Detection of prostate cancer: the impact of the European Randomized Study of Screening for Prostate Cancer (ERSPC)

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The European Randomized Study of Screening for Prostate Cancer (ERSPC) is a large, randomized controlled trial of screening versus control, conducted in eight European countries (Belgium, Finland, France, Italy, the Netherlands, Spain, Sweden, and Switzerland). This article focuses on important aspects relating to recent findings from the ERSPC about two topics: first, leadtime and overdiagnosis, and second, prostate-specific antigen (PSA) as a test for repeated screening.

The ERSPC together with the prostate cancer arm of the Prostate, Lung, Colon and Ovary (PLCO) screening trial of the National Cancer Institute in the United States are set to show or exclude an effect of screening on prostate cancer mortality. Both studies are progressing according to plan. Definitive endpoint-related data can be expected between 2005 and 2010 depending on the difference in prostate cancer mortality that may be shown between the screening and control arms. The ERSPC will allow a risk-to-benefit analysis including parameters of quality of life and cost.

Overdiagnosis with present prostate cancer screening regimens is high. This amount of overdiagnosis is likely to be unacceptable for most healthcare policy makers and providers. Addressing overdiagnosis will be a major research task for urologists for the years to come. Present screening needs to be more "selective" for cases that have aggressive patterns and are likely to lead to clinical diagnosis of prostate cancer and/or death. The test characteristics of prostate-specific antigen (PSA) change after one use. The positive relation between PSA levels and positive predictive value (PPV) and detection rates in first screening rounds are lost. This may be compatible with the observation that tumor volumes in second round screening are smaller, and larger tumors are harvested. Tumor volume becomes a negative predictor in round 2, indicating that a large proportion of elevated PSA values are caused by benign prostatic hyperplasia (BPH) rather than by prostate cancer. While the outcome of the ongoing randomized studies is uncertain, screening tests cannot be refused to men who are well-informed and accept to take the risk of experiencing more harm than benefit as a result of a positive screening test result.

Key Words: prostate cancer, screening, randomized study leadtime, overdiagnosis

Introduction

Screening for prostate cancer remains a controversial issue in 2005. A direct effect of screening on prostate cancer mortality at an acceptable cost of loss of quality of life and money has not been shown, so far. Trends of a decrease of prostate cancer mortality in several western countries have occurred. In the United States, since 1994 a continuous trend in decrease in prostate cancer mortality is observed at an average of about 4% per year between 1994 and 2000.[1] In the Tyrol area in Austria, a 32% difference between observed and expected prostate cancer mortality was found between 1993 and 1999.[2] While these data are encouraging, many countries, however, consider the available evidence as insufficient to introduce population-based screening programs for prostate cancer. While the ongoing randomized studies[3,4] await their final

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results, there is consensus that the application of available tests for early detection cannot be refused to well-informed men. The production of validated information, therefore, is a top priority at this time.

The European study

The European Randomized Study of Screening for Prostate Cancer (ERSPC) is a large, randomized controlled trial of screening versus control, conducted in eight European countries (Belgium, Finland, France, Italy, the Netherlands, Spain, Sweden, and Switzerland). The study started in 1993 and recruited 205,897 men by the end of 2004. It covers the age group 50-74 with variations between participating countries. The screening interval is 4 years with the exception of Sweden where re-screening takes place after 2 years. An overview of recruitment and cancer detection to date is shown in Table 1.

Due to different legislations in European countries, it was necessary to use two different randomization schemes, which are summarized in Figure 1. In Belgium, the Netherlands, Spain, and Switzerland a written informed consent is necessary prior to randomization. The remaining countries require informed consent only for men who participate in the active screening group. Screening is PSA driven. A biopsy is indicated for men who have a PSA level of 3.0 ng/mL or higher. This has resulted in biopsies of 20%-23% of participants and a positive predictive value (PPV) of about 25% in the first round of screening. The acceptance of biopsy has been high and varies between 70% and 95%. Quality-of-life studies evaluating each step of the study from invitation to participate until treatment are conducted in the Netherlands and in Finland.

The most recent estimate of the study's power is shown in Figure 2.[6] Power, of course, depends on the difference in prostate cancer mortality between the screening and control group. The figure shows estimates for differences ranging between 20% and 50%. If mortality reductions in the order of magnitude

TABLE 1. **Summary of ERSPC recruitment 1993-2004**

	Number of men*	Number of cancers*
Screening arm	95,247	3,723
Control arm	110,650	1,811
Total	205,897	5,534

*age range 50 to 74 years

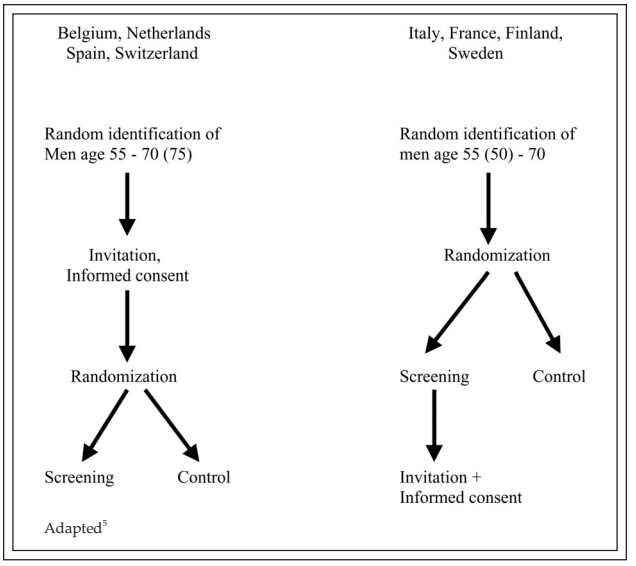

Figure 1. Randomization procedures in ERSPC.

seen in the United States or in the Innsbruck area would occur in the ERSPC trial, the curve representing a reduction of 30% might apply. In this case, the trial would have 80% power in 2004. For this reason, endpoint evaluations are scheduled for at least every 2 years from the end of 2004 onward. The power calculation takes into account the 20% contamination by opportunistic screening in the control group.

The ERSPC is organized in a decentralized fashion. Supervision of quality control and performance of the study is delegated to several committees. The study is run by a scientific committee with two voting members per country. The Data Monitoring Committee (DMC) is an independent supervisory

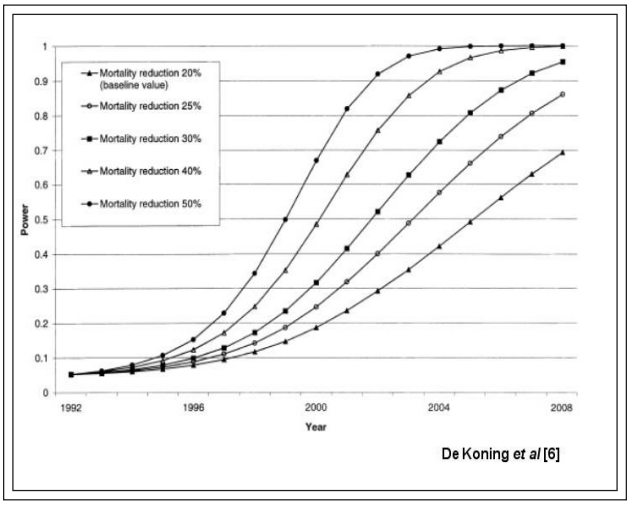

Figure 2. The power of ERSPC – effect of different assumptions of intervention effects.

committee working in close co-operation with individuals working with data from the central database. This database is located at the University of London and is not associated with a screening center.

Many aspects of the ERSPC have recently been summarized in a separate supplement.[6] More than 260 publications have resulted from ERSPC so far on many different aspects of screening. A summary can be found on the ERSPC web site at: www.erspc.org.

The article focuses on important aspects relating to recent findings of the ERSPC about two topics: first, leadtime and overdiagnosis, and second, PSA as a test for repeated screening.

Recent findings of the European study

Leadtime and overdiagnosis

Screening for any disease, by definition, produces a leadtime, which can be defined as the time between a positive screening test and the point in time at which clinical diagnosis might have occurred. Randomized screening studies offer the opportunity to evaluate lead times. Several such estimates have been carried out.7-9 It is estimated that lead times in prostate cancer are in the range of 5-12 years. Draisma utilized the micro simulation technique (MISCAN). Some of his resulting data about leadtime and about overdetection — which can be defined as detecting a disease that does not appear during the lifetime of the individual — are summarized in Table 2. Both parameters are age-dependent. Surprisingly, lead times produced with yearly screening as opposed to screening every 4 years are quite similar. The same is true for the rates of overdiagnosis.

The period of time that the diagnosis of prostate cancer is advanced with respect to a potential clinical entity is obviously of great relevance for the outcome of the ongoing screening studies. The ERSPC has chosen a follow-up period of 10 years. This period of time may be too short to observe the expected differences. On the other hand, leadtime may differ for different prognostic subgroups. Cases with the most favorable prognostic factors may have much longer lead times. Most likely, men who are overdiagnosed with prostate cancer are those with more favorable prognostic factors, for example, they are older and likely to die from other causes. An overdiagnosis of 50% means that half of the men who are diagnosed will never experience prostate cancer as a clinical entity during their lifetimes.

Overdiagnosis can be looked at in two different ways. Some groups[7-9] evaluate overdiagnosis as cancers that are otherwise not diagnosed during a lifetime. Other recent estimates are available.[10,11] Overdiagnosis can also, however, be defined as the diagnosis of cancers that will not lead to death. This definition was applied by McGregor[12] who estimated that 84 of 100 screening-detected cancers may not result in death by age 85. This means that 16 of 100 people with cancers detected by screening may be saved from dying from their disease. The data translate into an incidence-to– mortality ratio of 6.25. Clearly, even if screening was shown by the ongoing randomized studies to lower prostate cancer mortality at an acceptable price in terms of quality of life and economic cost, this amount of overdiagnosis is probably unacceptable for healthcare policy makers and providers. To make screening more "selective" for cases that are likely to gain importance during a lifetime or lead to death can be considered as the major research goal in this field.

PSA as a test for repeated screening

A recent article by Stamey and co-workers suggests that in the situation of frequent screening as it is taking place in the United States, PSA loses its predictive

TABLE 2. **Leadtime and overdiagnosis of prostate cancer – ERSPC (Rotterdam)**

Screening	Leadtime years, mean (range)	Overdetection % (range)
Yearly		
age 55-67	12.3 (11.8-13.3)	50 (46-57)
age 55-75	11.6 (11.1-12.6)	56 (54-61)
Every 4 years		
age 55-67	11.2 (10.8-12.1)	48 (44-55)
age 55-75	10.3 (9.9-11.2)	54 (51-59)

Adapted fron Draisma et al 2003[8]

value.[13] Is the era of PSA- based screening over? What is the value of PSA in the setting of repeated screening? The ERSPC is set to make a major contribution to this issue because of a fixed re-screening interval and repeated screens over more than 8 years. Data from the ERSPC Rotterdam will be used to illustrate this issue.

During the initial years of the ERSPC (Rotterdam), a PSA value > 4.0 ng/mL and/or a positive digital rectal examination (DRE) or transrectal ultrasonography (TRUS) were used as an indication for biopsy. This was changed in 1997, after screening about one-half of the participants in the first round. The data on round 1, shown in Table 3, need to be interpreted based on this background. The detection rate seen with the original regimen versus with the later use of PSA $\geq$ 3.0 ng/mL as the only biopsy indication were similar — 4.8% and 5.3%, respectively. The Table gives a comparison of test characteristics of PSA-driven screening in the first and second rounds. PPVs and detection rates are expressed per PSA range in rounds 1 and 2. The PPVs and the detection rates of the total population are significantly lower in the second round compared to the first round (p values of 0.0001 and 0.0005, respectively). The decrease of the number of eligible participants in round 2 is due to passing the age limit of 74 years, death, acute disease, and other factors. It is evident from the data shown in Table 3 that PPVs and detection rates in round 1 are positively related to rising PSA values. This relationship is lost in round 2, as has been pointed out previously.[15] An analysis of factors that might determine prostate cancer detection after prior use of PSA was carried out.[16] PSA, PSA velocity, prostate volume, TRUS, DRE and age were all weak predictors of outcome with odds ratios ranging between 0.73 and 2.15. In multivariate analysis and backward deletion, PSA velocity was the only parameter excluded.[17] In a recent study, the rate of progression of PSA to the arbitrary biopsy cut-off of 3.0 ng/mL and its relation to the diagnosis of prostate cancer was evaluated. PSA progression to levels above 3 ng/mL strongly depended on PSA levels during the first round. Only 0.9% of cases who presented with a PSA below 1 ng/mL, but 48% of those who presented with PSA values between 2 and 2.9 ng/mL progressed to PSA values above 3 ng/mL. The PPV increased with increasing PSA ranges in round 1 and amounted to 26.3% for all those who progressed to levels above 3 ng/mL.[18]. The cancer detection rate strongly depended on the PSA values in round 1.[16] This was interpreted as showing that a PSA value of 3 ng/mL maintains its predictive value while excluding very large numbers of men (5,109 of 5,771) who presented with PSA below 3 ng/mL in round 1 from biopsy.

Stamey's observation was largely based on the loss

TABLE 3. **PSA, PPV, and detection rates in screening rounds 1 and 2***

PSA ng/ml	Screened N A	Biopsies N (%) B	Cancers N C	PPV (%) C/B	Det. rate (%) C/A
Round 1					
< 3.0	15,852	918 (5.8)	79	8.6	0.5
3.0-3.9	1,426	791 (55.5)	179	22.6	12.6
4.0-9.9	2,235	2,005 (89.7)	526	26.3	23.5
>=10	457	403 (88.2)	231	57.3	50.6
Total	18,970	4,117 (20.6)	1,105	24.7	5.1
Round 2					
< 3.0	10,026	693 (6.9)	109	15.7	
3.0-3.9	949	830 (87.5)	174	21	
4.0-9.9	1,362	1,215 (89.2)	234	19.3	17.2
>=10	183	166 (90.7)	32	19.3	17.5
Unknown					
Total	12,520	166 (90.7)	549	18.9	4.6

Source: ERSPC (Rotterdam)[5]

* screening interval = 4 years; PPV = positve predictive value

The PPV is obtained by dividing the number of cancers (column C) by the number of biopsies (column B). The detection rate is obtained by dividing column C by the number of men screened (column A).

of a correlation of PSA at the time of diagnosis with the volume of the so-called index lesion. Data from the ERSPC Rotterdam, however, show that the correlation between PSA and tumor volume as determined by planemetrical techniques applied to 4-mm step sections is significant in round 1 and remains significant in round 2. Tumor volumes are larger in round 1, and the difference to round 2 is statistically significant.

Summary

Lead-time depends on age, screen intervals and procedures used; it amounts to 10-12 years. Overdiagnosis with screening is seen in at least 50% of cases depending on the intensity of screening and age. PSA levels correlate with the related PPV. This relationship gets lost with repeated screening. □

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