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# A Detailed Evaluation of the Effect of Prostate-specific Antigen–based Screening on Morbidity and Mortality of Prostate Cancer: 21-year Follow-up Results of the Rotterdam Section of the European Randomised Study of Screening for Prostate Cancer

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**Abstract**

***Background:*** Considering the long natural history of prostate cancer (PCa), long-term results of the European Randomised Study of Screening for PCa (ERSPC) are crucial.
***Objective:*** To provide an update on the effect of prostate-specific antigen (PSA)-based screening on PCa-specific mortality (PCSM), metastatic disease, and overdiagnosis in the Dutch arm of the ERSPC.
***Design, setting, and participants:*** Between 1993 and 2000, a total of 42 376 men, aged 55–74 yr, were randomised to a screening or a control arm. The main analysis was performed with men aged 55–69 yr ($n$ = 34 831). Men in the screening arm were offered PSA-based screening with an interval of 4 yr.
***Outcome measurements and statistical analysis:*** Intention-to-screen analyses with Poisson regression were used to calculate rate ratios (RRs) of PCSM and metastatic PCa.
***Results and limitations:*** After a median follow-up of 21 yr, the RR of PCSM was 0.73 (95% confidence interval [CI]: 0.61–0.88) favouring screening. The numbers of men needed to invite (NNI) and needed to diagnose (NND) to prevent one PCa death were 246 and 14, respectively. For metastatic PCa, the RR was 0.67 (95% CI: 0.58–0.78) favouring screening. The NNI and NND to prevent one metastasis were 121 and 7, respectively. No statistical difference in PCSM (RR of 1.18 [95% CI: 0.87–1.62]) was observed in men aged ≥70 yr at the time of randomisation. In the screening arm, higher rates of PCSM and metastatic disease were observed in men who were screened only once and in a selected group of men above the screening age cut-off of 74 yr.
***Conclusions:*** The current analysis illustrates that with a follow-up of 21 yr, both absolute metastasis and mortality reduction continue to increase, resulting in a more favourable

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harm-benefit ratio than demonstrated previously. These data do not support starting screening at the age of 70–74 yr and show that repeated screening is essential.

***Patient summary:*** Prostate-specific antigen–based prostate cancer screening reduces metastasis and mortality. Longer follow-up shows fewer invitations and diagnoses needed to prevent one death, a positive note towards the issue of overdiagnosis.



## 1. Introduction

In the early 1990s, the European Randomised Prostate Cancer Screening Study (ERSPC) was initiated to determine the effect of prostate-specific antigen (PSA)-based screening on prostate cancer (PCa)-specific mortality (PCSM). After a follow-up of 16 yr, the ERSPC showed a relative risk reduction of 20% in PCSM in favour of screening [1]. Despite this level 1 evidence for PCSM reduction, PSA-based screening remains a controversial topic due to the high rate of overdiagnosis and subsequent overtreatment [2]. In recent years, the focus has also shifted to how to best screen for PCa [3].

In addition to reducing PCSM, another relevant aim of screening is to decrease the burden of PCa by averting or delaying metastatic disease (M+). Besides the effect of M+ on mortality [4], it is also important to consider the impact of M+ and subsequent treatment on quality of life [5,6]. Data from four centres of the ERSPC showed a relative reduction rate in M+ of 30% in favour of screening after 12 yr of follow-up [7]. However, the effect of screening on the risk of M+ was primarily seen at diagnosis but attenuated during follow-up [7]. The lack of an effect of screening during follow-up remains largely unexplained. Longer follow-up data may provide insight into which screened patients are at risk of developing M+ after diagnosis.

Therefore, the aim of the current study is to evaluate the long-term effect on the risks and benefits of PSA-based PCa screening using extended follow-up of the Rotterdam section of the ERSPC, a section of the ERSPC that is sufficiently powered [8]. Special attention is given to the timing of PCSM and M+ in relation to the (attendance to) screening algorithm.

## 2. Patients and methods

### 2.1. Study design and population

The ERSPC trial is a multicentre randomised study in which men were assigned randomly to a screening arm (S-arm) and a control arm (C-arm). We included men from the Rotterdam section, which is the second largest participating site. Methods of invitation, randomisation, and the applied screening algorithm including side studies have been described previously [9]. In short, the screening protocol consisted of PSA testing with a 4-yr interval and an upper age limit of 74 yr (maximum of five consecutive screening rounds). In general, a PSA level of $\geq$3.0 ng/ml triggered transrectal ultrasonography–guided biopsy.

The incidence of PCa detected outside the screening setting was obtained from yearly linkages with the Dutch Cancer Registry. PCa cases detected outside a screening visit were classified into cases of interval PCa (defined as PCa detected between two screening visits), PCa in nonattendees (ie, men who were invited for screening but did not attend), and PCa diagnosed in men who were not eligible for screening anymore due to the upper age limit. After diagnosis, detailed information on follow-up, such as disease progression or death, was collected by a semiannual chart review. For this report, follow-up was truncated at January 1, 2019 or at 21 yr after randomisation (since this was the median available follow-up of men who were still alive).

### 2.2. Outcomes

The primary outcome was PCSM. The cause of death among deceased men with PCa was determined through a fixed algorithm by an independent, blinded, cause of death committee [10]. The secondary outcome was the incidence of M+ in both study arms. The definition of M+ was determined by the presence of a positive bone or computed tomography scan or, if imaging data were not available, a PSA value of >100 ng/ml.

### 2.3. Statistical analyses

All men who consented were randomised and analysed regardless of their participation in accordance with the intention-to-screen principle. Primary analyses focused on the predefined ERSPC core age group (55–69 yr) and sensitivity analyses were performed for the whole cohort (55–74 yr). To account for competing events (other-cause mortality), cumulative incidence (CIN) rates for PCa diagnosis, M+, and PCSM of both study arms were calculated. The Poisson regression analysis was used to calculate the rate ratios (RRs) of PCSM and M+ between the two study arms [11]. Additionally, separate RRs were calculated for M+ at diagnosis (ie, detected <3 mo after PCa diagnosis) and M+ during follow-up (ie, detected >3 mo after PCa diagnosis). Time was incorporated in the Poisson models as the offset of the logarithmic transformation of the time between randomisation and the event of interest (ie, PCSM or M+), last follow-up visit, or the fixed end date (January 1, 2019). The Nelson-Aalen method was used to calculate cumulative hazard estimates for PCSM and M+ stratified by study arm [12]. To further clarify the timing of PCSM in the S-arm, men with screen-detected PCa in the first round were compared with those who had screen-detected PCa during subsequent screening rounds using a Cox regression analysis. The survival time in this model was defined as the time between diagnosis and PCa death. Men who died of other causes or were alive at the fixed end date (January 1, 2019) were censored. Additionally, Nelson-Aalen cumulative hazard estimates were calculated for PCSM in men who were diagnosed after discontinuing screening. The number needed to invite (NNI) to prevent one PCa death was calculated as 1 divided by the absolute risk difference in PCSM between study arms. The number needed to diagnose (NND) was defined as the NNI multiplied by the excess incidence of PCa in the screening group. All statistical analyses were performed in R Statistical Software version 4.1.1 [13].

## 3. Results

### 3.1. PCa detection, metastatic disease, and PCSM

A total of 42 376 men underwent randomisation of whom 20 984 were assigned to the S-arm and 20 916 to the

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C-arm (Fig. 1). Table 1 summarises the characteristics of the participants and the results of screening stratified by the core age group and the whole cohort. At 21 yr after randomisation, 2708 men (CIN: 16%; 95% confidence interval [CI]: 15–16) in the S-arm and 1706 men (CIN: 9.9%; 95% CI: 9.5–10) in the C-arm were diagnosed with PCa. This results in an excess incidence in the S-arm of 57 per 1000 men randomised.

Of those men with PCa, M+ was detected in 297 (21 yr post-randomisation CIN: 1.7%; 95% CI: 1.6–1.9) men in the S-arm and 439 men (21 yr post-randomisation CIN: 2.6%; 95% CI: 2.3–2.8) in the C-arm (see Fig. 2 for the Nelson-Aalen cumulative hazard). The rate of M+ at diagnosis was two times less among men randomised to the S-arm than that among men in the C-arm (RR: 0.45; 95% CI: 0.36–0.55). However, we did not found a reduction in M+ in follow-up between the two arms (RR: 1.10; 95% CI: 0.89–1.36). Overall, this results in an RR for M+ of 0.67 (95% CI: 0.58–0.78) in favour of the S-arm. The NNI and NND to avoid one case of M+ were 121 and 7, respectively (M+ in the ERSPC Rotterdam at various lengths of follow-up is presented in Supplementary Table 1). The sensitivity analysis for the whole cohort showed a lower overall reduction in M+: RR of 0.74 (95% CI: 0.65–0.84), NNI of 150, and NND of 8.

The CIN of all-cause death among all randomised core age men at 21 yr after randomisation was 47%. In total, 198 men died of PCa in the S-arm and 268 in the C-arm (see Fig. 3 for the Nelson-Aalen cumulative hazard). The CIN of PCSM at 21 yr after randomisation was 1.16% in the S-arm and 1.59% in the C-arm, which results in an RR of 0.73 (95% CI: 0.61–0.88), corresponding to a relative risk reduction of 27%. The absolute risk reduction in PCSM between the arms was 0.41%, resulting in an NNI of 246 and an NND of 14 (PCSM in the ERSPC Rotterdam at various lengths of follow-up is presented in Supplementary Table 2). A sensitivity analysis for the whole cohort showed a lower reduction in PCSM: RR of 0.83 (95% CI: 0.71–0.97), corresponding with a relative risk reduction of 17%, an NNI of 355, and an NND of 19. No statistical difference in PCSM (RR of 1.18 [95% CI: 0.87–1.62]) was observed in men aged ≥70 yr at the time of randomisation.

### 3.2. Detailed analyses of the PCa detection rate, metastatic disease, and PCSM in the S-arm

Figure 4 shows a detailed flow diagram of all men in the S-arm. Of the men diagnosed with PCa in the S-arm, 2282 (72%; median age at diagnosis: 68.3 yr [interquartile range {IQR}: 64.3.0–71.8]) were detected through the screening protocol. Nearly half of screen-detected cancers (47%) were diagnosed in the first screening round. However, in the fifth screening round, PCa was still found in 118 (7.1%) of the 1670 screened men. M+ at the time of diagnosis in screen-detected cancers was mainly found in the first round (2.5%), but was rare in subsequent rounds (0.8%; 1.3%, 0%, and 0%, respectively). Progression to M+ during follow-up occurred in a considerable number of PCa cases detected in the initial (108/1071; 10%) and second (31/549; 5.6%) screening rounds.

Furthermore, 759 PCa cases were diagnosed in the 17 115 men who were still alive after discontinuing screening (CIN: 4.4%; median age at diagnosis: 76.3 yr [IQR: 72.8–80.0]). In nonattenders, a total of 388 PCa cases were detected (CIN: 5.8%) after a median time of 10 yr (IQR: 7.5–14) after the last screening. Most of these cancers (51%) were detected in men who discontinued screening after the first round. However, the highest rate of PCSM (21%) with a low median time between diagnosis and PCa death (3.3 yr) was observed among those who never attended screening. The CIN of PCa in men that exceeded the upper age limit of 74 yr was 3.5% (median age at diagnosis: 79.1 yr [IQR: 76.0–82.1]). M+ at diagnosis in the S-arm occurred predominantly after discontinuation of screening (117/161 [73%]). These cases are equally divided between nonattenders and men who discontinued screening due to the upper age limit.

An analysis of the men who died of PCa in the S-arm shows that most of these men were screened only once ($n$ = 181, 64% of all PCSM cases). Of the 151 screen-detected PCa deaths, 108 (71%) were diagnosed in the first round. Twelve years after diagnosis, the risk of dying from PCa was significantly higher for these men than for men diagnosed in the second or third round (hazard ratio [HR]: 2.56; 95% CI: 1.56–4.19; cumulative hazard curve is presented in Supplementary Fig. 1). Furthermore, 26% (74/283) of the PCa deaths in the S-arm occurred in men who were diagnosed after discontinuing the screening protocol due to the upper age limit. Among these men, no statistically significant difference in M+ or PCSM was observed in those who were screened one, two, or three times at 12 yr after their last screen (Fig. 5). Of these 74 PCa deaths, 43% had an indication for biopsy at their last screen, of whom 38% refused the biopsy.

## 4. Discussion

Almost three decades after the Dutch arm of the ERSPC was established, we evaluated the effect of PSA-based screening on M+ and PCSM. With a median follow-up of 21 yr, the ERSPC Rotterdam shows a statistically significant PCSM relative rate reduction of 27% (95% CI: 12–39) among men aged 55–69 yr who underwent PSA-based screening compared with those who were offered no active screening. A smaller reduction of 17% (95% CI: 3.3–29) was observed in the whole cohort (aged 55–74 yr), and no statistical difference in PCSM was observed in men aged ≥70 yr at the time of randomisation. This is in line with previously reported data of the ERSPC [8], which showed that starting screening in men ≥70 yr does not result in a PCSM reduction. Furthermore, while the relative risk reduction of the core age group is somewhat lower than the ERSPC Rotterdam at a 16-yr follow-up PCSM reduction of 33% [1], the absolute risk difference of PCSM between the two arms has increased from 0.32% to 0.41%. This increase reflects the reduction in NNI (from 303 to 243 men) and NND (from 18 to 14 men), which is a favourable finding when it comes to the issue of overdiagnosis [2] and is also observed in the Swedish arm of the ERSPC after 22 yr of follow-up [14]. The NND in the current study is comparable with the one calculated by Basour-

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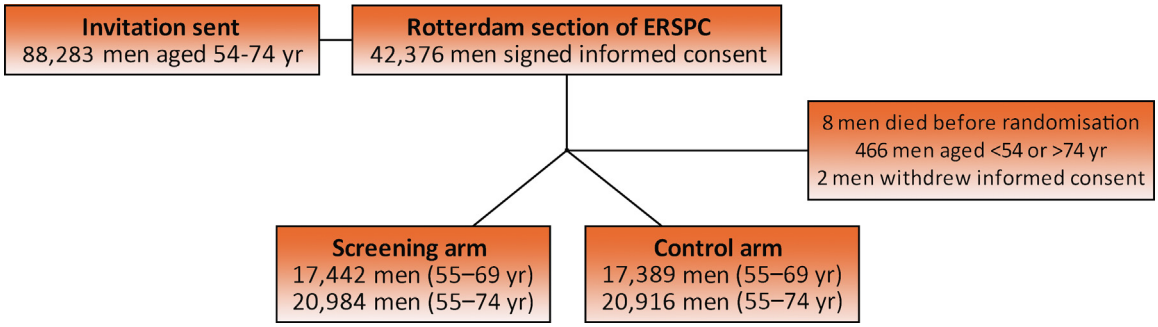


**Fig. 1 – Flowchart of the study. ERSPC = European Randomised Study of Screening for Prostate Cancer; PCa = prostate cancer.**

**Table 1 – Characteristics of patients and results of screening according to the age at randomisation**

| | Core age group (55–69 yr) | Whole cohort (55–74 yr) |
|---|---|---|
| Total patients, *n* | 34 831 | 41 900 |
| Age at randomisation (yr), median (IQR) | 61.7 (58.1–65.6) | 63.2 (58.7–68.2) |
| Control arm, *n* | 17 389 | 20 916 |
| Prostate cancer cases, *n* | 1706 | 2022 |
| Metastatic prostate cancer, *n* | 439 | 540 |
| At diagnosis, *n* | 278 | 342 |
| In follow-up, *n* | 161 | 198 |
| Prostate cancer–specific mortality, *n* | 268 | 341 |
| Screening arm, *n* | 17 442 | 20 984 |
| Prostate cancer cases, *n* | 2708 | 3180 |
| Metastatic prostate cancer, *n* | 297 | 402 |
| At diagnosis, *n* | 118 | 161 |
| In follow-up, *n* | 179 | 241 |
| Prostate cancer–specific mortality, *n* | 198 | 283 |
| Screened at least once, *n* (%) | 16 501 (95) | 19 764 (94) |
| Biopsied at least once, *n* (%) | 6324 (36) | 7375 (35) |
| Total screens, *n* | 43 077 | 46 988 |
| Positive tests, *n* (% of total screens) | 10 086 (23) | 11 481 (24) |
| Biopsies, *n* (% of positive tests) | 9283 (92) | 10 499 (91) |
| Mean rounds invited | 2.9 | 2.6 |
| Mean rounds screened | 2.6 | 2.3 |
| Excess incidence per 1000 men | 57 | 55 |
| Risk ratio prostate cancer (95% CI) | 1.58 (1.50–1.68) | 1.56 (1.49–1.65) |
| Rate ratio prostate cancer (95% CI) | 1.67 (1.58–1.78) | 1.66 (1.58–1.76) |

CI = confidence interval; IQR = interquartile range.

akos et al [15], which quantified overdiagnosis after three decades of PSA screening comparing pre- and post-PSA era data. With two estimation approaches, they calculated an NND of 11–14 even in the least optimistic scenario. Furthermore, a previous analysis of a pilot cohort of the ERSPC Rotterdam with only little PSA contamination in the C-arm showed even more favourable results with a reduction in PCSM of 52% and an NND of 3 [16]. While the degree of contamination was not assessed in the current study, a previous report of the ERSPC Rotterdam showed that 4.3% of PCSM in the C-arm was attributed to contamination. Correcting for this (and nonattendance) resulted in a mortality reduction of 51% in favour of organised screening [17].

Moreover, although overdiagnosis poses a concern in traditional PSA-based screening, this harm may be mitigated by contemporary protocols using risk stratification tools such as biomarkers, magnetic resonance imaging, and multivariable risk calculators before biopsy [18–20]. Although we need to wait for the long-term effects of population-based screening with such a risk stratification approach [21,22], the first results showed a huge potential for these new tools to reduce unnecessary biopsy procedures and overdiagnosis of insignificant PCa [23,24,25]. At the same time, in case of low-risk disease, overtreatment can be avoided with active surveillance as a safe alternative to active treatment [26].

Besides the reduction in PCSM, our study showed a relative rate reduction in overall M+ of 33% for the core age group and 26% in the whole cohort. These findings are comparable with the previously published results of four ERSPC centres [7] in which a relative reduction of 30% (core age group) was found after a median follow-up of 12 yr. However, with increased follow-up available, the reduction of overall metastasis coincides with a lower NNI (121 vs 328 men) and NND (7 vs 12 men). The relative reduction is mainly caused by the prevention of M+ at diagnosis in the S-arm. This finding is supported by a recent report in which increased rates of M+ at diagnosis were observed after the US Preventive Services Task Force had recommended against PSA-based screening [27].

Nonetheless, the overall reduction in M+ is attenuated due to increasing numbers of M+ during follow-up in the S-arm. A possible explanation for this observation might be the cross-sectional design effect of the trial by offering a first PSA test to men aged anywhere between 55 and 74 yr. The high prevalence of latent advanced-stage PCa in this population might have caused a lead-time bias, considering half (51%) of the M+ cases detected during follow-up of the S-arm were observed in men who were diagnosed in the first screening round. In other words, many of the cases diagnosed at the first screening round are labelled as having organ-confined disease, while in fact, the process of developing M+ has already begun. By starting screening at a fixed age <60 yr, these cancers might be detected in the window of cure [28]. Moreover, men diagnosed in the first round have a considerably higher rate of PCSM than those

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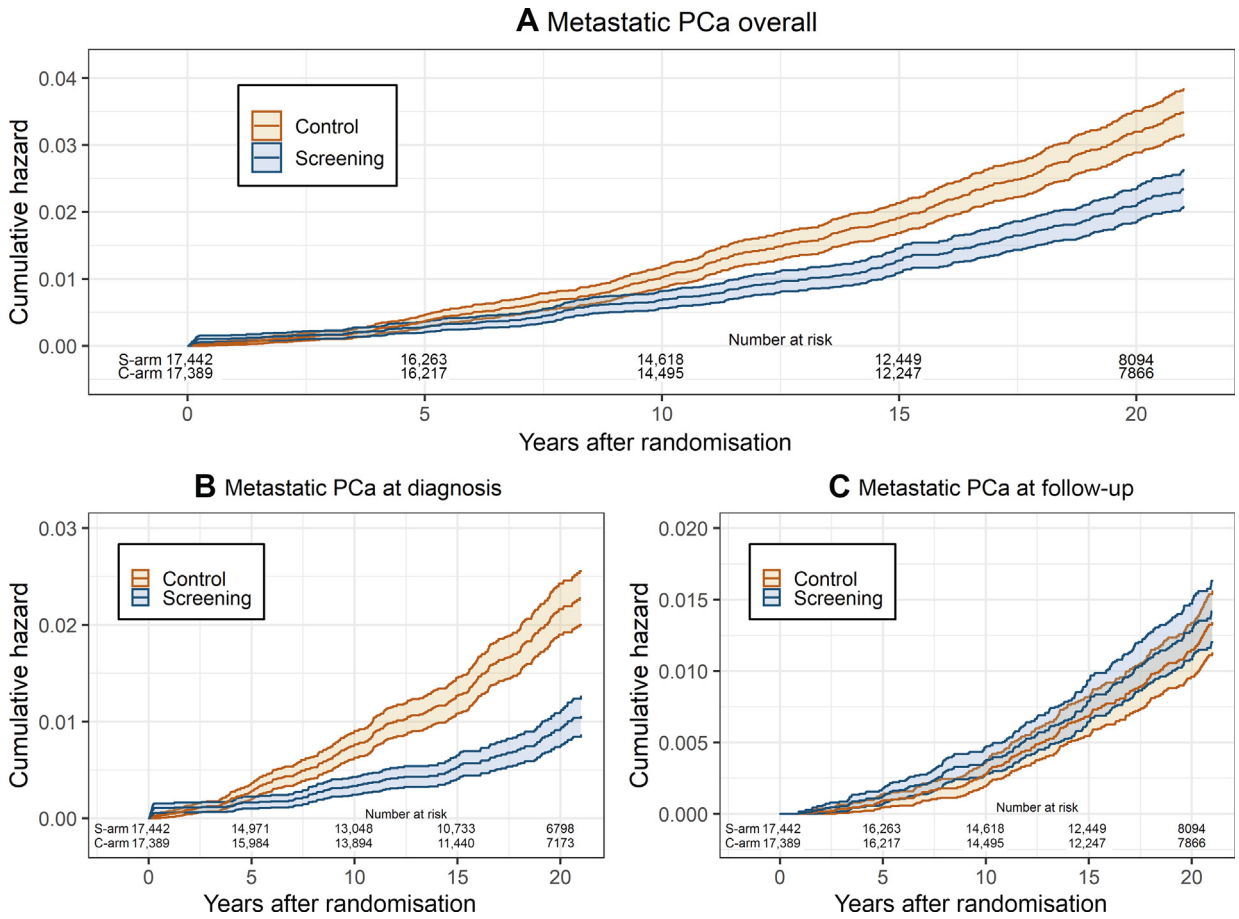


**Fig. 2 – Nelson-Aalen cumulative hazard estimates of metastatic prostate cancer (A) overall, (B) at diagnosis, and (C) at follow-up for the ERSPC core age group (55–69 yr) including 95% confidence intervals. C-arm = control arm; ERSPC = European Randomised Study of Screening for Prostate Cancer; PCa = prostate cancer; S-arm = screening arm.**

diagnosed at subsequent screening rounds (HR 2.56; 95% CI: 1.56–4.19 for PCSM at 12 yr after diagnosis). This observation is supported by the Finnish ERSPC arm [29] and the CAP trial, which also showed no significant reduction in PCSM after a single PSA test [30].

The rates of M+ and PCSM were also particularly high for men who underwent active screening but were diagnosed after the age cut-off of 74 yr. Among these men, we found no significant difference in PCSM at 12 yr after their last screening visit with regard to the number of times these men were screened. So even though men were screened multiple times, lethal cancers are still diagnosed after screening. The median time between the last screening visit and diagnosis for the men in this group who eventually died of their disease was 7 yr. This corresponds with the results of the Göteborg trial, which showed that after termination of screening (at an upper age limit of 69 yr), the incidence of high-risk PCa gradually increased in the S-arm and approximated the incidence of the C-arm 9 yr after discontinuing screening [31]. Since the protective effect of screening seems to fade after less than a decade, the question is raised whether the upper age limit to continue screening should be raised. On a population-based level, this would implicate an even higher, unacceptable, number of overdiagnosis since age and PCa overdiagnosis are strongly correlated [32]. Additionally, it is important to consider the cost efficacy and harm-benefit ratio in population-based screening and to accept that not all PCSM cases can be prevented. However, the number of PCSM cases in elderly with limited comorbidity and life expectancy of at least 10–15 yr may be reduced with a more targeted approach, such as reducing the number of men who refused an indicated biopsy (16% in this group) or continuing follow-up of men with a negative biopsy despite a suspiciously high PSA [33].

Our study has some limitations. In this study, only data from the Rotterdam section were analysed, although it was not designed as a stand-alone trial. However, initial calculations of sample size and power for the ERSPC study in 1992 solely on the basis of Dutch data showed that 20 000 men randomised in each arm would be required to show a 25% PCa mortality reduction with a 80% power at 10 yr of follow-up, ignoring potential noncompliance and contamination [8]. Additionally, this is the only centre that collects detailed follow-up data on (secondary) treatment and metastases after diagnosis of all cancers in both arms. Strength of this study includes the long follow-up time and the fact that almost half of the men have reached the endpoint (i.e. death) at the time of analysis. In addition,

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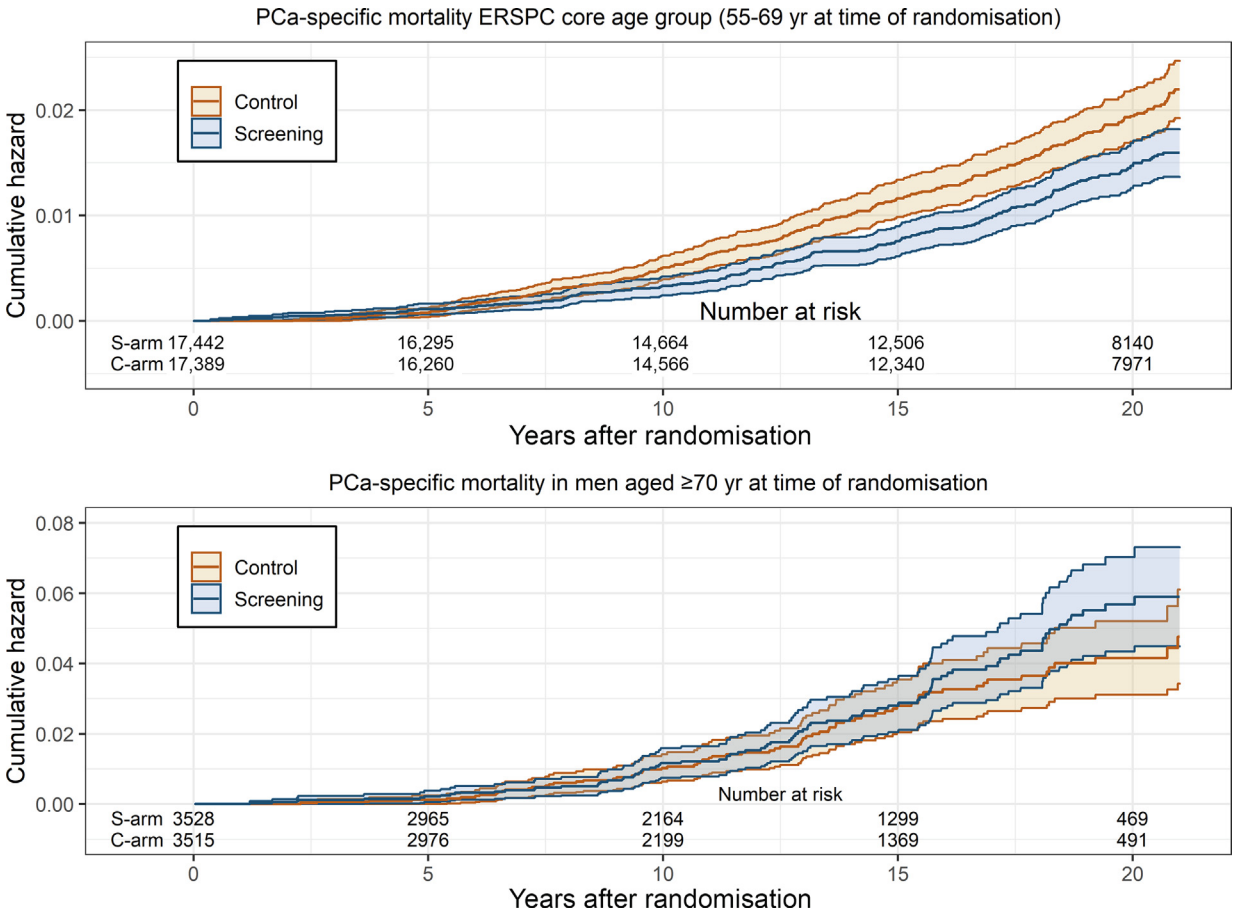


**Fig. 3 – Nelson-Aalen cumulative hazard estimates of prostate cancer–specific mortality for the ERSPC core age group (55–69 yr) and men aged ≥70 yr at the time of randomisation including 95% confidence intervals. C-arm = control arm; ERSPC = European Randomised Study of Screening for Prostate Cancer; PCa = prostate cancer; S-arm = screening arm.**

the cause of death is determined through a fixed algorithm by an independent committee, which is essential for any cause-specific mortality study.

## 5. Conclusions

Considering the long natural history of PCa, the current analysis shows that after extended follow-up, both absolute metastasis and PCSM reduction continue to increase in favour of PSA-based screening. Although coinciding overdiagnosis still remains a dilemma, the NNI and NND decline with longer follow-up. Starting screening at age 70–74 yr is too late, and repeated screening is crucial for a population-based screening protocol.

***Author contributions*:** Ivo I. de Vos 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.
*Acquisition of data*: Roobol.
*Analysis and interpretation of data*: de Vos, Meertens, Remmers, Hogenhout, Roobol.
*Drafting of the manuscript*: de Vos, Meertens.
*Critical revision of the manuscript for important intellectual content*: de Vos, Meertens, Hogenhout, Remmers, Roobol.
*Statistical analysis*: de Vos, Remmers.
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*Supervision*: Roobol.
*Other*: None.

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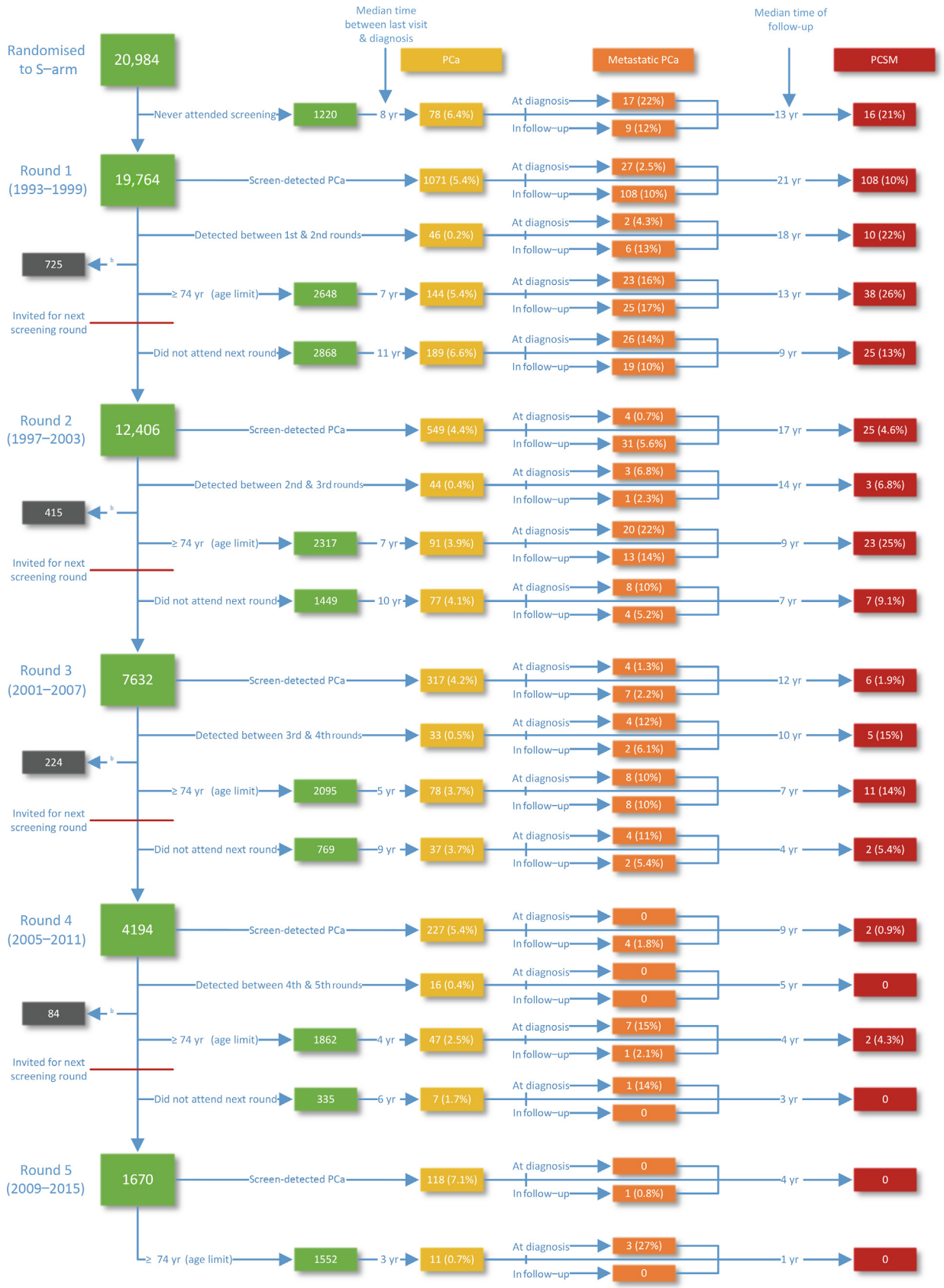


**Fig. 4 – Detailed flow diagram of all men in the screening-arm. C-arm = control arm; PCa = prostate cancer; PCSM = prostate cancer–specific mortality; S-arm = screening arm. [a] Median time between diagnosis and January 1, 2019. [b] Deceased in between rounds due to other causes.**

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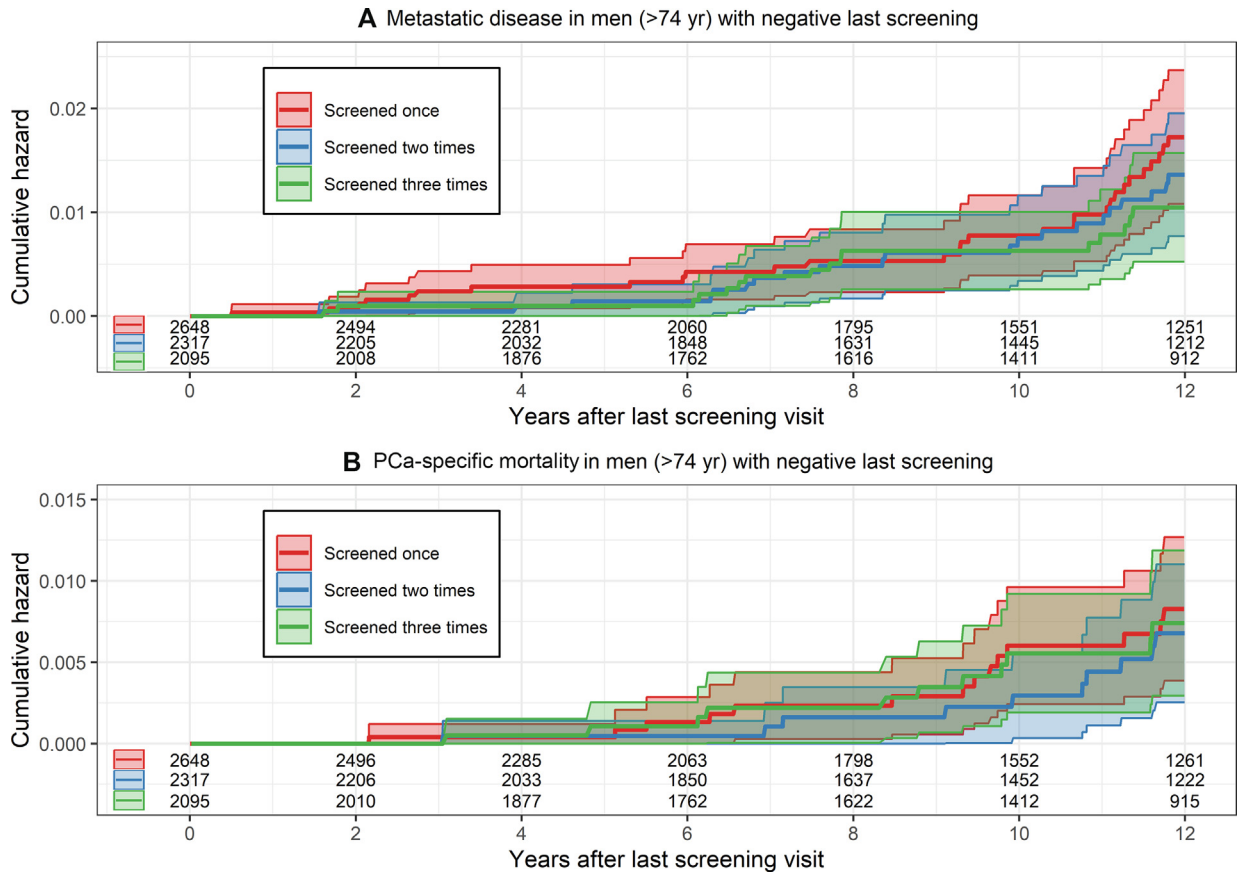


**Fig. 5 – Nelson-Aalen cumulative hazard estimates of (A) metastatic prostate cancer and (B) prostate cancer–specific mortality in men in whom no prostate cancer was detected during screening and who were no longer eligible for screening due to the upper age limit.**

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## Peer Review Summary

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