



Screening and prostate cancer mortality: results of the European Randomised Study of Screening for Prostate Cancer (ERSPC) at 13 years of follow-up

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Summary

Background The European Randomised study of Screening for Prostate Cancer (ERSPC) has shown significant reductions in prostate cancer mortality after 9 years and 11 years of follow-up, but screening is controversial because of adverse events such as overdiagnosis. We provide updated results of mortality from prostate cancer with follow-up to 2010, with analyses truncated at 9, 11, and 13 years.

Methods ERSPC is a multicentre, randomised trial with a predefined centralised database, analysis plan, and core age group (55–69 years), which assesses prostate-specific antigen (PSA) testing in eight European countries. Eligible men aged 50–74 years were identified from population registries and randomly assigned by computer generated random numbers to screening or no intervention (control). Investigators were masked to group allocation. The primary outcome was prostate cancer mortality in the core age group. Analysis was by intention to treat. We did a secondary analysis that corrected for selection bias due to non-participation. Only incidence and no mortality data at 9 years' follow-up are reported for the French centres. This study is registered with Current Controlled Trials, number ISRCTN49127736.

Findings With data truncated at 13 years of follow-up, 7408 prostate cancer cases were diagnosed in the intervention group and 6107 cases in the control group. The rate ratio of prostate cancer incidence between the intervention and control groups was 1.91 (95% CI 1.83–1.99) after 9 years (1.64 [1.58–1.69] including France), 1.66 (1.60–1.73) after 11 years, and 1.57 (1.51–1.62) after 13 years. The rate ratio of prostate cancer mortality was 0.85 (0.70–1.03) after 9 years, 0.78 (0.66–0.91) after 11 years, and 0.79 (0.69–0.91) at 13 years. The absolute risk reduction of death from prostate cancer at 13 years was 0.11 per 1000 person-years or 1.28 per 1000 men randomised, which is equivalent to one prostate cancer death averted per 781 (95% CI 490–1929) men invited for screening or one per 27 (17–66) additional prostate cancer detected. After adjustment for non-participation, the rate ratio of prostate cancer mortality in men screened was 0.73 (95% CI 0.61–0.88).

Interpretation In this update the ERSPC confirms a substantial reduction in prostate cancer mortality attributable to testing of PSA, with a substantially increased absolute effect at 13 years compared with findings after 9 and 11 years. Despite our findings, further quantification of harms and their reduction are still considered a prerequisite for the introduction of population-based screening.

Funding Each centre had its own funding responsibility.

Introduction

The European Randomised study of Screening for Prostate Cancer (ERSPC) has shown significant reductions in prostate cancer mortality after 9 years¹ and 11 years of follow-up.² Despite these results, screening for prostate cancer is controversial because of adverse effects such as overdiagnosis, which is estimated to include 40–50% of screen-detected cases and often results in overtreatment with subsequent side-effects.^{3–5} However, a modelling study, partly based on ERSPC data, showed that with a 4-year screening interval a gain of 52 life-years and a gain of 41 quality-of-life-adjusted life-years (QALYs) was achieved per 1000 men, despite some reduction in quality of life

due to overdiagnosis and long-term side-effects of treatment.⁵

We report updated results of mortality from prostate cancer with follow-up to 2010, with analyses truncated at 9 years, 11 years, and 13 years of follow-up. For the first time, we include France in the analysis of incidence of prostate cancer at 9 years of follow-up, but not in the analysis of mortality because of incomplete follow-up to the end of 2010.

Methods

Study design and participants

The ERSPC is a multicentre, randomised, screening trial with the main aim to compare mortality from prostate

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cancer in an intervention group invited to screening with a control group with no intervention offered. The trial was initiated in 1993 in the Netherlands and in Belgium.^{6,7} Five other centres (in Sweden, Finland, Italy, Spain, and Switzerland) joined the study between 1994 and 1998. Two French centres started in 2000 and 2003.

Eligible participants were men aged 50–74 years at the time of randomisation. Only men who were randomised, but had a death date before randomisation were excluded. Recruitment was completed by the end of 2003, except in France with recruitment up to 2005. The screening interval of 4 years (2 years in Sweden) was chosen on the basis of lead time estimated to be more than 8 years at the time of trial initiation.^{8,9} Measurement of prostate-specific antigen (PSA) in serum, with a cutoff of 3·0 ng/mL or more, was the main screening test and indication for biopsy (an ancillary test was used for men with PSA 3·0–3·9 ng/mL in Finland and Italy). Sextant biopsies were initially recommended for screen-positive men, in line with practice recommendations during the initiation of ERSPC. Screening was discontinued after three screening rounds in Belgium, Finland, and Spain, and after two rounds in France, but continued up to five rounds in the Netherlands and ten in Sweden. During 1994 and 1995, performance criteria were established as indicators of successful conduct of the trial. These criteria included a pilot study, randomisation with concealed allocation, adherence to the common trial protocol,

participation in quality control assessments, and continuous conduct of the study (recruitment, screening, and data collection).¹⁰ An independent quality control committee was in charge of the supervision of compliance with the performance criteria. Full access to the ERSPC data, including disease-specific mortality outcome, was provided by the protocol after the first endpoint publication.¹ Because of different legal regulations in four countries (Belgium, The Netherlands, Spain, and Switzerland) upfront written informed consent was used. In the remaining countries, Finland, Sweden, Italy, and France, randomisation preceded with informed consent, which was only applied to men to be offered screening. Ethical approval was obtained by each of the individual participating countries as reported previously.^{1,2}

Randomisation and masking

The ERSPC trial protocol has been published previously.^{1,2,10,11} In short, eligible participants were identified from population registers and randomisation was done individually based on computer-generated random numbers (with 1:1 allocation, except in Finland where an intervention to control ratio of roughly 1:1·5 was used). Because of different legal regulations, randomisation after informed consent was used in some and randomisation before consent in other countries.^{10,11} Allocation of participants to the trial groups was masked to the investigators.

Outcomes

The primary endpoint of the study was prostate cancer mortality.¹² Overall mortality was assessed mainly to ensure comparability between trial groups, because no reduction in overall mortality was anticipated from the intervention (in view of the small proportion of all deaths caused by prostate cancer). Data for overall mortality were obtained by linkage to national registries. Deaths from prostate cancer were ascertained by local independent causes of death committees who assessed all deaths in men diagnosed with prostate cancer or those who had prostate cancer as a cause of death on the death certificate, masked to trial group, and following the same algorithm in all centres.¹³ If consensus was not reached, the international causes of death committee was consulted. Of assessed deaths, those classified as definitely prostate cancer and probably prostate cancer and intervention related deaths were used as the outcome events in the analysis. Death certificates were used in Finland after a very high concordance with committee assignments was shown ($\kappa > 0\cdot9$).¹⁴ Analyses were truncated at 9 and 11 years; screening effect is also reported in men actually screened, with adjustment for selection bias.

Safety assessments were done by the independent Data Monitoring Committee. Stopping rules were an excess of overall or prostate cancer mortality in the intervention group compared with the control group.¹⁵

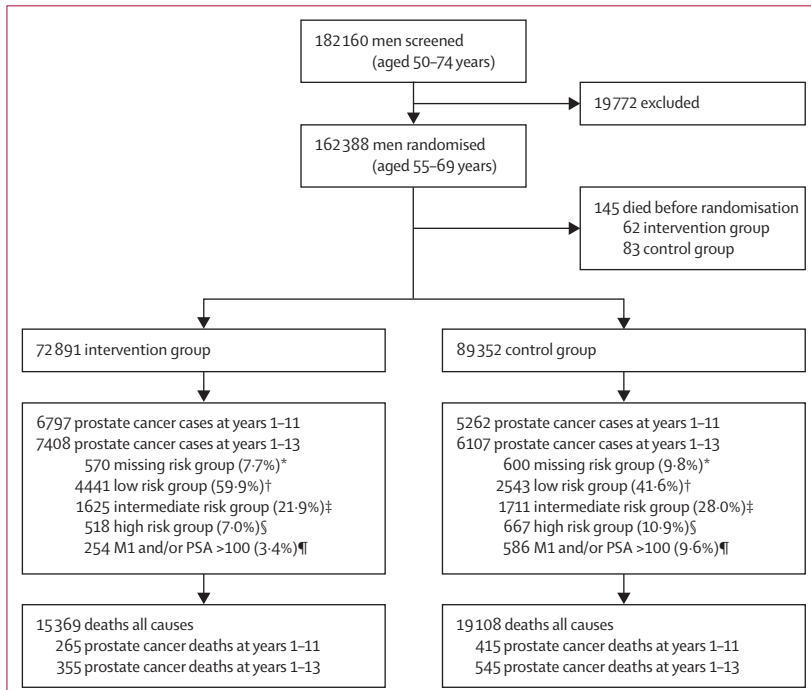


Figure 1: Trial profile (core age group, excluding France)

GS=Gleason score. M1=evidence of metastases on imaging or a PSA value of >100 ng/mL. PSA=prostate-specific antigen. *Missing=missing T stage or GS, not M1 or PSA >100. †Low risk=T1, and T2 and with GS ≤6. ‡Intermediate risk=T1, and T2 with GS 7 and T3 with GS ≤7. §High risk=T1, and T2, and T3 with GS 8-10 and T4 with any GS. ¶M1 or PSA >100 might occur, any T stage, or GS.

	Netherlands	Belgium	Sweden	Finland	Italy	Spain	Switzerland	Total (excluding France)	France (Herauld)	France (Tarn)	Total
Period of randomisation	Nov, 1993–March, 2000	June, 1991–Dec, 2003	Dec 31, 1994 (all randomised on same day)	Jan, 1996–Jan, 1999	Oct, 1996–Oct, 2000	Feb, 1996–June 1999	Sept, 1998–Aug, 2003	..	June, 2003–March, 2005	Dec, 2000–June, 2004	..
Median age at randomisation (years, IQR)	61.7 (58.0–65.6)	63.0 (60.2–66.2)	59.7 (57.2–62.4)	58.7 (54.8–62.7)	61.8 (58.4–65.9)	60.4 (57.4–64.2)	61.1 (57.8–65.1)	60.2 (57.1–64.2)	62.0 (58.8–65.9)	62.0 (57.9–66.1)	61.1 (57.9–66.1)
Randomised (n)	34 833	8 562	11 852	80 379	14 517	2 197	9 903	162 243	57 662	21 349	241 254
Screening (n, %)	17 443 (50%)	4 307 (50%)	5 901 (50%)	31 970 (40%)	7 266 (50%)	1 056 (48%)	4 948 (50%)	72 891 (45%)	28 793 (50%)	10 879 (51%)	112 563 (47%)
Control (n, %)	17 390 (50%)	4 255 (50%)	5 951 (50%)	48 409 (60%)	7 251 (50%)	1 141 (52%)	4 955 (50%)	89 352 (55%)	28 869 (50%)	10 470 (49%)	128 691 (53%)
Screened at least once (n, %)	16 502 (95%)	3 908 (91%)	4 478 (76%)	23 771 (74%)	5 730 (79%)	1 056 (100%)	4 810 (97%)	60 255 (83%)	7 164 (25%)	4 143 (38%)	71 562 (64%)
Screen tests done (n)	39 345	6 446	15 468	52 142	12 731	1 846	12 062	140 040	7 164	5 358	152 562
Mean screens per man screened (SD)	2.4 (1.1)	1.6 (0.7)	3.5 (1.7)	2.2 (0.8)	2.2 (0.8)	1.7 (0.5)	2.5 (0.7)	2.3 (1.0)	1.0 (0)	1.3 (0.5)	2.1 (1.1)
Positive tests (n, %)	9 301 (24%)	1 058 (16%)	2 897 (19%)	5 925 (11%)	1 443 (11%)	354 (19%)	2 596 (22%)	23 574 (17%)	1 091 (15%)	821 (15%)	25 486 (17%)
Biopsies (n)	8 332	752	2 510	5 404	902	263	2 025	20 188	315	418	20 921
Biopsies/positive tests (%)	89.6%	71.1%	86.6%	91.2%	62.5%	74.3%	78.0%	85.6%	28.9%	50.9%	82.1%
Prostate cancer cases											
Screening cohort total (n)	2 180	417	738	3 018	396	87	572	7 408	1 196	559	9 163
Screen detected (n)	1 809	187	570	1 631	197	60	429	4 883	163	121	5 167
Interval and non-attender (n)	371	230	168	1 387	199	27	143	2 525	1 033	438	3 996
Screen detected cancers/biopsy (%)	21.7%	24.9%	22.7%	30.2%	21.8%	22.8%	21.2%	24.2%	51.7%	28.9%	24.7%
Cumulative incidence (total cancers/all randomised to screening group, %)	12.5%	9.7%	12.5%	9.4%	5.5%	8.2%	11.6%	10.2%	4.2%	5.1%	8.1%
Prostate cancer											
Control group (n)	1 070	321	469	3 609	289	52	297	6 107	1 094	506	7 707
Cumulative incidence (%)	6.2%	7.5%	7.9%	7.5%	4.0%	4.6%	6.0%	6.8%	3.8%	4.8%	6.0%
Mean follow-up (years, SD)	11.5 (2.8)	10.8 (3.1)	11.7 (3.0)	11.4 (3.0)	11.3 (2.7)	11.9 (2.3)	9.8 (2.0)	11.3 (2.9)	6.2 (1.1)	7.3 (1.5)	9.7 (3.4)
Median follow-up (years, IQR)	13.0 (11.4–13.0)	13.0 (9.0–13.0)	13.0 (0)	13.0 (12.0–13.0)	12.6 (10.7–13.0)	12.7 (12.2–12.9)	10.2 (8.7–11.2)	13.0 (11.7–13.0)	6.4 (8.7–11.2)	7.5 (0)	11.3 (6.6–13.0)

Table 1: Randomisation, participants, and results of screening all centres (core age group, cutoff date Dec 31, 2010, data truncated at 13 years of follow-up)

Statistical analysis

The primary analysis assessed prostate cancer mortality and addressed the upfront agreed core age group (55–69 years), with follow-up through to 2010 truncated at 9 years, 11 years, and 13 years. All results were calculated with the control group for Finland, which was weighted by roughly 1:1.5. The analysis was done on the basis of intention to treat (or intention to screen), comparing

groups formed by randomisation regardless of compliance with the assignment. Rate ratios (RR) were calculated with Poisson regression. Reported p values are two-sided. Additionally, an analysis of mortality in men screened corrected for selection bias due to non-participation was done.¹⁶ France was excluded from all analyses of prostate cancer mortality because of incomplete follow-up. France was included in a secondary

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	Intervention group			Control group			Rate ratio* (95% CI)	Rate difference per 1000 person-years* (95% CI)	Rate difference per 1000 men*
	Prostate cancer (n)	Person-years	Rate per 1000 person-years	Prostate cancer (n)	Person-years	Rate per 1000 person-years			
Years 1–9 including France	7902	835 353	9.46	5726	984 993	5.81	1.64 (1.58–1.69)	3.69 (3.42–3.95)	26.5
Years 1–9	6147	585 627	10.50	4127	736 688	5.60	1.91 (1.83–1.99)	5.00 (4.68–5.32)	39.0
Years 1–11	6797	692 186	9.82	5262	873 415	6.02	1.66 (1.60–1.73)	3.90 (3.61–4.20)	35.5
Years 1–13	7408	775 527	9.55	6107	980 474	6.23	1.57 (1.51–1.62)	3.44 (3.16–3.72)	34.8

*Control group for Finland weighted by 1:1.5.

Table 2: Prostate cancer incidence in the intervention and control groups during three time periods truncated (all centres, core age group, France excluded except for years 1–9)

Intervention group	Control group			Rate ratio* (95% CI)	p value	Rate difference per 1000 person-years* (95% CI)	Rate difference per 1000 men*	Adjusted rate ratio in attenders* (95% CI)	p value			
	Prostate cancer deaths (n)	Person-years	Rate per 1000 person-years							Prostate cancer deaths (n)	Person-years	Rate per 1000 person-years
Years 1–9	193	614 590	0.31	278	751 777	0.37	0.85 (0.70 to 1.03)	0.10	-0.06 (-0.12 to 0.01)	-0.46
Years 1–11	265	732 133	0.35	415	896 367	0.46	0.78 (0.66 to 0.91)	0.002	-0.10 (-0.17 to -0.04)	-1.02	0.71 (0.58 to 0.88)	0.001
Years 1–13	355	825 018	0.43	545	1 011 192	0.54	0.79 (0.69 to 0.91)	0.001	-0.11 (-0.18 to -0.05)	-1.28	0.73 (0.61 to 0.88)	0.0007

*Adjusted by centre and for the randomisation ratio 1:1.5 intervention group versus control group in Finland.

Table 3: Prostate cancer mortality in the intervention and control groups during three time periods truncated (all centres, core age group, France excluded except for years 1–9)

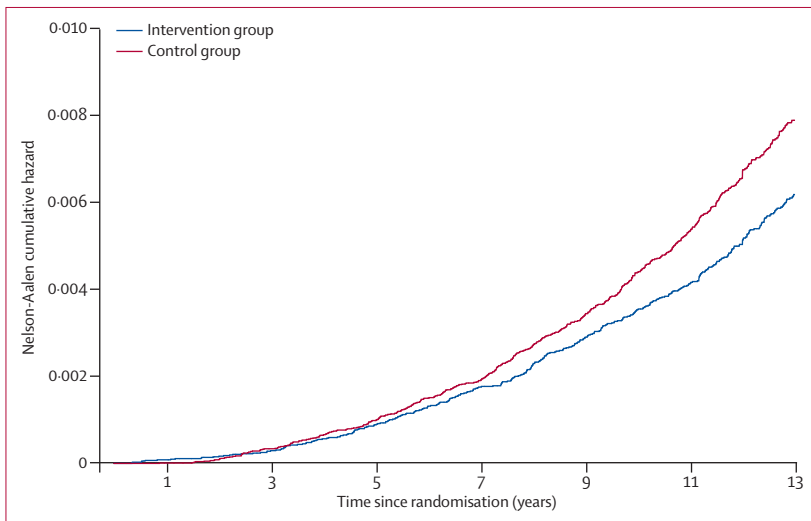


Figure 2: Nelson-Aalen estimates of cumulative prostate cancer mortality (all centres, excluding France)

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analysis of incidence of prostate cancer with 1–9 years’ follow-up. Appendix pp 13–16, 20, 21 shows the analysis considering all available ages. Appendix p 17 shows a further secondary analysis of the results per centre for the core age group excluding France. No adjustment of significance for α -spending in sequential analyses was

applied because the present analysis is protocol based and not driven by statistical significance.^{17,18} Cumulative prostate cancer mortality by group was calculated with the Nelson-Aalen method.¹⁷ Number needed to invite (NNI) to avert one prostate cancer death was calculated as the inverse of the absolute risk reduction, and the number needed to detect (NND) as the NNI multiplied by the excess incidence of prostate cancer in the intervention group. Analyses were done with Stata version 12.1.

This trial is registered with Current Controlled Trials, number ISRCTN49127736.

Role of the funding source

The funders of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. Access to data was limited to the independent data centre led by SMM. None of the investigators had access to outcome data outside the planned official reports of the data centre. FHS produced the primary version and was responsible for submitting the report.

Results

In the core group of men aged 55–69 years, excluding France, 162 388 were randomly assigned, of whom 145 died between randomisation and screening. With data truncated at 13 years of follow-up, 7408 prostate

	Intervention group			Control group			Rate ratio (95% CI)	p value
	Deaths (n)	Person-years	Rate per 1000 person-years	Deaths (n)	Person-years	Rate per 1000 person-years		
All-cause mortality								
Core age group	15369	825018	18.6	19108	1011192	18.9	1.00 (0.98–1.02)	0.82
All ages	18251	935185	19.5	21992	1120432	19.6	1.00 (0.98–1.02)	0.98
Prostate cancer mortality								
Age groups (years)								
≤54	6	64265	0.09	7	62312	0.11	0.84 (0.28–2.49)	0.75
55–59	114	411834	0.28	174	524314	0.33	0.81 (0.93–1.03)	0.09
60–64	121	240895	0.50	159	280404	0.57	0.90 (0.71–1.15)	0.41
65–69	120	172289	0.70	212	206474	1.03	0.69 (0.55–0.87)	0.002
70≥	66	45903	1.44	58	46928	1.24	1.17 (0.82–1.66)	0.40
Core age group	355	825018	0.43	545	1011192	0.54	0.79 (0.69–0.91)	0.001
All ages	427	935185	0.46	610	1120432	0.54	0.83 (0.73–0.94)	0.004

Test for heterogeneity for prostate cancer mortality: all ages $\chi^2=6.26$ $p=0.18$; core age group: $\chi^2=2.31$ $p=0.32$.

Table 4: All cause and prostate cancer mortality by age at randomisation (France excluded)

cancer cases were diagnosed in the intervention group and 6107 cases in the control group (figure 1).

The median age at randomisation was 60.2 years (table 1). The overall compliance with biopsies was 85.6%, 20 188 of 23 574 screen-positive tests. On average, men in the intervention group were screened 2.3 times (ranging from 1.6 times in Belgium with a 7-year interval to 3.5 times in Sweden with a 2-year interval). Of the screen-positive men who underwent a biopsy, 4883 (24.2%) were diagnosed with prostate cancer within 12 months after testing (table 1).

With follow-up truncated at 13 years, prostate cancer incidence was 9.55 per 1000 person-years in the intervention group and 6.23 in the control group (table 2).

With follow-up truncated at 13 years, prostate cancer mortality was 0.43 per 1000 person-years in the intervention group and 0.54 per 1000 person-years in the control group (RR of 0.79, 95% CI 0.69–0.91, $p=0.001$; table 3, figure 2). We recorded a similar RR after 11 years (table 3). After adjustment for non-participation, we noted an RR of 0.71 (95% CI 0.58–0.88, $p=0.001$) after 11 years and 0.73 (0.61–0.88, $p<0.0007$) after 13 years (table 3).

The absolute risk reduction in prostate cancer mortality at 13 years of follow-up in the intervention group compared with the control group, after adjustment for the randomisation ratio of 1:1.5 in Finland was 0.11 prostate cancer deaths per 1000 person-years or 1.28 prostate cancer deaths per 1000 men, which yielded an NNI of 781 (95% CI 490–1929) and an NND of 27 (17–66). The NNI and NND were substantially decreased from follow-up to 9 years (NNI 1410, NND 48) and 11 years (NNI 979 [95% CI 594–2770], NND 35 [21–96]).¹² All-cause mortality did not differ between the two trial groups (table 4).

In addition to the core age group, we noted a significant reduction in prostate cancer mortality for all 181999 men aged 50–74 years at entry (excluding France; table 4). The

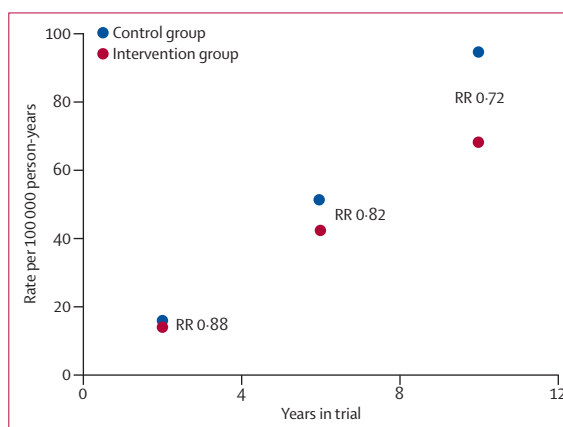


Figure 3: Nelson-Aalen estimates of cumulative prostate cancer in both groups by 4-year periods (all centres, excluding France)

effect of screening did not significantly differ across 5-year bands in the core age group or across the entire age range, but, most likely by chance, we noted a significant reduction in prostate cancer mortality in the 65–69 year age group. We recorded a non-significant increase in prostate cancer mortality in the 70 year and older screening group (table 4); however, men in this age group were screened only once, which might explain the absence of an effect of starting to screen late in life.

Figure 3 shows prostate cancer mortality for the two trial groups in 4-year intervals from date of randomisation. At 0–4 years the RR was 0.88 (95% CI 0.58–1.34), which decreased to 0.82 (0.64–1.06) at 4–8 years, and further decreased to 0.72 (0.59–0.88) at 8–12 years.

An analysis of prostate cancer mortality in the intervention and control groups in the core age group of individual centres showed significant RRs only for Sweden (0.62 [95% CI 0.41–0.92]) and the Netherlands

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See Online for appendix

Panel: Research in context**Systematic review**

In most parts of the world, prostate cancer is a frequent or the most frequent cause of death from cancer. The prostate-specific antigen test was shown early during the 1990s to enable diagnosis of the disease at an early stage. This led to widespread use worldwide despite many uncertainties. The ERSPC study group therefore decided in 1994 to establish a randomised controlled trial of screening for prostate cancer. A similar study, the Prostate, Lung, Colon, Ovary (PLCO) Screening Trial was initiated around the same time. Follow-up of the European Randomised study of Screening for Prostate Cancer (ERSPC) has been published previously in 2009¹ and 2012.² Results have changed substantially, mainly concerning the absolute effect of screening on prostate cancer mortality at the evaluations done after 10 and 13 years and with respect to the initial evaluation after 8 years of follow-up. The number needed to invite changed from 1410 to 781 and the number needed to detect from 48 to 27 for follow-up periods of 9–13 years. The relative difference in mortality between the intervention group and control group remained similar at 22% and 21%, but the level of significance increased (from $p=0.04$ to $p=0.001$ with 9 years vs 11 years of follow-up). The recent Cochrane analysis of all screening trials is subject to ongoing debate, mainly concerning the comparability of ERSPC with other screening trials.¹⁹

Interpretation

Our data show a significant relative reduction in prostate cancer mortality when comparing the screening group and control group of 21% and 27% in men who participated in the study. The main weakness of screening is a high rate of overdiagnosis and overtreatment.⁵ We conclude that the time for population-based screening has not arrived. In the present situation, early diagnosis cannot be refused to men who are well informed and request to be tested. Information must concentrate on the occurrence of overdiagnosis, which is also the main target of future research. Multiparametric MRI and the developments of new markers are the hope for the future. In the meantime available instruments with multivariate risk stratification must be applied.

(0.67 [0.51–0.88]; appendix pp 17). A more extensive comparison including adjustments for non-compliance is pending.

Discussion

The results of our primary analysis, based on extended follow-up up to 13 years, showed no further increase in the relative effect of screening on prostate cancer mortality after 11 years,² but an enhanced absolute mortality reduction per 1000 men randomised (panel). In line with ERSPC rules of participation and reporting,⁸ France was included in the analysis of incidence, but not in that of mortality, because of incomplete follow-up to the end of 2010. The absolute effect—ie, absolute risk reduction—is a key indicator of the effectiveness of screening and should guide decision making for both policy and patients. At 13 years' follow-up, the NNI and NND were substantially decreased from that at 9 and 11 years' follow-up (NNI at 9 years vs 13 years, 1410 and 781). For comparison, the corresponding figures of NNI estimated for breast cancer screening trials are 1339–2000 based on 13 year follow-up.²⁰

In terms of relative effect, most of the screening effect was achieved during 1–11 years' follow-up, with little further divergence occurring during years 11–13.

Mortality from prostate cancer was significantly lower in the screened group than in the control group in the

core age group and for all ages. Our previous reports^{1,2} did not include data for France because of short follow-up. French data are shown here for the first time in an analysis of incidence up to 9 years of follow-up. The French centres have mean follow-up periods of only 6.2 years and 7.3 years, the lowest compliance with biopsy indications, contributed with only one to two rounds of screening, and their incidence data are suggestive of a very high contamination rate (prostate cancer incidence RR 1.1 for the screening group, table 1). Inclusion of these centres in the analysis of data truncated at 9 years gave a lower RR of prostate cancer incidence (table 2).

We recorded differences in the screening effect between centres, but none were significant (appendix pp 17, France excluded). Reduction in prostate cancer mortality was significant in the Swedish and Dutch centres, but not in the others. Data for Finland, the largest component, still do not show a significant reduction in mortality. Differences between centres are most likely due to differences in length of follow-up, underlying incidence and mortality, and contamination in the control group, but possibly also to performance of screening and duration of intervention.

Possible mechanisms that might explain the absence of further increase in the relative effect by screening in the 1–11 year versus 1–13 year periods could include non-compliance in the intervention group and contamination in the control group by screening. A decreasing difference in the frequency of screening between the intervention group and control group, as shown in the narrowing difference between the intervention and control groups is prostate cancer incidence (table 2), is likely to play an additional part. Additionally, patients with latent advanced prostate cancer at the time of randomisation (effect of advanced incurable cases detected in the first screen on prostate cancer mortality)²¹ could be at the end of their treated natural course. Additionally, compliance with biopsy sampling or variations in treatment could have an effect.

Complete adjustment for contamination and non-participation according to Cuzick and colleagues¹⁶ is not possible at present because of unavailability of opportunistic PSA-testing data in the control group in some centres.

The change in frequency of stage T1c disease in the control group with time might serve as a surrogate. An increase in the detection rate of stage T1c prostate cancer per 1000 person-years within the core age group in the control group from 0.85 during year 1 to 3.58 during year 12 was noted (appendix pp 18, excluding France).

Possibly, follow-up is still too short to see the full effect of PSA screening, in view of the long natural history of screen-detected prostate cancer. Although follow-up from randomisation was 13 years, the median follow-up from diagnosis of prostate cancer was only 6.4 years in the intervention group and 4.3 years in the control group

(data not shown), and previous studies have shown that the natural course of early prostate cancer is usually in the range of 15–25 years.^{22,23}

Differences in the treatment of prostate cancer with similar tumour characteristics between the two groups of the trial could, in theory, explain apparent differences assigned to screening. A previous analysis, however, showed that this hypothesis is unlikely.²⁴ This analysis showed only one major difference in treatment between the groups, an increased rate of radiotherapy combined with endocrine treatment in favour of the control. An update of the assessment of treatments per group and per centre is in preparation. Additionally, an alternative analysis applying the excess mortality method has been done and reported.²⁵ This analysis takes into account the differences in deaths that could be related to treatment. The results of this analysis do not differ from the data reported here.

As previously reported, we noted no difference in all-cause mortality. As identified in other trials of cancer (except for regional screening for cervix cancer), all cause mortality is not a useful endpoint for assessment of screening, but similar mortality rates support the comparability of the trial groups.

Overdiagnosis occurs in roughly 40% of cases detected by screening,^{3,4} resulting in a high risk of overtreatment with unavoidable side-effects, which is a major adverse consequence of prostate cancer screening. Our results show a 1.57-fold increased incidence in the screening group (absolute excess 3.44 per 1000 person-years), which is consistent with earlier assessments.^{1,2} Yet our modelling study⁵ showed a favourable balance of benefits (mortality reduction) and harms (positive net effect despite a smaller gain in QALYs than life-years overall). The model estimate of overdiagnosis is 41%. However, if we assume no overdiagnosis, QALYs gained per 1000 men screened annually increased from 56 to 79. Further research is urgently needed on methods to reduce overdiagnosis preferably by avoiding unnecessary biopsy procedures, and reduction in the very large number of men who must be screened, biopsied, and treated to help only a few patients. One promising approach to decrease overdiagnosis is the development of multiparametric MRI technology applied to the prostate.

Our study has limitations, including heterogeneity between centres that is not excluded by analysis of homogeneity in terms of screening protocol and performance, contamination in the control group (range 23–40%), and the short follow-up (>70% of all participants of the study population are still alive).

Despite evidence for the effectiveness of PSA screening to reduce prostate cancer mortality in our study, the uncertain balance between benefits and harms needs to be considered in decisions about population screening. Informed decision making, with well designed decision aids, is necessary for individuals

who consider PSA-based screening for prostate cancer. Another issue that requires consideration is the different outcome of the ERSPC and the prostate screening group of the Prostate, Lung, Colon and Prostate Cancer screening trial (PLCO),²⁶ of which a recent update again reported no effect on prostate cancer mortality despite more diagnoses of prostate cancer in the screening group than in the control group. The comparability of the two trials is subject to substantial debate.^{19,27} Complications of diagnostic procedures have recently been reported in two other publications.^{28,29}

The fact that the time for population-based screening has not yet arrived should not prevent clinicians and other health-care providers from considering the application of PSA-driven testing for men who wish to undergo such study. For now, extensive, well balanced information should be provided and discussed with patients, preferably on the basis of validated decision aids. Instruments to decrease the proportion of unnecessary biopsies and the risk of overdiagnosis in the form of risk calculators are freely available on the internet. A promising approach lies in the development of multiparametric MRI imaging technology of the prostate, which at present claims to selectively diagnose aggressive prostate cancers and avoid the diagnosis of many non-significant cancers (eg, well differentiated T1c tumours with small volumes on biopsy which are unlikely to progress or kill).

In conclusion, with data truncated at 13-years' follow-up, our study continues to show a significant 21% relative reduction in prostate cancer mortality in favour of screening, with one prostate cancer death averted per 781 men invited and 27 excess cases detected. The relative risk reduction in men actually screened was 27% after adjustment for selection effects. Despite our findings, further quantification of harms and their reduction are still considered a prerequisite for the introduction of population-based screening.

Contributors

All authors contributed by providing data to the independent data centre twice a year, including substantial numbers of participants, as shown in appendix p 3, and by critically revising the manuscript for important intellectual content. FHS has been the initiator of ERSPC and was instrumental in its coordination since 1993, has contributed together with the Rotterdam study group to the data collection, was responsible for all international coordination of ERSPC during the 13-year follow-up period reported in the publication, and wrote the report. JH was responsible for the Swedish input of ERSPC including data collection and study design, and contributed to analysis of results and interpretation and revision of the report. MJR was responsible for collection, quality, and transfer of ERSPC Rotterdam data to the central database of ERSPC in the UK, and critically revised the report for statistical analyses and intellectual content. TLJT contributed to the study design, data collection, data interpretation, and critical commenting of the report. MZ critically revised the report for statistical analyses and intellectual content. VN was responsible for the collection, quality, and transfer of ERSPC Antwerp data to the central database of ERSPC, and critically revised the report. MK was responsible for data collection and quality of ERSPC Switzerland, data transfer to the central database of the ERSPC in UK, study execution

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in Switzerland and ERSPC as a whole (member of scientific committee), and critical revision of the manuscript for statistical analyses and intellectual content. ML was a coinvestigator for the Spanish section of ERSPC study. LM was responsible for the collection, quality, and transfer of ERSPC Finland data to the central database of ERSPC in the UK. HL contributed to the study design, data collection, data analysis, data interpretation, and the preparation, review, and final approval of the report. LJD was responsible for the collection, quality, and transfer of data from Antwerp centre, and critical revision of the report. FR was responsible for data collection and quality of ERSPC Switzerland, study execution in Switzerland and ERSPC as a whole (member of scientific committee), and critical revision of the report for intellectual content. AP was a coinvestigator for the Spanish section of ERSPC study. CHB was responsible for data collection and review of the report. SC provided substantial contributions to the analysis and interpretation of data, substantially and critically revised the report for important intellectual content, and approved the final version of the report. DP was responsible for collection, quality, and transfer of ERPC Florence data to the central database of ERSPC in the UK. AV was responsible for data collection and review of the report. XR was responsible for data collection. MH was responsible for critical review of the report for statistical analyses and intellectual content. U-HS was responsible for the PSA determinations and approved the report. PK was responsible for the collection and quality of ERSPC Finland pathology data to the central database of ERSPC in the UK. KT was responsible for data collection, data interpretation, and critical revision of the report. GA was responsible for critical revision of the report, data interpretation, and intellectual content. AH was responsible for data collection and quality of ERSPC Switzerland, study execution in Switzerland and ERSPC as a whole, and critical revision of the report for intellectual content. THvdK was responsible for data collection, critical review of the report, and approval of the final report. RHNvS was responsible for literature search, data collection, sample handling, PSA measurements, and review of the report. HJdK was responsible for study design, data collection, data interpretation, and writing. SM contributed to the data analysis, data interpretation, and writing of the report. AA was the principal investigator of the Finnish trial with contribution to the study design and data collection, is a coordinator of ERSPC, participated in the drafting of the report, critical revision of the content of the report, planning of the statistical analyses, and approved the final version of the report.

Declaration of interests

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