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RESEARCH

Randomised prostate cancer screening trial: 20 year follow-up

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ABSTRACT

Objective To assess whether screening for prostate cancer reduces prostate cancer specific mortality.

Design Population based randomised controlled trial.

Setting Department of Urology, Norrköping, and the South-East Region Prostate Cancer Register.

Participants All men aged 50-69 in the city of Norrköping, Sweden, identified in 1987 in the National Population Register (n=9026).

Intervention From the study population, 1494 men were randomly allocated to be screened by including every sixth man from a list of dates of birth. These men were invited to be screened every third year from 1987 to 1996. On the first two occasions screening was done by digital rectal examination only. From 1993, this was combined with prostate specific antigen testing, with 4 µg/L as cut off. On the fourth occasion (1996), only men aged 69 or under at the time of the investigation were invited.

Main outcome measures Data on tumour stage, grade, and treatment from the South East Region Prostate Cancer Register. Prostate cancer specific mortality up to 31 December 2008.

Results In the four screenings from 1987 to 1996 attendance was 1161/1492 (78%), 957/1363 (70%), 895/1210 (74%), and 446/606 (74%), respectively. There were 85 cases (5.7%) of prostate cancer diagnosed in the screened group and 292 (3.9%) in the control group. The risk ratio for death from prostate cancer in the screening group was 1.16 (95% confidence interval 0.78 to 1.73). In a Cox proportional hazard analysis comparing prostate cancer specific survival in the control group with that in the screened group, the hazard ratio for death from prostate cancer was 1.23 (0.94 to 1.62; P=0.13). After adjustment for age at start of the study, the hazard ratio was 1.58 (1.06 to 2.36; P=0.024).

Conclusions After 20 years of follow-up the rate of death from prostate cancer did not differ significantly between men in the screening group and those in the control group.

Trial registration Current Controlled Trials, ISRCTN06342431.

INTRODUCTION

The favourable outcome after radical surgery shown in a Scandinavian study comparing radical prostatectomy with watchful waiting[1] has stimulated the debate on early detection of prostate cancer, in particular by testing for prostate specific antigen. The Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial[2] and the European Randomised Study of Screening for Prostate Cancer (ERSPC)[3] were expected to provide final evidence for or against screening as a method to reduce mortality from prostate cancer. These two large studies, however, did not show unequivocal benefit from prostate specific antigen screening. The ERSPC trial showed a significant improvement in cancer specific survival for men in the screened group but with a high risk of overdiagnosis and overtreatment.[3] The Gothenburg randomised population based prostate cancer screening trial,[4] from one of the centres included in the ERSPC trial, found a risk ratio for prostate cancer specific death similar to that found in the ERSPC trial. The PLCO trial, on the other hand, did not show any benefit from screening,[2] probably because of a large degree of cross-over contamination. Follow-up in the PLCO might also have been too short to provide reliable data on mortality.

In 1987 a randomised controlled trial on screening for prostate cancer was started in Norrköping, Sweden. The study was started before prostate specific antigen testing was established as a method of screening so at the first two screening sessions only digital rectal examination was used. From 1993 this was combined with a prostate specific antigen test. The feasibility of a screening programme for prostate cancer has previously been reported.[5] We have also previously presented data on the reliability of digital rectal examination,[6] the cost effectiveness of screening for prostate cancer,[7 8] and the clinical consequences of screening.[9] Here we report on mortality 20 years after the start of study.

METHODS

The design of the study has been described elsewhere.[9] In 1987 all men aged 50-69 in Norrköping, Sweden, were identified in the National Population Register. The total study population was 9026 men. From this population, 1494 men were randomly allocated to be screened by including every sixth man from a list of dates of birth. The 7532 remaining men constituted the control group. All men in the study group were contacted by mail one week before each examination. Information regarding the study was also spread by

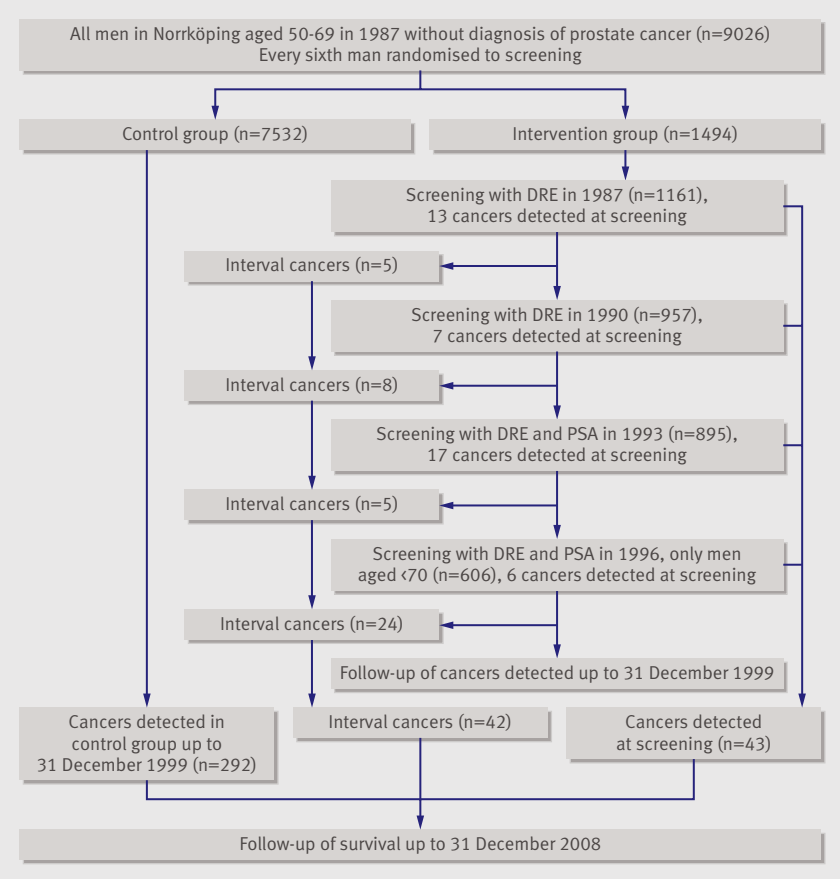

Fig 1 | Flow chart of study group enrolment. DRE=digital rectal examination, PSA=prostate specific antigen

local media. The sample size was calculated to allow us to assess the acceptance and feasibility of a prostate cancer screening programme.

At the first screening session in 1987 a specialist in urology and a general practitioner performed the digital rectal examinations. This double examination was done to determine the reliability of the examination between observers.[6] At subsequent sessions only general practitioners performed the examinations. At the third and fourth screening sessions, in 1993 and 1996, digital rectal examination was combined with a test for prostate specific antigen, with concentrations of >4 µg/L as the cut off. With the exception of men who had emigrated, the cohort allocated to screening remained the same for the first three sessions. In the fourth session, only men aged 69 or under at the time of the investigation were invited, which left a total of 606 men. All men, including those who did not participate in the fourth session, were included in the final analysis.

When the results of the digital rectal examination or prostate specific antigen test led to a suspicion of prostate cancer, the man underwent fine needle aspiration biopsy. The biopsy samples were taken from the peripheral zone of the apex, mid-prostatic region, and bases of both lateral lobes according to a sextant distribution. Directed biopsy samples were also taken in men in whom a nodule was palpated. If the biopsy result was negative, information was sent by mail. Men with positive cytology result were followed up by a urologist and treated according to the standardised management programme in the region. Investigations of men with prostate cancer included testing for prostate specific antigen, transrectal ultrasonography, and bone scan. Depending on the tumour stage and the general condition of the patient, men were offered radiotherapy or radical prostatectomy if it was considered possible to prolong survival.

The trial was made possible by the system of personal registration numbers,[10] each number being unique for each Swedish citizen, making it possible to trace all participants in the study in the population register, the South-East Region Prostate Cancer Register, and the Central Death Register.[11]

All cases of prostate cancer, whether detected in the screened or in the non-screened cohort, were registered in the South-East Region Prostate Cancer Register. This register is an extension of the National Cancer Register, which was founded in 1958 to enable continuous surveillance of the incidence of all oncological diseases. The personal registration numbers are used to link the South-East Region Prostate Cancer Register with the National Cancer Register. Whenever a new case of prostate cancer is registered in the South-East Region, the physician responsible for the patient submits a report according to a standardised protocol, including tumour stage according to the tumour, node, metastases (TNM) classification, tumour grade, and treatment, to the regional oncological centre for recording in the South-East Region Prostate Cancer Register.

Figure 1 shows the trial enrolment and study group assignment. Date of diagnosis, TNM categories, tumour grade, and treatment were registered in the South-East Region Prostate Cancer Register for all men with a diagnosis of prostate cancer in the screened and the non-screened cohort. All patients with cancer were treated according to a standardised management programme for prostate cancer common to the South East Region. Date and cause of death were also

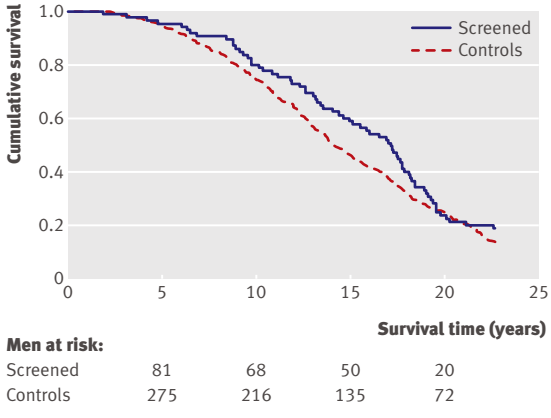

Fig 2 | Kaplan-Meier curves of overall survival for men diagnosed with prostate cancer in control group (n=292) and screened group (n=85). Log rank test P=0.14

Table 1 | Baseline data and mortality in men allocated to screening for prostate cancer or no screening (control group)

	No screening group	Screening group
No of men (excluding men with prostate cancer already diagnosed)	7532	1494
Age (years):		
50-54	1790	357
55-59	1809	360
60-64	2004	393
65-69	1929	384
No (%) of prostate cancers diagnosed, 1 January 1987 to 31 December 1999	292 (3.9)	85 (5.7)*
Mean (SD) age at diagnosis (years)	69.7 (5.7)	68.1 (5.6)†

*43 (2.9%) detected at screening; 42 (2.58%) interval cancers.
†66.5 (5.2) in men with cancer detected at screening; 69.9 (5.5) in men with interval cancers.

recorded in the register when applicable. The Central Death Register was checked for deaths not registered in the South-East Region Prostate Cancer Register. In September 2009 cause of death was registered in a blinded review of the patients' records for all men who died. All men in whom cancer was diagnosed up to 31 December 1999 were included in the analysis. Survival was followed until 31 December 2008.

Statistics

All analyses were performed based on intention to screen comparisons. We used Cox proportional hazard modelling to estimate hazard ratios for death from prostate cancer, with age and group allocation (screening/control) as covariates. To investigate whether the detection rate and subsequent mortality changed after the introduction of prostate specific antigen testing as a screening tool, we also tested a model with diagnosis before 1993 versus diagnosis after 1993 as a dichotomous time varying covariate. We used log rank to test differences in total and prostate cancer specific survival. The difference in deaths from prostate cancer between the two groups was tested by determining the risk ratio for prostate cancer specific death.

We also performed a subgroup analysis of men with a diagnosis in 1993 or later—that is, from the time that prostate specific antigen testing was introduced in the screening arm. All analyses were performed with SPSS 18.0.

The main outcome measure was the prostate cancer specific death risk ratio. The study was designed to detect a plausible reduction of prostate cancer specific mortality within 20 years from the start of the study from 1.5% to 1.0% in the screening group. A total of 1050 patients in the screening group would be required to detect this difference (80% power, two sided 5% significance level). To allow for non-compliance in the screening group and contamination in the control group, 1400 men were included in the screening group.

No interim analyses with mortality as end point were performed.

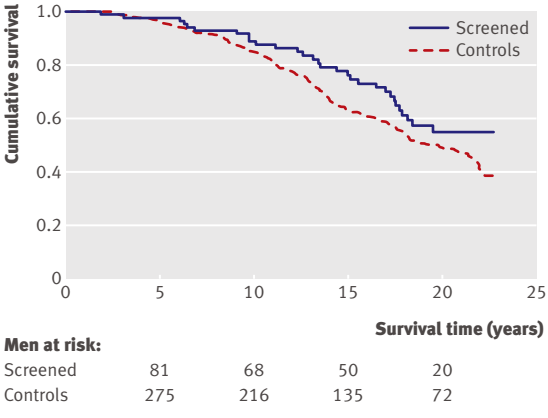

Fig 3 | Kaplan-Meier curves of prostate cancer specific survival for men diagnosed with prostate cancer in control group (n=292) and screened group (n=85). Log rank test P=0.065

RESULTS

In 1987, 1161 of 1492 (78%) invited men underwent screening. The numbers were 957/1363 (70%) in 1990 and 895/1210 (74%) in 1993. In 1996, men born before 1927 (n=512) were not invited to screening, leaving 606 men born 1927-37. Of these, 446 (74%) attended the screening. The median follow-up time was 75 months.

Eighty five cases (5.7%) of prostate cancer were diagnosed in the screened group and 292 (3.9%) in the control group (table 1). In the intervention group, 43 tumours were found at screening and 42 in the interval between examinations (table 2). The percentage of men with localised tumours (T1-2, N0/NX, M0) was significantly higher in the screened group (56.5%) than in the control group (26.7%, P<0.001). The rates of non-localised tumours were 37/1494 (2.5%) in the screening group and 213/7532 (2.8%) in the control group (P=0.44).

The prostate cancer specific mortality was 30/85 (35%) for men with prostate cancer diagnosed in the screening group and 130/292 (45%) for men with prostate cancer diagnosed in the control group. The overall mortality for men with prostate cancer was 69/85 (81%) in the screening group and 252/292 (86%) in the control group. The median cancer specific survival was 201 months in the screened group and 133 months in the control group. The risk ratio for death from prostate cancer was 1.16 (95% confidence interval 0.78 to 1.73).

The log rank test did not show a significantly longer prostate cancer survival (P=0.065) or overall survival (P=0.14) for men with prostate cancer diagnosed in the screening group (figs 2 and 3). Figure 4 shows the cumulative mortality. In a Cox proportional hazard analysis, the hazard ratio for death from prostate cancer was 1.23 (0.94 to 1.62; P=0.13) and 1.58 (1.06 to 2.36; P=0.024) after adjustment for age at start of the study. With the addition of the period of diagnosis as 1987-92 or 1993-9 as a dichotomous time dependent variable and adjustment for age at the start of the study, the hazard ratio was 1.59 (1.07 to 2.38; P=0.022). The period of diagnosis as a time dependent variable was not found to be a significant covariate in univariate analysis.

Table 2 | Distribution of tumour stage, tumour grade, and treatment in men with prostate cancer according to allocation to screening or no screening (control). Figures are numbers (percentages)

	No screening group	Screening group		
		All cancers	Cancers detected at screening	Interval cancers
Tumour stage:				
Localised tumours (T1-2, N0/NX, and M0)	78 (26.7)	48 (56.5)	36 (83.7)	12 (28.6)
Advanced tumours (T3-4, N1, or MX/M1)	213 (73.3)	37 (43.5)	7 (16.3)	30 (71.4)
Tumour grade:				
G1	94 (32.2)	43 (50.6)	24 (55.8)	19 (45.2)
G2	149 (51.0)	31 (36.5)	19 (44.2)	12 (28.6)
G3	43 (14.7)	11 (12.9)	0 (0)	11 (26.2)
GX/tumour grade not recorded	6 (2.1)	0 (0)	0 (0)	0 (0)
Treatment:				
Watchful waiting	101 (34.6)	37 (43.5)	21 (48.8)	16 (38.1)
Hormonal treatment	147 (50.3)	27 (31.8)	4 (9.3)	23 (54.8)
Radical prostatectomy	23 (7.9)	16 (18.8)	14 (32.6)	2 (4.8)
Brachytherapy	3 (1.0)	1 (1.2)	0 (0)	1 (2.4)
External radiotherapy	15 (5.1)	4 (4.7)	4 (9.3)	0 (0)
Not registered	3 (1.0)	0 (0)	0 (0)	0 (0)

DISCUSSION

In this randomised controlled trial, screening for prostate cancer did not seem to have a significant effect on mortality from prostate cancer after 20 years of follow-up. The relatively high cancer specific mortality seen in men with localised prostate cancer if they are followed up for long enough[12] makes not only the large sample size but also a sufficiently long follow-up time prerequisites for accurate interpretation of mortality data.

Strength of this study

The high compliance, uniform treatment, and complete data on tumour stage, tumour grade, and cause of death provided by the South-East Region Prostate Cancer Register and the Central Death Register all give strength to our findings. The personal registration number unique for each Swedish citizen[10] minimises the risk of dropouts and incomplete data because of change of address.

The completeness of the National Cancer Register has also been found to be high,[13] which supports the validity of the South-East Region Prostate Cancer Register. A validation of the South-East Region Prostate Cancer Register showed a high accuracy and completeness for all variables included.[14]

The extended prostate cancer registration, which covered the screened group as well as the control group, provided data on tumour stage, tumour grade, treatment, and mortality for both groups.[14] All men with a diagnosis of prostate cancer, whichever group they were allocated to, underwent the same standardised management programme. Uniform principles for registration, evaluation, and treatment decision minimise the risk of bias caused by local variations in management. All men in the screening group as well as in the control group were managed in the same urology unit. The incidence of prostate cancer was higher in the screening group, probably because of detection of a larger number of indolent tumours that do not reduce prostate cancer specific survival or overall survival.

Comparison with other studies

Opportunistic screening for prostate specific antigen is not practised as widely in Sweden as in the United States.[15-17] Until 1994, less than one test per man aged 50 or older was performed in Sweden.[18] The relatively low level of such testing in the background population reduced the chance of contamination as well as the prevalence of undetected indolent tumours in the screening group before the start of the study. The study started before testing was introduced in clinical practice,[18] which could have increased the lead time even more. Until 1987, prostate cancer was diagnosed almost exclusively at presentation with symptoms or incidentally at histopathological examination after transurethral prostate resection. The pre-screening prevalence of asymptomatic low grade tumours was therefore low.

Although screening with digital rectal examination and prostate specific antigen is an effective method for detecting early stages of prostate cancer, the high rate of overdiagnosis has to be considered before

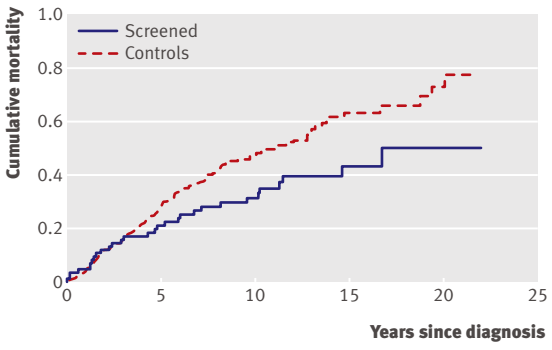

Fig 4 | Cumulative rates of prostate cancer specific mortality

WHAT IS ALREADY KNOWN ON THIS TOPIC

Previous studies have questioned the short term benefit of prostate cancer screening, but these lack long term follow-up

WHAT THIS STUDY ADDS

In a randomised controlled study on a population with little background opportunistic screening, complete registration of tumour stage, tumour grade, and treatment of both screening and control groups showed that the risk for overdetection and overtreatment in the screening group is considerable

widespread introduction of routine prostate cancer screening.[19] At the start of this trial, digital rectal examination and fine needle aspiration biopsy were used for tumour detection. Despite the fact that these methods have a lower sensitivity than prostate specific antigen testing and ultrasound guided biopsy, there was a significant shift towards detection of localised tumours in the intervention group.[9] The rate of diagnosis in the screened group, however, was lower than in the PLCO and ERSPC trials.[2-4]

Disease specific mortality is one of the most sensitive measures of the aggressiveness of a disease and the effectiveness of treatment. Determination of disease specific mortality, however, requires accurate determination of the underlying cause of death. In a review of the medical records of patients in the South-East Region Prostate Cancer Register, the validity of the death certificates that constitute the base for the cause of death was shown to be high.[20] This also supports the outcome of our study as we determined disease specific mortality from the South-East Region Prostate Cancer Register. Although the data in the ERSPC, as well as trials, have been carefully validated,[21] the criteria for defining death in prostate cancer are more vaguely defined.

The impact of screening on stage shift has been described in a previous report.[9] The tumours in the screening group were smaller and more often localised than in the control group. In contrast with the PLCO and ERSPC trials,[21] we had complete data on tumour stage for all men in the control group and the screened group. The screening had high acceptance in the population and a reasonable cost.[7 8] The actual cost of the tests, however, is only a part of the total cost of screening.[8 22] The total healthcare costs for prostate cancer treatment and other relevant costs in healthcare and in society should also be taken into consideration before the introduction of a widespread screening programme.

The population size in our study was smaller than the PLCO and ERSPC trials, but the longer follow-up, high attendance, and low rate of contamination caused the power to reach a similar level. The risk ratio for prostate cancer specific death in our study (1.16, 0.78 to 1.73) was close to that found in the PLCO trial (1.13, 0.75 to 1.70). The confidence interval of the risk ratio was narrow enough to conclude that screening and treatment of men with tumours detected through screening as practised in the present study is unlikely to reduce mortality from prostate cancer by more than a third. Though screening could lead to a reduction of up to a third in mortality from prostate cancer, this would be at the risk of overdetection and overtreatment.[9]

Although the outcomes are somewhat contradictory, the results of our study and the PLCO and ERSPC studies indicate that, whether or not there might be a benefit from prostate cancer screening, a high rate of overdiagnosis is unavoidable.[2-4] In the ERSPC trial, it was estimated that screening for prostate cancer could advance the diagnosis by 10 years. Half of the cancers detected by screen would not have been diagnosed in the absence of screening.[22 23] To prevent one death from cancer, 1410 men would need to be screened and 48 treated.[3]

Policy implications

Before undergoing prostate specific antigen testing, asymptomatic men should be informed about the potential hazards of treatment with curative intent in case prostate cancer is diagnosed. These include erectile dysfunction, urinary incontinence, and bowel symptoms. The discomfort associated with prostate biopsy and the psychological effects of false positive results should also be considered.[24] The next goal for prostate screening should rather be to find ways of discriminating indolent tumours from high risk tumours and to develop less aggressive treatment for indolent tumours[25] rather than to optimise sensitivity of the diagnostic tests.

Conclusions

The risk ratio for prostate cancer specific death did not indicate significant benefit from prostate cancer screening. Although the population size in our study is not sufficient to draw definite conclusions, the power is sufficient to show major differences in prostate cancer specific survival.

Contributors: GS drafted the manuscript, with contributions from all other coauthors. EV organised the screening programme with OL and PC. EV also conceived the study design. JR did all the analyses. GS is guarantor.
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Ethical approval: This study was approved by the institutional review board of Linköping, Sweden, 1992. Participants gave informed consent for data sharing.
Data sharing: Technical appendix, statistical code, dataset and the full study protocol are available from gabriel.sandblom@ki.se.

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