EUROPEAN JOURNAL OF CANCER 46 (2010) 3102–3108

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

Lead-time in the European Randomised Study of Screening for Prostate Cancer

Patrik Finne [a], *Mahdi Fallah* [a,b], *Matti Hakama* [a,c], *Stefano Ciatto* [d], *Jonas Hugosson* [e], *Harry de Koning* [f], *Sue Moss* [g], *Vera Nelen* [h], *Anssi Auvinen* [a,*]

[a] *University of Tampere, School of Public Health, Tampere, Finland*
[b] *Tampere University Hospital, Finland*
[c] *Finnish Cancer Registry, Helsinki, Finland*
[d] *Istituto per lo Studio e la Prevenzione Oncologica, Florence, Italy*
[e] *Department of Urology, Sahlgrenska University Hospital, Gothenburg, Sweden*
[f] *Erasmus University Medical Centre, Department of Public Health, Rotterdam, The Netherlands*
[g] *Institute for Cancer Research, Sutton, Surrey, England, UK*
[h] *Public Health Department, Provincial Institute of Hygiene, Antwerp, Belgium*

ARTICLE INFO

Article history:
Received 31 May 2010
Received in revised form
19 September 2010
Accepted 20 September 2010

Keywords:
Prostate neoplasms
Mass screening
Prostate-specific antigen
Randomised trials

ABSTRACT

Background: Lead-time is defined as the time by which screening advances the diagnosis compared with absence of screening. A sufficiently long lead-time needs to be achieved so that cancer can be detected while still curable. A very short lead-time may indicate poor sensitivity of the screening test, while a very long lead-time suggests overdiagnosis.
Material and methods: In the first screening round, a total of 56,294 men aged 55–74 years were screened with serum prostate specific antigen (PSA) in five countries of the European Randomised Study of Screening for Prostate Cancer (ERSPC) with an overall detection rate (prevalence) of 2.8% (1972 prostate cancers). Prostate cancer incidence among 92,142 men randomly allocated to the control arm of the trial was also assessed. Lead-time was estimated as the time required to accumulate a similar cumulative risk of prostate cancer in the control arm to the detection rate in the intervention arm, i.e. from the ratio of detection rate (prevalence of screen-detected cases) and expected incidence (cumulative risk).
Results: Using a serum PSA cut-off of 4 ng/ml, the mean lead-time in the whole study population was estimated as 6.8 years (95% confidence interval (95% CI) 7.9–8.4). It was 8 years in The Netherlands, 6 in Sweden and Finland, 5 in Italy and 4 in Belgium. The mean lead-time was similar, 6–7 years, at ages 50–64 years, but close to 8 years among men aged 65–74 years. A lower PSA cut-off level of 3 ng/ml used in Sweden and The Netherlands prolonged the mean lead-time by approximately 1 year. Lead-time based on advanced prostate cancer only was slightly shorter, mean 5.3 years (95% CI 4.6–6.0). The lead-time for the second screening round was slightly shorter than that for the first (5.9, 95% CI 5.4–6.4), reflecting a similar relation between detection rate and control group incidence.
Conclusion: The lead-time for prostate cancer found in ERSPC substantially exceeded that found for breast, cervical and colorectal cancer screening. One round of prostate cancer

* *Corresponding author:* Address: Tampere School of Public Health, FI-33014 University of Tampere, Finland. Tel.: +358 3 3551 6883; fax: +358 3 3551 6057.
E-mail address: anssi.auvinen@uta.fi (A. Auvinen).
0959-8049/$ - see front matter
doi:10.1016/j.ejca.2010.09.034

screening can advance clinical diagnosis by 4–8 years. Overdiagnosis or detection of non-progressive tumours may contribute substantially to the lead-time.

1. Introduction

Screening for prostate cancer with prostate-specific antigen (PSA) has become more frequent in most Western countries, although it was only recently proven to reduce prostate cancer mortality.[1] Screening may reduce the disease burden if more effective treatment can be provided when the disease is detected in the pre-clinical state. The time by which screening advances the detection of prostate cancer (i.e. interval between the time of detection by screening and the time the case would have become detectable in the absence of screening) is called the lead-time.[2] Hence, lead-time represents a window of opportunity for curing a screen-detected case and reducing disease burden in the target population. The length of lead-time depends both on disease and on the screening test, because the interval between screening detectability and clinical surfacing is affected by both the natural history and the test properties. A closely related concept is the duration of the detectable preclinical phase (DPCP), which defines the maximum lead-time. The screening interval should be shorter than the DPCP.

Ideally, the lead-time is identical to the screening interval, assuming perfect sensitivity and no overdiagnosis or contamination (screening in the control arm). Under such condition, all interval cases arise during the screening interval (no cases are missed at screening) and therefore have a maximum lead-time equal to the length of the interval. Less than perfect sensitivity increases the lead-time, as does overdiagnosis by screening (by inflating the detection rate), while contamination biases the estimated lead-time downward through overestimation of the expected incidence.

Comparison of lead-time between different screening regimens indicates the potential effectiveness, assuming that all cancers detected would surface clinically. Due to the hypothetical or counterfactual nature of the concept (contrasting actual and potential disease occurrence), lead-time cannot be observed directly. Yet, a randomised screening trial offers an opportunity for obtaining a valid estimate of the expected incidence in the absence of screening from the control arm.

Lead-time can be estimated by comparing the incidence of prostate cancer in a screened population to that in a control population, i.e. ratio of detection rate at screening to the expected incidence. In this way, the lead-time in the first round of the Finnish prostate cancer screening trial was shown to be 5–7 years.[3] Similarly, a lead-time of 4.5–8 years was estimated by comparing the results of a Swedish early detection programme with prostate cancer incidence in a control group.[4]

Other approaches have also been used for estimating the lead-time. A simulation study based on the Dutch screening trial estimated lead-time using a stochastic natural history model.[5] It gave an estimate of 11 years for the mean lead-time for screening with a 4-year interval. Serum bank studies can provide estimates based on time from blood sample to diagnosis of cancer, and in such studies lead-times between 5 and 10 years have been reported.[6,7] Several modelling studies have estimated lead-time from incidence and mortality rates, without individual screening data. They have given estimates from 5 to 7 years.[8–10] A recent British study estimated lead-time as 5–14 years, depending on differentiation (Gleason grade).[11]

We estimated lead-time of prostate cancer screening based on the relation of detection rate and control arm incidence among nearly 150,000 men from five centres within the ERSPC trial.

2. Material and methods

The five largest participant centres of ERSPC (registered as Current Controlled Trials ISRCTN 49127736) were included in the study.[12] Altogether 56,294 men aged 50–75 years were screened during the first screening round in the intervention arm of the trial (Table 1). The control group of 92,142 men accrued 710,347 person-years during a follow-up time up to 13 years. Cancer incidence data were available up to 31/12/2003 in Italy, 31/12/2005 in Finland, 31/03/2006 in Sweden, 30/09/2004 in Belgium and 31/12/2004 in The Netherlands.

In Belgium, Finland and Italy, a serum PSA 4 ng/ml or higher was defined as a positive screening result, resulting in referral to prostate biopsy (though in Belgium a lower cut-off level of 3 ng/ml was adopted in 1999). In these three centres, digital rectal examination and/or transrectal ultrasonography (in Italy and initially also in Belgium) or proportion of free PSA (in Finland) was used as ancillary referral criterion in the intermediate PSA range (3–3.9 ng/ml in Finland and 2.5–3.9 ng/ml in Italy).[7] In Sweden, the cut-off of serum PSA was 3 ng/ml, and in The Netherlands the cut-off was lowered from 4 ng/ml to 3 ng/ml in 1997. The central database of ERSPC provided data on the number of prostate cancers detected in screening and control arms, and the number of person-years accrued in the control arm.

2.1. Calculating cumulative risk of prostate cancer in the control arm

Cumulative risk of prostate cancer in the control arm was calculated as a function of the follow-up time given by the formula:

$$F(t) = 1 - \exp(-\lambda_1 - \lambda_2 \ldots - \lambda_i)$$

where λ_i is the incidence rate during the year i of follow-up. Incidence density rate of prostate cancer in the control arm was estimated as the number of cancer cases divided by the number of person-years during each year of follow-up. Cumulative risk of prostate cancer can be defined as the probability of being diagnosed with prostate cancer within a given period of time assuming no death due to other causes than prostate cancer in that period.

Table 1 – Screening protocol by country.

Country	Age range at entry	Screening interval (years)	Screening regimen	
			Prostate specific antigen (PSA) 3.0–3.9	PSA ⩾ 4.0 (ng/ml)
Finland	55–67	4	F/T PSA	Biopsy
The Netherlands	55–74	4	Biopsy[a]	Biopsy
Sweden	51–66	2	Biopsy	Biopsy
Italy	55–70	4	DRE and TRUS for PSA 2.5–3.9	Biopsy
Belgium	55–74	4	Biopsy[b]	Biopsy

F/T PSA: ratio of free to total PSA with a cut-off of 0.16. DRE: digital rectal examination. TRUS: transrectal ultrasound.
[a] From 1997 onwards, earlier also DRE and TRUS as primary screening test for all men.
[b] From 1999 onwards; 1995–1997 cut-off 4 ng/ml; DRE is used as a primary screening test for all men.

2.2. *Advanced prostate cancer*

A separate analysis was conducted restricted to advanced cancer, defined in terms of clinical TNM stage (T3-4, N1 or M1).

2.3. *Estimating the lead-time*

We estimated lead-time of prostate cancer screening as the time required to accrue a similar cumulative prostate cancer risk in the control arm to the detection rate in the screening arm (number of screen-detected cancer cases relative to the number of screened men). This approach can be seen as a refined version of the traditional prevalence:incidence ratio, which provides a crude measure of the lead-time. The difference is mainly due to the fact that prostate cancer is common enough for the simple estimate of cumulative incidence over the follow-up time ($\Sigma\lambda_i$ or sum of annual incidence rates) to diverge from the exponential formula ($1 - \exp[-\Sigma\lambda_i]$, as above).

For the first round, follow-up of the men in the control arm started at randomisation and for the second round at the time of the initiation of the second round of screening.

Confidence intervals were estimated by simulations, assuming that the numbers of screen-detected cases, as well as incident cases in the control arm, follow a Poisson distribution (entering both frequencies as random variables into the function with 10,000 iterations).

The trial protocol was reviewed by the pertinent ethical committees in each participating centre.

3. Results

The detection rate of prostate cancer screening using a cut-off of serum PSA of 4 ng/ml varied between 1.4% and 4.0% in the five countries (Table 2). Including also those cases detected with lower PSA levels, the detection increased slightly, ranging from 1.6% in Italy to 5.1% in The Netherlands.

The prevalence/incidence ratio based on serum PSA ⩾ 4 ng/ml in the first round was 3.2 years in Belgium, 5–6 in Sweden, Italy and Finland and 8.6 in The Netherlands. In all countries combined, the mean P:I ratio was estimated as 6.8 years (95% confidence interval (95% CI) 6.5–7.2).

A cumulative risk of prostate cancer corresponding to the detection in the screened group based on a PSA cut-off level of 4 ng/ml was reached in 4 years in Belgium, 5 years in Italy, 6 years in Sweden and Finland and 8 years in The Netherlands (Fig. 1). In the whole study population, the detection probability of the first screening was reached in the control arm in slightly less than 7 years (6.8, 95% CI 6.4–7.3 years, Table 2).

With a PSA cut-off of 4 ng/ml, the estimated lead-time was approximately 8 years among 65–74-year-old men, while it was 6–7 years in the younger age groups. The screen-detected prostate cancers with serum PSA 3.0–3.9 ng/ml prolonged the estimated lead-times by approximately 1 year (not shown).

An additional analysis conducted based on advanced/aggressive cases only gave a considerably shorter mean lead-time in some centres, while no substantial difference was seen in others (Table 3). The analysis restricted to advanced cases yielded substantially shorter lead-time in Finland, Sweden and Italy (by a third to a half). Some shortening occurred also in The Netherlands and Belgium, but only by approximately a tenth. The mean lead-time for all five centres combined was 5.3 years (95% CI 4.6–6.0).

In the second screening round, detection remained comparable to the first round (Table 2). The detection rate was lower only in The Netherlands, while yields were higher in Belgium (and to a lesser extent also in Finland). Correspondingly, lead-time was overall only slightly shorter than for the first round (5.9 years, 95% CI 5.4–6.4). In Belgium, the detection rate was substantially higher and lead-time markedly longer than at the first round. This was probably attributable to the long screening interval (7 years due to temporary discontinuation for lack of funding) resulting in men being substantially older and a long time window for *de novo* cancers to arise. Slightly longer lead-time was seen also in Finland, while in The Netherlands the lead-time was considerably shorter than at the first round.

4. Discussion

We estimated lead-time in five centres within the European Randomised Study of Prostate Cancer Screening, with slightly different screening regimens. The estimated lead-time ranged 4–8 years between centres. Analysis restricted to advanced cases gave shorter lead-times for all centres. The mean lead-time for the second screening round was overall slightly shorter than at the initial screen, but the relation varied in different centres. It is not possible to conclude whether the long lead-time reflects mainly overdiagnosis, but it indicates a higher yield in the screening arm relative to the control arm (expected incidence).

Table 2 – Numbers of men and prostate cancers with detection rates among the screened group (rounds 1 and 2) and cumulative incidence in the control group by centre, European Randomised Study of Screening for Prostate Cancer.

	Control arm (8-year follow-up)				Screening arm, round 1				Screening arm, round 2		
	Men	Cancer cases	Cumulative risk (%)	Incidence rate (10^5)	Screened men	Screen-detected cancer cases*	Lead-time, years (95% CI)	P:I ratio	Screened men	Screen-detected cancer cases	Lead-time, years (95% CI)
Country	*n*	*n*			*n*	*n* (%)			*n*	*n* (%)	
Finland	48,407	1399	2.9	401	20,796	506 (2.4)	6.4 (5.7–7.1)	6.1	16,247	447 (2.8)	7.1 (6.3–8.0)
The Netherlands	21,138	678	3.2	478	19,970	804 (4.0)	8.3 (7.5–9.2)	8.6	12,531	260 (2.1)	4.9 (4.2–5.7)
Sweden	9954	284	2.9	376	5855	110 (1.9)	5.8 (4.5–7.4)	5.0	4685	60 (1.3)	4.7 (3.5–6.2)
Italy	7477	113	1.5	279	5106	71 (1.4)	5.2 (3.8–7.1)	5.5	3903	53 (1.4)	5.1 (3.4–7.6)
Belgium	5166	197	3.8	607	4567	88 (1.9)	4.2 (3.1–5.7)	3.2	1560	64 (4.1)	7.1 (5.2–9.6)
Total	92,142	2671	2.9	418	56,294	1603 (2.8)	6.8 (6.4–7.3)	6.8	38,926	884 (2.3)	5.9 (5.4–6.4)

* The detection rate shown is obtained for serum PSA cut-off of 4 ng/ml.

In theory of screening, it is assumed that the target condition progresses from a pre-clinical detectable phase (PCDP) to a clinical state.[1,13,14] Lead-time indicates the amount of time gained by screening, i.e. how much earlier disease is detected through screening compared with absence of screening. A closely related concept is sojourn time, which refers to the duration of the PCDP (the maximum lead-time). The prevalence:incidence ratio as well as the prevalence:risk ratio we used may be considered a measure of the mean sojourn time (duration of PCDP). However, it can also be taken to represent lead-time based on the assumption that lead-times follow a negative exponential probability distribution owing to its memoryless nature, i.e. the time to event is unaffected by the time from the past event. Hence, the expected time to an event is independent of the time since its previous occurrence. In other words, if the time from onset to clinically diagnosis is exponentially distributed, the distribution of the time from detection by screening to clinical diagnosis does not depend on the time from onset to screen-detection, but is again exponentially distributed with the same mean. This allows the interpretation of the time to accrue incidence similar to the screening as the lead-time. The exponential distribution is commonly used for modelling lead-time also in more refined analyses also incorporating sensitivity,[16,17] as it relates naturally to stochastic event history process by implying Poisson-distributed disease incidence.

The potential benefit of a screening programme is proportional to the lead-time acquired by early diagnosis, but this relationship is not straight forward because of the interrelation between lead-time, sensitivity and overdiagnosis. Overdiagnosis is detection of disease that would not have reached the clinical state during the lifetime of the person with a screen-detected disease. As overdiagnosis is thought to be more common in prostate cancer screening (up to half of the screen-detected cases[5,8,15]) than breast or colorectal cancer screening (not including *in situ* or pre-malignant lesions), it has a strong influence on lead-time. The extent of overdetection can be estimated if both lead-time and mortality from other disease are known, given that there are no indolent (non-progressive) cases. Yet, detection of non-progressive tumours may substantially inflate the estimated lead-time, and for instance autopsy studies have shown very high prevalence of latent prostate cancers.[18] Several studies have attempted to estimate both lead-time and overdiagnosis, dealing separately with cases that would be expected to surface clinically.[5,7–10] Our approach does not allow distinction of the effects of sensitivity and overdiagnosis.

To deal with overdiagnosis, we conducted a separate analysis of advanced cancers only in both arms, assuming that these represent cases very likely to surface clinically and involve little if any overdiagnosis. The lead-time in this analysis was 3–5 years, with the exception of The Netherlands with substantially longer lead-time (7.5 years). The shorter lead-time reflecting lower incidence of such cancers among screened men relative to the control group may be attributable to inflation of lead-time for all cases and/or a stage shift as the result of screening. A short lead-time for aggressive cancer is highly plausible, as it may indicate more rapid growth and progression, resulting in shorter pre-clinical detectable phase. The fact that the lead-time is nevertheless

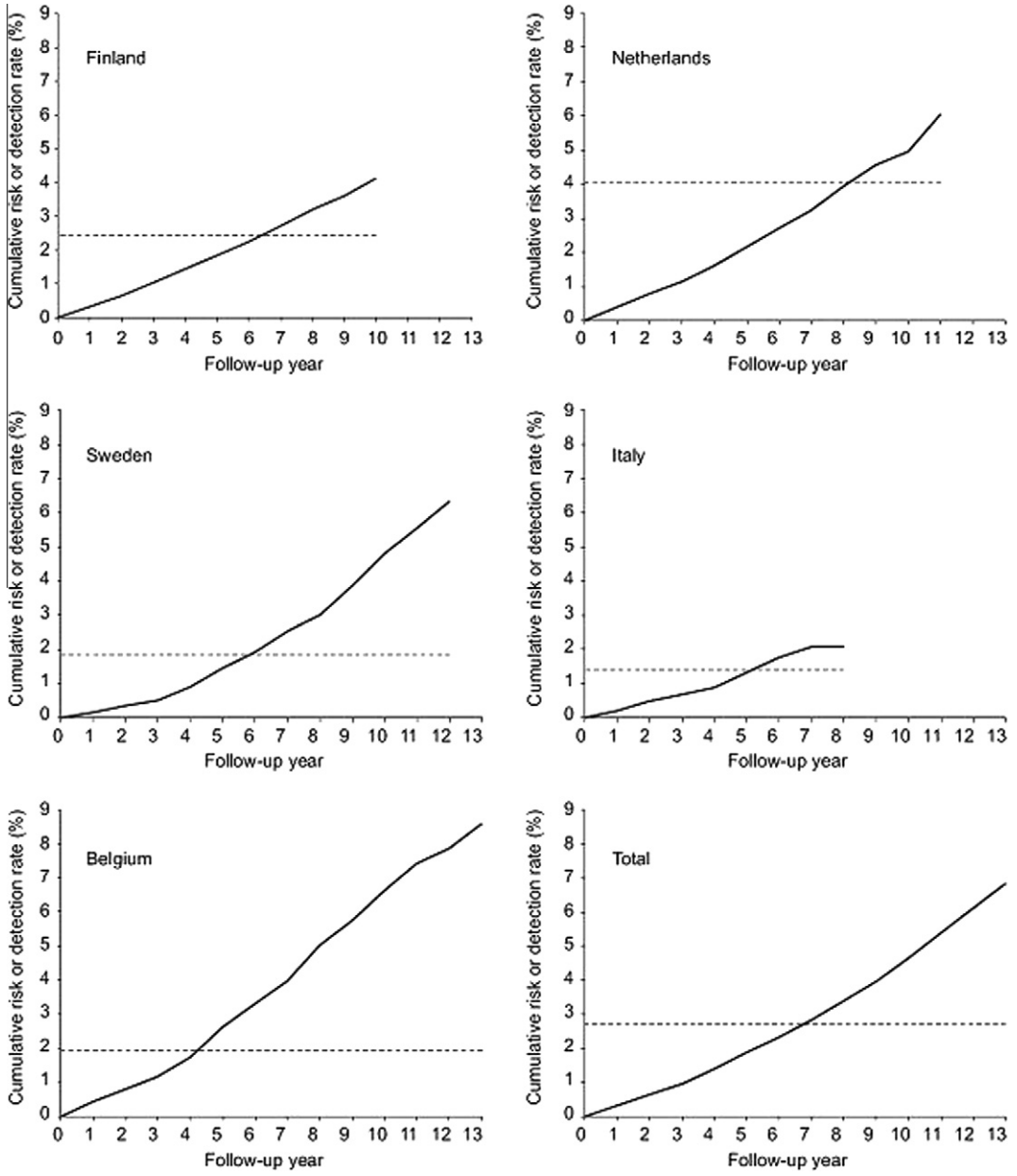

Fig. 1 – Cumulative risk of prostate cancer detection in control arm (solid line) in relation to detection rate of prostate cancer in the first screening round (dotted line) by country.

substantial (similar to or longer than screening interval) suggests that these cases can also be detected early by screening. Even though these cases are likely to be clinically relevant, they may not be entirely free from overdiagnosis, as some deaths from other causes are likely to occur prior to the expected clinical detection.

The shortest mean lead-time was estimated for Belgium. This is related to the fact that it had a relatively low detection rate, but prostate cancer incidence in the control arm was higher than that for the other centres. The longest mean lead-time was found for The Netherlands with the highest detection rate. This could reflect a high sensitivity or overdiagnosis owing to consistently low PSA cut-off and use of additional tests. No straight forward relation was observed between the PSA cut-off level used and the length of lead-time, which may be partly due to other differences in screening protocols or in baseline risk of prostate cancer.

The highest cumulative risk of prostate cancer and incidence rate in the control arm were found in Belgium and The Netherlands. This may be related to the volunteer-based design, which may have led to recruitment of high-risk men and/or contamination. This is also suggested by the fact that the rates in the control arm in these countries are well above national incidence rates. Contamination (unorganised screening in the control arm) may increase the prostate cancer incidence in the control arm and hence shorten the estimated lead-time.[19]

The lead-time for the second screening round was not substantially shorter than that for the first round, which was unexpected, as the prevalence screen is usually assumed to

Table 3 – Lead-time calculated from the ratio of detection rate and cumulative risk based on advanced cancers only (T3-4, N1 or M1).

		Control arm (8-year follow-up)			Screening arm			Lead-time, years (95% CI)
Country	Men *n*	Advanced cases *n*	Cumulative risk (%)	Incidence rate (10^5)	Screened men *n*	Screen-detected advanced[#] *n*	Detection rate[#]	
Finland	48,407	383	0.8	110	20,796	73	0.4	3.3 (2.5–4.2)
The Netherlands	21,138	196	0.9	139	19,970	205	1.0	7.5 (6.2–9.1)
Sweden	9954	75	0.7	99	5855	11	0.2	3.5 (1.5–4.6)
Italy	7477	30	0.4	116	5106	14	0.3[a]	3.4 (1.6–6.2)
Belgium	5166	52	1.2	143	4567	39	0.9[a]	4.0 (2.6–6.0)
TOTAL	92,142	743	0.8	116	56,294	331	0.6	5.3 (4.6–6.0)

[a] Cases with missing stage information 72% in Italy and 57% in Belgium. Numbers of cases and detection rates estimates assuming a similar stage distribution among cases with known and missing stage information.

[#] Cases with ⩾PSA 4 ng/ml only.

capture most of the slowly growing cancers. The detection rate in the second round was generally slightly lower than at the initial screen. This may indicate either a large pool of non-progressive lesions (undetected at first screen) or a rapid influx of new cases to such a pool. However, the incidence in the control arm did not substantially increase during the screening interval, which could reflect the fact that incidence rates plateaued or even started to decrease in several populations in the turn of the century.

We used a simple, pragmatic approach to estimate lead-time and evaluate how much earlier cancer cases are detected by organised screening, relative to the absence of such effort. In such setting, any opportunistic screening is incorporated into the control group providing reference incidence. Another approach would be to relate disease detection by screening to complete absence of any screening. We did not have incidence data from such 'intact' (non-screened) populations. Historical incidence rates of prostate cancer from pre-PSA era could be used to obtain such estimates. Yet, such estimate would presume no genuine increase in disease risk (due to factors other than screening).

Previous screening studies have estimated lead-time as 6–12 years. Our approach for calculating the prevalence:risk ratio instead of prevalence:incidence ratio (using the exponential formula) corrects the overestimation of large probabilities and gives therefore slightly smaller expected occurrence and consequently somewhat longer lead-time estimates. A Finnish study using similar methods, but shorter follow-up, reported a lead-time of 6–7 years.[3] A more sophisticated simulation study using material from the Dutch screening trial suggested lead-time of 11 years.[5] Population models have been constructed using the United States of America (USA) incidence and mortality rates suggest mean lead-times around 6 years.[8–10]

In serum bank studies, lead-time is calculated retrospectively only for cancer cases, which decreases the estimated time. On the other hand, lead-time is usually calculated since PSA reaching the cut-off level (usually 4 ng/ml), while at screening the PSA distribution ranges higher above the threshold. This is likely to prolong the estimated lead-time.

In conclusion, a single screening round within the European Randomised Prostate Cancer Screening trial can advance diagnosis by 4–8 years, which is consistent with calculations based on mathematical models and substantially longer than for breast, cervical and colorectal cancer screening. All centres showed shorter lead-times for aggressive cancer, while results based on the second round were similar to the initial screen. Overdiagnosis contributes substantially to lead-time

Conflict of interest statement

None declared.

Acknowledgements

We thank Elham Kharazmi MD, PhD, for her assistance in data analyses.

The European Randomised Study of Prostate Cancer Screening (ERSPC) has received funding as unrestricted grant from Beckman-Coulter Inc. The funding source has had no role in decisions about publication, their contents or timing and has no involvement in preparing the publications of the trial.

REFERENCES

1. Schröder FH, Hugososn J, Roobol M, et al. Effect of screening on prostate cancer mortality: first results from the European Randomized study of Screening for Prostate Cancer (ERSPC). *N Engl J Med* 2009;**360**:1320–8.
2. Hakama M, Auvinen A. Cancer screening. In: Heggenhougen K, editor. *International encyclopedia of public health*. Elsevier; 2008. p. 464–80.
3. Auvinen A, Määttänen L, Stenman UH, et al. Lead-time in prostate cancer screening (Finland). *Cancer Causes Control* 2002;**13**:279–85.
4. Törnblom M, Eriksson H, Franzén S, et al. Lead time associated with screening for prostate cancer. *Int J Cancer* 2004;**108**:122–9.
5. Draisma G, Boer R, Otto SJ, et al. Lead times and overdetection due to prostate-specific antigen screening: estimates from the

European Randomized study of Screening for Prostate Cancer. *J Natl Cancer Inst* 2003;**95**:868–78.
6. Stenman UH, Hakama M, Knekt P, et al. Serum concentrations of prostate specific antigen and its complex with alpha 1-antichymotrypsin before diagnosis of prostate cancer. *Lancet* 1994;**344**:1594–8.
7. Gann PH, Hennekens CH, Stampfer MJ. A prospective evaluation of plasma prostate-specific antigen for detection of prostatic cancer. *JAMA* 1995;**273**:289–94.
8. Etzioni R, Penson DF, Legler JM, et al. Ovediagnosis due to prostate cancer specific antigen screening. *J Natl Cancer Inst* 2002;**94**:981–90.
9. Telesca D, Etzioni R, Gulati R. Estimating lead time and overdiagnosis associated with PSA screening from prostate cancer incidence trends. *Biometrics* 2008;**64**:10–9.
10. Tsodikov A, Szabo A, Wegelin J. A population model of prostate cancer incidence. *Stat Med* 2006;**25**:2846–66.
11. Parker C, Muston D, Melia J, Moss S, Dearnaley D. A model of the natural history of screen-detected prostate cancer, and the effect of radical treatment on overall survival. *Br J Cancer* 2006;**94**:1361–8.
12. de Koning HJ, Auvinen A, Berenguer Sanchez A, et al. Large-scale randomized prostate cancer screening trials: program performances in the European Randomized Screening for Prostate Cancer trial and the prostate, lung, colorectal and ovary cancer trial. *Int J Cancer* 2002;**97**:237–44.
13. Zelen M, Feinleib M. On the theory of screening for chronic diseases. *Biometrika* 1969;**56**:601–14.
14. Cole P, Morrison AS. Basic issues in population screening for cancer. *J Natl Cancer Inst* 1980;**64**:1263–72.
15. Davidov O, Zelen M. Overdiagnosis in early detection programs. *Biostatistics* 2004;**5**:603–13.
16. Walter SD, Day NE. Estimation of the duration of a preclinical state using screening data. *Am J Epidemiol* 1983;**118**: 865–86.
17. Day NE, Walter SD. Simplified models of screening for chronic disease: estimation procedures for mass screening programs. *Biometrics* 1984;**40**:1–14.
18. Sakr WA, Grignon DJ, Crissman JD, et al. High grade prostatic intraepithelial neoplasia (HGPIN) and prostatic adenocarcinoma between the ages of 20–69: an autopsy study of 249 cases. *In Vivo* 1998;**8**:439–43.
19. Ciatto S, Zappa M, Villers A, et al. Contamination by opportunistic screening in the European Randomized study of Prostate Cancer Screening. *BJU Int* 2003;**92**(Suppl. 2): 97–100.