White Paper: To Screen or Not to Screen?

Prof Chris Bangma, one of the ERSPC directors, sets this challenge for health authorities in the light of their recent study into the benefits of population based screening for prostate cancer.

Summary
Screening the general population for prostate cancer based on PSA (prostate specific antigen) reduces prostate cancer specific mortality by at least 20 %. This is the finding of the European Randomised Study for Screening of Prostate Cancer (ERSPC) when it monitored 162.000 men aged 55 to 69 over a period of nine years.

For the first time, serious consideration has to be given to population-based screening. But health authorities will need to include additional arguments such as the overall financial cost and the quality of life gained by screening.

Screening increases the risk of overdiagnosis, by finding indolent (not life threatening) tumours, and therefore putting the patient at risk of unnecessary treatment. For a calculation of this risk, the online Prostate Risk Indicator is available – (www.prostaatwijzer.nl, www.urosource.org)

Introduction: prostate cancer and PSA
Prostate cancer (Pca) is the most frequent malignant tumour in men in the western world, and the most common cause of death (www.iarc.org). Statistics on incidence and mortality show a gradual increase over the last decade. The increasing incidence may have various causes. The number of elderly men is increasing, so is the median age of the population. Awareness amongst men and their partners of the availability of PSA as marker for prostate diseases including prostate cancer (Pca) has grown in parallel [1].

Until the early nineties prostate cancer was diagnosed as a result of symptomatic metastases, or when found during digital rectal examination (DRE) for aspecific urinary complaints. In addition, the metastatic marker Acid Phosphatase would usually be elevated. The introduction of the PSA test, led to a far earlier diagnosis. At the same time, programmes initiating population-based screening for cervix or mammary gland cancer also had the effect of raising awareness of prostate cancer and whether this too could be detected and treated at a curable stage.

Evaluation of Pca screening: results of the ERSPC
The increasing incidence and mortality of Pca world wide was the base for starting a study to evaluate the changes on specific mortality as an effect of population based screening in men aged 55-69. As a benchmark, it took the criteria for population screening, as defined by Wilson and Junger (Wilson JMG, Junger G. Principles and Practice of Screening for Disease. Geneva: WHO 1968). PSA based screening followed by prostate biopsies was the most appropriate method to find early Pca at a curable stage. Curative treatments like radiotherapy and radical surgery were available, and later on brachytherapy was added. Technically, radical surgery had improved, though side effects like stress incontinence and erectile dysfunction remained considerable [2] . Also, radiotherapy had its acute and chronic side effects [3]. PSA screening appeared to be cost effective, non-invasive, and judged a good method for mass screening.

After a number of pilots in 1992-1993, the multicentre European study ERSPC (European Randomised Study for Screening of Prostate Cancer) was initiated by Prof Louis Denis and Prof Fritz Schröder in eight countries (Belgium, Finland, France, Italy, Netherlands, Spain, Sweden, Switzerland). It was coordinated from Erasmus Medical Centre in Rotterdam [4]. The primary endpoint of the study was defined as Pca-specific mortality, and the study size was based on a difference between the randomised intervention (screening) group and the controls of 25 % with a statistical power of 0.80 [5]. The study was ultimately conducted among 162.243 men aged 55 to 69, randomised into two different arms. In the intervention arm, screening was conducted by the determination of serum PSA, and a value of ≥ 3,0 ng/ml (Beckman Coulter Hybritech assay) was an indication for sextant prostatic biopsies followed by histology. All protocols and quality control have been published extensively previously [6]

In March 2009, the first international report on the reduction of mortality by screening was published based on an intention-to-screen analysis [7]. After a mean follow-up of nine years in both groups, a significant mortality reduction of 20 % was observed in the intervention group. In order to prevent 1 prostate cancer death, 1410 men needed to be screened, which is comparable with breast cancer screening. However in contrast to screening studies in other cancers, the ERSPC study into prostate cancer specific mortality showed that in order to prevented 1 man from dying of prostate cancer, 48 men had to be diagnosed with prostate cancer in excess of the control group. There was no reduction in overall mortality.

These results are starkly in contrast with the simultaneously published results of the PLCO study from the USA [8]. The PLCO studied the mortality of prostate, lung, cervix, and ovary cancer screening in a randomised fashion. The PLCO study showed no mortality differences between its randomised arms for prostate cancer after seven years of follow-up.

Why the difference? Unfortunately, the study was compromised in various ways so it is unlikely this study will ever be able to confirm the ERSPC findings. This is because a large proportion of men in the control arm of the study had already undergone a PSA determination before or during the study, and therefore that arm of the study has to be regarded as contaminated. In fact 52 % of men in the control arm underwent inadvertently a PSA test, (likely to be due to the awareness of PSA testing for prostate cancer in the USA at the start of the study in the early nineties). The real difference between the men that actually obtained PSA screening in the intervention arm (85%), and those that were included in the control arm were only 33 %. As the PLCO sample size was only 77,000 individuals in total, this critically compromises the power of the study.

Techniques and methods for prostate cancer screening

In the ERSPC protocol, a PSA value > 3ng/ml was an indicator for requiring a follow up with a prostate biopsy. About 20 % of men in the screened population obtained at least one set of biopsies. For men aged 55-60 the biopsy incidence was 15 %, while for men aged 70-74 this was 35 %. In about 80 % of the men given a biopsy no tumour was diagnosed. Although the side effects of prostate biopsies are considered to be minor in most cases, (hematuria and haemospermia of short duration, urinary tract infections [9]), the low specificity of PSA for positive biopsies appears to be unacceptable for use in a population based screening setting. This is the same for DRE and transrectal ultrasonography [10]. Additional methods are therefore needed to identify those men without an obviously detectable cancer, in order to decrease the psychological effects of invasive diagnostic procedures.

When no cancer could be detected at first screening, men were invited for a second screen after four years (in Sweden two years) according to an identical protocol.

Remarkably, though the PSA level in the first round correlated well with the incidence of detected cancers, PSA did not have predictive value in the follow-up visits of screening [11].

Prostate cancers detected in the time interval between two screening visits were indicated as 'interval carcinomas'. These interval tumours only occurred at very low frequency (in 0.03 % of the intervention group [12]), and presented with a tumour stage that allows successful curative therapy. Diminishing the length of the screening interval from four to two years showed no reduction in the number of interval cancers. It is likely that some cancers always show up during screening intervals, independent of its duration.

The result of screening: overdiagnosis of indolent tumours

Previously it was observed in the ERSPC that approximately 50 % of cancers detected with the above described screening method are cancers that are not likely to cause harm during life, as they grow to slow and continue to have a low Gleason score (less than 7) [13]. These tumours are called 'indolent' .One would prefer to be able to avoid detecting these tumours in the first place for psychological reasons. Overdiagnosis might initiate treatment (including its side effects) that may not be necessary but is driven by uncertainty of the ultimate outcome of the natural course of the tumour [14]. Currently there are no prognostic parameters in biomaterials (urine, blood, tissue) that can predict the exact outcome of a tumour.

Based on the population data of the ERSPC, a nomogram has been constructed using age, PSA, prostate volume, and the characteristics from tissues obtained by prostate biopsy to calculate the probability of the presence of an indolent tumour. In 30 % of screen detected cancers, indolent tumours can be predicted with a probability of at least 70 % [15]. Using this probability cut-off for the initiation of a conservative form of treatment called active surveillance (see below), about 6 % of non-indolent tumours are going to be regarded as indolent, and will (initially) be treated as indolent cancers until they are recognised as significant.

The consequence of identifying a likely indolent tumour is to refrain from invasive therapy like radiotherapy or surgery till the moment that the tumour shows progressive growth, and a shift towards invasive therapy is then indicated. This approach is called 'active surveillance'. Tumour growth is monitored by serial 3-monthly PSA measurements and annually repeated biopsies [16]. A freely accessible protocol has been made available on the web for online monitoring and treatment recommendations, and is indicated by the name PRIAS (www.prias-project.nl).

So far evaluation of men that have followed surveillance showed that metastases have been diagnosed in only one out of 200 men at the time of the shift towards invasive therapy [17]. Active Surveillance therefore appears to be a safe treatment option, but the median follow-up of series has been restricted to eight years only.

Population based screening, is it indicated?

The recent results of the ERSPC alone cannot decide the question of whether population based screening is indicated. This is because we still do not know the quality of life gained by mortality being reduced; and this can only be determined in the light of the extra years that men will live with the diagnosis of prostate cancer after early diagnosis. Also in terms of health economics it is not known whether screening is cost effective, and in what form. Health authorities will need this information before they can decide to initiate mass screening programs. Till that time, offering screening to the individual is allowed in most European countries (except The Netherlands).

Individual screening: doctor, do I have to be screened?

1) The information, the risks
For the medical practices, the individual requests for screening appears currently more important than the quest for population based programs. Individual men want to decide whether to be screened or not. These men should be informed about the benefits and disadvantages of screening, especially overdiagnosis. Use of the Prostate Risk Indicator (www.prostaatwijzer.nl, www.urosource.org) forces the user to read validated information on prostate cancer and screening before being able to calculate his individual risk compared to that of the general population.

2) *PSA, the assay*
If a decision is made to screen a patient, a PSA will be taken in order to estimate the probability of a positive prostate biopsy. PSA of the Prostate Risk Indicator is based on the assay and traditional stable calibrators of Beckman Coulter (BC). After 1995 many PSA-assays have been gradually recalibrated towards a WHO standard. This WHO calibrator differs by 20 % from the BC calibrators, and resulting PSA values are 20 % lower compared to BC measurements [18]. This implies that one has to multiply a WHO calibrated PSA value by 1.2 in order to obtain a Beckman Coulter result that fits with the risk assessment of the Prostate Risk Indicator.

3) A*ge and family history*
In Sweden it has been observed that if PSA is lower than 0.6 ng/ml up to the age of fifty, the chance of getting a metastatic prostate cancer in the next 25 years is less than 5 % [19]. This relates to a study of PSA available from the period 1974 to 1986 in over 20.000 men. A serum PSA obtained from men in a younger age category is less influenced by the effects of benign prostatic hypertrophy, making it likely to be a relevant prognostic factor for Pca.

Above the age of 70, co-morbidity plays an important role when deciding on screening. PSA increases with age, and tumours detected are larger and have higher Gleason score compared to tumours at an earlier age. Approximately 10 % of tumours detected in elderly are high risk tumours. A longer duration of tumour growth is likely to result in larger and less differentiated tumours. Even so, a large number of tumours in elderly are low risk, and their clinical course is usually asymptomatic. To estimate co-morbidity one of the most frequently used scales is the Charlson Index (www.medalreg.com) . Usually, physicians predict life expectancy poorly [21], which gives room for improvement.

The interest of the patient and his doctor is not only death by prostate cancer, but particularly whether he suffers symptoms. The effect of screening on preventing metastatic disease will shortly be further evaluated by ERSPC.

Current guidelines for diagnostic procedures
In many current national guidelines, a problem with micturition is an indication that a DRE is advisable. An abnormal DRE indicates the need to perform a prostate biopsy for histology. However, in some cases it may be preferable to refrain from biopsies, such as the age or co-morbidity of the patient, so that treatment is not always appropriate for an asymptomatic man even with a cancer is diagnosed. When the PSA is lower than 1.0 ng/ml, there is a very small chance that an abnormal DRE is caused by tumour [22]. International guidelines for this are likely to be changed as a result of the ERSPC study.

Conclusion

Increased awareness of prostate cancer and the availability of PSA testing, has stimulated the quest for more accurate and early detection. For an individual, the Prostate Risk Calculator can be useful, after being given balanced information on the benefits and disadvantages of screening. It is possible that the already high incidence of individual screening might be used in the future as an argument against more organised population screening programs. However, any fundamental changes to national health policy will have to take into account the extent of overdiagnosis, the quality of life after early detection, and the financial ramifications of population-based screening.

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