EUROPEAN UROLOGY 75 (2019) 374–377

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Brief Correspondence

Results of Prostate Cancer Screening in a Unique Cohort at 19 yr of Follow-up

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Article info

Article history:
Accepted October 26, 2018

Associate Editor:
James Catto

Keywords:
Cancer-specific mortality
Metastatic disease
Prostate cancer
PSA-based screening

Abstract

We assessed the effect of screening in the European Randomized study of Screening for Prostate Cancer (ERSPC) Rotterdam pilot 1 study cohort with men randomized in 1991–1992. A total of 1134 men were randomized on a 1:1 basis to a screening (S) and control (C) arm after prostate-specific antigen (PSA) testing (PSA ≥10.0 ng/ml was excluded from randomization). Further PSA testing was offered to all men in the S-arm with 4-yr intervals starting at age 55 yr and screened up to the age of 74 yr. Overall, a PSA level of ≥3.0 ng/ml triggered biopsy. At time of analysis, 63% of men had died. Overall relative risk of metastatic (M+) disease and prostate cancer (PCa) death was 0.46 (95% confidence interval [CI]: 0.19–1.11) and 0.48 (95% CI: 0.17–1.36), respectively, in favor of screening. This ERSPC Rotterdam pilot 1 study cohort, screened in a period without noteworthy contamination, shows that PSA-based screening could result in considerable reductions of M+ disease and mortality which if confirmed in larger datasets should trigger further discussion on pros/cons of PCa screening.

Patient summary: In a cohort with 19 yr of follow-up, we found indications for a more substantial reduction in metastatic disease and cancer-specific mortality in favor of prostate cancer screening than previously reported. If confirmed in larger cohorts, these findings should be considered in the ongoing discussion on harms and benefits of prostate cancer screening.

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Main report

The European Randomized study of Screening for Prostate Cancer (ERSPC) has shown that prostate-specific antigen (PSA)-based screening results in a significant prostate cancer (PCa) mortality reduction at 13 yr of follow-up (FU) [1]. In contrast to the ERSPC, the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial did not show a cancer-specific mortality reduction due to screening in their intention-to-screen analysis [2]. However, recently published (modeling) analyses show that the ERSPC and PLCO trials in fact provide compatible evidence that screening reduces PCa mortality [3,4]. Despite these observed reductions, unnecessary testing and overdiagnosis

https://doi.org/10.1016/j.eururo.2018.10.053
0302-2838/

still preclude PSA-based PCa screening from adoption as public health policy. However, the results of the ERSPC and PLCO trials may be affected by a relatively short FU and PSA contamination. Here, we assessed the effect of PSA-based PCa screening in an ERSPC Rotterdam study cohort (pilot 1 study) with men randomized in the period 1991–1992 (an era in which PSA testing was uncommon) and enabling us to report on the basis of long-term FU.

ERSPC Rotterdam started with a series of five pilot studies in October 1991. Full capacity screening started in June 1994. In this work, we describe the results of the first pilot study of ERSPC Rotterdam. The participants of this ERSPC pilot 1 study are not included in the Rotterdam section of the main ERSPC trial. The other pilot studies were not included in the current analyses due to their period of randomization, length of FU, and substantial differences in administrative procedures/screening processes. The pilot 1 study protocol characteristics are described in earlier publications [5,6]. Briefly, 3331 men aged 55–74 yr selected from the population registry of Rotterdam were invited for screening. The only exclusion criterion was a previous PCa diagnosis. Men who responded (n = 1186; recruitment rate of 35.6%) by returning the intake questionnaire and who provided signed informed consent were included and randomized after PSA testing (n = 1134) on a 1:1 basis to a screening (S) and control (C) arm. Men (n = 30) with a PSA level ≥10.0 ng/ml were excluded from randomization and directly referred to their general practitioner. The screening protocol consisted of PSA, digital rectal examination, and transrectal ultrasound (TRUS) and was offered to all men in the S-arm with a 4-yr interval and applying the upper age limit of 74 yr (maximum of five consecutive screening rounds). In general, a PSA level ≥3.0 ng/ml triggered TRUS-guided biopsy. The primary endpoint was PCa-specific mortality. We also assessed the clinical/pathological features of the cancers detected (at time of diagnosis) and calculated the relative risk (RR) of metastatic (M+) disease (defined as N1 and/or M1 and/or PSA >100 ng/ml), including M+ disease at diagnosis and during FU. Finally, we retrospectively randomized the initially excluded men (PSA ≥10.0 ng/ml) using the bootstrap procedure (n = 5000 iterations) to calculate risk reductions including all PSA values (hypothetical situation). Descriptive statistics were used to evaluate patient/tumor characteristics. Cumulative progression to M+ disease and PCa-specific mortality by arm were calculated using the Nelson-Aalen method [7]. Numbers needed to screen (NNS) to avert one M+ disease and PCa death were calculated as the inverse of the absolute risk reduction and number needed to diagnose (NND) as the NNS multiplied by the excess PCa incidence in the S-arm. All analyses were performed using R, version 3.4.3.

Of the 1134 men with a PSA level <10.0 ng/ml, 553 (49%) were randomized to the S-arm and 581 (51%) to the C-arm. Median PSA level at baseline in S- and C-arms was 1.2 ng/ml (interquartile range [IQR]: 0.5–2.2) and 1.1 ng/ml (IQR: 0.5–2.1), respectively. Further PSA measurements in the C-arm are not available. The median age at randomization and FU time was 64 (IQR: 60–69) and 19 yr (IQR: 12–24), respectively. Cumulative PSA contamination rate in the C-arm was estimated to be ±4.5% (questionnaire data), with the first 4 yr a rate of 1.8%. In the S-arm, 71 PCas were detected versus 57 PCas in the C-arm (Table 1). Excess incidence due to screening is 32 PCa cases per 1000 men randomized. The M+ disease was detected in three men in the S-arm versus eight men in the C-arm. During FU, seven men in the S-arm and 16 men in the C-arm progressed to M+ disease, resulting in an overall RR of M+ disease of 0.46 (95% confidence interval [CI]: 0.19–1.11) and a 19 yr-specific RR of M+ disease of 0.42 (95% CI: 0.16–1.08), in favor of screening (Fig. 1A). At time of analysis, 63% (718/1134) of all men had died. Five men in the S-arm and 11 men in the C-arm died because of PCa. Overall RR of PCa death in men allocated to the S-arm relative to the C-arm was 0.48 (95% CI: 0.17–1.36); 19 yr-specific RR of PCa death was 0.47 (95% CI: 0.14–1.50]) in favor of screening (Fig. 1B). The absolute risk reduction in M+ disease and PCa mortality was 14.9 (95% CI:–2–32) and 9.9 (95% CI:–5–25) per 1000 men, respectively. NNS to avert one M+ disease and PCa death was 67 (95% CI: 30–ND) and 101 (95% CI: 39–ND), respectively. NND was three

Table 1 – The clinical/pathological features (TNM-staging, Gleason grading) of the cancers detected (at time of diagnosis). Survival status and cause of death from both the screening and control arm of the men included and randomized with a prostate-specific antigen (PSA) level <10.0 ng/ml (n = 1134) as well as of the men excluded because of a PSA level ≥10.0 ng/ml (n = 30)

	Screening arm (n = 553)		Control arm (n = 581)		Total excluded men (n = 30)	
	No.	%	No.	%	No.	%
T-stage						
T1	29	41	20	35	5	26
T2	27	38	24	42	8	42
T3	14	20	7	12	5	26
T4	1	1	6	11	1	5
N-stage						
NX	37	52	34	60	8	42
N0	34	48	19	33	9	47
N1	–	–	4[a]	7	2[b]	11
M-stage						
MX	25	35	25	44	4	21
M0	43	61	25	44	12	63
M1	3	4	7[a]	12	3[b]	16
PSA >100 ng/ml	–	–	–	–	5[c]	26
Gleason score						
3 + 3	39	55	26	46	–	–
≥3 + 4	23	32	28	49	1	5
Unknown	9	13	3	5	18	95
Survival status–all men						
Alive	189	34	227	39	4	13
Death	364	66	354	61	26	87
Survival status–PCa men						
Alive	50	70	40	70	3	16
Death	21	30	17	30	16	84
Cause of death						
PCa	5	1	11	3	5	19
Other cause	359	99	343	97	21	81

PCa = prostate cancer; PSA = prostate-specific antigen.
[a] Three men had both N1 and M1 disease.
[b] One man had both N1 and M1 disease.
[c] One man had both M1 disease and PSA >100 ng/ml at time of diagnosis.

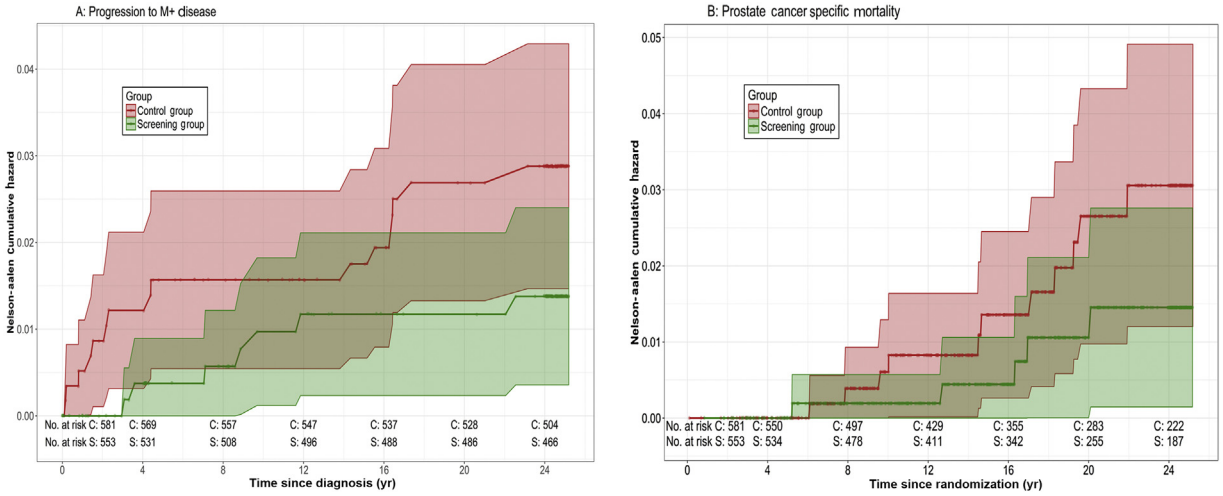

Fig. 1 – (A) Nelson-Aalen estimates of cumulative progression to metastatic disease (including 95% confidence intervals) for the men randomized with a PSA level <10.0 ng/ml. (B) Nelson-Aalen estimates of cumulative prostate cancer-specific mortality (including 95% confidence intervals) for the men randomized with a PSA level <10.0 ng/ml.
C-arm = control arm; M+ disease = metastatic disease; PSA = prostate-specific antigen; S-arm = screening arm.

(101/1000 × 32). In the S-arm, 75% of the PCa underwent treatment versus 25% underwent surveillance. In the C-arm, 53% of the PCa cases underwent treatment versus 30% underwent surveillance (in 17% of the cases in C-arm, the choice of treatment was unknown).

Among the 30 men initially excluded from randomization, 19 were diagnosed with PCa including eight with M+ disease (Table 1). Of these men, 26 (87%) died including five PCa deaths. Retrospectively randomizing these 30 men resulted in an overall RR (in favor of screening and averaged over 5000 randomization procedures) of M+ disease and PCa death of 0.57 (95% CI: 0.27–1.20) and 0.59 (95% CI: 0.25–1.44), respectively.

This ERSPC Rotterdam pilot 1 study cohort, systematically screened in a period largely without PSA contamination and with more than 60% of the men deceased, confirms that PSA-based PCa screening reduces M+ disease and PCa-specific mortality. The reductions are, although statistically insignificant, considerable and if confirmed in larger datasets should again be weighed against the harms of unnecessary testing and overdiagnosis.

Previous ERSPC reports on lead time of advanced disease (±3 yr), M+ disease developing despite screening, and reduction of M+ disease preceding PCa mortality reduction are also confirmed, proving the validity of our findings [8,9]. The reductions in M+ disease and PCa mortality are, however, substantially larger than the main ERSPC trial (54% vs 30% and 52% vs 21%, respectively) [1–4]. This could be explained by the relatively long FU of this study implying that FU in the ERSPC trial could still be too short to see the full effect of screening, given the long natural history of screen-detected PCa (15–25 yr) and the fact that there was almost no PSA contamination in the C-arm of this study [10].

We note that inclusion of men with high PSA values and therefore more likely to have disease beyond cure even if detected earlier resulted in the decrease in relative reduction of both M+ disease and PCa-specific mortality.

The strengths of the present study include the relatively long FU, almost no PSA contamination, and more than 60% of men deceased at time of analysis. Therefore, this study is an appropriate comparison between screening and no screening and can be regarded as a good indicator of the full effect of PCa screening. Limitations to this work include the small sample size and low event rates necessitating confirmation of our findings in the ongoing randomized trials. It can, however, not be excluded that the magnitude of the RRs in this pilot study will be confirmed in the main ERSPC trial when having the availability of 19 yr of FU.

In conclusion, long-term data predominantly coming from an era with hardly any contamination show that PSA-based PCa screening could result in a considerable reduction of both M+ disease and PCa-specific mortality which, if confirmed in larger datasets, should refuel the discussion on harms and benefits of PCa screening.

Author contributions: Daniël Fernando Osses 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, van der Kwast, Roobol.
Acquisition of data: Schröder, van der Kwast, Roobol.
Analysis and interpretation of data: Osses, Roobol.
Drafting of the manuscript: Osses.
Critical revision of the manuscript for important intellectual content: Osses, Remmers, Schröder, van der Kwast, Roobol.
Statistical analysis: Remmers, Roobol.
Obtaining funding: None.
Administrative, technical, or material support: None.
Supervision: Schröder, Roobol.
Other (specify): None.

Financial disclosures: Daniël Fernando Osses 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: The Dutch part of ERSPC was funded by the Dutch Cancer Society (KWF 94-869, 98-1657, 2002-277, 2006-3518, 2010-4800), The Netherlands Organisation for Health Research and Development (ZonMw-002822820, 22000106, 50-50110-98-311, 62300035), The Dutch Cancer Research Foundation (SWOP), and an unconditional grant from Beckman-Coulter-Hybritech Inc.

Acknowledgments: We would like to thank participants and all members of the ERSPC Rotterdam study group for their contribution.

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