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A 16-year Follow-up of the E**uropean** R**andomized study of** S**creening for** P**rostate** C**ancer**

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Abstract

Background: The European Randomized study of Screening for Prostate Cancer (ERSPC) has previously demonstrated that prostate-specific antigen (PSA) screening decreases prostate cancer (PCa) mortality.

Objective: To determine whether PSA screening decreases PCa mortality for up to 16 years and to assess results following adjustment for non-participation and number of screening rounds attended.

Design, setting, and participants: Multicentre population-based randomised screening trial in eight European countries. Report includes 182,160 men, followed-up until 2014 (maximum of 16 years), with a predefined core age group of 162,389 men (55-69 years), selected from population registry.

Outcome measurements and statistical analysis: Outcome was PCa mortality, also assessed with adjustment for non-participation and number of screening rounds attended.

Results and limitations: Rate ratio (RR) of PCa mortality was 0.80 (95% CI 0.72-0.89, p<0.001) at 16 years. Difference in absolute PCa mortality increased from 0.14% at 13 years to 0.18% at 16 years. The number of screening invitations needed to prevent one PCa death was 570 at 16 years compared to 742 at 13 years. The number needed to diagnose was reduced to 18 from 26 at 13 years. Men with PCa detected during the first round evidenced higher prevalence of PSA > 20 ng/mL (9.9% compared to 4.1% in the second round, p<0.001) and higher PCa mortality (HR=1.86, p<0.001) compared to those detected subsequently.

Conclusions: Findings corroborate earlier results that PSA-screening significantly reduces PCa mortality, showing larger absolute benefit with longer follow-up and a reduction in excess incidence. Repeated screening may be important to reduce PCa mortality on a population level.

Patient summary: In this report, we looked at the outcomes from prostate cancer in a large European population. We found that repeated screening reduces the risk of dying from prostate cancer.

Introduction

The European Randomised study of Screening for Prostate Cancer (ERSPC) was initiated 1993 with the primary aim to investigate the effect of regular prostate-specific antigen (PSA) screening on prostate cancer (PCa) mortality. Findings were previously reported on three occasions as pre-specified in the study protocol at 9, 11, and 13 years of follow-up [1-3]. The latest report (2014) showed that PSA screening increased PCa incidence 1.6-fold and the relative reduction in PCa mortality was 21% at 13 years of follow-up[3]. This is the 16-year main endpoint follow-up in order to quantify the long-term harms and benefits of screening. Secondary aims were to investigate how variations in screening attendance and duration of screening (one test only versus repeated testing) affected PCa mortality and if this could explain the observed variations in outcome between different screening trials as well as between different ERSPC centres [3, 4].

Material (Patients) and Methods

Study design and participants

The ERSPC, described previously[1-3], is a multicentre randomised screening trial for PCa in eight European countries (Figure 1). It started in Belgium and the Netherlands (1993), and the last country to join was France in 2003. Minor variations in screening protocols between centres were accepted, but compulsory criteria for participation were defined,[5] including PSA as the primary screening test, followed by systematic prostate biopsies for men with elevated PSA; a core age group of men 55-69 years at randomisation; repeated screening invitations, and regular data delivery to an independent central database (age groups between 50 and 74 years were invited in some centres). Stopping age for screening invitations varied between 67 and 78 years. Most centres used a four-year interval, but

Sweden and France used a two-year interval and Belgium a 7-year interval. A minimum of two and a maximum of eight invitations was used for the core age group and the duration of screening (time from the first to the last invitation) varied between four (oldest men in Finland) and 16 years (the Netherlands and Sweden). Primary screening tool was PSA. To achieve high quality, a uniform PSA method was chosen (Hybritech, Tandem R). A quality assurance program was designed to guarantee accuracy of the test across centres. Additional screening tools were employed in some centres. In the Netherlands, digital rectal examination (DRE) was used during 1993 - 1996 in men with PSA 1.0-4.0 ng/mL. In Finland, DRE was used in 1996-1998 and the ratio of free to total PSA since 1999 in men with a PSA 3.0-3.9 ng/mL. Since 1996, most centres used a PSA-level ≥ 3.0 ng/mL as definition of a positive screening test. Men with a positive screening test were recommended digital rectal examination (DRE), trans-rectal ultrasound of the prostate, and systematic prostate biopsies. Initially, sextant biopsies were the standard, but this was later changed to 10-12 cores. A summary of the characteristics by centre is provided in Table 1. French data were excluded from the combined analysis, as these two centres failed to comply with a primary criterion (screening participation >50%) (Table 1)[6]. Ethical approval was obtained separately for each participating country.

Randomisation and masking

Two types of randomisations were used: randomisation before consent (Zelen-type effectiveness design in Sweden, Finland, and Italy) or randomisation after consent (efficacy design in the other countries). Randomisation was done by computer-generated random numbers with eligible participants identified in population registers. Trial group allocation was masked for determination of the main outcome.

Outcomes

Primary outcome was PCa mortality. For deceased men with PCa, medical records were evaluated by a Cause of Death Committee (COD) using a standardised flow-chart to establish COD[7]. The COD committee was masked regarding randomisation arm. Official causes of death were used in Finland since 2003 after demonstrating a very high concordance with that obtained by the local COD committee[8]. PCa incidence was monitored by country for cancer and vital status. All randomised men were linked with Cancer registers and biannually reported to the Central Database. For men with PCa, TNM-stage, PSA, Gleason score, and primary treatment were abstracted from medical records. A scientific committee established quality criteria and other committees monitored the conduct, progress of the trial, PSA-harmonization, and assignment of Gleason grades[5]. This report includes follow-up through Dec 31, 2014 or a maximum of 16 years after randomisation.

Statistical analysis

Primary analysis

The primary analysis evaluated PCa mortality and focused on the core age group 55-69 years, with follow-up through 2014 truncated at 9, 11, 13, and 16 years. The main analysis was carried out according to the intention-to-screen principle, i.e., comparing groups formed by randomisation (regardless of assignment compliance). Incidence and mortality rates and risks were calculated by dividing number of events with number of person-years and number of men, respectively. Rate ratios (RR) (ratio of incidence per person-years), risk ratios (ratio of incidence per man) and the corresponding differences were calculated using Poisson regression analysis, with the control arm for Finland weighted by 1:1.5 due to unequal allocation (agreed upon when Finland joined the trial) . Confidence intervals for rate and risk differences were calculated by Wald´s method, with standard errors derived by the delta

method. For NNI, the confidence intervals were derived as one over the intervals for the differences in risk of PC mortality. *P*-values are two-sided. No adjustment of significance for alpha-spending in sequential analyses was applied because the present analysis is protocol-based and not driven by statistical significance[9, 10]. Number needed to invite (NNI) to avert one PCa death was calculated as the inverse of the absolute risk difference in PCa deaths. The number needed to detect (NND) as the NNI multiplied by the excess incidence of prostate cancer in the screening group. Both the graphs on cumulative PCa incidence and mortality in the control and screening arms and the graph on survival after screen-detected PCa are based on Nelson-Aalen estimates of survival. Cumulative incidence and mortality curves adjusted for the competing risk of death of other causes follow the approach in Cuzick and colleagues [11, 12].

Secondary analysis

In a secondary analysis, PCa mortality was assessed from diagnosis in those men diagnosed within the program. Men with screen-detected cancer in round one were compared to screen-detected men during subsequent screening rounds. Cox regression analysis was used. To evaluate the effect of attending at least one screening round, adjusted RRs were calculated with adjustment for non-participation[12]. The proportion of complete non-attendees (i.e., never participating) in the screening group, and the PCa mortality among them was calculated. The control group is then considered to consist of a non-attender part of the same size and with the same PCa mortality rate as the non-attender part of the screening group, allowing us to calculate the adjusted mortality rate among those who participated at least once.

Additionally, we estimated an adjusted RR in men who attended at least twice. Here, we defined two groups of attendees, (1) all men who participated only once, and (2) men

participated at least twice. The proportion of men attending one screen only and the PCa mortality in this group were calculated. The underlying PCa mortality in this group (screened only once) in the absence of screening is unknown but a recent study showed no effect of one screen only [4]. We therefore carried out analyses based on mortality reductions in men screened once only of 0% (there was no benefit to men with cancer detected at the first screen) up to 25% (i.e., the benefit of the first screen was the same as that at later screens). This trial is registered with Current Controlled Trials, number ISRCTN49127736.

Statistical analyses were performed in R Statistical Software (Version 3.3.1; Foundation for Statistical Computing, Vienna, Austria).

Results

Primary analyses

A total of 182,160 men were randomised, of whom 162,389 were part of the core age group 55-69 years. Figure 1 shows the trial profile. Men randomized to the screening arm were screened on average 1.94 times (2.3 times in screening attendees), and of those participating, 28% were screen-positive at least once (Table 1). Median follow-up (excluding France; from randomisation to a minimum of 16 years, December 31, 2014, and date of death) was 15.5 years and median follow-up from diagnosis to PCa cases was 8.8 years in the screening arm (10.3 in screen-detected and 4.5 in clinically detected) compared to 5.4 years in the control arm. Cumulative PCa-specific incidence at 16 years was 13.3% in the screening arm and 10.3% in the control arm (Kaplan Meier estimates). Hence, PCa incidence in the control arm compared to the screening arm increased during longer follow-up, however, still remained 1.4-fold higher in the screening arm after 16 years (Table 2).

The RR of PCa mortality between the arms was 0.80 at 16 years (95% CI 0.72-0.89, p<0.001), and compared to 9, 11, and 13 years of follow-up, did not change (Table 3). The absolute difference between the trial arms increased from 0.14% at 13 years to 0.18% at 16 years. NNI was 570 and NND was 18 men (Table 3). PCa mortality by age at randomisation (5-year age groups) are presented in Table 4 (Appendix). Of the individual centres, a significant mortality reduction was seen in Sweden (RR 0.63, 95% CI 0.44-0.88, p=0.008) and the Netherlands (RR 0.67, 95% CI 0.53-0.85, p=0.001) (Table 5, Appendix). Table 6 (Appendix) shows the distribution of PSA-levels at diagnosis in the different screening rounds.

Secondary analyses

PCa-specific survival for cases detected during the first screening round was significantly worse compared to those diagnosed at subsequent screening rounds (HR=1.86, p<0.001)

(Figure 3). The PCa mortality reduction in those who attended at least one screening-round was 25% (RR 0.75, 95% CI 0.66-0.75). The calculated PCa mortality reduction for those attending the screening program at least twice was 48% (RR 0.52, 95% CI 0.42-0.63) if no mortality reduction was postulated from one-test only, 43% (RR 0.57, 95% CI 0.47-0.70) if a mortality reduction of 10% was postulated, and 25% (RR 0.75, 95% CI 0.60-0.92) if first screening was as effective as the following rounds (Table 7, Appendix).

Discussion

This ERSPC update with three additional years of follow-up shows that the absolute reduction in PCa mortality still increases with longer duration of follow-up, while the relative risk reduction remains unchanged at 20% since the initial report based on 8.8 years of follow-up[1-3]. PCa incidence in the control group is gradually catching up with the screening arm, but at 16 years, a 41% excess incidence remains in the screening arm. Results illustrate that both incidence and mortality differences continue to change between the two arms and demonstrate why extended follow-up is required to better understand the long-term risks and benefits of PCa screening[13]. Despite a median follow-up of 15.5 years from randomisation, median follow-up from diagnosis (i.e., 8.8 years in the screening arm and 5.4 years in controls) is quite modest given the natural course of PCa as many screening-detected cancers are of low or intermediate risk with a long natural course[14]. Deaths among men with PCa diagnosed after screening termination will also affect the long-term impact of the screening trial, which will be observed in future follow-up.

The NNI to prevent one PCa death was 570 at 16 years compared to 1947 at 9 years and 742 at 13 years[1-3], an important decrease, emphasising the long-term impact of PCa screening. These figures differ from earlier publications as in our first two, no truncation at 9 and 11 years was performed.

The number of cases needed to diagnose for averting one PCa death is declining from 48 in our first report at 9 years to 18 in this update at 16 years. With extended follow-up, the NND will likely continue to decrease. Although difficult to compare screening programs, at 16 years, the NND in the Swedish centre was as low as 7 and comparable to that of breast cancer[15]. Nevertheless, the considerable NND reflects the abiding high excess incidence among screened men, indicating a substantial rate of over-diagnosis, even with many years

of follow-up. The continued decline in NND many years after termination of PCa screening also reflects the long lead-time of screen-detected PCa[16].

For screening decisions, this long symptom-free period has to be considered relative to early treatment with immediate side-effects that might negatively affect quality of life[17].

To detect roughly 5000 cancers, more than 20,000 biopsies were performed, corresponding to a PPV of 24% and a quarter of participants biopsied at least once, demonstrating the low specificity of PSA as a screening test. Development and use of more specific tests such as PHI, 4Kscore, and risk-calculators must be prioritised but also improving the diagnostic work-up with less invasive diagnostic methods such as MRI [18].

As in previous publications, we found a large difference in PCa mortality reduction between centres within ERSPC, with the largest effect observed in Sweden and the Netherlands[1-3]. In current analysis, these two centres show a relative reduction in PCa mortality by approximately 35 percent. With different screening protocols and screening lengths between centres, outcomes were evaluated by number of screening rounds. PCa mortality in first screening round-diagnosed men had a significantly worse outcome compared to those detected at subsequent rounds (Figure 3). One explanation is that many first screening round-diagnosed men had incurable disease whereas this was much less common in men detected at subsequent screening rounds. This is supported by the finding that the number of cancers detected with a PSA > 20 was 182 in round one (10% of all PCa cases detected in that screening round), 72 cases (4.1%) in round two, and only 42 cases (3.2%) in round three (Table 6, Appendix). As PCa with a PSA > 20 ng/mL to a high degree represents incurable PCa, our data show that the majority of such cancers were in fact diagnosed during the first screening round. In this analysis, interval cancers were not added to the cancer cases designated to rounds two or three which could be questioned. However,

the rate of aggressive interval cancers is rare in PCa screening and incorporation of these cases into the calculations will only marginally change the overall result[19].

These results suggest that a possible small beneficial effect of a one-time screen only may "drown" in the high mortality rate of existing prevalent incurable PCa cases while repeated screening over long duration is necessary for achieving a substantial and measurable PCa mortality reduction. Several lines of evidence support this view.

Cases detected within ERSPC during the first round later frequently developed metastasis, indicating that many of these men diagnosed during the first round were detected too late and screening could not prevent disease progression[20].

A screening trial (Stockholm, 1988-89) invited 2,400 men ages 55-70 only once and found no difference in PCa mortality after 20 years to a non-screened source population, however, statistical power was limited[21]. Similar results were observed in the present study: men aged 70-74 were only invited once, and in this age-group, no effect on PCa mortality was seen (Table 4, Appendix). No PCa mortality reduction was shown after 15 years in the U.S. PLCO trial and applied only six years of screening[22]. Despite several other components of this study may explain the PLCO null result, including large control group contamination, the short screening period may have contributed[23, 24]. Within ERSPC, Finland showed only a small mortality reduction (RR 0.91) compared to the Netherlands (RR 0.67) and Sweden (RR 0.63). In Finland, the oldest age group where a quarter of the men was only invited twice, the mean number of screening visits was 1.6. In the Netherlands, all men in the core age group were invited at least three times and the youngest up to five times with on average 2.3 screening visits. In Sweden, all men were also invited at least three times and the youngest eight times with on average 2.6 screenings. These were three larger centres in ERSPC with different screening intensity thus indicate that the length and

intensity of screening is directly correlated to the mortality reduction (Table 1). The recently published CAP study invited 189 386 cluster-randomised men to a one-time screening of whom 40% participated. They found no significant effect on PCa mortality (RR 0.96, CI 0.85-1.08)[4] (average follow-up 10 years). The data encouraged us to analyse the effect of repeated screens assuming various effects from one test only (Table 7, Appendix). Men attending at least one screening round had after correction for non-attendance a PCa mortality reduction of 25% and those who attended at least two screenings had a decrease of 48% if assuming no effect of one-time screening. This model may explain the large differences in PCa mortality reduction observed between the centres within ERSPC but other explanations may also contribute, e.g., the rate of opportunistic screening in the control group (e.g., Finland)[25]. This report shows that cancers detected in round one have a poorer prognosis but this is partly due to the ERSPC study design where men started screening in various age cohorts with a median age of 60 at randomisation. Older men screened for the first time evidence higher risk of being diagnosed with incurable disease[26]. In a running screening program, men are invited from earlier age (50-55 years) and the risk of missing the “window of cure” is probably lower. Furthermore, randomised screening trials will underestimate the true effect of an effective population-based screening program[27].

Our study has limitations including heterogenous populations with different background risks between centres, possibly influencing the results. Another limitation is the increased uptake of opportunistic screening in Europe, which could underestimate the true effects of screening.

Conclusions

This 16-year report from ERSPC shows that the absolute effect of screening on PCa mortality increases with longer follow-up. The excess PCa incidence among screened men is decreasing but is still rather high. The PCa mortality reduction seems to be related to the duration of screening and a one-time screening test is suggested to have little or no effect on PCa mortality due to a prevalence pool of more advanced disease in which treatment is unlikely to provide major benefits.

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1 Table 1. Characteristics of the study overall and by centre*

2

	Belgium	Finland	Italy	Netherlands	Spain	Sweden	Switzerland	Total (excl. France)	France, Herault	France, Tarn	Total
Age at randomisation, years (median, IQR)	63 (60, 66)	59 (55, 63)	62 (58, 66)	62 (58, 66)	60 (57, 64)	60 (57, 62)	61 (58, 65)	60 (57, 64)	62 (59, 66)	62 (58, 66)	61 (58, 65)
Randomised (n)	8562	80379	14515	34833	2197	11852	9903	162241	57643	21350	241234
Screening, n (%)	4307 (50%)	31970 (40%)	7265 (50%)	17443 (50%)	1056 (48%)	5901 (50%)	4948 (50%)	72890 (45%)	28784 (50%)	10879 (51%)	112553 (47%)
Control, n (%)	4255 (50%)	48409 (60%)	7250 (50%)	17390 (50%)	1141 (52%)	5951 (50%)	4955 (50%)	89351 (55%)	28859 (50%)	10471 (49%)	128681 (53%)
Follow-up, years (median, IQR)	16.0 (11.1, 16.0)	16.0 (13.8, 16.0)	15.0 (13.2, 16.0)	15.6 (13.8, 16.0)	15.6 (15.1, 15.9)	16.0 (13.9, 16.0)	13.0 (11.6, 14.2)	15.5 (13.0, 16.0)	9.4 (8.9, 9.6)	10.5 (9.8, 10.5)	13.2 (9.5, 16.0)
Screened at least once, n (%)	3908 (91%)	23771 (74%)	5730 (79%)	16502 (95%)	1056 (100%)	4484 (76%)	4810 (97%)	60261 (83%)	8121 (28%)	4143 (38%)	72525 (64%)
Screening tests done (n)	6446	52142	12731	40358	1846	15475	12068	141066	10060	5358	156484
Screening rounds per man (mean)	1.5	1.6	1.8	2.3	1.7	2.6	2.4	1.9	0.3	0.5	1.4
Positive tests (n)	1058	5925	1443	9552	354	2896	2599	23827	1627	821	26275
Men with positive tests, n (%)	914 (21%)	4635 (14%)	1054 (15%)	6793 (39%)	326 (31%)	1537 (26%)	1729 (35%)	16988 (23%)	1560 (5%)	760 (7%)	19308 (17%)
Biopsies (n)	752	5404	902	8541	263	2509	2027	20398	468	418	21284
Biopsies / positive tests (%)	71%	91%	63%	89%	74%	87%	78%	86%	29%	51%	81%
Men with biopsy at least once, n (%)	684 (75%)	4336 (94%)	741 (70%)	6187 (91%)	244 (75%)	1430 (93%)	1494 (86%)	15116 (89%)	468 (30%)	410 (54%)	15994 (83%)
Prostate cancer cases, screening group											
Prostate cancer cases overall in screening group, total (n)	482	3500	560	2376	92	814	620	8444	1718	747	10909
Screen-detected cancers (n)	188	1632	197	1868	60	576	436	4957	229	128	5314

Interval cancers and cancers among non-attendees (n)	294	1868	363	508	32	238	184	3487	1489	619	5595
Screen-detected cancers / biopsy (%)	25%	30%	22%	22%	23%	23%	22%	24%	49%	31%	25%
Cumulative incidence in screening group†, (%)	11.2%	11.0%	8.0%	13.6%	8.7%	13.8%	12.6%	11.7%	6.0%	6.9%	9.8%
Prostate cancer cases, control group											
Prostate cancer cases overall in control cohort, total (n)	393	4546	452	1325	60	592	364	7732	1541	690	9963
Cumulative incidence in control group (%) †	9.2%	9.4%	6.5%	7.6%	5.3%	9.9%	7.4%	8.7%	5.4%	6.6%	7.8%

* From randomisation to a minimum of 16 years, December 2014, and date of death.
† Calculated as total cases / randomized, excluding subjects with PCa before randomisation.

Table 2. Prostate cancer incidence at various lengths of follow-up

		Years 1-9	Years 1-11	Years 1-13	Years 1-16
Screening group	Prostate cancer (n)	6172	6852	7655	8444
	Person-years	584776	695850	797774	918300
	Rate per 1000 person-years	10.6	9.8	9.6	9.2
	Risk per 1000 men	85	95	106	117
Control group	Prostate cancer (n)	4154	5333	6384	7732
	Person-years	735777	877302	1007337	1162062
	Rate per 1000 person-years	5.6	5.6	5.6	5.6
	Risk per 1000 men	5.6	5.6	5.6	5.6
Rate ratio (95% CI)		1.90 (1.83 - 1.98)	1.65 (1.59 - 1.71)	1.54 (1.49 - 1.59)	1.41 (1.36 - 1.45)
Rate difference per 1000 person-years (95% CI)		5.0 (4.7, 5.3)	3.9 (3.6, 4.1)	3.4 (3.1, 3.6)	2.7 (2.4, 2.9)
Risk ratio (95% CI)		1.85 (1.78 - 1.93)	1.60 (1.54 - 1.66)	1.49 (1.44 - 1.54)	1.36 (1.32 - 1.41)
Risk difference per 1000 men (95% CI)		39 (37, 42)	35 (33, 38)	35 (32, 38)	31 (28, 34)

Table 3. Prostate cancer mortality at various lengths of follow-up

		Years 1-9	Years 1-11	Years 1-13	Years 1-16
Screening group	Prostate cancer deaths (n)	191	268	371	520
	Person-years	612723	735205	848802	985382
	Rate per 1000 person-years	0.31	0.36	0.44	0.53
	Risk per 1000 men	2.6	3.7	5.1	7.2
Control group	Prostate cancer deaths (n)	280	419	570	793
	Person-years	749801	899370	1038723	1207411
	Rate per 1000 person-years	0.37	0.47	0.55	0.66
	Risk per 1000 men	3.1	4.7	6.4	8.9
Rate ratio (95% CI)		0.84 (0.70 - 1.00)	0.78 (0.67 - 0.91)	0.79 (0.69 - 0.90)	0.80 (0.72 - 0.89)
p-value		0.053	0.001	<0.001	<0.001
Rate difference per 1000 person-years (95% CI)		-0.06 (-0.12 - 0.00)	-0.10 (-0.17- -0.04)	-0.12 (-0.18 - -0.05)	-0.13 (-0.20 - -0.07)
Rate ratio, attenders		0.78 (0.63, 0.96)	0.72 (0.60, 0.86)	0.73 (0.63, 0.85)	0.75 (0.66, 0.85)
p-value		0.022	<0.001	<0.001	<0.001
Risk ratio (95% CI)		0.84 (0.70 - 1.00)	0.78 (0.67 - 0.91)	0.79 (0.70 - 0.90)	0.80 (0.72 - 0.90)
Risk difference per 1000 men (95% CI)		-0.5 (-1.0, 0.0)	-1.0 (-1.7, -0.4)	-1.3 (-2.1, -0.6)	-1.8 (-2.6, -0.9)
NNI (95% CI)		1947 (963 - Inf)	962 (598 - 2463)	742 (478 - 1650)	570 (380 - 1137)
NND		76	34	26	18

NNI=Number needed to invite to screening to prevent one prostate cancer death
NND=Number needed to invite to diagnose to prevent one prostate cancer death

15 Inf=infinity

16

17

18