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What explains the differences between centres in the European screening trial? A simulation study

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ABSTRACT

Background: The European Randomised study of Screening for Prostate Cancer (ERSPC) is a multicentre, randomised screening trial on men aged 55–69 years at baseline without known prostate cancer (PrCa) at randomisation to an intervention arm invited to screening or to a control arm. The ERSPC has shown a significant 21% reduction in PrCa mortality at 13 years of follow-up. The effect of screening appears to vary across centres, for which several explanations are possible. We set to assess if the apparent differences in PrCa mortality reduction between the centres can be explained by differences in screening protocols.
Methods: We examined the centre differences by developing a simulation model and estimated how alternative screening protocols would have affected PrCa mortality.
Results: Our results showed outcomes similar to those observed, when the results by centres were reproduced by simulating the screening regimens with PSA threshold of 3 versus 4 ng/ml, or screening interval of two versus four years. The findings suggest that the differences are only marginally attributable to the different screening protocols.
Conclusion: The small screening impact in Finland was not explained by the differences in the screening protocols. A possible reason for it was the contamination of and the unexpectedly low PrCa mortality in the Finnish control arm.

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1. Introduction

The European Randomised study of Screening for Prostate Cancer (ERSPC) is a multicentre, randomised screening trial assessing mortality from prostate cancer (PrCa) in an intervention arm invited to prostate-specific antigen (PSA)-based screening compared with a control arm without intervention. The trial was initiated in 1993–1996 in seven European countries (N = 162,243): the Netherlands, Sweden and Finland (responsible for 78% of the total number of men included), and smaller centres in Switzerland, Belgium, Italy and Spain. In an updated analysis, the ERSPC has recently shown a significant 21% reduction in PrCa mortality at 13 years of follow-up [1].

Interestingly, the screening effect does not appear to be constant across the trial centres, with the largest reduction in PrCa mortality in Sweden, followed by the Netherlands and a non-significant 10% decrease in Finland [1–4].

We aim to assess if, and to what extent, the apparent differences in PrCa mortality reduction between the centres can be explained by differences in screening protocols. Both Netherlands and Sweden used a PSA threshold of 3 ng/ml as indication for prostate biopsy, while in Finland it was set at 4 ng/ml (with an ancillary test at PSA 3.0–3.9 ng/ml). The screening interval was four years in Finland and the Netherlands, and two years in Sweden. Although PSA is measured in screening at regular intervals in accordance with centre-specific protocols, the PSA level is known to increase with age and any prostate disease. Thus, a screen-positive man

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could have reached the value used as threshold in screening at an earlier time, but this remains unobservable until the protocol-scheduled measurement. The time to detection of an elevated PSA affects the probability of developing advanced disease and the risk increases with less frequent screening or a higher PSA threshold, which may in turn increase PrCa mortality and reduce the screening effect.

To assess the impact of the screening regimen on screening outcomes, we developed a longitudinal model for PSA and a simulation model for the prediction of PrCa death under different hypothetical conditions. The joint use of these two models allowed estimation of the effects of different screening protocols on PrCa mortality in three largest ERSPC centres.

2. Materials and methods

2.1. Data sets analysed

The present analysis was based on 126,829 men aged 55–69 years at baseline without known PrCa at randomisation from the Netherlands, Sweden and Finland, including 55,199 men assigned to the intervention arm. The follow-up time was truncated at 12 years, during which 5565 (10.1%) men were diagnosed with PrCa in the intervention and 4777 (6.7%) in the control arm. A total of 252 (0.4%) men in the intervention arm and 426 (0.6%) men in the control arm died from PrCa. The median age of the participants at randomisation was 59 years, but the Netherlands centre comprised older men (median age 62 years) than those in Sweden and Finland. Full ERSPC study details are given in Schröder et al. [1].

2.2. Statistical methods

We (i) developed and fitted a longitudinal model on PSA depicting the continuous PSA development over time (velocity or doubling time) in men with and without PrCa and (ii) using the estimated PSA levels, simulated the screening and PrCa outcomes under various hypothetical screening protocols. For example, a simulation following the Swedish protocol at all centres should show the potential effect of a two-year screening interval, i.e. to what extent the differences are attributable to the frequency of screening.

The model for PSA development was built and estimated on PSA data obtained in the ERSPC study, and the same data was used to interpolate/predict individual development of PSA. More specifically, a linear mixed model was fitted for PSA (transformed as log [PSA + 1]) to depict the continuous PSA development of each man with at least one PSA measurement. The fixed effect part of the model consisted of linear and quadratic age, and of an assumed change in the quadratic part five years before the diagnosis of PrCa. The change was allowed to vary according to the Gleason score (<7, 7 or >7) of the PrCa. Thus, the individual profiles consisted of piecewise exponential components estimated from the data, allowing a rapid increase starting five years before the diagnosis of PrCa. The choice of five years was based on initial empirical investigation of the data, choosing alternative annual change points and taking the change point which fitted the data best. Man-specific random effects were introduced for the intercept, linear and quadratic terms in the model to realistically capture observable deviations from the mean profile and to account for the natural heterogeneity in the population, and hence, the covariance structure. Based on the individual-specific fitted PSA curves, we estimated the change in PSA concentration for men from randomization up to PrCa diagnosis or 12 years of follow-up, whichever came first. By generating the PSA histories, we could estimate the time when a man with a PrCa would enter the detectable preclinical phase of the disease, i.e. the cancer become potentially detectable by screening and when the hypothetical screening protocol would have been able to detect the elevated PSA, resulting in detection of the cancer by screening (diagnosis and subsequent commencement of treatment).

The simulation model for PrCa mortality was built sequentially. First, we estimated the probability of PrCa death during the first two years after randomization. Second, among those who survived the first two years, we estimated the probability of PrCa death between two and four years. Following this sequential construction, a set of probabilities was estimated from the data up to the last interval from 10 to 12 years. As multiple time intervals were obtained on the same individuals, these probabilities were estimated by using generalized estimating equations models with a complementary log-log link function including baseline age, centre, time interval, estimated log of PSA at the beginning of the time interval, and finally, information on whether the individual was screen-positive at the beginning of the time interval, as covariates. Men with no PSA measurements (non-participants and control arm) were not included in the estimation of the model parameters.

Once the set of probabilities was established, we simulated hypothetical data by bootstrap resampling from this model under the following scenarios:

- The Swedish screening protocol with two-year screening interval addressing whether PrCa mortality in the screening arms of the Netherlands and Finland would have been improved relative to the control arm. In this scenario, the Finnish individuals would have become screen positive earlier as the delay to reach the threshold of 3 ng/ml would have been shorter due to more frequent screening and lower threshold, and the Dutch men due shorter screening interval.
- No screening-scenario expected to result in similar PrCa mortality in the intervention and the control arms. This means that men would have never become screen positive, regardless of the longitudinal development of PSA. The scenario was intended to show whether the effects of screening have been correctly estimated by the simulation model.
- Simulation with similar procedures as actually applied in each centre. This was used as a second validation of the simulation model expected to yield results similar to those actually observed.

Men in the control arm in each centre were used as observed, without simulation.

The times of death overall were assumed to be uniformly distributed on the time interval when PrCa death occurred.

The simulation model is particularly designed for ERSPC and addressing the current research question and is similar to the FHCRC model in the implementation of PSA model part (https://resources.cisnet.cancer.gov/registry/packages/psapc-fhcrc/). Full details are given in the Appendix.

3. Results

The PSA model indicated statistically significant differences between the centres, with the highest levels in Finland, followed by Sweden and the Netherlands in that order (Table A.2). The linear component for age in the model indicated a steady increase in the average PSA levels with a quadratic age component depicting a small, but statistically significant deceleration in the velocity. Men with Gleason score >7 tumors showed the largest acceleration in the PSA development five years prior to the actual diagnosis, but substantial changes were also observed in men with Gleason score 7 or <7 cancers. The random effects part of the model (not shown)

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