Mortality results from the Göteborg randomised population-based prostate-cancer screening trial

Jonas Hugosson, Sigrid Carlsson, Gunnar Aus, Svante Bergdahl, Ali Khatami, Pär Lodding, Carl-Gustaf Pihl, Johan Stranne, Erik Holmberg, Hans Lilja

Summary

Background **Prostate cancer is one of the leading causes of death from malignant disease among men in the developed world. One strategy to decrease the risk of death from this disease is screening with prostate-specific antigen (PSA); however, the extent of benefit and harm with such screening is under continuous debate.**

Methods **In December, 1994, 20 000 men born between 1930 and 1944, randomly sampled from the population register, were randomised by computer in a 1:1 ratio to either a screening group invited for PSA testing every 2 years (n=10 000) or to a control group not invited (n=10 000). Men in the screening group were invited up to the upper age limit (median 69, range 67–71 years) and only men with raised PSA concentrations were offered additional tests such as digital rectal examination and prostate biopsies. The primary endpoint was prostate-cancer specific mortality, analysed according to the intention-to-screen principle. The study is ongoing, with men who have not reached the upper age limit invited for PSA testing. This is the first planned report on cumulative prostate-cancer incidence and mortality calculated up to Dec 31, 2008. This study is registered as an International Standard Randomised Controlled Trial ISRCTN54449243.**

Findings **In each group, 48 men were excluded from the analysis because of death or emigration before the randomisation date, or prevalent prostate cancer. In men randomised to screening, 7578 (76%) of 9952 attended at least once. During a median follow-up of 14 years, 1138 men in the screening group and 718 in the control group were diagnosed with prostate cancer, resulting in a cumulative prostate-cancer incidence of 12·7% in the screening group and 8·2% in the control group (hazard ratio 1·64; 95% CI 1·50–1·80; p<0·0001). The absolute cumulative risk reduction of death from prostate cancer at 14 years was 0·40% (95% CI 0·17–0·64), from 0·90% in the control group to 0·50% in the screening group. The rate ratio for death from prostate cancer was 0·56 (95% CI 0·39–0·82; p=0·002) in the screening compared with the control group. The rate ratio of death from prostate cancer for attendees compared with the control group was 0·44 (95% CI 0·28–0·68; p=0·0002). Overall, 293 (95% CI 177–799) men needed to be invited for screening and 12 to be diagnosed to prevent one prostate cancer death.**

Interpretation **This study shows that prostate cancer mortality was reduced almost by half over 14 years. However, the risk of over-diagnosis is substantial and the number needed to treat is at least as high as in breast-cancer screening programmes. The benefit of prostate-cancer screening compares favourably to other cancer screening programs.**

Funding **The Swedish Cancer Society, the Swedish Research Council, and the National Cancer Institute.**

Lancet Oncol 2010; 11: 725–32

Published Online
July 1, 2010
DOI:10.1016/S1470-2045(10)70146-7

See Reflection and Reaction page 702

Department of Urology (Prof J Hugosson MD, S Carlsson MD, G Aus MD, S Bergdahl MD, A Khatami MD, P Lodding MD, J Stranne MD), **and Oncology** (E Holmberg PhD), **Institute of Clinical Sciences, Sahlgrenska Academy at University of Göteborg, Sweden**; **Department of Pathology, Institute of Biomedicine, Sahlgrenska Academy at University of Göteborg, Sweden** (C G Pihl MD); **Department of Laboratory Medicine, Lund University, University Hospital, Malmö, Sweden** (Prof H Lilja MD); **and Department of Clinical Laboratories, Urology, and Genitourinary Oncology** (H Lilja), **Memorial Sloan-Kettering Cancer Center, New York, NY, USA**

Correspondence to:
Prof Jonas Hugosson, Institute of Clinical Sciences, Department of Urology, Sahlgrenska University Hospital, Bruna stråket 11 B, 41345 Göteborg, Sweden
jonas@urol.se

Introduction

The European Randomised Study of Screening for Prostate Cancer (ERSPC) compared a group of men invited for prostate-cancer screening based on prostate-specific antigen (PSA) with a control group without any active intervention. Interim analyses, based on a median follow-up of 9 years,[1,2] showed that men randomised to active screening had a significant reduction in prostate-cancer mortality; rate ratio (RR) 0·80 (95% CI 0·65–0·98, adjusted p=0·04).[1] The number of men needed to be screened (NNS) to prevent one death from prostate cancer was 1410 (or 1068 in men who were actually screened[1]), which is similar to breast and colorectal cancer screening.[3–6] However, the number of men needed to treat (NNT) to prevent one death was high (48 men), which might be explained by only 9 years of follow-up or by screening that resulted in the detection of a large proportion of indolent cancers.

These reports provide the first level one evidence that PSA-based prostate-cancer screening can reduce prostate-cancer mortality. An open question, however, is whether the modest benefit in reduced cancer mortality documented thus far outweighs the harms of over-detection. This issue is emphasised by the report from another large screening trial, the US-based Prostate, Lung, Colorectal, and Ovarian Cancer (PLCO) screening trial, which found no difference in prostate-cancer mortality between men randomised to screening and those in the control group at 11·5 years of follow-up.[7] Other randomised studies have either been too small[8,9] or criticised for methodological problems.[10,11]

The Göteborg randomised population-based prostate-cancer screening trial is a prospective randomised trial, planned and started in 1995, assessing the effects of PSA-based screening every 2 years. The trial is truly population-based, as individuals from the population

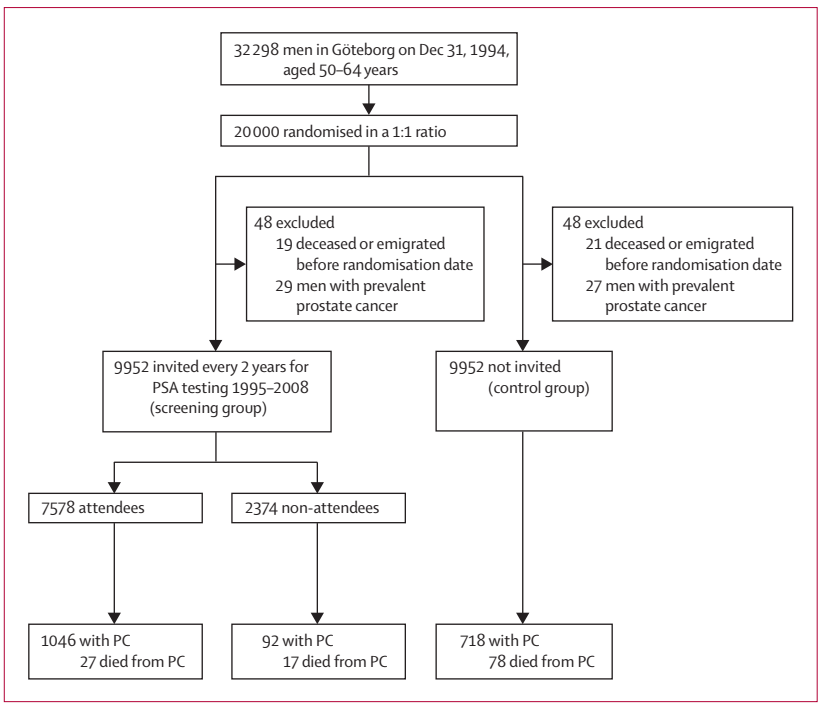

Figure 1: **Trial profile**
PSA=prostate-specific antigen. PC=prostate cancer.

register were randomised to screening or control groups without prior information, which results in a more representative study than randomisation after informed consent. The study design allows the analysis of both how a screening programme will be accepted by the population and its effectiveness in terms of prostate-cancer mortality reduction at a population level. The trial was designed and initiated independently from the ERSPC, although it was subsequently agreed to include a subset of participants in the ERSPC. According to the ethical committee approval from 1994, an analysis of this study was planned for after 15 years. The present report is the first publication from the Göteborg trial assessing prostate-cancer mortality.

Methods

Participants

As of Dec 31, 1994, the population register documented 32 298 men born between 1930 and 1944 (age 50–64, median 56 years) living in the city of Göteborg, Sweden. By computer randomisation 20 000 of these men were identified and allocated to either the intervention arm (screening group) or to a control group. The number of men in each birth cohort (1930–34, 1935–39, and 1940–44) was calculated to be proportional to the distribution in the original cohort. This resulted in larger birth cohorts from the 1940s than those from the early 1930s. The ethical review committee at the University of Göteborg approved this study in 1994.

Randomisation and masking

The randomisation procedure was done at the Department of Statistics at the University of Göteborg. 10-digit personal identifiers were the only available personal data for those doing the computer randomisation. No informed consent was needed from those in the control group. Masking of the group assignment was only done for the cause of death committee. However, possible discrepancies, caused by group assignments, were analysed for differences in the treatments given.

Procedures

Invitations to screening began in January, 1995, and in 1996 the study became associated with the ERSPC without any changes in the protocol. Results from the men born between 1930 and 1939 have been published within the previous ERSPC report.[1]

Men allocated to the screening group were invited for PSA testing every second year, until they reached the upper age limit;[12] the mean age at last invitation to screening was 69 years (67–71). The written invitation informed men about the study design, the complexity of PSA screening, and the voluntary nature of participation. Blood was processed within 3 h of venipuncture, frozen, and shipped frozen on dry ice for analyses within 2 weeks of the blood draw. Total PSA was measured using dual-label DELFIA Prostatus total/free PSA-assay (Perkin-Elmer, Turku, Finland). Calibration of this assay changed in 2004 to reflect the WHO 96/670 calibrator;[13,14] a correction factor was applied to the earlier measurements, and all figures given in this paper are in accordance with this calibration.

The PSA threshold needed to invite men to further urological work-up was 3·4 ng/mL (WHO corrected value; the nominal value was 3·0 ng/mL) between 1995 and 1998; in 1999 the threshold was changed to 2·9 ng/mL (nominal value 2·5 ng/mL) for consistency with other ERSPC sites. Due to the change of assay-calibrator, the threshold changed again to 2·5 ng/mL at the start of 2005.

Men with PSA below the threshold did not have further assessment, but were invited again after 2 years. Only men with PSA at or above the threshold were invited for further urological work-up, which included digital rectal examination (DRE), trans-rectal ultrasound (TRUS) examination, and laterally directed sextant biopsies. For men diagnosed with prostate cancer, the protocol did not specify any particular treatment; further evaluation and treatment was at the discretion of their physicians. Men with a benign finding at biopsy were invited for screening again after 2 years. Men with persistently raised PSA concentrations were recommended to have a new prostate biopsy at each visit at which PSA was raised. Seven screening rounds were completed by the end of 2008. Minor changes in the screening algorithm have been made during the study period.[15]

In both arms of the study, the incidence of prostate cancer was checked by linking with the West Swedish

Regional Cancer Registry every third month from the start of the study. In 2009, we linked with all six regional cancer registries in Sweden and obtained data for prostate cancers diagnosed from Jan 1, 1995, through to Dec 31, 2008. For every man with prostate cancer, all available medical documentation was retrieved to establish tumour stage, treatment, and disease course. Additionally, for all deceased men we obtained a copy of the cause of death (COD) certificate. Two cases of prostate cancer, not registered in the regional cancer registries, were detected from COD certificates. Linkage with the population register was done every third month to identify all men who died or emigrated. The last date of follow-up was the date of death, date of emigration, or Dec 31, 2008.

COD for men diagnosed with prostate cancer was determined by an independent COD committee. The committee did a blinded review of all cases diagnosed with prostate cancer, including all medical records, pathology reports, and autopsy protocols, according to a standard algorithm used in the ERSPC.[16] The COD certificates were not available to the COD committee. Deaths classified as definitive prostate-cancer deaths, intervention-related deaths (ie, deaths from diagnostic procedures or treatment), or probable prostate-cancer deaths were regarded as deaths caused by prostate cancer, whereas other classifications were regarded as non-prostate cancer deaths.

Statistical analysis

The main outcome measures were absolute and relative-risk reduction in cumulative prostate-cancer mortality between study arms. Secondary measures were the cumulative prostate-cancer incidence and the proportion of screening attendees. A pre-study power calculation (two-sided test; $p<0·05$ and 80% power) was done with the assumption of a 70% participation rate. A 40% mortality difference between the study arms was calculated to become significant 15 years after the study began (Dec 31, 2009). A new power calculation in 2009 incorporated the observed 76% participation rate in the Swedish branch of the published ERSPC results;[1] the new calculation suggested that the study has sufficient power to allow analyses to be done a year early.

Cumulative incidences of prostate cancer in the screening and control groups were plotted as 1 minus the Kaplan-Meier estimator. The corresponding hazard ratio (HR) for the incidence of prostate cancer between the groups was estimated by Cox regression and the proportional hazard assumption was tested with Schoenfeld residuals.[17] A time-dependent covariate approach was used to estimate the HR at different time periods after the start of screening to avoid violation of the proportional hazard assumption. The Nelson-Aalen method was used to calculate the cumulative hazard for prostate-cancer mortality.[18] Poisson-regression analysis was used to estimate the mortality-rate ratio in the screening group versus the control group. All p values were two-sided. NNS was calculated as 1 divided by absolute reduction in prostate-cancer mortality. As this study is an intention-to-screen analysis, we refer to NNS as the number needed to invite for screening. The NNT was calculated as 1 divided by (absolute reduction in prostate-cancer mortality multiplied by excess prostate-cancer incidence); we renamed this measure as number needed

	Screening visit							Total
	1st	2nd	3rd	4th	5th	6th	7th	
1st invitation round (1995–96)								
Number of men invited	..	..	..	..	..	..	..	9890
Number of men participating	5855	..	..	..	..	..	..	5855
Number of men with raised PSA	661	..	..	..	..	..	..	661
Number of men with PC	144	..	..	..	..	..	..	144
2nd invitation round (1997–99)								
Number of men invited	..	..	..	..	..	..	..	9525
Number of men participating	580	4680	..	..	..	..	..	5260
Number of men with raised PSA	66	543	..	..	..	..	..	609
Number of men with PC	15	98	..	..	..	..	..	113
3rd invitation round (1999–2000)*								
Number of men invited	..	..	..	..	..	..	..	6920
Number of men participating	460	632	2283	..	..	..	..	3375
Number of men with raised PSA	79	130	621	..	..	..	..	830
Number of men with PC	29	23	108	..	..	..	..	160
4th invitation round (2001–02)								
Number of men invited	..	..	..	..	..	..	..	7873
Number of men participating	291	549	2251	1531	..	..	..	4622
Number of men with raised PSA	49	63	125	497	..	..	..	734
Number of men with PC	13	13	19	87	..	..	..	132
5th invitation round (2003–04)								
Number of men invited	..	..	..	..	..	..	..	6598
Number of men participating	207	342	547	1880	1138	..	..	4114
Number of men with raised PSA	38	62	54	110	351	..	..	615
Number of men with PC	9	11	6	20	65	..	..	111
6th invitation round (2005–06)								
Number of men invited	..	..	..	..	..	..	..	5733
Number of men participating	117	188	296	468	1556	850	..	3475
Number of men with raised PSA	34	34	51	61	104	418	..	702
Number of men with PC	13	6	14	11	20	81		145
7th invitation round (2007–08)								
Number of men invited	..	..	..	..	..	..	..	4148
Number of men participating	68	94	145	241	374	1157	535	2614
Number of men with raised PSA	20	11	24	42	64	87	294	542
Number of men with PC	8	3	3	11	10	11	45	91
Total (1995–2008)								
Total number of invitations in the study	..	..	..	..	..	..	..	50 687
Number of men participating	7578	6334	3794	4393	3325	2452	1439	29 315†
Number of men with raised PSA	947	843	875	710	519	505	294	4693‡
Number of men with PC	231	154	150	129	95	92	45	896

PSA=prostate-specific antigen. PC=prostate cancer. *The low attendance rate in the third invitation round was because men with total PSA<1 ng/mL in the second invitation round were not invited (except those born 1930–31). †The total number of PSA tests done in the study. ‡The total number of PSA tests exceeding the PSA cutoff during the study.

***Table 1*: Number and outcome of participants in relation to screening visit**

	Control group (n=9952)	Screening group (n=9952)		
		All (n=9952)	Attendees (n=7578)	Non-attendees (n=2374)
Number of men with prostate cancers diagnosed (%)	718 (7·2%)	1138 (11·4%)	1046 (13·8%)	92 (3·9%)
Tumour grouping (%)				
Low risk*	199 (2%)	604 (6·1%)	590 (7·8%)	14 (0·6%)
Moderate risk†	249 (2·5%)	363 (3·6%)	339 (4·5%)	24 (1%)
High risk‡	126 (1·3%)	96 (1%)	76 (1%)	20 (0.8%)
Advanced disease§	87 (0·9%)	46 (0·5%)	25 (0·3%)	21 (0·9%)
Unknown¶	57 (0·6%)	29 (0·3%)	16 (0·2%)	13 (0·5%)

*T1, not N1 or M1, and Gleason score ≤6 and prostate-specific antigen <10 ng/mL.†T1–2, but not N1 or M1, with a Gleason score ≤7, prostate-specific antigen <20 ng/mL or both; and not meeting the criteria for low risk.‡T1–4, but not N1 or M1, with a Gleason score ≥8, prostate-specific antigen <100 ng/mL, or both; and not meeting the criteria for low or moderate risk.§N1 or M1, or prostate-specific antigen ≥100 ng/mL.¶Includes seven cases detected at autopsy.

Table 2: **Prostate cancers diagnosed in the study groups**

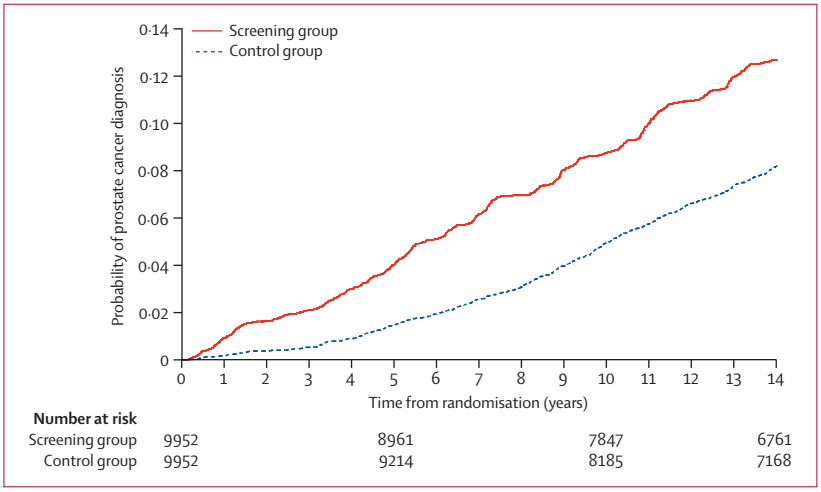

Figure 2: **Cumulative incidence of prostate cancer in the screening group and in the control group**

to diagnose, because many patients were not actually treated. The analyses were done using Stata, release 11. This study is registered with controlled-trials.com, number ISRCTN54449243.

Role of the funding source

The funding sources had no role in the study design and conduct, collection, management, analysis, and interpretation of the data, or writing of the report. The funding sources had no access to the database, which is kept at the Sahlgrenska University Hospital. All authors of this manuscript have had full access to the database. JH had the final responsibility to submit the paper for publication.

Results

The trial profile is shown in figure 1. Subsequent to randomisation, we excluded from analysis 56 men with a prior diagnosis of prostate cancer, 34 who had died, and six who had emigrated but had not been removed from the population register at the time of randomisation. Thus, the screening and control groups each consisted of 9952 evaluable men. In the screening group, 7578 (76%) of 9952 men participated in at least one screening round (attendees; table 1). These men received 29 315 PSA tests during the study period. In 2469 (33%) of 7578 attendees, PSA was raised above the threshold at least once and a total of 4693 elevated PSA tests were recorded during the study (table 1). In men with raised PSA, 2298 (93%) of 2469 had prostate biopsy at least once; 4153 biopsy procedures were done in the study. The maximum follow-up time of 14 years was reached by 15 501 (78%) of the randomised men.

Prostate cancer was diagnosed in 1138 (11·4%) men in the screening group and 718 (7·2%) in the control group (table 2). Of those men with detected prostate cancer in the screening group, 896 (78·7%) of 1138 were diagnosed as a result of an invitation to the study (table 1). Of these 896 men, 231 were detected at their first screening visit and 665 during subsequent screening rounds. At the first screening visit 3671 (48·4%) of 7578 had PSA below 1·00 ng/mL, 2960 (39·1%) of 7578 had a PSA between 1·00 and 2·99 ng/mL, and 947 (12·5%) of 7578 had a PSA of 3·00 ng/mL or greater; the risk of being diagnosed with prostate cancer during follow-up was 2·6%, 17·6%, and 45·5% respectively. The cumulative incidence of prostate cancer at 14 years was 12·7% in the screening group versus 8·2% in the control group (HR 1·64, 95% CI 1·50–1·80; p<0.0001; figure 2). During the first year, after the start of screening, the HR was 5·2 (95% CI 3·1–8·6), which subsequently decreased to 3·7 (95% CI 2·2–6·2) at 1–2 years, 2·6 (95% CI 1·9–3·6) at 2–4 years, 2·1 (95% CI 1·7–2·7) at 4–6 years, 1·7 (95% CI 1·3–2·1) at 6–8 years, and 1·2 (95% CI 1·0–1·3) at 8 years or more (figure 2).

Most of the prostate cancers diagnosed in the screening group were early-stage disease (table 2). The number of men with advanced prostate cancer (metastases or PSA >100 ng/mL at diagnosis) was lower in the screening group than in the control group (46 men *vs* 87; p=0·0003; table 2). Notably, in non-attendees in the screening group, a high proportion of cancers were advanced at diagnosis (table 2).

The difference in stage distribution was mirrored by the treatment difference, with more hormonal therapy used in the control group than in the screening group and more surveillance or treatment with curative intent in the screening group than in the control group (table 3). However, in men with low- and moderate-risk tumours, the proportion having curative treatment was similar between groups: 476 (49·2%) of 967 in the screening group and 228 (50·8%) of 448 in the control group. In the men diagnosed with prostate cancer, the median follow-up after diagnosis was 6·7 (IQR 3·1–9·5) years in the screening group and 4·3 (2·1–7·1) years in the control group. The COD committee and COD certificates were highly concordant in assessing whether the deaths

were caused by prostate cancer. According to the COD committee review, 78 men in the control group died from prostate cancer (77 according to death certificates) compared with 44 in the screening group (45 according to death certificates). Within the screening group, 27 (0·4%) of 7578 prostate-cancer-specific deaths were registered among attendees versus 17 (0·7%) of 2374 non-attendees (figure 1; table 4). Of the attendees who died from prostate cancer, 13 were diagnosed with prostate cancer at first screening (prevalence screen); the youngest of these men was 59 years of age at diagnosis. Attendees who were older than 60 years of age at study entry seemed to have a higher risk of dying from prostate cancer (19 prostate-cancer deaths in attendees in the screening group *vs* 35 prostate-cancer deaths in the control group) compared with men younger than 60 years of age at study entry (8 prostate cancer deaths in attendees in the screening group *vs* 43 prostate cancer deaths in the control group) (table 4).

The RR of dying from prostate cancer was 0·56 (95% CI 0·39–0·82; p=0·002) in the screening group compared with the control group (figure 3). The absolute cumulative-risk reduction (Kaplan-Meier estimates) of death from prostate cancer at 14 years was 0·40% (95% CI 0·17–0·64), from 0·90% in the control group to 0·50% in the screening group. A secondary analysis showed that the RR of death from prostate cancer for attendees compared with the control group was 0·44 (95% CI 0·28–0·68; p=0·0002) and the RR of death from prostate cancer for non-attendees compared with the control group was 1·05 (95% CI 0·62–1·78 p=0·84). The number of men with prostate cancer who died from unrelated causes was 109 (9·6%) of 1138 in the screening group and 54 (7·5%) of 718 in the control group. However, the follow-up time was longer for the men diagnosed with prostate cancer in the screening group than the control group (6·7 *vs* 4·3 years). Therefore, the cumulative risk (Kaplan-Meier estimates) of non-prostate cancer deaths measured from the date of prostate-cancer diagnosis was similar at 10 years, 13·1% in the screening group and 15·0% in the control group (log-rank test p=0·50).

The NNS to prevent one prostate-cancer death was 293 (95% CI 177–799), whereas the NNT was 12. If the calculations were restricted to attendees, the respective numbers were 234 (95% CI 154–492) and 15.

Discussion

The aim of this prospective, population-based randomised screening study was to assess the effectiveness of a screening programme in which men were first randomised and then asked to participate. The design gives more representative results than does randomisation after informed consent, and mirrors the situation when screening is introduced in the population. The study yielded two major findings. First, a PSA-based screening programme is acceptable to men aged 50 years or older, with 76% attending at least once. Second, with such a participation rate, a screening programme will decrease prostate-cancer mortality by as much as half over 14 years' follow-up.

Half of the attendees who died from prostate cancer were diagnosed at their first screening visit and many of these men were 60 years of age or older at study entry. In a programme in which all men started screening at 50 years of age, some men could instead be diagnosed at a curable stage; therefore, potential for larger mortality reduction exists (table 4).[12]

	Control group (n=718)	Screening group (n=1138)		
		All (n=1138)	Attendees (n=1046)	Non-attendees (n=92)
Primary radical prostatectomy*	241 (33·6%)	468 (41·1%)	439 (42·0%)	29 (31·5%)
Primary radiation	75 (10·4%)	93 (8·2%)	81 (7·7%)	12 (13·0%)
Primary endocrine treatment	162 (22·6%)	80 (7·0%)	47 (4·5%)	33 (35·9%)
Primary surveillance followed by curative treatment†	36 (5·0%)	142 (12·5%)	141 (13·5%)	1 (1·1%)
Primary surveillance followed by endocrine treatment	20 (2·8%)	23 (2·0%)	21 (2·0%)	2 (2·2%)
Surveillance at last follow-up	152 (21·2%)	314 (27·6%)	301 (28·8%)	13 (14·1%)
Not treated‡	32 (4·5%)	18 (1·6%)	16 (1·5%)	2 (2·2%)

Data are n (%). *Includes nine cryosurgeries and six cystoprostatectomies. †Includes two cystoprostatectomies. ‡Includes seven cases detected at autopsy.

Table 3: **Treatments for prostate cancer, by study group**

	Total	Control group	Screening group		
			All	Attendees	Non-attendees
1930–34					
Total number	5563	2789	2774	2064	710
Number with PC	615	259	356	318	38
Number of deaths	1689	853	836	488	348
Number of PC deaths	62	35	27	19	8
1935–39					
Total number	6284	3161	3123	2420	703
Number with PC	654	252	402	372	30
Number of deaths	1284	650	634	360	274
Number of PC deaths	47	35	12	6	6
1940–44					
Total number	8057	4002	4055	3094	961
Number with PC	587	207	380	356	24
Number of deaths	990	479	511	267	244
Number of PC deaths	13	8	5	2	3
Total					
Total number	19 904	9952	9952	7578	2374
Number with PC	1856	718	1138	1046	92
Number of deaths	3963	1982	1981	1115	866
Number of PC deaths	122	78	44	27	17

PC=prostate cancer.

Table 4: **Outcome of men in relation to birth cohort at entry to the study**

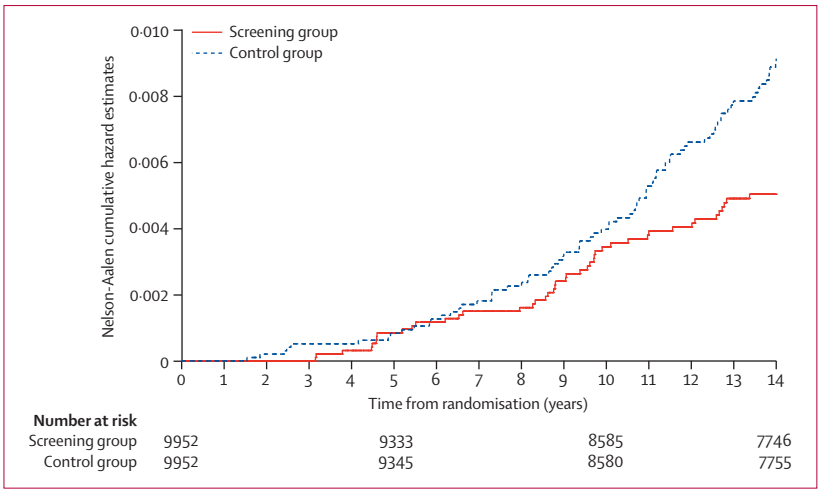

Figure 3: **Cumulative risk of death from prostate cancer using Nelson-Aalen cumulative hazard estimates**

This study shows a much higher mortality reduction than in previous studies: an RR of 0·56 in this study compared with 0·80 in the ERSPC (0·84 if the Swedish cohort is withdrawn),[1] and no reduction in the PLCO study.[7] Several factors might account for this. First, the men in our study were younger (median age 56 years at baseline) than in both previous publications (median age >60 years). Younger men are less likely than older men to have incurable prostate cancer at the first screening and are therefore more likely to gain the full benefit of screening. Second, the PSA threshold for biopsy was lower in our study than in most other ERSPC branches and in the PLCO trial. However, DRE was never used as a screening tool in our study, but was used by most ERSPC centres at the first screening round and in the design of PLCO trial. Addition of DRE in our study might have resulted in an even larger mortality reduction than seen in our study, although only a few incurable cancers were found in men who attended the programme, and some of these incurable cancers were still non-palpable at diagnosis.[12] Third, the interval of screening in this study (every 2 years) was shorter than in the other ERSPC branches (every 4 years), although longer than in the PLCO trial (every year). Fourth, this study had a much higher rate of biopsy for men with a positive screening result (93% *vs* 30–40% in PLCO[19]), a much lower rate of PSA testing before the start of the study (estimated as 3% *vs* 44% in PLCO), and probably a lower rate of contamination in the control group than in the PLCO trial. Fifth, the present study has much longer follow-up than do the ERSPC and PLCO studies (median 14 years from randomisation *vs* 9 years for ERSPC,[1] and 11·5 years for PLCO[7]).

Up to 10 years of follow-up, the Nelson-Aalen plot in our study resembles that which was published in the ERSPC study, suggesting that most of the benefit from screening occurs after 10 years (figure 3). This is to be expected from a disease with long a lead-time and a long natural course.[20,21]

Although the median follow-up from randomisation is long, the follow-up time measured from prostate-cancer diagnosis is rather short; 6·7 years for attendees versus 4·3 years for controls in this study compared with 6·3 versus 5·2 years in the PLCO study.[7]

The reasons as to why our study shows an important mortality reduction and the PLCO trial did not, despite a similar follow-up after diagnosis in the two studies, might in part be explained by the absence of pre-screening in our study, which meant many aggressive cancers were still detectable. Furthermore, contamination in the control group was low—at least during the first 5 years of our study. An indication of these important differences is that despite the randomisation of 76 693 men in the PLCO trial versus 19 904 in our study, only 174 prostate-cancer deaths were recorded in the PLCO trial[7] compared with 122 in our study. The men in the PLCO trial were also older.

The RR of 0·56 within 14 years corresponds to an absolute risk reduction of 0·40% and no effect on overall mortality (similar number of men at risk at 14 years, [figure 3] and similar number of total deaths in the study group [table 4]). These low mortality figures are related to the young age of participants at the start of the study and the comparatively short follow-up after prostate-cancer diagnosis. Because about 5% of deaths among Swedish men are caused by prostate cancer,[22] it is obvious that we have so far studied only the early effects of screening. If the relative-risk reduction is sustained over time the mortality reduction, even measured in terms of absolute-risk reduction, might become important. An indication of this is the large difference between the arms in the number of men needing endocrine treatment—182 (1·8%) in the control group versus 103 (1·0%) in the screening group. The fact that 79 more men in the control group were treated with endocrine treatment than in the screening group might also be regarded as an important advantage. The increased ratio of unrelated deaths reported in the screening group compared with the control group (9·6% *vs* 7·5%) is explained by the longer follow-up of patients with prostate cancer in the screening group than in the control group, because there is no difference in non-prostate-cancer mortality if Kaplan-Meier estimates are calculated from diagnosis.

The high rate of attendance to this PSA-based screening programme is corroborated by findings from several uncontrolled trials. Bartsch and co-workers[23] reported that 86·6% of men accepted an offer of a free PSA test and that 85·0% of those with raised PSA concentrations consented to additional urological assessment with prostate biopsies.[23] Moreover, all centres in the ERSPC study reported a high acceptance rate for screening.[1] The screening procedures with PSA testing and prostate biopsy are seldom associated with severe psychological distress, even for men with repeatedly raised PSA concentrations.[24,25] We therefore conclude that acceptance is not an obstacle for a population-based prostate-cancer-screening programme.

Differences between screening and control groups in cancer stage and grade show the cancer stage migration introduced by a PSA-based screening programme. Although 1·6 times as many prostate cancers were diagnosed in the screening group, the absolute number of patients with advanced disease was lower in the screening group than in the control group. Therefore, screening caused a true stage migration and resulted in a different distribution of treatments between the two groups. However, in men with early cancer (low- and moderate-risk cancer), treatment with curative intent was as common in the control and screening groups (51% *vs* 49%), suggesting that the mortality difference resulted from screening and not from different treatments.

At 14 years of follow-up, the number who needed to be invited to screening (corresponding to NNS) to prevent one prostate cancer death was 293, and the number who needed to be diagnosed (corresponding to NNT) was 12. These figures, and the RR of 0·56 in our study, can be compared with those of the commonly recommended practices of screening for breast and colon cancer. Because these figures are time-dependent, we focus this comparison on studies with similar follow-up periods. For mammography, a 2009 meta-analysis of randomised trials showed a number needed to invite to screening of 377 (credible interval 230–1050) for women aged 60–69 years and 1339 (credible interval 322–7455) for women aged 50–59 years, and RRs of 0·68 and 0·86 respectively at 11–20 years of follow-up.[5] Individual studies included in the meta-analysis, as well as other mammography studies, have shown similar numbers.[3,26–33] In a 2009 Cochrane review, the NNT for mammography was 10 over 10 years.[3] For colorectal-cancer screening by faecal occult-blood test, the RRs varied between 0·67 and 0·87 in four randomised trials[34–37] and was 0·84 overall in both a 2008 Cochrane review[4] (after 11·7–18·4 years) and a meta-analysis by Towler and colleagues[6] (after 7·8–13·0 years). Towler and colleagues[6] estimated the NNS after 10 years to be 1173 (95% CI 741–2807). Moreover, a multicentre study has reported an RR of 0·69 for colorectal-cancer mortality, with flexible-sigmoidoscopy screening for colorectal cancer, and an NNS of 489 at a median follow-up of 11·2 years.[38] The NNT cannot be calculated for comparison because screening for colorectal cancer is associated with a reduced colorectal-cancer incidence.

The NNT in our study is substantially lower than that in the ERSPC study,[1] which suggests that the NNT is very dependent on the length of follow-up. It is not easy to predict at which follow-up period the NNT will stabilise. Furthermore, since NNT in prostate-cancer screening mainly reflects the risk of over-diagnosis, it is not easy at this point to make estimates of this risk but it is probably not as high as some have feared,[39] at least if screening is restricted to the age groups included in this study. As many as 314 (30%) screening attendees were in active surveillance at last follow-up in this study. The strategy of active surveillance will at least reduce the risk of over-treatment and the risk associated seems low.[40]

Since the benefit from prostate-cancer screening takes a long time to achieve—only marginal benefits are gained within the first 10 years of starting prostate-cancer screening—one should be cautious to recommend that all elderly men have PSA screening. As the risk of over-diagnosis and over-treatment are still the major concerns in prostate-cancer screening, inviting men over the age of 70 for PSA screening seems questionable.

In summary, in this trial prostate-cancer screening was well accepted by the general population and can result in a relevant reduction in cancer mortality, greater than that reported in screening for breast or colorectal cancer. Nevertheless, PSA screening is associated with a long and varying lead time, resulting in a risk of over-diagnosis that is substantial but still of a largely unknown magnitude.

Contributors

JH 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. JH is the principal investigator of the study and was responsible for planning of the study. HL participated in the conception and design of the study and contributed with supervision and administrative support. JH and HL were responsible for funding. JH, AK, PL, JS, SB, and C-GP collected data. JH, GA, SC, AK, PL, JS, and SB did the biopsy procedures. C-GP did the pathological examination of all specimens in the study. EH, JH, SC, HL, and GA analysed the data (extraction of results and the statistical analysis). JH, JS, SC, HL, and GA interpreted the data. SC performed the literature search. JH, SC, GA, HL, JS wrote, JH, SC, GA, HL, PL, AK, SB revised, and EH and C-GP reviewed the paper.

Conflict of interest

HL holds patents for free PSA and hK2 assays, and has received honoraria from GlaxoSmithKline. JH has received lecture fees from GlaxoSmithKline and Abbott Pharmaceuticals. All other authors declared no conflicts of interest.

Acknowledgments

This study was supported by the Swedish Cancer Society (Contract numbers 09 0107, 080315, and 083455), the Swedish Research Council (Medicine) (20095) and the National Cancer Institute grant number (R21-CA127768-01A1). Grants were also received from the Stichting af Jochnick Foundation, Catarina and Sven Hagstroms family foundation, Gunvor and Ivan Svensson's foundation, Johanniterorden, King Gustav V Jubilée Clinic Cancer Research Foundation, Sahlgrenska University Hospital, Abbott Pharmaceuticals (Sweden), and Schering Plough (Sweden). We also acknowledge the Sidney Kimmel Centre for Prostate and Urologic Cancers, David H Koch through the Prostate Cancer Foundation, and Fundación Federico SA for their funding support. We thank the COD committee (Bo Johan Norlén, Silas Pettersson, and Eberhard Varenhorst); Helén Ahlgren; Maria Nyberg; Charlotte Becker, Gun-Britt Eriksson, Kerstin Håkansson, and Mona Hassan Al-Battat for expert assistance with immunoassays; Björn Zackrisson, Erik Pileblad, Rebecka Godtman, and Anna Grenabo Bergdahl for various aspects in this screening project and especially for helping with all biopsies performed; Janet Novak for her assistance with editing the manuscript, which was paid for by Memorial Sloan-Kettering Cancer Center; and Andrew Vickers for valuable criticism and suggestions.

References

1 Schroder FH, Hugosson J, Roobol MJ, et al. Screening and prostate-cancer mortality in a randomized European study. *N Engl J Med* 2009; **360:** 1320–28.

2 Roobol MJ, Kerkhof M, Schroder FH, et al. Prostate cancer mortality reduction by prostate-specific antigen-based screening adjusted for nonattendance and contamination in the European Randomised Study of Screening for Prostate Cancer (ERSPC). *Eur Urol* 2009; **56:** 584–91.

3 Gotzsche PC, Nielsen M. Screening for breast cancer with mammography. *Cochrane Database Syst Rev* 2009; **4:** CD001877.

4 Hewitson P, Glasziou P, Watson E, Towler B, Irwig L. Cochrane systematic review of colorectal cancer screening using the fecal occult blood test (hemoccult): an update. *Am J Gastroenterol* 2008; **103:** 1541–49.

5 Nelson HD, Tyne K, Naik A, , et al. Screening for breast cancer: an update for the U.S. Preventive Services Task Force. *Ann Intern Med* 2009; **151:** 727–37.

6 Towler B, Irwig L, Glasziou P, Kewenter J, Weller D, Silagy C. A systematic review of the effects of screening for colorectal cancer using the faecal occult blood test, hemoccult. *BMJ* 1998; **317:** 559–65.

7 Andriole GL, Grubb RL, 3rd, Buys SS, Chia D, Church TR, Fouad MN, et al. Mortality results from a randomized prostate-cancer screening trial. *N Engl J Med* 2009; **360:** 1310–19.

8 Sandblom G, Varenhorst E, Lofman O, Rosell J, Carlsson P. Clinical consequences of screening for prostate cancer: 15 years follow-up of a randomised controlled trial in Sweden. *Eur Urol* 2004; **46:** 717–23.

9 Kjellman A, Akre O, Norming U, Tornblom M, Gustafsson O. 15-year followup of a population based prostate cancer screening study. *J Urol* 2009; **181:** 1615–21.

10 Labrie F, Candas B, Cusan L, et al. Screening decreases prostate cancer mortality: 11-year follow-up of the 1988 Quebec prospective randomized controlled trial. *Prostate* 2004; **59:** 311–18.

11 Ilic D, O'Connor D, Green S, Wilt TA. Screening for prostate cancer: A Cochrane systematic review. *Cancer Causes Control* 2007; **18:** 279–85.

12 Bergdahl AG, Aus G, Lilja H, Hugosson J. Risk of dying from prostate cancer in men randomized to screening: differences between attendees and nonattendees. *Cancer* 2009; **115:** 5672–79.

13 World Health Organization. WHO Expert Committee on Biological Standardization. Forty-eighth report. WHO technical report series, no. 889. Geneva, Switzerland: World Health Organization, 1999.

14 Rafferty B, Rigsby P, Rose M, Stamey T, Gaines Das R. Reference reagents for prostate-specific antigen (PSA): establishment of the First International Standards for free PSA and PSA (90:10). *Clin Chem* 2000; **46:** 1310–17.

15 ERSPC website. http://media.erspc-media.org/sweden/ (accessed May 5, 2010).

16 De Koning HJ, Blom J, Merkelbach JW, et al. Determining the cause of death in randomized screening trial(s) for prostate cancer. *BJU Int* 2003; **92** (suppl 2): 71–78.

17 Grambsch P, Therneau T. Proportional hazards tests and diagnostics based on weighted residuals. *Biometrika* 1994; **81:** 515–26.

18 Aalen O. Nonparametric inference for a family of counting processes. *Ann Stat* 1978; **6:** 701–26.

19 Grubb RL, 3rd, Pinsky PF, Greenlee RT, et al. Prostate cancer screening in the Prostate, Lung, Colorectal and Ovarian cancer screening trial: update on findings from the initial four rounds of screening in a randomized trial. *BJU Int* 2008; **102:** 1524–30.

20 Tornblom M, Eriksson H, Franzen S, et al. Lead time associated with screening for prostate cancer. *Int J Cancer* 2004; **108:** 122–29.

21 Albertsen PC, Hanley JA, Fine J. 20-year outcomes following conservative management of clinically localized prostate cancer. *JAMA* 2005; **293:** 2095–101.

22 The National Board of Health and Welfare, 2009. Official Statistics of Sweden. Causes of death 2007. http://www.socialstyrelsen.se/publikationer2009/dodsorsaker2007 (accessed June 25, 2010).

23 Bartsch G, Horninger W, Klocker H, et al. Tyrol prostate cancer demonstration project: early detection, treatment, outcome, incidence and mortality. *BJU Int* 2008; **101:** 809–16.

24 Brindle LA, Oliver SE, Dedman D, et al. Measuring the psychosocial impact of population-based prostate-specific antigen testing for prostate cancer in the UK. *BJU Int* 2006; **98:** 777–82.

25 Carlsson S, Aus G, Wessman C, Hugosson J. Anxiety associated with prostate cancer screening with special reference to men with a positive screening test (elevated PSA) - results from a prospective, population-based, randomised study. *Eur J Cancer* 2007; **43:** 2109–16.

26 Miller AB, To T, Baines CJ, Wall C. The Canadian National Breast Screening Study-1: breast cancer mortality after 11 to 16 years of follow-up. A randomized screening trial of mammography in women age 40 to 49 years. *Ann Intern Med* 2002; **137:** 305–12.

27 Miller AB, To T, Baines CJ, Wall C. Canadian National Breast Screening Study-2: 13-year results of a randomized trial in women aged 50-59 years. *J Natl Cancer Inst* 2000; **92:** 1490–99.

28 Nystrom L, Andersson I, Bjurstam N, Frisell J, Nordenskjold B, Rutqvist LE. Long-term effects of mammography screening: updated overview of the Swedish randomised trials. *Lancet* 2002; **359:** 909–19.

29 Moss SM, Cuckle H, Evans A, et al. Effect of mammographic screening from age 40 years on breast cancer mortality at 10 years' follow-up: a randomised controlled trial. *Lancet* 2006; **368:** 2053–60.

30 Tabar L, Fagerberg G, Chen HH, et al. Efficacy of breast cancer screening by age. New results from the Swedish Two-County Trial. *Cancer* 1995; **75:** 2507–17.

31 Shapiro S, Venet W, Strax P, Venet L, Roeser R. Ten- to fourteen-year effect of screening on breast cancer mortality. *J Natl Cancer Inst* 1982; **69:** 349–55.

32 Frisell J, Lidbrink E, Hellstrom L, Rutqvist LE. Followup after 11 years--update of mortality results in the Stockholm mammographic screening trial. *Breast Cancer Res Treat* 1997; **45:** 263–70.

33 Bjurstam N, Bjorneld L, Warwick J, et al. The Gothenburg Breast Screening Trial. *Cancer* 2003; **97:** 2387–96.

34 Kronborg O, Jorgensen OD, Fenger C, Rasmussen M. Randomized study of biennial screening with a faecal occult blood test: results after nine screening rounds. *Scand J Gastroenterol* 2004; **39:** 846–51.

35 Lindholm E, Brevinge H, Haglind E. Survival benefit in a randomized clinical trial of faecal occult blood screening for colorectal cancer. *Br J Surg* 2008; **95:** 1029–36.

36 Mandel JS, Church TR, Ederer F, Bond JH. Colorectal cancer mortality: effectiveness of biennial screening for fecal occult blood. *J Natl Cancer Inst* 1999; **91:** 434–37.

37 Scholefield JH, Moss S, Sufi F, Mangham CM, Hardcastle JD. Effect of faecal occult blood screening on mortality from colorectal cancer: results from a randomised controlled trial. *Gut* 2002; **50:** 840–44.

38 Atkin WS, Edwards R, Kralj-Hans I, et al. Once-only flexible sigmoidoscopy screening in prevention of colorectal cancer: a multicentre randomised controlled trial. *Lancet* 2010; **375:** 1624–33.

39 Albertsen PC. The unintended burden of increased prostate cancer detection associated with prostate cancer screening and diagnosis. *Urology* 2009; **75:** 399–405.

40 Khatami A, Aus G, Damber JE, Lilja H, Lodding P, Hugosson J. PSA doubling time predicts the outcome after active surveillance in screening-detected prostate cancer: results from the European randomized study of screening for prostate cancer, Sweden section. *Int J Cancer* 2007; **120:** 170–74.