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Brief Correspondence

The Impact of Design and Performance in Prostate-Specific Antigen Screening: Differences Between ERSPC Centers

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Abstract

The European Randomized study of Screening for Prostate Cancer (ERSPC) has shown a 20% relative reduction in prostate cancer mortality after 16 yr [rate ratio (RR) 0.80], but centers varied by attendance, screen interval, biopsy compliance, contamination in the control arm, and treatments. We used a microsimulation model, calibrated to the ERSPC individual-level data, to predict influence of study features on the results. The relative reduction in prostate cancer mortality would have been somewhat larger with improved study features: increased attendance (90% attendance in all volunteer-based and 70% in all population-based centers, resulting in RR 0.77), a 2-yr screen interval (RR 0.75), and an 80% biopsy compliance (RR 0.79). The RR would have been substantially lower with a 30% attendance (RR 0.92), 40% biopsy compliance (RR 0.90), or 100% contamination (RR 0.85). The variations in results by trial center may reflect differences in study design and performance and results of our simulations highlight the effect of quality indicators in prostate-specific antigen screening in different settings.

Patient summary: We evaluated the effect of various features of prostate-specific antigen (PSA) screening on its effectiveness. The compliance to PSA testing and those having a biopsy after an elevated PSA substantially influence the prostate cancer mortality.

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The European Randomized study of Screening for Prostate Cancer (ERSPC) has shown a 20% relative reduction in prostate cancer mortality after 16 yr [1]. However, the results differed between centers, varying from a prostate cancer mortality rate ratio (RR) of 0.63 in Sweden to 0.99 in Italy. These differences could reflect variations in screening protocols, deviations from the quality criteria defined at the start of the trial, or variations in opportunistic screening and treatment [2,3].

In some centers the randomized population was volunteer based (efficacy design) and attendance exceeded 90%. In the other centers a population-based effectiveness design

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was used with randomization before consent and the attendance was 60–70%. After the first round, the attendance was lower. The a priori defined quality criteria were 90% attendance for the volunteer-based centers and 70% for the population-based centers. In France, the attendance was only around 30% [4].

The screening interval in the trial was 4 yr, except in Sweden (2 yr). In Belgium, the interval between the first and second screen was 6 yr.

The biopsy compliance varied between 40% (in the third round in Italy) and 91% (Finland), whereas the quality criterion was that more than 80% of the men recommended for biopsy should be biopsied.

The level of contamination in the ERSPC was estimated in some studies, ranging from 7% to 40% per year across centers [5–8]. In Finland, 63% of the men in the control arm had a prostate-specific antigen (PSA) test during the first 12 yr of the trial [9].

Treatment decisions were left to the treating physicians of each patient. This could have resulted in differences in treatment and therefore affect prostate cancer mortality reduction by trial center [11].

The aim of this study is to evaluate what the impact of the quality indicators has been on the overall ERSPC results.

For this analysis, we used the Erasmus MIcrosimulation SCreening ANalysis (MISCAN) prostate cancer model based on 16-yr follow-up data of the ERSPC (excluding France). MISCAN is a stochastic model that simulates individual life histories. The model has been described extensively before and is described in Appendix A [10].

The output of the model was the prostate cancer incidence and mortality in both arms by year of follow-up. After calibration, the predicted prostate cancer mortality RR at 16 yr of follow-up was 0.79 versus 0.80 observed in the ERSPC (Appendix Fig. 1).

We started with this base model and then changed several parameters one by one in the model, representing the attendance, screening interval, biopsy compliance, contamination, and curative treatment and including France (Table 1).

The predicted prostate cancer mortality RRs for all scenarios are presented in Fig. 1. The RRs varied from 0.92 for the 30% attendance scenario to 0.73 for the scenario

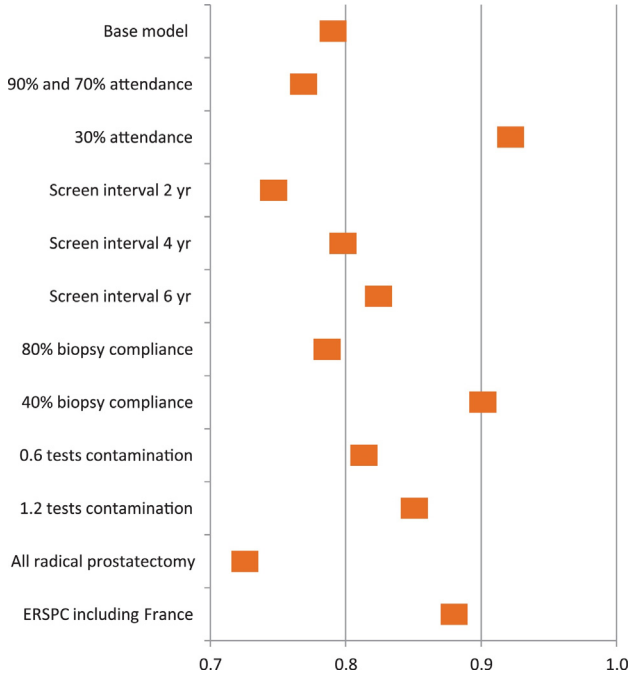

Fig. 1 – Predicted prostate cancer mortality rate ratio in the European Randomized study of Screening for Prostate Cancer (ERSPC) trial after 16 yr of follow-up for the various scenarios.

in which all men in the screen arm with locoregional cancer were treated by radical prostatectomy. With inclusion of the French centers, the whole ERSPC study would show a prostate cancer mortality RR of 0.88. The impact of screening on incidence and prostate cancer mortality by year of follow-up for all scenarios are presented in Appendix Figs. 2–7.

The lower attendance after 4 yr did not yet substantially influence prostate cancer mortality. An earlier study already found that the differences in prostate cancer mortality reduction between the centers could not be explained by the differences in attendance [2]. However, a very low attendance of 30%, as in France, would lead to a substantially lower incidence in the screen arm and also a lower prostate cancer mortality reduction.

The screening interval had a large impact on the incidence in the early years, but a smaller effect on prostate

Table 1 – The inputs used in the base model and the 11 alternative scenarios

	Base model	Alternative scenario
Attendance	By age, center, and round On average 82% in the first round	1. 90% per round for The Netherlands, Belgium, Spain, and Switzerland and 70% per round for Italy, Finland, and Sweden 2. 30% per round
Interval	By center and round (2–6 yr)	3. All 2 yr 4. All 4 yr All 6 yr
Biopsy compliance	By age, center, and round On average 86% in the first round	6. 80% 7. 40%
Contamination	Mean of 0.3 tests per man in the control arm during the first 16 yr of follow-up	8. Mean of 0.6 tests per man Mean of 1.2 tests per man
Curative treatment	Treatment based on age and stage	10. All men in the screen arm and locoregional stage receive radical prostatectomy
France	Not included	11. Included (on average 30% attendance per round)

cancer mortality at 16 yr. Possibly its influence on prostate cancer mortality will be larger with a longer follow-up.

The overall biopsy compliance was more than 80% in the first round of the ERSPC, decreasing slightly to 70–75% in the third round, but the decline did not substantially influence the prostate cancer mortality. A very low biopsy compliance of 40% would have had a substantial impact on both incidence and mortality.

Contamination in the control arm substantially increased the incidence and reduced the prostate cancer mortality in the control arm, leading to a smaller prostate cancer mortality reduction by screening.

In a hypothetical situation, in which all men in the screen arm with a localized cancer would have been treated by radical prostatectomy, the prostate cancer mortality reduction would have increased to 27%. However, this would substantially diminish quality of life, due to complications and adverse effects of treatment.

This study has several limitations that involve the choice and uncertainty in the many parameters needed for the model. For example, Surveillance, Epidemiology, and End Results (SEER) data on prostate cancer survival are used, instead of European data, because there is no large European data set available for the survival in the period before screening started. We had to make assumptions on opportunistic screening. A sensitivity analysis could help in quantifying the uncertainty in the model parameters. However, for this analysis it is particularly complicated. When adjusting parameters, the point estimate of the prostate cancer mortality reduction in the base model will also change, complicating the interpretation of the results of the other scenarios. Besides, we modeled only a limited number of scenarios, based on the ERSPC trial. Therefore, for example, we did not assess the effect of different screen ages, because those were roughly similar in the ERSPC centers.

In conclusion, the ERSPC would have shown only a slightly larger prostate cancer mortality reduction if all centers had complied with the quality criteria for attendance or biopsy compliance, or if a 2-yr screening interval had been used. By contrast, the prostate cancer mortality reduction could have been substantially lower if the attendance, biopsy compliance, or contamination had been similar to the center with the lowest performance. The magnitude of the impact of the specific features estimated here may, together with information on overdiagnosis and overtreatment, be helpful in predicting the effectiveness of any (future) PSA testing program.

Author contributions: Eveline A.M. Heijnsdijk has 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: Adolfsson, Auvinen, Roobol, Hugosson, de Koning.
Acquisition of data: Adolfsson, Auvinen, Roobol, Hugosson, de Koning.
Analysis and interpretation of data: Heijnsdijk.
Drafting of the manuscript: Heijnsdijk.
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Statistical analysis: Heijnsdijk.
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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.eururo.2019.04.007.

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