Prostate Cancer

Prostate Cancer Mortality Among Elderly Men After Discontinuing Organised Screening: Long-term Results from the European Randomized Study of Screening for Prostate Cancer Rotterdam

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Abstract

Background: The optimal timing for discontinuing screening of prostate cancer (PCa) in elderly men is currently not known and remains debated.
Objective: To assess prostate cancer–specific mortality (PCSM) in elderly men who previously underwent prostate-specific antigen (PSA)-based screening and to identify those who may benefit from continued screening.
Design, setting, and participants: A total of 7052 men, who participated in the screening arm of the Rotterdam section of the European Randomized Study of Screening for Prostate Cancer and were aged 70–74 yr at their last screening visit after undergoing a maximum of three screening rounds without being diagnosed with PCa, were included.
Outcome measurements and statistical analysis: The cumulative incidence of PCSM by the age of 85 yr was assessed. Additionally, a competing risk regression was performed to assess the potential predictors of PCSM.
Results and limitations: The median follow-up was 16 yr. The cumulative incidence of PCSM by the age of 85 yr was 0.54% (95% confidence interval [CI]: 0.40–0.70) in all men, 0.11% (95% CI: 0.05–0.27) in men with PSA <2 ng/ml, 0.85% (95% CI: 0.47–1.5) in men with PSA 2–3 ng/ml, and 6.8% (95% CI: 3.1–15) in men with PSA $\geq$6.5 ng/ml and no previous benign biopsy. PSA (subdistribution hazard ratio [sHR]: 2.0; 95% CI: 1.7–2.3), previous benign prostate biopsy (sHR: 0.41; 95% CI: 0.23–0.72), and hypertension (sHR: 0.48; 95% CI: 0.25–0.91) were significantly associated with PCSM.
Conclusions: Men aged 70–74 yr who have previously undergone PSA-based screening without receiving a PCa diagnosis have a very low risk of dying from PCa by the age of 85 yr. These data suggest that screening may be discontinued in men with PSA <3.0 ng/ml or previous benign prostate biopsies. Those with higher PSA levels and no prior biopsies may consider continued screening if life expectancy exceeds 10 yr.

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Patient summary: This study shows that men who participated in a prostate cancer screening trial have a very low risk of dying from prostate cancer if they have not been diagnosed with prostate cancer by the age of 74 yr.

1. Introduction

The prevalence of prostate cancer (PCa) and high-risk PCa is strongly associated with age [1]. With the global rise in life expectancy and population [2], the worldwide PCa burden is expected to grow to almost 2.4 million new cases by 2040, with a corresponding twofold increase in disease-specific deaths to 740 000 men compared with those in 2020 [3]. While screening for PCa may potentially reduce this burden [4], it is also associated with overdiagnosis, particularly in older men or those with comorbidities [5]. This has been demonstrated by the long-term results of the European Randomized Study of Screening for Prostate Cancer (ERSPC), which showed that repeated prostate-specific antigen (PSA)-based screening significantly reduces the incidence of metastatic PCa and PCa-specific mortality (PCSM) in men aged 55–69 yr, whereas no significant reduction (rate ratio of 1.18 [95% confidence interval {CI}: 0.87–1.62]) was observed in men who were first screened between the ages of 70 and 74 yr [6]. Nevertheless, even among men aged 55–69 yr at randomisation who underwent repeated screening, a considerable number of men still developed lethal PCa after the screening age cut-off of 74 yr [6]. Thus, the optimal age for discontinuing screening in men who have already undergone screening remains a topic of debate, with competing views of early detection, quality of life, and avoidance of overdiagnosis and overtreatment [7].

Current guidelines vary in their recommendations as to when screening should be discontinued in elderly men. Guidelines by both European and American associations of urology recommend that PCa screening can be continued in men with life expectancy of at least 10–15 yr after counselling on the possible benefits and drawbacks [8,9]. Additionally, the US Preventive Services Task Force took a more cautious stance in 2018 by recommending against routine PSA-based screening in all men aged 70 yr due to competing risks from other causes of death [10]. Despite these recommendations, screening rates in this elderly population remain high, with up to 50% of men continuing to undergo screening [11]. Such opportunistic screening in elderly men has limited the impact on PCSM and leads to higher rates of overdiagnosis, resulting in an unfavourable harm-benefit ratio [6,12].

Therefore, this study aims to assess PCSM in men aged 70–74 yr who previously underwent protocolled PSA-based screening and to identify a specific subgroup that may benefit from continued screening using long-term follow-up data from the Rotterdam section of the ERSPC.

2. Patients and methods

The ERSPC is a multicentre, population-based, randomised trial designed to study the effect of PSA-based screening on PCSM. The Dutch arm of the ERSPC, the ERSPC Rotterdam, began randomising men aged 55–74 yr in 1993. The methods of invitation and randomisation, and the applied screening algorithm have been described previously [13]. In brief, men in the intervention group received PSA testing every 4 yr until the age of 74 yr, with a maximum of five screening rounds. If their PSA level was ≥3.0 ng/ml (ie, positive screen), sextant transrectal ultrasonography (TRUS)-guided biopsies were advised. At each screening visit, participants completed a questionnaire assessing comorbidities. The incidence of PCa detected outside the screening setting was obtained through yearly linkages with the Dutch Cancer Registry. After diagnosis, follow-up data, such as disease progression or death, were collected by a semiannual chart review. If a PCa patient died, a specially constituted committee determined the cause of death via a fixed algorithm [14].

In this study, we evaluated men who were aged 70–74 yr at their last screening visit after a maximum of three consecutive screening rounds (1993–2007) and who completed screening without a PCa diagnosis (Fig. 1). The date of inclusion was determined as the date of the last screening visit, and follow-up was truncated on January 1, 2020. Men who underwent screening more than three times were excluded from the primary analysis, as their available length of follow-up was not yet sufficient to cover at least 15 yr. They were, however, included in a sensitivity analysis to assess the effect of the number of previous screening rounds.

2.1. Statistical analyses

The primary outcome of the study was the cumulative incidence of PCSM by the age of 85 yr, since follow-up was complete for 97% of the men at this time point. The 10- and 15-yr cumulative incidences of PCSM were also calculated. The high rate of other-cause mortality makes a competing risk analysis the preferred method for determining the cumulative incidence of PCSM, as traditional methods tend to overestimate the probability when competing events are present [15]. To account for the competing risk, we employed the Fine-Gray method, considering death from other causes as the competing event [16]. The follow-up time was calculated from the date of the last screening visit until the date of death or censoring (January 1, 2020). Additionally, the cumulative incidence was stratified by the number of previous screenings. A sensitivity analysis was conducted, including men who were screened four or five times, focusing on the cumulative incidence of PCSM by the age of 82 yr.

Furthermore, cumulative incidences were also stratified by the presence of any previous benign prostate biopsies (ie, performed in any of the screening rounds) and PSA at the last screening visit. PSA cut-offs were based on the biopsy threshold used in the screening protocol, which was 3 ng/ml, and the age-specific reference value of 6.5 ng/ml for men in their 70s [17].

To assess the potential predictors of PCSM, a competing risk regression was performed. Covariates included PSA at the last screening, presence of any previous benign prostate biopsies, and the presence of a
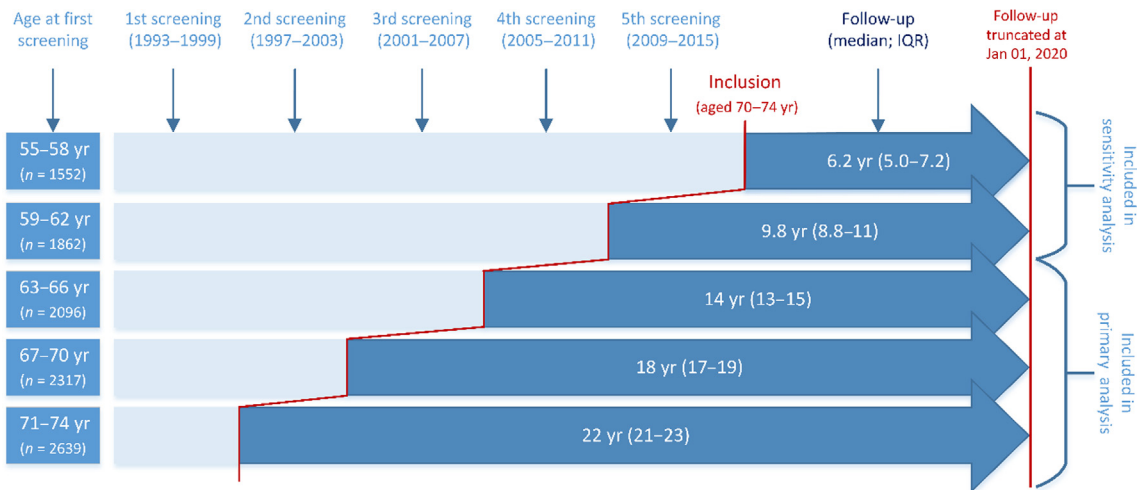
Fig. 1 – Flowchart of the study. Men aged 55–74 yr were randomised in 1993 and underwent PSA testing every 4 yr until the age of 74 yr, with a maximum of five screening rounds per participant. With follow-up starting from the date of their last screening visit, the primary analyses included men with a maximum of three screening rounds, while a sensitivity analysis involved men who had up to five screening rounds. IQR = interquartile range.

Table 1 – Patient characteristics

Patient characteristics	n = 7052
Age at last visit (yr)	73 (72–74)
Year last screening	2000 (1998–2004)
Times screened with 4 yr interval	
1	2639 (37)
2	2317 (33)
3	2096 (30)
PSA (ng/ml) at last screen	1.6 (0.90–3.0)
PSA ≥3.0	1856 (26)
Previous benign prostate biopsy	
0	4898 (69)
1	1533 (22)
≥2	621 (10)
Positive family history[a]	511 (7.2)
Hypertension[a]	1819 (26)
Heart disease[a]	2055 (29)
Diabetes[a]	688 (9.8)
Prostate cancer diagnosis	324
Time last screen – diagnosis (yr)	7.0 (4.0–11)
Risk group at diagnosis	
Low risk	75 (23)
Intermediate risk	80 (25%)
High risk	113 (35)
Metastatic disease	56 (17)
Progression to metastatic disease after initial diagnosis	51
Time last screen – metastatic disease (yr)	11 (7.5–14)
Prostate cancer–specific mortality	81
Age at death (yr)	85 (82–89)
Time last screen – death (yr)	13 (9.7–16)
Other-cause mortality	5277
Age at death (yr)	83 (78–87)
Time last screen – death (yr)	10 (5.7–14)

PSA = prostate-specific antigen.
Data are presented as median (interquartile range) and frequency (%).
[a] Participant reported.

family history of PCa, hypertension, heart disease, and diabetes. The discriminative ability of the model was assessed with the time-dependent area under the curve (AUC) at 10 and 15 yr after the last screening [18]. In addition, the 10-yr predicted risks of PCSM were visualised by PSA level and presence of previous benign biopsies at the time of the last screening. This time point was chosen since it aligns with the minimum life expectancy recommended by the guidelines for PSA screening [8,9]. All statistical analyses were performed in R statistical software version 4.1.2.

3. Results

We evaluated a total of 7052 men (Table 1). At the last screening, the median PSA was 1.7 ng/ml (interquartile range [IQR]: 0.90–3.1), and 1856 (26%) men had a positive screen at the last screening. Moreover, 2154 (31%) men had previously undergone at least one biopsy procedure with benign outcome during the screening period. Throughout the follow-up period, a total of 5277 men died. The median duration of available follow-up for those who remained alive was 16 yr (IQR: 14–18), and their median age at the end of follow-up was 88 yr (IQR: 86–91).

During the follow-up period, a total of 324 men were diagnosed with PCa after a median time period between the last screening visit and diagnosis of 7.0 yr (IQR: 4.0–11). A total of 107 men were found to have metastases, with 56 identified at the time of diagnosis and 51 experiencing disease progression after the initial diagnosis. Ultimately, 81 men died from the disease. The cumulative incidence of PCSM by the age of 85 yr was 0.54% (95% CI: 0.40–0.70; Fig. 2A), with no significant differences observed between the number of previous screens (Fig. 2B). The cumulative incidence and survival curves for 10 and 15 yr are presented in Supplementary Table 1 and Supplementary Figure 1. The median time between the last screen and PCSM was 13 yr (9.7–16), and their median age at death was 85 yr (82–89). The cumulative incidence of other-cause mortality by the age of 85 yr was 52% (95% CI: 50–53). A sensitivity analysis including men with four or five previous screens showed no significant difference in the cumulative incidence of PCSM by the age of 82 yr (Supplementary Fig. 2).

Figure 3 displays the cumulative incidence curves of PCSM stratified by PSA at the last screening and the biopsy history. By the age of 85 yr, the cumulative incidence of
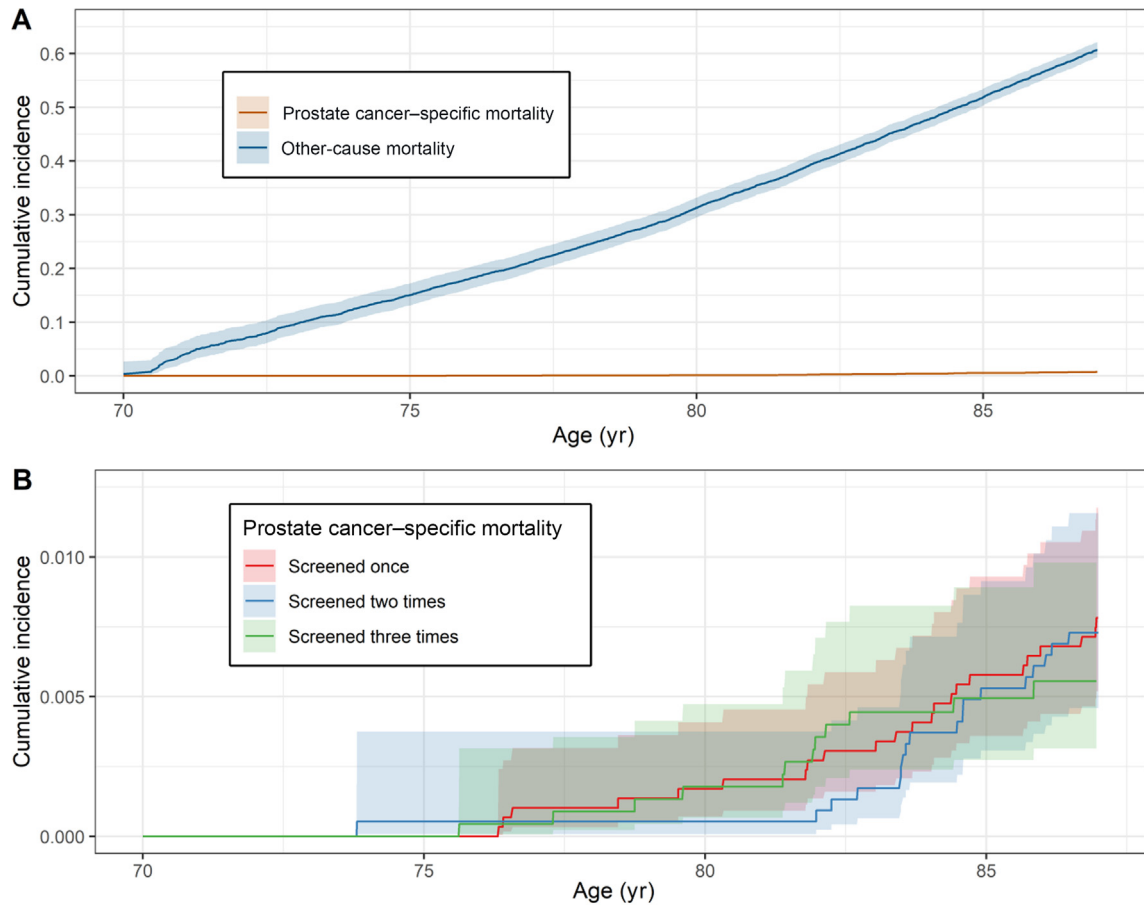
Fig. 2 – (A) Cumulative incidence of prostate cancer–specific mortality and other-cause mortality after the last screening visit and (B) magnification of the cumulative incidence of prostate cancer–specific mortality stratified by the number of previous screening visits.
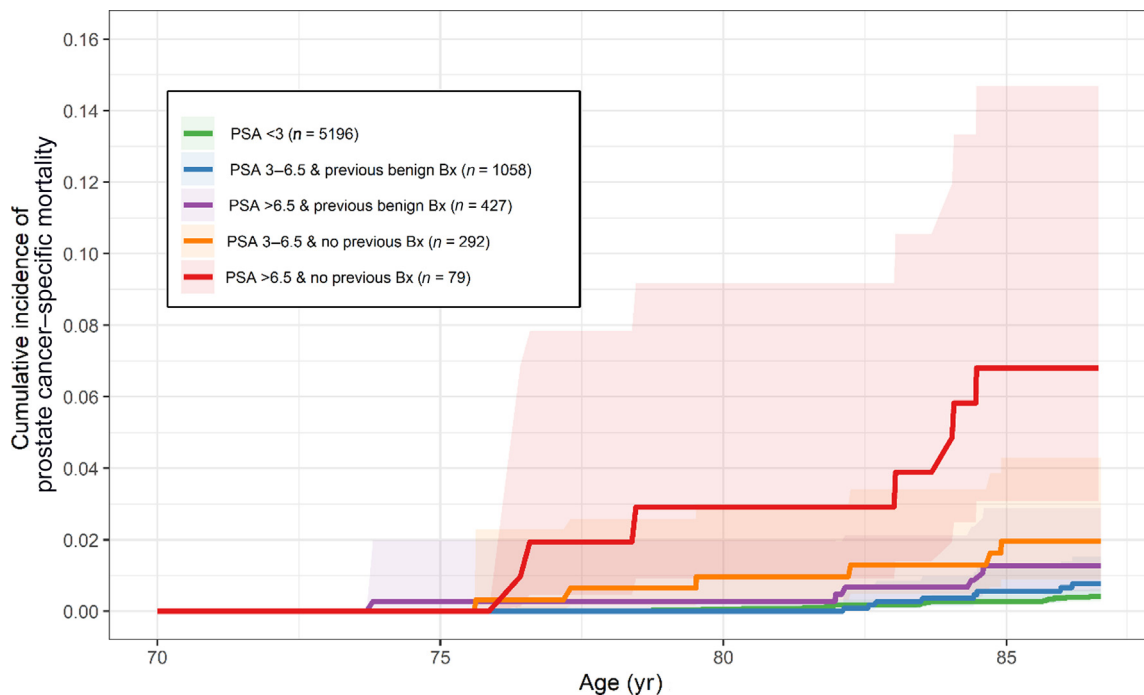

Fig. 3 – Cumulative incidence of prostate cancer–specific mortality stratified by PSA level and presence of previous benign biopsies at the time of last screening. Bx = prostate biopsy; PSA = prostate-specific antigen.

PCSM was 0.11% (95% CI: 0.05–0.27) in men with PSA <2 ng/ml, 0.85% (95% CI: 0.47–1.5) in men with PSA 2–3 ng/ml, 0.56% (95% CI: 0.25–1.2) in men with PSA 3–6.5 ng/ml and a previous benign biopsy, 1.3% (95% CI: 0.56–2.9) in men with PSA >6.5 ng/ml and a previous benign biopsy, 2.0% (95% CI: 0.88–4.3) in men with PSA 3–6.5 ng/ml and no previous biopsy, and 6.8% (95% CI: 3.1–15) in men with PSA ≥6.5 ng/ml and no previous biopsy. The cumulative incidences at 10 and 15 yr after the last visit are presented in Supplementary Table 1 and Supplementary Figure 3.

Statistically significant predictors associated with PCSM in the multivariable model are PSA at the last screening (per doubling; subdistribution hazard ratio [sHR]: 1.98; 95% CI: 1.68–2.33), previous benign prostate biopsy (sHR: 0.41; 95% CI: 0.23–0.72), and hypertension (sHR: 0.48; 95% CI: 0.25–0.91; Table 2). A nonlinear relationship of PSA with PCSM did not improve the model fit statistically. The time-dependent AUCs at 10 and 15 yr after the last screen are 0.80 (95% CI: 0.72–0.87) and 0.73 (95% CI: 0.67–0.79), respectively.

Figure 4 presents the predicted probabilities of PCSM at 10 yr after the last screening based on the PSA level at the last screen and whether the individual has previously undergone benign prostate biopsies, along with a density plot of the PSA levels within the cohort. Additionally, Supplementary Table 2 presents the predicted probabilities of PCSM at 10 yr after the last screening for several hypothetical patients. Based on the model, 228 (3.2%) men have a 10-yr predicted probability of PCSM of >1%.

4. Discussion

Our current data are, to the best of our knowledge, the first to provide insight into when and how to discontinue PCa screening in previously screened elderly men in whom the risk of overdiagnosis and subsequent overtreatment is a major concern due to the competing risk of other-cause mortality [5,19]. In this population-based cohort among men aged 70–74 yr at the last screening visit, who had previously undergone protocolled PSA-based screening and were followed until a median age of 88 yr, the absolute risk

of PCSM was very low. The cumulative incidence of 0.54% by the age of 85 yr within this study is notably lower than the 1.9–2.3% overall probability of PCSM by the age of 85 yr for men in Europe and the USA [20,21].

The risk of PCSM was found to be significantly correlated with the PSA level at the last screening round. Previous studies established the predictive value of baseline PSA among men aged 55–69 yr for the risk of lethal disease and suggested a reduced screening frequency for individuals with low baseline PSA levels [22,23]. Our present findings extend beyond this observation and provide evidence that screening can safely be discontinued in elderly men with PSA below 3 ng/ml, since PCSM by the age of 85 yr was rare (<1%) among these men. Although 39% of all PCSM events by the age of 85 yr occurred within this group, the high proportion of men involved (74% in this cohort) and the relatively low number of PCSM cases (n = 16) indicate that continuing screening in this particular group is unlikely to improve the harm-benefit ratio significantly. This notion is further supported by a study that assessed the risk of PCSM following a transurethral resection of the prostate with benign histology [24]. Using data from a large population-based registry with a median age of 72 yr at the time of the procedure, the authors reported a 15-yr cumulative incidence of PCSM of only 0.8% among men with a PSA level below 10 ng/ml and concluded that these men do not require extensive monitoring.

Additionally, we observed a significant correlation between a patient's history of prostate biopsy and the risk of PCSM. In men with prior benign biopsies, the cumulative incidence of PCSM by age 85 yr (ranging from 0.56% to 1.3% depending on PSA) aligns with long-term follow-up studies on men with benign systematic TRUS-guided biopsies. In two population-based screening trials, the Swedish arm of the ERSPC and the American Prostate, Lung, Colorectal, and Ovarian trial, the 20-yr cumulative incidences of PCSM ranged from 1.1% to 1.2% after adjusting for the competing risk of death from other causes [25,26]. Another analysis, encompassing all men in Denmark with a history of benign TRUS-guided biopsies, reported a 15-yr cumulative incidence of PCSM of 1.3% among men with a PSA level below 10 ng/ml and a median age of 66 yr at the time of the initial biopsy [27]. Furthermore, worth noting is that many men in these historical cohorts predominantly underwent conventional sextant-core biopsies. Modern screening approaches commonly involve a 12-core biopsy protocol and magnetic resonance imaging (MRI)-targeted biopsy, which have been shown to minimise undersampling and subsequently enhance diagnostic accuracy [28]. The improved early detection of clinically significant tumours with this contemporary way of screening will likely result in even lower PCSM rates than those observed in the historical cohorts.

Nevertheless, it is important to acknowledge that despite the protective effect of prior screening, some elderly men may still be diagnosed with a lethal form of PCa. Consequently, we aimed to identify a particular subgroup that may potentially benefit from on-going screening. Restricting screening only to those with a high risk of PCSM by implementing a risk-based approach might result in reduced PCSM while limiting overdiagnosis. According to

Table 2 – Competing risk regression of prostate cancer–specific mortality

	sHR	95% CI	*p* value
PSA (per doubling)	1.98	1.68–2.33	<0.001
Previous benign prostate biopsy			
No	Reference		
Yes	0.41	0.23–0.72	0.002
Positive family history			
No	Reference		
Yes	1.54	0.78–3.06	0.2
Hypertension			
No	Reference		
Yes	0.48	0.25–0.91	0.024
Heart disease			
No	Reference		
Yes	0.94	0.41–1.58	0.7
Diabetes			
No	Reference		
Yes	0.97	0.41–2.25	0.9

CI = confidence Interval; sHR = subdistribution hazard ratio.
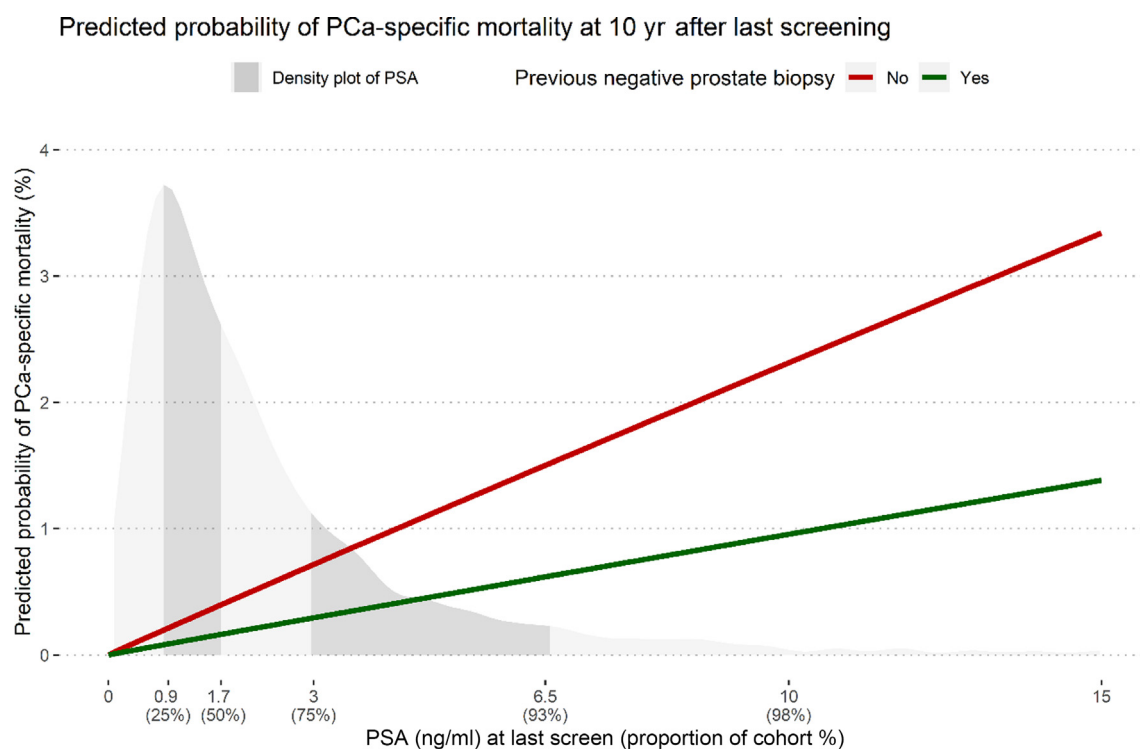
Fig. 4 – Predicted probability of prostate cancer–specific mortality at 10 yr after the last screening including a density plot showing the distribution of the PSA values within the cohort. PCa = prostate cancer; PSA = prostate-specific antigen.

our multivariable model, elevated PSA at the last screening is associated with a higher risk of PCSM, whereas a history of previous benign prostate biopsies is linked to a lower risk of PCSM. Interestingly, hypertension showed a significant association with a decreased risk of PCSM, whereas no similar link was found for the comorbidities of heart disease and diabetes. One possible explanation could be that these comorbidities were self-reported through a questionnaire, which may have led to potential misclassification. Nonetheless, it indicates that discontinuation of screening is likely to be safe in men with a low PSA level and/or hypertension. Conversely, as also demonstrated by the relatively high cumulative incidence of PCSM of 6.8% in men with PSA ≥ 6.5 ng/ml and no previous biopsy, continued screening might be beneficial for men with a high PSA level at the last screen who have not undergone biopsies previously. This highlights the need for multivariable risk stratification in deciding whether to continue screening rather than a univariable approach using an age cut-off. However, the intention is not to advocate for the strict application of a specific risk threshold from our model in clinical decision-making. Instead, these data should facilitate shared decision-making, taking into account personal factors such as the individual's life expectancy, comorbidity, and quality of life [29].

Moreover, a major challenge also resides in deciding whether screening should be continued based on an individual's predicted life expectancy. Current guidelines recommend to only apply PCa screening in men who are very healthy, with an estimated life expectancy of at least 10 yr [8,9]. This recommendation is substantiated by the median duration of 13 yr between the last screening and

PCSM observed in our current study. When determining whether an individual would be eligible for continued screening based on life expectancy, it is crucial to not rely solely on the age of the patient. Factors such as performance status, overall vitality, and the individual's willingness and ability to undergo potential treatment procedures resulting from continued screening should also be taken into consideration. Risk calculators that have been developed to assess a patient's life expectancy may aid in shared decision-making [30,31].

Our study's strengths include its long-term follow-up and the fact that almost all (97%) men reached the study endpoint (ie, dead or alive by the age of 85 yr). Additionally, a dedicated committee of urologists determined the cause of death for each PCa patient based on a thorough examination of their complete medical files, which ensures a reliable cause of death assessment. Our study also has several limitations. The ERSPC Rotterdam screening protocol utilised a sextant-core biopsy set, which may limit the direct applicability of our findings to the contemporary practice, where MRI-targeted biopsies are commonly applied. However, since MRI-targeted biopsies reduces undersampling, it may be expected that modern screening would result in even lower mortality rates of PCa than those observed in our cohort. Another limitation is the lack of data on the cohort's PSA testing after discontinuing the screening study, which prevents us from ruling out the possibility that the low rate of PCSM has been influenced by continued PSA testing beyond age 74 yr. One could argue that their prior testing may lead them to continue screening, while on the contrary, increased awareness of PSA testing's pros and cons may make them more inclined to stop testing. Additionally,

the Dutch general practitioners' guidelines are notably restrictive to PSA testing, which could suggest a relatively low prevalence in the Netherlands [32]. Furthermore, it should be noted that the observational nature of these data, without an intervention, does not offer evidence that on-going screening in men considered to be at a high risk will necessarily result in reduced PCSM. Prior studies link older age to an increased risk of high-grade PCa [33,34]. This raises the question of whether continued screening in these men will actually lead to a shift towards more favourable stages and create an opportunity for curative treatment, which is an essential prerequisite for screening to reduce PCSM effectively.

5. Conclusions

Men aged 70–74 yr who have undergone protocolled PSA-based screening without being diagnosed with PCa face a very low risk of PCSM. PCa screening in the elderly requires a personalised approach due to the large risk of overdiagnosis, with careful consideration of the individual's screening history, comorbidities, and life expectancy. Our observations question the value of on-going PSA screening for men aged ≥70 yr with PSA <3.0 ng/ml or with a history of benign prostate biopsies. Our data also raise doubts about the continuation of screening in elderly men with hypertension, necessitating further investigation into the precise impact of different comorbidities. For men with a higher PSA level without prior biopsies, continued screening may be appropriate if their life expectancy exceeds 10 yr.

Peer Review Summary

Peer Review Summary and Supplementary data to this article can be found online at https://doi.org/10.1016/j.eururo.2023.10.011.

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