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Prostate Cancer – Editor's Choice

Relationship Between Baseline Prostate-specific Antigen on Cancer Detection and Prostate Cancer Death: Long-term Follow-up from the European Randomized Study of Screening for Prostate Cancer

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Abstract

Background: The European Association of Urology guidelines recommend a risk-based strategy for prostate cancer screening based on the first prostate-specific antigen (PSA) level and age.
Objective: To analyze the impact of the first PSA level on prostate cancer (PCa) detection and PCa-specific mortality (PCSM) in a population-based screening trial (repeat screening every 2–4 yr).
Design, setting, and participants: We evaluated 25 589 men aged 55–59 yr, 16 898 men aged 60–64 yr, and 12 936 men aged 65–69 yr who attended at least one screening visit in the European Randomized Study of Screening for Prostate Cancer (ERSPC) trial (screening arm: repeat PSA testing every 2–4 yr and biopsy in cases with elevated PSA; control arm: no active screening offered) during 16-yr follow-up (FU).
Outcome measurements and statistical analysis: We assessed the actuarial probability for any PCa and for clinically significant (cs)PCa (Gleason ≥7). Cox proportional-hazards regression was performed to assess whether the association between baseline PSA and

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PCSM was comparable for all age groups. A Lorenz curve was computed to assess the association between baseline PSA and PCSM for men aged 60–61 yr.

Results and limitations: The overall actuarial probability at 16 yr ranged from 12% to 16% for any PCa and from 3.7% to 5.7% for csPCa across the age groups. The actuarial probability of csPCa at 16 yr ranged from 1.2–1.5% for men with PSA <1.0 ng/ml to 13.3–13.8% for men with PSA ≥3.0 ng/ml. The association between baseline PSA and PCSM differed marginally among the three age groups. A Lorenz curve for men aged 60–61 yr showed that 92% of lethal PCa cases occurred among those with PSA above the median (1.21 ng/ml). In addition, for men initially screened at age 60–61 yr with baseline PSA <2 ng/ml, further continuation of screening is unlikely to be beneficial after the age of 68–70 yr if PSA is still <2 ng/ml. No case of PCSM emerged in the subsequent 8 yr (up to age 76–78 yr). A limitation is that these results may not be generalizable to an opportunistic screening setting or to contemporary clinical practice.

Conclusions: In all age groups, baseline PSA can guide decisions on the repeat screening interval. Baseline PSA of <1.0 ng/ml for men aged 55–69 yr is a strong indicator to delay or stop further screening.

Patient summary: In prostate cancer screening, the patient's baseline PSA (prostate-specific antigen) level can be used to guide decisions on when to repeat screening. The PSA test when used according to current knowledge is valuable in helping to reduce the burden of prostate cancer.

1. Introduction

Prostate-specific antigen (PSA)-based screening for prostate cancer (PCa) is associated with, besides a decrease in metastatic disease and PCa-specific mortality (PCSM) [1,2], an increase in the incidence of PCa, as demonstrated in the Prostate, Lung, Colorectal and Ovarian screening trial (PLCO) after correcting for contamination [3] and in the European Randomized Study of Screening for Prostate Cancer (ERSPC) trial [2]. A considerable proportion of the excess incidence due to PSA-based screening concerns overdiagnosis, for which detection and subsequent treatment most likely only result in harm. The European Association of Urology (EAU) guidelines recommend that men should not undergo PSA testing without counseling on the potential risks and benefits; if the decision is to perform a PSA test, a risk-based strategy should be followed [4]. This risk-based strategy was further elaborated in the EAU 2021 position paper and in the recent recommendations on early detection of PCa [5–7]. A very low PSA level has implications for further testing, with a screening interval of up to 8 yr for those younger than 60 yr and a recommendation to refrain from further testing for those aged ≥60 yr [8–10]. The Göteborg-1 trial recently showed that age is a predictor for finding screen-detected Gleason ≥7 PCa [11]. It is obvious that both a man's initial PSA level and his remaining life span are crucial in the balance between further testing to avoid missing a diagnosis within the window of curability and overdiagnosis with subsequent overtreatment. The general idea is that men with life expectancy of <10–15 yr are unlikely to benefit from (further) screening.

The Malmö Preventive Project data [8,12] underlying these recommendations are either from a time period where PSA testing was virtually nonexistent or from studies with relatively short follow-up. Furthermore, life expectancy has increased since then [13]. As an example, a Dutch man aged 60 yr in 1994 had average life expectancy of 18.9 yr, while a man aged 60 yr in 2020 had average life expectancy of 22.7 yr [14].

The aim of the present study was to analyze the relationship between baseline PSA on PCa incidence and PCSM for men aged 55–59, 60–64, and 65–69 yr at the time of first screening using data from ERSPC with repeated screening and 16 yr of follow-up. Since the EAU guidelines recommend postponing further PSA testing in men with PSA <2.0 ng/ml at age 60 yr, we focused on men aged 60–61 yr at screening and assessed long-term outcomes in relation to their baseline PSA and screening interval.

2. Patients and methods

The ERSPC study has already been described in detail [2,15–17]. In short, in this multicenter randomized screening trial, a PSA level ≥3.0 ng/ml was considered as a positive screening test and was followed by transrectal ultrasound–guided systematic prostate biopsies. Screening was performed predominantly at an interval of 4 yr (range 2–7) up to the age of 70 yr (range 50–75). The core age group consisted of men aged 55–69 yr at the time of randomization.

2.1. Statistical analyses

Statistical analyses were conducted for men aged 55–59, 60–64, and 65–69 yr at the time of the first screening round. We compared the probability of any PCa and of clinically significant (cs)PCa, defined as Gleason ≥7 (graded according to the pre-2005 International Society of Urological Pathology criteria), and the probability of screen-detected PCa. Men who did not participate in the first screening round and men who were diagnosed with PCa or died before randomization were excluded from the analyses. As in the previous ERSPC manuscripts on PCSM, we did not include the data from France because of limited follow-up. Follow-up was truncated at 16 yr after randomization [2].

Actuarial probabilities were calculated for any PCa and for csPCa up to 16 yr after randomization, stratified by age group. For any PCa, censoring included men who died before they had a diagnosis or were still alive

16 yr after randomization. For csPCa, censoring also included those diagnosed with Gleason 6 PCa. For the probability of screen-detected and interval PCa, censoring included men without a diagnosis within 16 yr. To assess whether the relation between baseline PSA and PCSM was similar for men aged 55–59, 60–64, and 65–69 yr, we fitted a Cox proportional-hazards regression model including the main effect of PSA level and age group, and a model including the main effect of PSA level and age group and an interaction term between PSA and age group. We tested whether the model with the interaction had a better fit to the data using the likelihood ratio test. We evaluated the discriminative performance using the time-dependent area under the receiver operating characteristic curve (AUC) at 16 yr with nearest-neighbor estimation [18,19].

The EAU guidelines recommend postponing follow-up to 8 yr for men with PSA <2.0 ng/ml at age 60 yr. Therefore, we plotted time-dependent Lorenz curves to visually assess the association between baseline PSA for men aged 60 or 61 yr at the time of first screening and PCSM 16 yr later. In addition, we evaluated in detail the recommendation to postpone screening by at least 8 yr for men considered to be at low risk. A Lorenz curve was plotted for men aged 60–61 yr with baseline PSA <2.0 ng/ml who attended their next screening approximately 8 yr (range 7.5–8.5) later, so men at repeat screening were then aged 68–70 yr (some men who were late in their 61st yr on screening were aged 70 yr at repeat screening). This second Lorenz curve starts at the time after repeat screening (ie, 8 yr after initial screening) and covers an additional follow-up period of 8 yr.

3. Results

3.1. PCa incidence and mortality in the age groups by PSA level

Our cohort consisted of 25 598 men aged 55–59 yr, 16 898 men aged 60–64 yr, and 12 936 men aged 65–69 yr randomized to screening who underwent a PSA test in the first screening round (Table 1). A total of 12 825 men aged 55–59 yr (50%), 6579 men aged 60–64 yr (39%), and 4209 men aged 65–69 yr (33%) had PSA <1.0 ng/ml. A total of 2863 men aged 55–59 yr, 2401 men aged 60–64 yr, and 1856 men aged 65–69 yr were diagnosed with any PCa over a maximum period of 16 yr. The overall cumulative incidence of screen-detected PCa at 16 yr after randomization ranged between 7.5% and 9.5%.

The overall actuarial probability of csPCa at 16 yr was 3.7% (95% confidence interval [CI] 3.5–4.0%) for men aged 55–59 yr, 5.1% (95% CI 4.8–5.5%) for men aged 60–64 yr, and 5.7% (95% CI 5.2–6.1%) for men aged 65–69 yr (Supplementary Fig. 1). In more detail, in the group with PSA ≥3.0 ng/ml, the actuarial probabilities of csPCa were considerably higher: 13% (95% CI 12–15%) for men aged 55–59 yr, 14% (95% CI 12–15%) for men aged 60–64 yr, and 13% (95% CI 12–15%) for men aged 65–69 yr. In the group with baseline PSA <1.0 ng/ml, the actuarial probability of any PCa after 16 yr was 3.0% at most. Almost half of these cancers were defined as csPCa.

The relationship between baseline PSA and PCSM among all screened men was not the same for all age groups ($p < 0.001$). The hazard ratio for PCSM on doubling of baseline PSA was 2.46 (95% CI 2.24–2.71) for men aged 55–59 yr (AUC = 0.71), 2.23 (95% CI 2.03–2.46) for men aged 60–64 yr (AUC = 0.71), and 2.04 (95% CI 1.89–2.20) for men aged 65–69 yr (AUC = 0.71).

3.2. Baseline PSA at age 60–61 yr in relation to PCSM at 16-yr follow-up

A total of 5096 men were aged 60–61 yr at the time of their first screening attendance. Within 16 yr of follow-up, 26 men died of PCa (actuarial probability of PCSM at 16 yr is 0.58, 95% CI 0.36-0.80). The Lorenz curve (Fig. 1A) shows that 92% of lethal PCa cases occurred among men with a PSA above the median of 1.21 ng/ml. The percentage of PCa deaths below the PSA cutoff of 2.0 ng/ml was 35% ($n = 9$).

Table 1 – Results by age group and baseline PSA level

Age group by PSA level	Men (*N*)	PCa cases (*n*)	Actuarial probability at 16 yr, % (95% CI)		Cumulative incidence at 16 yr, % (95% CI)		csPCa cases (*n*)	Confirmed PCa deaths/PCa patients who died, *n*/*N* (%)	Median time, yr (IQR)	
			PCa	csPCa	SD PCa	Interval PCa			FS to Dx	Dx to death
Age 55–59 yr	25 598	2863	12 (11–12)	3.7 (3.5–4.0)	7.6 (7.3–8.0)	4.2 (4.0–4.5)	840	108/430 (25)	8.0 (4.2–10.3)	5.4 (2.4–8.2)
PSA										
<1.0 ng/ml	12 825	318	2.7 (2.4–3.0)	1.3 (1.1–1.5)	1.2 (1.0–1.3)	1.6 (1.4–1.8)	149	10/42 (24)	11.9 (8.6–13.2)	1.7 (1.1–3.5)
1.0–1.9 ng/ml	7812	880	12 (11–13)	4.4 (3.9–4.9)	7.5 (6.9–8.1)	4.6 (4.1–5.1)	298	25/102 (25)	8.6 (7.2–12.0)	3.4 (2.0–6.3)
2.0–2.9 ng/ml	2330	569	26 (24–28)	6.6 (5.5–7.7)	18 (16–19)	8.0 (6.9–9.2)	127	15/67 (22)	7.5 (4.3–8.9)	5.0 (1.9–6.7)
≥3.0 ng/ml	2631	1096	43 (41–45)	13 (12–15)	30 (29–32)	12 (11–14)	266	58/219 (26)	3.4 (0.6–7.1)	7.1 (4.2–10.5)
Age 60–64 yr	16 898	2401	15 (15–16)	5.1 (4.8–5.5)	10.0 (9.5–10.5)	5.5 (5.1–5.9)	728	129/536 (24)	5.0 (1.9–8.8)	6.3 (3.0–9.6)
PSA										
<1.0 ng/ml	6579	169	3.0 (2.6–3.5)	1.5 (1.2–1.8)	1.1 (0.9–1.4)	1.9 (1.5–2.3)	81	11/25 (44)	10.5 (8.2–12.9)	3.2 (1.5–5.1)
1.0–1.9 ng/ml	5236	572	12 (11–13)	4.7 (4.1–5.4)	7.5 (6.7–8.2)	4.9 (4.2–5.5)	203	25/97 (26)	8.4 (5.0–12.2)	3.5 (1.6–6.1)
2.0–2.9 ng/ml	2098	469	25 (23–27)	7.4 (6.2–8.7)	16 (15–18)	8.3 (7.1–9.6)	124	20/77 (26)	6.7 (4.3–8.7)	6.7 (3.3–9.0)
≥3.0 ng/ml	2985	1191	42 (40–44)	14 (12–15)	29 (28–31)	12 (11–14)	320	73/337 (22)	2.7 (0.3–5.8)	7.4 (4.2–10.4)
Age 65–69 yr	12 936	1856	16 (15–17)	5.7 (5.2–6.1)	9.5 (9.0–10.1)	6.5 (6.0–6.9)	589	130/649 (20)	4.2 (0.3–7.8)	6.5 (3.3–9.9)
PSA										
<1.0 ng/ml	4209	88	2.7 (2.1–3.2)	1.2 (0.8–1.6)	0.4 (0.2–0.6)	2.2 (1.7–2.8)	37	10/25 (40)	9.1 (5.8–12.2)	3.6 (1.3–6.5)
1.0–1.9 ng/ml	3773	283	9.0 (8.0–10.0)	3.8 (3.1–4.5)	3.5 (2.9–4.2)	5.5 (4.6–6.3)	107	18/74 (24)	8.0 (4.2–11.6)	4.3 (1.6–7.3)
2.0–2.9 ng/ml	1762	298	20 (18–22)	8.2 (6.7–9.7)	10.6 (9.1–12.1)	9.0 (7.5–10.6)	108	13/89 (15)	4.9 (4.2–8.9)	4.9 (2.3–7.6)
≥3.0 ng/ml	3192	1187	40 (38–41)	13 (12–15)	28 (26–30)	12 (10–13)	337	89/461 (19)	0.9 (0.2–4.6)	7.3 (4.2–10.7)

PCa = prostate cancer; csPCa = clinically significant PCa; CI = confidence interval; IQR = interquartile range; FS = first screening; Dx = diagnosis; PSA = prostate-specific antigen; SD = screening-detected.

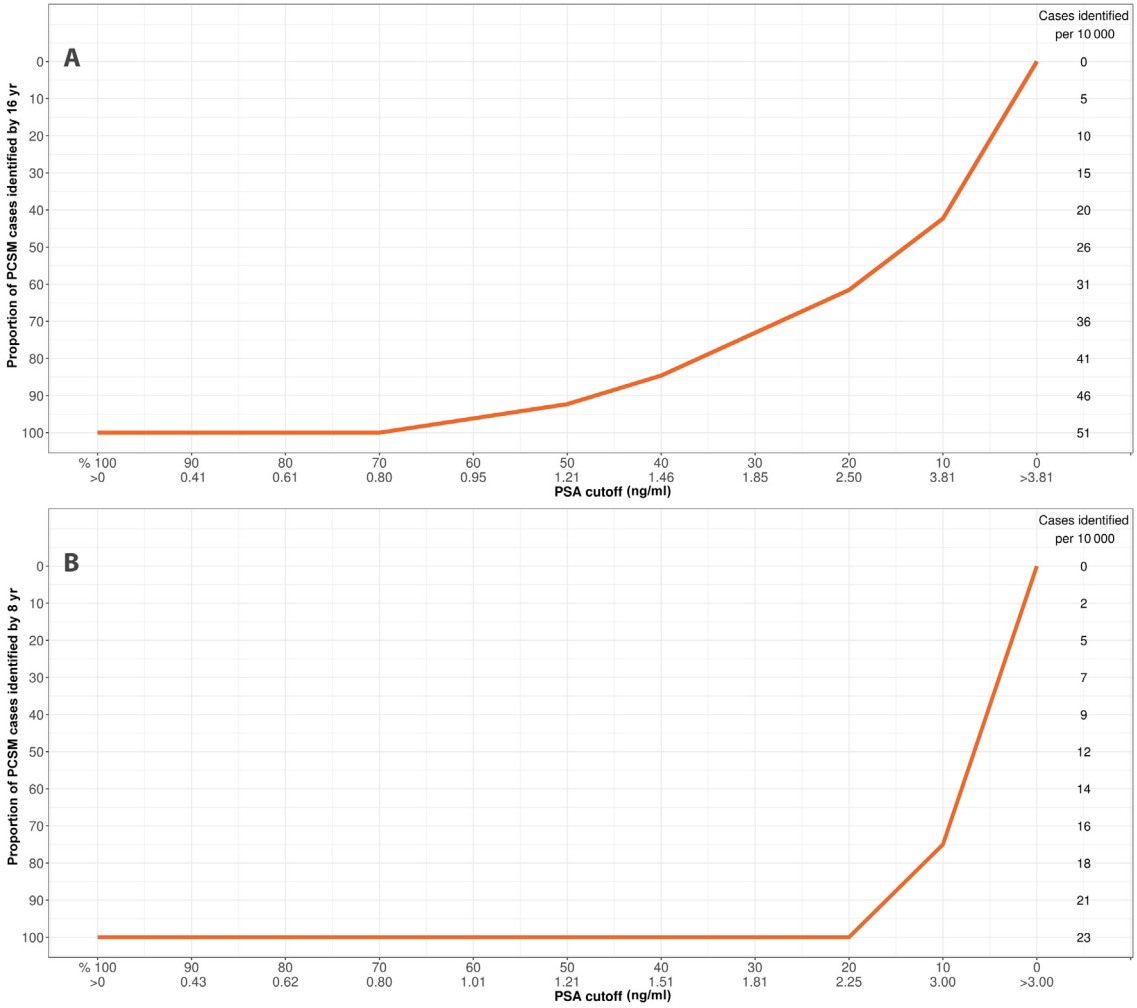

Fig. 1 – Lorenz curves of the association between baseline prostate-specific antigen (PSA) and prostate cancer–specific mortality (PCSM).

3.3. *Effect of an 8-yr screening interval on PCSM 8 yr later*

Of the men aged 60–61 yr at the time of their first screening attendance, 3699 had PSA <2.0 ng/ml (73%). These men were followed over the next 8–16 yr. During the first 8-yr follow-up period, 228 men died and 1732 declined further attendance. However, all men were followed via links to the national cancer registries. This resulted in a probabilities at 16 yr of 1.7% (95% CI 1.3–2.1) for PCa diagnosis and 0.03% (95% CI 0.00–0.09) for PCSM. Among the 1739 men who did not drop out, receive a PCa diagnosis, or die, their PSA level at repeat screening 8 yr later (range 7.5–8.5 yr) increased in comparison to baseline by a median of 0.36 ng/ml (interquartile range [IQR] 0.04–0.90). The median PSA 8 yr later was 1.2 ng/ml (IQR 0.7–2.0).

The Lorenz curve for these 1739 men shows that with another additional 8 yr of follow-up (ie, 8–16 yr after the first screening), all lethal PCa cases (n = 4) occurred in men with PSA >2.25 ng/ml at repeat screening (8 yr after initial screening), a PSA cutoff that represents 20% of the total cohort of 1739 men. A total of 725 men (42%) attended a subsequent screening test after 8.5 yr.

4. Discussion

We assessed the relationship between baseline PSA at age 55–69 yr and subsequent PCa detection and PCSM. In this PSA-based (repeated) screening setting, the overall actuarial probability at 16 yr was 12–16% for any PCa and 3.7–5.7% for csPCa. Among the men aged 65–69 yr with baseline PSA <1.0 ng/ml, the cumulative incidence of screen-detected PCa at 16 yr was only 0.4%, most likely because these men were screened only once. For men with baseline PSA <1.0 ng/ml at age 55–69 yr, the actuarial probability of any PCa at 16 yr was 2.7–3.0%. This low actuarial probability confirms that men with low initial PSA at age 55–69 yr are unlikely to reach the commonly applied PSA biopsy threshold of 3.0 or 4.0 ng/ml and be subsequently diagnosed with (cs)PCa. This is consistent with earlier results from the PLCO [20] and ERSPC [10] trials. While the actuarial probability is low for men with these baseline PSA levels, almost half of these cancers were csPCa. Men with an initial low PSA are unlikely to have benign enlargement of their prostate. Thus, when their PSA level increases and reaches the threshold for biopsy, this is an indication of cancer progression. As a

result, there is less overdiagnosis in this subgroup. Conversely, men with benign enlargement of their prostate are likely to have elevated PSA and can be diagnosed with indolent tumor. These findings could also underlie our results showing that some men have low PSA for many years (median time from first screening to diagnosis is 12 yr for those aged 55–59 yr with PSA <1.0 ng/ml) and died relatively shortly after diagnosis (median 1.7 yr). These findings would call for an improved screening algorithm for these men, who represent approximately 35% of those aged 55–75 yr [21]. However, this should not be achieved simply by lowering the PSA biopsy threshold, as it has been estimated that the number needed to screen to avoid one man with PSA <2.0 ng/ml dying from PCa is nearly 25 000 and the corresponding number needed to treat is 724 [22]. These numbers illustrate the scarce benefits of aggressive investigation for men with low PSA. Men eligible for repeat screening and prostate biopsy because of PSA above the threshold contribute to overdiagnosis. Here, repeat biopsies over a period of 8 yr (3 consecutive screening visits at an interval of 4 yr each) accounted for a quarter of all biopsies but yielded only <10% of all csPCa cases [23].

The association between baseline PSA and PCSM differed marginally (and not likely to be clinically relevant) between the 64–69-yr and 54–59-yr age groups, but not between the 60–64-yr and 55–59-yr groups. Finally, two-thirds of all PCa deaths in the group aged 60–61 yr occurred in the 25% of men with baseline PSA >2.0 ng/ml. The fact that approximately one-third of PCa deaths occurred in a group of men deemed at low risk (PSA <2.0 ng/ml) may cast doubt on the relatively long screening interval proposed. However, considering the number of men involved (N = 5096) and the number of PC deaths (n = 26), more intensive PSA testing is unlikely to improve the harm/benefit ratio. More interesting is the Lorenz curve for men aged 68–70 yr with low PSA (<2 ng/ml since their first screening at age 60–61 yr). According to the EAU guidelines, repeat screening should be considered after a long interval or omitted entirely. Our results show that with 8 yr of additional follow-up during which 42% of all men attended a subsequent screening visit, no PCa deaths occurred in the group with PSA $\leq$2.25 ng/ml. These observations question the value of repeated PSA screening for men aged $\geq$68–70 yr and PSA <2.0 ng/ml even if they are considered to have life expectancy of >15 yr.

Our results are in line with the study by Preston et al [24], who showed that baseline PSA among men aged 40–59 yr could predict PCSM, and results from the Swedish serum bank study using data from the Malmö Preventive Project [25]. In our study, the median PSA level (1.2 ng/ml) could predict 80% of PCSM cases and is comparable to the median PSA of 1.06 ng/ml in their setting. It must be noted, however, that the PCSM rate was lower in ERSPC. To elaborate, the median PSA predicted 27 PC deaths per 1000 men in the Swedish study started in the early 1980s, while in the current prospective screening study the rate was 4.6 PC deaths per 1000 men. It is plausible that this result can be attributed to PSA-based screening versus an unscreened population in Sweden, as well as differences in follow-up length (16 yr vs $\geq$20 yr) and the high Swedish mortality in comparison to other European countries. Our results show slightly lower actuarial probability of csPCa than in PLCO [26]. In PLCO, the actuarial probability at 13 yr for men aged 55–60 yr with baseline PSA of 1.0–1.9 ng/ml was 11% for any PCa (12% at 16 yr in our study) and 5.4% for csPCa (4.4% at 16 yr in our study).

Our study has some limitations. The ERSPC trial applied an upper age limit for screening and thus the numbers of screening visits differ among the age groups analyzed here. In addition there is a period effect, which suggests that men aged 55–59 yr were at most 71–75 yr after 16 yr, while men aged 65–69 yr were at most 81–85 yr after 16 yr. This limits direct comparison of detection and mortality rates between the age groups. In addition, the subgroup of men aged 60–61 yr with PSA <2.0 ng/ml was relatively limited in size, which makes it hard to generalize the results. Furthermore, the contemporary diagnostic pathway for PCa includes measurement of prostate volume and the use of magnetic resonance imaging. Contemporary screening studies will provide insight into a risk-adapted screening strategy [27–30]. Results from these studies will provide information on reduction in overdiagnosis using risk-adapted screening and on the starting age, as investigated in the PROBASE trial. The sample size, controlled setting, and follow-up length and detail are strengths of our study.

5. Conclusions

In conclusion, long-term ERSPC data support the EAU guideline recommendations regarding risk-based early detection of PCa among men aged 60 yr with PSA <2.0 ng/ml. The PSA test when used according to current knowledge is valuable in helping to reduce the burden of PCa and can be used as an aid in decisions to discontinue repeat screening. When implementing currently available knowledge in daily practice, selective identification of men at risk of developing or having aggressive PCa, including elderly men, should remain the focus for further research.

Author contributions: Sebastiaan Remmers 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: Roobol, Remmers.
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Analysis and interpretation of data: All authors.
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Peer Review Summary

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References

[1] Schröder FH, Hugosson J, Carlsson S, et al. Screening for prostate cancer decreases the risk of developing metastatic disease: findings from the European Randomized Study of Screening for Prostate Cancer (ERSPC). Eur Urol 2012;62:745–52.
[2] Hugosson J, Roobol MJ, Mansson M, et al. A 16-yr follow-up of the European Randomized study of Screening for Prostate Cancer. Eur Urol 2019;76:43–51.
[3] Gulati R, Tsodikov A, Wever EM, et al. The impact of PLCO control arm contamination on perceived PSA screening efficacy. Cancer Causes Control 2012;23:827–35.
[4] 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.
[5] Van Poppel H, Hogenhout R, Albers P, van den Bergh RCN, Barentsz JO, Roobol MJ. Early detection of prostate cancer in 2020 and beyond: facts and recommendations for the European Union and the European Commission. Eur Urol 2021;79:327–9.
[6] Van Poppel H, Hogenhout R, Albers P, van den Bergh RCN, Barentsz JO, Roobol MJ. A European model for an organised risk-stratified early detection programme for prostate cancer. Eur Urol Oncol 2021;4:731–9.
[7] Van Poppel H, Roobol MJ, Chapple CR, et al. Prostate-specific antigen testing as part of a risk-adapted early detection strategy for prostate cancer: European Association of Urology position and recommendations for 2021. Eur Urol 2021;80:703–11.
[8] Carlsson S, Assel M, Sjoberg D, et al. Influence of blood prostate specific antigen levels at age 60 on benefits and harms of prostate cancer screening: population based cohort study. BMJ 2014;348:g2296.
[9] Gelfond J, Choate K, Ankerst DP, Hernandez J, Leach RJ, Thompson IM. Intermediate-term risk of prostate cancer is directly related to baseline prostate specific antigen: implications for reducing the burden of prostate specific antigen screening. J Urol 2015;194:46–51.
[10] Roobol MJ, Roobol DW, Schroder FH. Is additional testing necessary in men with prostate-specific antigen levels of 1.0 ng/mL or less in a population-based screening setting? (ERSPC, section Rotterdam). Urology 2005;65:343–6.
[11] Godtman RA, Kollberg KS, Pihl CG, Månsson M, Hugosson J. The association between age, prostate cancer risk, and higher Gleason score in a long-term screening program: results from the Göteborg-1 prostate cancer screening trial. Eur Urol 2022;82:311–7.
[12] Vickers AJ, Ulmert D, Sjoberg DD, et al. Strategy for detection of prostate cancer based on relation between prostate specific antigen at age 40–55 and long term risk of metastasis: case-control study. BMJ 2013;346:f2023.
[13] Wang H, Dwyer-Lindgren L, Lofgren KT, et al. Age-specific and sex-specific mortality in 187 countries, 1970–2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012;380:2071–94.
[14] CBS. Levensverwachting; geslacht, leeftijd (per jaar en periode van vijf jaren) [Life expectancy; gender, age (per year and period of five years)] updated 2022-06-23. https://opendata.cbs.nl/statline/#/CBS/nl/dataset/37360ned/table?fromstatweb.
[15] Schroder 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.
[16] Schroder FH, Hugosson J, Roobol MJ, et al. Prostate-cancer mortality at 11 years of follow-up. N Engl J Med 2012;366:981–90.
[17] 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.
[18] Blanche P, Kattan MW, Gerds TA. The c-index is not proper for the evaluation of t-year predicted risks. Biostatistics 2019;20:347–57.
[19] Heagerty PJ, Lumley T, Pepe MS. Time-dependent ROC curves for censored survival data and a diagnostic marker. Biometrics 2000;56:337–44.
[20] Crawford ED, Paul FP, David C, et al. Prostate specific antigen changes as related to the initial prostate specific antigen: data from the Prostate, Lung, Colorectal and Ovarian cancer screening trial. J Urol 2006;175:1286–90.

[21] Bul M, van Leeuwen PJ, Zhu X, Schroder FH, Roobol MJ. Prostate cancer incidence and disease-specific survival of men with initial prostate-specific antigen less than 3.0 ng/ml who are participating in ERSPC Rotterdam. Eur Urol 2011;59:498–505.
[22] van Leeuwen PJ, Connolly D, Tammela TL, et al. Balancing the harms and benefits of early detection of prostate cancer. Cancer 2010;116:4857–65.
[23] Bokhorst LP, Zhu X, Bul M, Bangma CH, Schroder FH, Roobol MJ. Positive predictive value of prostate biopsy indicated by prostate-specific-antigen-based prostate cancer screening: trends over time in a European randomized trial. BJU Int 2012;110:1654–60.
[24] Preston MA, Batista JL, Wilson KM, et al. Baseline prostate-specific antigen levels in midlife predict lethal prostate cancer. J Clin Oncol 2016;34:2705–11.
[25] Vickers AJ, Cronin AM, Bjork T, et al. Prostate specific antigen concentration at age 60 and death or metastasis from prostate cancer: case-control study. BMJ 2010;341:c4521.
[26] Kovac E, Carlsson SV, Lilja H, et al. Association of baseline prostate-specific antigen level with long-term diagnosis of clinically significant prostate cancer among patients aged 55 to 60 years: a secondary analysis of a cohort in the Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trial. JAMA Netw Open 2020;3:e1919284.
[27] Arsov C, Albers P, Herkommer K, et al. A randomized trial of risk-adapted screening for prostate cancer in young men—results of the first screening round of the PROBASE trial. Int J Cancer 2022;150:1861–9.
[28] Krilaviciute A, Albers P, Lakes J, et al. Adherence to a risk-adapted screening strategy for prostate cancer: first results of the PROBASE trial. Int J Cancer 2023;152:854–64.
[29] Rannikko A, Leht M, Mirtti T, et al. Population-based randomized trial of screening for clinically significant prostate cancer ProScreen: a pilot study. BJU Int 2022;130:193–9.
[30] Eklund M, Jäderling F, Discacciati A, et al. MRI-targeted or standard biopsy in prostate cancer screening. N Engl J Med 2021;385:908–20.