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Design-corrected variation by centre in mortality reduction in the ERSPC randomised prostate cancer screening trial

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Abstract

Objectives—To calculate design-corrected estimates of the effect of screening on prostate cancer mortality by center. in the European Randomised Study of Screening for Prostate Cancer (ERSPC).

Setting—The ERSPC, a large multi-centre trial, has shown a 21 % reduction in prostate cancer mortality in men invited to screening with follow up truncated at 13 years. Centers either used pre-consent randomisation (effectiveness design) or post-consent randomisation (efficacy design).

Methods—We included six centers: three with an effectiveness design, and three with an efficacy design. The analysis included follow-up until the end of 2010, or a maximum of 13 years. The effect of screening was estimated in terms of both effectiveness (the mortality reduction in the target population) and efficacy (the reduction in those actually screened).

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Declaration of conflicting interests

Dr Stenman declares the following conflicts of interest: Co-holder of patent for free PSA. Consulting for PerkinElmer-Wallac, Abbott Diagnostics, Orion Diagnostics.

Results—The overall crude prostate cancer mortality risk ratio in the intervention arm vs control arm for the six centers was 0.79 ranging from a 14% increase to a 38% reduction. The risk ratio was 0.85 in centers with a pre-consent randomisation design and 0.73 in those with a post-consent design. After correcting for the design, overall efficacy was 27%; 24% in pre-consent and 29% in post-consent centers; the range between centers was from an increase of 12% to a reduction of 52%.

Conclusion—The estimated overall effect of screening in attenders (efficacy) was a 27% reduction in prostate cancer mortality at 13 years of follow up. The variation in efficacy between centers was greater than the range in risk ratio without correction for design. The center specific variation in the mortality reduction could not be accounted for by the randomisation method.

The ERSPC is registered with Current Controlled Trials, number ISRCTN49127736.

Keywords

Prostate cancer; screening; prostate specific antigen; study design

Introduction

The method of randomisation in the European Randomised Study of Screening for Prostate Cancer (ERSPC) trial varied between centers[1]. In some centers, a target population of men was identified and randomly sampled (Finland) or allocated (Sweden, Italy, France) to the intervention or control arms of the trial. Those in the intervention arm were invited to screening. In other centers (the Netherlands, Spain, Belgium and Switzerland) the men in the target population were first invited to consent to participate in the trial. Only those consenting were randomised to either the intervention or the control arm, and those randomised to the intervention arm were invited for screening. These designs are called pre and post consent randomisation, or effectiveness design and efficacy design, respectively. It has been suggested that randomisation methods may have introduced a bias in the results published by ERSPC[2].

Efficacy means the effect on outcome in theoretically optimal conditions (for example with 100% compliance/attendance), while effectiveness is the effect on outcome in a real life population setting. In screening and in other public health activities, the difference between these designs stems mainly from the extent of non-response. Attendance of those randomised to the intervention arm is generally higher with the efficacy design because the subjects have already indicated their willingness to take part in the study. The attendance proportion is a major determinant of the impact of population screening on mortality outcomes. However coverage, the proportion of those in the total target population who are screened may be less in trials with a post-consent randomisation design than with a pre-consent design, because of the two phase process of both consenting and attending. There may also be differences in the underlying risk (of either all cause or disease specific mortality) in the randomised populations due to the ‘healthy volunteer’ effect[3], although there is no evidence that this affects the relative risk due to the intervention.

The choice of design will depend on both ethical and practical constraints. In the ERSPC, the choice was in line with different national legal regulations. Ethical review board views are also reflected in local legislation. Some review boards regard it to be unethical to run a study without consent of the controls, and only an efficacy study is possible. Some however take the view that, as in any case the whole population is not covered by the trial (for example there may be restrictions by study area, calendar time, age and other characteristics), the choice of design can be made on scientific grounds, i.e. which of the designs provides data of more scientific value.

In fact, both designs are related to the scientific question of the effect of an intervention, whilst serving different purposes. The post-consent randomisation (efficacy) design in prostate cancer screening is addressing the question of effect in those who choose to be screened (or those who are actually screened) compared to a control group of men offered the normal health care practice, which will include opportunistic PSA-testing[4]. For brevity, we call this as a clinical purpose; it relates closely to the issue of clinical practice. The post-consent randomisation (effectiveness) design addresses the question of the effect of a screening programme as public health policy in the target population compared to normal clinical practice without a screening programme. Therefore, the corresponding purpose can be defined as a public health one.

Previously we have reported a 21% reduction in prostate cancer mortality at 11 and 13 years of follow-up in men aged 55–69 years invited to screening[5, 6]. This overall estimate did not take into consideration the two different designs of the included centres. Attendance for screening will tend to be lower with the pre-consent randomisation design, although even with post-consent randomisation there will be some non-attenders. After correction for non-attendance and adjustment for selection bias due to a likely higher mortality in non-attenders for screening, the overall efficacy was estimated at 27% at 13 years of follow up. However, large differences in the uncorrected prostate cancer mortality reduction between centers were observed, from a 14% increase (Switzerland) to a 38% reduction (Sweden) [5, 6.]

The reason for the differences in effect between the centers is likely to be multifactorical. In this paper we correct only for the design of effectiveness or efficacy. We also discuss the implications of these two different study purposes on the design and on the analysis of a screening study. We report the design-corrected efficacy and the effectiveness of screening for prostate cancer in the ERSPC screening trial by center, with follow-up until 31.12.2010, censored at 13 years. Specifically, we address the question of variation in effect between centers that can be accounted for by the different designs.

Method

Population

The ERSPC trial involved 182,160 men of which 162,388 were in the core age group of 55 to 69 years at the time of randomisation. The two French centres were excluded from the present analyses because of short follow-up (median 6.4 and 7.5 years respectively), and Spain was excluded because of the small number (2197) of men randomised. The final

number of men, period of recruitment and median length of follow-up by center are given in Table 1.

The total population, in the intervention and control arms combined, varied by center from 80,379 in Finland to 8,562 in Belgium. The duration of recruitment was from two years in Sweden to 12 years in Belgium. Data for overall mortality were obtained by linkage to national registries. Causes of death were evaluated in a blinded manner by an independent cause of death committee following a standard algorithm[7], except in Finland where death certificates causes were used after a very high concordance with committee assignments was shown.

Definitions

We define the outcome as death from prostate cancer, and attendance as attendance in response to first invitation to screening.

We use the following notations:

M(p) = mortality from prostate cancer in the whole target population (for the post-consent randomisation (efficacy) design, this includes the population from whom men were recruited, which is generally not known).

M(v) = mortality from prostate cancer in the men consenting to take part (post-consent randomisation (efficacy) design)

M(a) = mortality from prostate cancer in the attendees to screening

M(na) = mortality from prostate cancer in non-attendees (among invitees to screening)

α = person years in attendees as a proportion of the person years in the invited target population (pre-consent randomisation (effectiveness) design)

γ = person years in attendees as a proportion of the person years in those consenting and randomised to the intervention arm (post-consent randomisation (efficacy) design)

Invited are those randomised to the intervention arm in the total target population (effectiveness design) or in the consenters (post-consent randomisation (efficacy) design). We further denote:

$M_0(.)$ = prostate cancer mortality assuming no screening offered

$M_1(.)$ = prostate cancer mortality assuming screening offered

For each of . = p, v, a and na.

The basic relations, that link the quantities above, are

(pre-consent randomisation design)

$$M_0(p)=\alpha M_0(a)+(1-\alpha)M_0(na) \quad (1)$$

(post-consent randomisation design)

$$M_0(v)=\gamma\, M_0(a)+(1-\gamma)\, M_0(na) \quad (2)$$

These relations provide estimates of the mortality rate in the attenders in the absence of screening, by subtracting from the mortality in the control arm the mortality equivalent to that in the non-attenders in the intervention arm, and thus take account of selection bias.

With these denotations we can define

$$\text{Effectiveness} \quad E(p)=1-M_1(p)/M_0(p) \quad (3)$$

$$\text{Efficacy} \quad E(a)=1-M_1(a)/M_0(a) \quad (4)$$

Estimation of effectiveness

The pre-consent randomisation design provides a direct estimate of effectiveness. In the formula (3) $M_1(p)$ is the prostate cancer mortality in the total (invited) intervention arm and $M_0(p)$ is the mortality from prostate cancer in the control arm. Both quantities are known from the data.

The post-consent randomisation design does not provide data on effectiveness. To estimate effectiveness would require the person years in the consenters as a proportion of those in the total target population, together with the mortality in non-consenters, to be known, in addition to the trial data itself. This information is rarely available, and was not available in all ERSPC centers. More importantly, the inclusion of a two-phase screening process both consenting and attending means that such an estimate would lack real life applicability. In real life only a single phase will exist: that of attending, or responding to the invitation. In an efficacy trial the sum of non-consenters and non-attenders will differ from the number of non-attenders in an effectiveness trial because of the difference in motivation. Conceptually, to estimate effectiveness from an efficacy trial requires restrictive assumptions, and we do not present any such estimates for the pre consent centers in the ERSPC trial.

Estimation of efficacy

Transformation in the pre-consent randomisation (effectiveness) design to the efficacy E(a), takes place with the basic relation (1) that has previously been described elsewhere[8], and which takes account of selection bias due to differential mortality in non-attenders as well as the dilution due to non-attendance itself.

$$E(a)=1-M_1(a)/M_0(a)$$
$$=1-\alpha\, M_1(a)/(M_0(p)-(1-\alpha)M_0(na))$$

Here $M_0(na)$ is the mortality in those randomised in the intervention arm but who did not attend. $M_1(a)$ is the mortality in attenders, i.e. in those actually screened, $M_0(p)$ is the mortality in the control arm and α is the person year proportion of attenders in the screening arm. All these quantities are directly estimable from the data.

Even with the post-consent randomisation design, some correction is necessary to produce an estimate of efficacy with 100% attendance, since not all of those who consented and were randomised to the intervention arm actually attended, and some selection bias may still be present. The expected mortality in those attending can be estimated in a similar way to the pre-consent randomisation design, by means of the basic relation in the consenters (2) between the risk of death among non-attenders and controls. Simple arithmetic yields

$$E(a)=1-M_1(a)/M_0(a)$$
$$=1-\gamma M_1(a)/(M_0(v)-(1-\gamma)M_0(na))$$

Here $M_1(a)$ is the mortality among those screened (the attenders), the $M_0(v)$ is the mortality in the control arm of those consenting and $M_0(na)$ is the mortality in the consenters in the intervention arm who did not attend, and γ is the person year proportion of attenders in intervention arm. All these components are known and estimable from the data.

Results

The total numbers of men, person years and prostate cancer deaths in attenders, non-attenders and controls by center are given in the table 2.

The crude indicator of screening effect, prostate cancer mortality risk ratio (RR), calculated on an intention to treat basis (i.e. number of prostate cancer deaths divided by the respective person years in the intervention arm vs control arm) was RR = 0.79 (95% CI 0.69–0.91) (calculated with the control population for Finland weighted by 1:1.5) It showed substantial variation between centers from RR = 1.14 to RR = 0.62, the crude effect, (1−RR), therefore ranging from a reduction of 38% to an increase of 14%. Within the centers with a pre-consent randomisation design reductions ranged from 38% to 9%, whilst in those with an post-consent randomisation design the crude effect ranged from a 33% reduction to a 14% increase. Overall, the relative risk was larger in centers with pre-consent randomisation (RR=0.85) than in those with post-consent randomisation design (RR=0.73) (Table 3).

For estimates of efficacy in attenders, the overall risk ratio was 0.72 (95% CI 0.60–0.87), and the efficacy (1−RR)*100 increased to 28%. It was smaller in centers with pre-consent randomisation design (26%) than in those with post-consent randomisation design (29%). The range of 1−RR was 0.66 (from 0.52 to −0.14).

Discussion

We have calculated adjusted estimates of mortality reduction for the ERSPC centers in order to improve comparability between centers. Randomisation in the ERSPC centers was by two different methods. Post-consent randomisation was practised in Belgium, the Netherlands and in Switzerland, and pre-consent randomisation in Finland, Italy and Sweden. In Italy and Sweden a random allocation in 1:1 ratio was followed, whereas in Finland 32 000 of more than 80 000 men were randomly sampled to the screening arm. It has been suggested that the randomisation methods may have introduced a bias [2] and resulted in too large an estimated effect with pre-consent randomisation[9] and, that therefore the pooling of ERSPC centers may be inappropriate[10]. While the purpose of randomisation per se is to remove bias, application of different randomised designs may cause incomparability. In the present study, we correct for the incomparability and relate the randomisation method to the effect in those actually screened or in the target population i.e. to the purpose of the trial. The correction for efficacy had a greater impact in centers with a pre-consent randomisation (effectiveness) design than in those with a post-consent randomisation (efficacy) design (post-consent.

The different designs correspond to different contexts of screening; In practice, both designs compare an organised screening programme to the routine clinical practice which will include opportunistic screening. Opportunistic or spontaneous PSA-testing, either in the intervention or in the control arm, is called contamination. The performance of the test in the absence of such spontaneous use is difficult to measure once a test is approved, but any attempt to correct for contamination methodologically will have the potential for bias[8]. With post-consent randomisation, knowledge of the randomisation may affect the probability of having a spontaneous test in those allocated to the control group, resulting in more treatment and possibly an effect on mortality, but in a non-measurable way. It is therefore possible that the efficacy design underestimates the effect in those actually screened,. In the effectiveness design where individuals in the control arm are not contacted, the randomised study itself is less likely to affect the PSA-testing in the controls. We have not made such an assumption-based correction in this study.

Post-consent randomisation is specifically designed to provide an estimate of efficacy. However, the relative risk of prostate cancer death between the arms should still be corrected for the nonattendance in those consenting.

Pre-consent randomisation is designed to estimate effectiveness in the target population, but at the same time it provides an estimate of efficacy. Therefore, any changes related to the screening (exposure) and to the treatment and, hence, to death are likely to be more comparable with the population at large in the effectiveness trial than in the efficacy one. Furthermore, it is difficult to see how the exposure to any medical services in a randomised trial that is identical in the controls and in the population at large would violate any ethical rules.

The Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening trial conducted in the United States, enrolled over 150,000 subjects at 10 different screening centres, some of which used a ‘single consent’ process (post-consent randomisation) and some a ‘dual

consent process where randomisation was carried out after initial consent to follow up, and subjects randomised to the intervention arm were asked to consent again to screening[11]. The odds ratio of non-compliance was 2.2 in the dual consent centres even after adjustment for other factors. Contamination by screening in the control arm was a major issue in the prostate screening trial in PLCO[12], but data on contamination according to the consent process have not been published.

We believe that from a scientific point of view the pre consent randomised design without explicitly consenting the controls is superior to the post consent randomised design, because as demonstrated above the former can be used to provide results on both the clinical problem of efficacy and on the public health question of effectiveness, whereas the latter provides results only on efficacy. However the method above only provides adjusted estimates of efficacy in those accepting the first invitation to screening, and more sophisticated methods are required to study the effect of different patterns of subsequent screening attendance.

Even after correcting for the differences in design by estimation of efficacy, considerable variation remained between centres. As discussed elsewhere, possible reasons for this variation include differences in the extent of contamination by PSA screening in the control group, and variations in screening protocol including the number of screens and the length of the screening interval[6].

Efficacy was estimable in all ERSPC centers with minor restrictive assumptions. After correction for non-attendance and selection bias the overall efficacy (effect in attenders) was a 28% reduction in prostate cancer mortality; the effect estimate in the ERSPC of 21% in men invited[6] was a mixture of effectiveness and efficacy. Efficacy (effect in attenders) was larger in centers with post-consent randomisation than in those with pre-consent randomisation design, but the difference in the overall estimate of efficacy between the two groups of centers was substantially smaller than that in the crude estimate of relative mortality risks. However the correction for study design did not reduce the variation between individual centers, suggesting that center specific variation in the mortality reduction could not be accounted for by the randomisation method.

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Table 1

Number of men in the target population and screening arm, years of intake and mean years of follow-up by center in ERSPC. Core age group, follow-up to 31.12.2010, censored at 13 years

Center	Target population	Assigned to screening arm	Years of recruitment	Median of follow-up (years)
Pre-consent randomisation				
Finland	80,379	31,970	1996–1999	13
Italy	14,517	7,266	1996–2000	12.6
Sweden	11,852	5,901	1994–1995	13
Post-consent randomisation				
Belgium	8,562	4,307	1991–2003	13
Netherlands	34,833	17,443	1993–2000	13
Switzerland	9,903	4,948	1998–2003	10.2

Table 2

Number of men, person years and number of prostate cancer deaths by arm, attendance status and center in ERSPC. Core age group 55–69 years, follow-up to 31.12.2010, censored at 13 years

Center	Number of men			Person years			Prostate cancer deaths		
	Screening		Controls	Screening		Controls	Screening		Controls
	Attendees*	Non-attendees		Attendees	Non-attendees		Attendees	Non-attendees	
pre-consent randomisation									
Finland	20789	11181	48,409	246603	118926	553046	97	73	284
Italy	4961	2305	7,251	57082	25375	81715	17	9	32
Sweden	3649	2252	5,951	44376	24776	69498	22	16	62
Total	29399	15738	61611	348061	169077	704259	136	98	378
post-consent randomisation									
Belgium	3744	563	4,255	41199	5740	45932	17	1	23
Netherlands	16502	941	17,390	190108	9850	199165	78	7	126
Switzerland	4731	217	4,955	46459	1929	48253	16	0	14
Total	24977	1721	26600	277766	17519	293350	111	8	163

*Responders to the first invitation

Table 3

Effectiveness (in the population) and efficacy (in attenders) and by ERSPC center and arm. Core age group 55–69 years, follow-up until 31.12.2010, censored at 13 years

Center	Prostate cancer mortality by arm			Attendance proportion	Effectiveness	Efficacy
	Rate per 1000 person-years		RR (95% CI)		% mortality reduction (95% CI)	% mortality reduction (95% CI)
	Screening	Control				
pre-consent randomisation						
Finland	0.47	0.51	0.91 (0.75–1.10)	0.65	9	15 (−18 – 37)
Italy	0.32	0.39	0.81 (0.48–1.35)	0.68	19	26 (−43 – 56)
Sweden	0.55	0.89	0.62 (0.41–0.92)	0.62	38	52 (15–73)
Total			0.85 (0.72–0.99)		15	26 (2 – 43)*
post-consent randomisation						
Belgium	0.38	0.50	0.77 (0.41–1.42)	0.88	n.e.	24 (−45 – 54)
Netherlands	0.43	0.63	0.67 (0.51–0.88)	0.95	n.e.	35 (13 – 52)
Switzerland	0.33	0.29	1.14 (0.56–2.33)	0.96	n.e.	−14 (−135 – 45)
Total			0.73 (0.57–0.92)		n.e.	29 (9 – 45)
Total	0.43	0.54	0.79 (0.69–0.91)	0.76		28 (13 – 40)*

n.e. not estimable

* with adjustment for the control population in Finland