of screening. The proportion of interval cancers that progress to M+ ranges from 2.8% to 4.1% of all PCa diagnosed within the interval.

3.3. Risk factors and treatments applied

In Table 4, the M+ cases identified during follow-up within the screening arm were classified according to the method of detection. When risk groups have been redesigned and

Table 3 – Total number of prostate cancer (PCa) cases, total number of PCa cases that progress to M+, and PCa cases that progress to M+ within 5 yr after diagnosis, according to mechanism of detection in the screening arm

| Method of detection | PCa cases detected, n | PCa with progression to M+, n | Total PCa, % | PCa cases that progress within 5 yr after diagnosis, n (% of total M+ cases) | PCa cases that progress within 5 yr after diagnosis, % of total PCa cases |
|---------------------|-----------------------|-------------------------------|--------------|--|---|
| Screen detected | | | | | |
| Round 1 | 1330 | 87 | 6.5 | 33 (37.9) | 2.5 |
| Round 2 | 1045 | 10 | 1.0 | 7 (70.0) | 0.7 |
| Round 3 | 627 | 4 | 0.6 | 3 (75.0) | 0.5 |
| Nonattendees | 247 | 13 | 5.3 | 4 (30.7) | 1.6 |
| Interval 0–4 | 146 | 6 | 4.1 | 5 (83.3) | 3.4 |
| Interval 4–8 | 248 | 7 | 2.8 | 5 (71.4) | 2.0 |
| Interval 8–12 | 256 | 8 | 3.1 | 7 (87.5) | 2.7 |
| Total screening arm | 3940 | 135 | 3.4 | 64 (47.4) | 1.6 |

PCa = prostate cancer.

Table 4 – Prostate cancer cases that progress to M+ during follow-up by method of detection and by risk group at time of diagnosis in the screening arm

| Method of detection | Risk group at time of detection | | | Missing data on stage and/or grade, n (%) | Total, n |
|---------------------|---------------------------------|---------------------------|-------------------|---|----------|
| | Low risk*, n (%) | Intermediate risk*, n (%) | High risk*, n (%) | | |
| Screen detected | | | | | |
| Round 1 | 8 (9.2) | 52 (59.8) | 17 (19.5) | 10 (11.5) | 87 |
| Round 2 | – | 8 (80.0) | 2 (20.0) | – | 10 |
| Round 3 | – | 4 (100.0) | – | – | 4 |
| Nonattendees | 1 (7.7) | 6 (46.2) | – | 6 (46.2) | 13 |
| Interval 0–4 | – | 2 (33.3) | – | 4 (66.7) | 6 |
| Interval 4–8 | – | 1 (14.3) | 2 (28.6) | 4 (57.1) | 7 |
| Interval 8–12 | 1 (12.5) | 4 (50.0) | – | 3 (37.5) | 8 |
| Total screening arm | 10 (7.4) | 77 (57.0) | 21 (15.6) | 27 (20.0) | 135 |

PCa = prostate cancer.
 * Risk groups:
 Low risk: clinical stage T1, T2 with Gleason score ≤ 6 .
 Intermediate risk: clinical stage T1, T2 with Gleason score 7, and T3 with Gleason score ≤ 7 .
 High risk: clinical stage T1, T2, or T3 with Gleason score 8–10 or clinical stage T4 with any Gleason score.
 M1 and/or prostate-specific antigen (PSA) >100 at diagnosis: any clinical stage or Gleason score with M1 and/or PSA >100 .

Table 5 – Initial treatment of all prostate cancer (PCa) detected (without M+ at diagnosis) and PCa that progressed during follow-up per risk group and in the screening arm

| Screening arm | Surgery, % | Radiotherapy, % | AS, % | Hormones, % | Other, % | Total, n |
|--|------------|-----------------|-------|-------------|----------|-------------------|
| Low risk | 38.9 | 23.7 | 34.4 | 2.3 | 0.7 | 2566 |
| Low risk with later progression to M+ | 32.0 | 40.0 | 28.0 | – | – | 25 |
| Intermediate risk | 47.1 | 34.6 | 9.7 | 8.6 | – | 628 |
| Intermediate risk with later progression to M+ | 37.9 | 48.3 | – | 13.8 | – | 29 |
| High risk | 43.2 | 34.6 | 4.9 | 17.3 | – | 243 |
| High risk with later progression to M+ | 27.5 | 47.5 | 2.5 | 22.5 | – | 40 |
| Total PCa cases not M+ at diagnosis | 40.7 | 26.4 | 27.8 | 4.5 | 0.5 | 3437 [*] |
| Total PCa cases that progressed during follow-up | 31.9 | 45.7 | 8.5 | 13.8 | – | 94 ^{**} |

AS = active surveillance; PCa = prostate cancer.
 * A total of 382 cases are missing due to missing data on T stage, Gleason score, or treatment.
 ** A total of 41 cases are missing.

reevaluated including PSA, no major differences have been seen. For reasons of consistency, we prefer to use the definitions applied by Schröder et al. [1,2]. Most M+ cases occurred in the intermediate-risk group and after the initial screen, again pointing toward the presence of unfavorable cases in spite of using the prior diagnosis of PCa as an exclusion criterion for participation.

Treatment may have had a potential influence on the progression to M+ disease. Data on treatment are shown in Table 5 for the screening arm. The data suggest more frequent use of radiotherapy in men with progression to M+ disease. These data are not suitable for statistical testing due to missing data, lack of information on subsequent treatment, and a relatively rough subdivision (ie, age, comorbidity).

Table 6 – Age at diagnosis, deaths from prostate cancer, and times from diagnosis to M+ and from M+ to death for subgroups and the total population

| | At diagnosis | | During follow-up | | Total | |
|---|------------------|------------------|----------------------|----------------------|----------------------|----------------------|
| | Screening arm | Control arm | Screening arm | Control arm | Screening arm | Control arm |
| <i>n</i> | 121 | 280 | 135 | 130 | 256 | 410 |
| Age at diagnosis, yr, mean (range) | 68.3 (57–79) | 68.7 (55–80) | 64.1 (55–78) | 67.8 (56–82) | 66.0 (55–79) | 68.4 (55–82) |
| Time from diagnosis to M+ | <3 mo | <3 mo | 5.61 yr (0.27–14.21) | 4.04 yr (0.38–13.06) | 2.96 yr (0.07–14.21) | 1.28 yr (0.14–13.06) |
| Time from M+ to death, yr, mean (range) | 2.60 (0.04–7.44) | 2.41 (0.01–9.45) | 2.13 (0.03–8.85) | 1.31 (0.01–7.60) | 2.33 (0.03–8.85) | 2.04 (0.01–9.45) |
| Death, <i>n</i> | 64 | 162 | 86 | 81 | 150 | 243 |
| Death from PCa, % | 76.6 (n = 49) | 77.2 (n = 125) | 83.7 (n = 72) | 90.1 (n = 73) | 80.6 (n = 121) | 81.5 (n = 198) |

PCa = prostate cancer.

Finally, Table 6 gives an overview of the numbers of men with M+ disease per subgroup (at diagnosis, during follow-up, and overall), indicating age distribution and ranges as well as times from M+ to death and death rates from PCa. Men diagnosed with M+ during follow-up in the control arm were older than those in the screening arm. The time from diagnosis of PCa to M+ status is shorter in the control arm. The time from M+ to death is shortest in the control arm in cases that progress during follow-up.

4. Discussion

Our results show an absolute risk reduction of 3 M+ PCa cases per 1000 men, corresponding to a relative risk reduction of 30% ($p = 0.001$) in favor of screening. This reduction in M+ disease must be balanced against the downside of screening, mainly the rate of overdiagnosis in the screening arm, estimated at $\geq 50\%$ in the setting of the ERSPC [4]; in the current analysis, a potential rate of overdiagnosis of 55.6% was shown. This report is next to that of Kilpeläinen et al. [10], which is limited to one center and a shorter mean follow-up of only 9 yr; it is the first report analyzing the effect of screening on metastatic PCa in a prospective randomized setting. In addition, a few nonrandomized studies have addressed the issue [4–6]. The data confirm absolute and/or relative reductions of metastatic disease within the three different populations studied. The absolute risk reduction of 3 metastatic cases per 1000 men seen in our study, which is equivalent to a relative risk reduction of 30%, is modest but clinically relevant, especially if one considers the relative risk reduction of 42% seen after correction for nonattendance in men actually screened.

To provide a better balance between benefits and harms of screening for PCa, approaches to decrease overdiagnosis and other negative quality-of-life effects remain an important task. The use of available risk-stratifying instruments to decrease “unnecessary” diagnostic measures is a realistic option [11]. The relative risk reduction of 30% is lower than the relative risk reduction of 41% reported in 2009 for the whole of ERSPC with a 9-yr follow-up [1]. The reason for this is that M+ at diagnosis does not reflect the complete picture with respect to the relative decrease of M+ disease by screening. This detailed analysis shows that an almost equal number of PCa cases in both arms progress to M+ disease during follow-up, reducing the effect on M+ at diagnosis from 50% to 30% overall.

Next to establishing the effect of screening on the risk of developing M+ PCa, the exploration of factors that may influence the reduction of M+ disease is of importance. We show an increase of M+ disease overall in the screening arm as of year 7. This is explained in large part by nonparticipation and ending screening at age 70. The findings given in Figure 3 confirm that most metastatic progression occurs after the sixth year of follow-up (Table 2) in cancers diagnosed at the first screen. The data show, however, that very few (only 9 of 59) M+ cases might have been avoided by more aggressive screening. This late increase of M+ cases at diagnosis in the screening arm has the potential to decrease the overall effect of screening.

The finding that the rate of PCa cases progressing to M+ disease during follow-up is equal in both arms is new and is relevant for the understanding of screening studies and of screening for PCa in general. A potential explanation for the late, unexpected high rate of M+ disease in screen-detected cases is lead-time bias and the observation that, in the screening arm, many of the cases diagnosed at the first screen are already far advanced at the time of diagnosis. Unfortunately, our data cannot fully explain the lack of an effect of screening on M+ disease occurring during follow-up. Follow-up may, however, still be too short, and our conclusion may change in the future if the trend seen in Figure 2c after year 12 continues. Differences in potentially curative treatments between nonprogressive and progressive cancers in the screening arm may contribute to the reported observations.

4.1. Strengths and weaknesses

The main strength of our report is the fact that we are providing the only available data on an effect of screening on metastatic disease in a randomized controlled setting. Our data provide clinically useful information for men who consider being tested for PCa.

It is regrettable that we have to report on a selective group of centers and not on the ERSPC study as a whole. The different effectiveness of screening on the occurrence of M+ disease at diagnosis and during follow-up remains largely unexplained. The findings are clinically relevant but do not change the main downsides of screening, specifically overdiagnosis, that so far have prevented the introduction of screening for PCa in most countries. In addition, the lack of information on secondary treatments such as androgen deprivation is a weakness of our study. The 12-yr median follow-up is probably still too short for definite conclusions on the effect of screening on M+ PCa.

5. Conclusions

Our study shows relative reductions of 30% and 42% in M+ disease by screening for the whole population and for men who are screened, respectively, after 12 yr of follow-up. This benefit must be balanced against potential harms of screening.

Author contributions: Fritz H. Schröder had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Schröder, Hugosson, Carlsson, Tammela, Määttänen, Auvinen, Kwiatkowski, Recker, Roobol.

Acquisition of data: Schröder, Hugosson, Carlsson, Tammela, Määttänen, Auvinen, Kwiatkowski, Recker, Roobol.

Analysis and interpretation of data: Roobol, Schröder.

Drafting of the manuscript: Schröder.

Critical revision of the manuscript for important intellectual content: Schröder, Hugosson, Carlsson, Tammela, Määttänen, Auvinen, Kwiatkowski, Recker, Roobol.

Statistical analysis: Roobol.

Obtaining funding: Schröder, Hugosson, Carlsson, Tammela, Määttänen, Auvinen, Kwiatkowski, Recker, Roobol.

Administrative, technical, or material support: Schröder, Hugosson, Carlsson, Tammela, Määttänen, Auvinen, Kwiatkowski, Recker, Roobol.

Supervision: None.

Other (specify): None.

Financial disclosures: Fritz H. Schröder certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

Funding/Support and role of the sponsor: None.

References

- [1] Schröder FH, Hugosson J, Roobol MJ, et al. Screening and prostate-cancer mortality in a randomized European study. *N Engl J Med* 2009;360:1320–8.
- [2] Schröder FH, Hugosson J, Roobol MJ, et al. Prostate-cancer mortality at 11 years of follow-up. *N Engl J Med* 2012;366:981–90.
- [3] Hugosson J, Carlsson S, Aus G, et al. Mortality results from the Göteborg randomised population-based prostate-cancer screening trial. *Lancet Oncol* 2010;11:725–32.
- [4] Draisma G, Boer R, Otto SJ, et al. Lead times and overdiagnosis due to prostate-specific antigen screening: estimates from the European Randomized Study of Screening for Prostate Cancer. *J Natl Cancer Inst* 2003;95:868–78.
- [5] Aus G, Bergdahl S, Lodding P, Lilja H, Hugosson J. Prostate cancer screening decreases the absolute risk of being diagnosed with advanced prostate cancer—results from a prospective, population-based randomized controlled trial. *Eur Urol* 2007;51:659–64.
- [6] Cooperberg MR, Broering JM, Carroll PR. Risk assessment for prostate cancer metastases and mortality at the time of diagnosis. *J Natl Cancer Inst* 2009;101:878–87.
- [7] Etzioni R, Gulati R, Falcon S, Penson DF. Impact of PSA screening on the incidence of advanced stage prostate cancer in the United States: a surveillance modelling approach. *Med Decis Making* 2008;28:323–31.
- [8] Heidenreich A, Bellmunt J, Bolla M, et al. EAU guidelines on prostate cancer. Part I: screening, diagnosis, and treatment of clinically localised disease. *Actas Urol Esp* 2011;35:501–14.
- [9] Aalen OO. Nonparametric inference for a family of counting processes. *Ann Stat* 1978;6:701–26.
- [10] Kilpeläinen TP, Auvinen A, Määttänen L, et al. Results of the three rounds of the Finnish Prostate Cancer Screening Trial—the incidence of advanced cancer is decreased by screening. *Int J Cancer* 2010;127:1699–705.
- [11] Roobol MJ, Steyerberg EW, Kranse R, et al. A risk-based strategy improves prostate-specific antigen-driven detection of prostate cancer. *Eur Urol* 2010;57:79–85.