# PSA screening – a review of recent studies

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In spite of the absence of level one evidence for its effectiveness, the use of screening has been prevalent worldwide with rates of around 70% in the US and 20–40% in European countries. Prostate specific antigen (PSA) and digital rectal examination (DRE) are the most commonly applied screening tests. PSA was introduced into clinical medicine in 1987 and evidence for potential effectiveness in the early detection of prostate cancer emerged in the early 1990s after PSA driven biopsy indications revealed a significant down staging of prostate cancer at the time of diagnosis [1]. In the meantime, level one evidence for an effectiveness of prostate cancer screening in terms of lowering prostate cancer specific mortality has emerged [2]. The findings of this study will be presented and discussed and put into perspective with other emerging evidence of the effects of prostate cancer screening on a population based and individual basis.

## Background information

### *Definitions*

Screening entails the application of testing to potentially healthy populations. The expected outcome is the improvement of the health status of a population with respect to disease outcomes. Since results of screening and screening trials are based on populations, they may not necessarily predict the outcome of an individual that wishes to be screened. Individual screening upon request has been termed 'opportunistic screening' or 'early detection'. Obviously, the outcome of opportunistic screening is the individual health benefit.

Prostate cancer is the most common cancer and most frequent cause of cancer death in men. The Globocan 2002 statistics [3] revealed that, worldwide, 697,000 prostate cancers were diagnosed, while 221,000 died of the disease. The incidence mortality ratio worldwide is 3:1 but this was shown to increase, with PSA driven screening, to 7:1 in the US. Obviously, even a modest improvement of prostate cancer mortality by screening would lead to very large numbers of men being saved the suffering associated with advanced disease and the potential of death from prostate cancer.

### *Prostate specific antigen (PSA)*

PSA remains the most important test for diagnosing prostate cancer in spite of an increasing understanding of its disadvantages. Within the prostate cancer prevention trial (PCPT) control arm, more than 5000 men aged 55 or older with an initial PSA of less than 3.0 ng/ml were followed for a period of 7 years and biopsied for a rise of PSA to >4.0 ng/ml, an abnormal rectal examination or the end of the 7-year study period [4]. A detection rate of 21.9% resulted. The data also show that there is no PSA range identifiable which shows matching sensitivity and specificity values. Any cut-off value of PSA use will always miss cancers and will miss a certain proportion of aggressive cancers. Cut-off values of 2.5 or 3.0 ng/ml as biopsy indications, for example, will miss 56 or 64% of detectable cancers and 33 and 42% of potentially aggressive cancers, respectively (Gleason $\geqslant$7). A complete review of these data is given in Table 1. The detection rate of 21.9% contrasts sharply with a lifetime risk of prostate cancer mortality of 3% and shows that a large proportion of cancers, otherwise only found at autopsy, are detected in this setting. Clearly, biopsying all men by age without consideration of PSA levels is not an option. Screening algorithms will have to be designed which would diagnose indolent disease but also allow the detection of aggressive cancers in a curable state at subsequent examinations.

## The European Randomised Study of Screening for Prostate Cancer (ERSPC)

This randomised screening study has recently reported a first analysis including the evaluation of prostate cancer mortality in the screening versus control arm [2]. The study has included a randomised sample of

182,160 men aged 50–74, of whom 162,367 fall into the core age group of 55–69 which is subject to the recent publication. This core age group was decided within the European consortium of eight countries at the time of initiation in 1994. The screening interval was 4 years in 87% of the population; one centre (Sweden) utilised a 2-year interval. Sextant lateralised biopsies were recommended for PSA values $\geqslant$3.0 ng/ml. Two centres utilised a cut-off of 4.0 ng/ml with ancillary tests (DRE, FT-ratio) in the PSA range 3.0–4.0 ng/ml. The participating countries were Belgium, Finland, France, Italy, The Netherlands, Spain, Sweden and Switzerland. Considering the decentralised data collection, a number of independent monitoring committees were installed, which included an independent Data Monitoring Committee. The causes of death evaluation were blinded and standardised. A power calculation was published early during the course of the study with adjustment of the sample size to non-compliance and contamination. The Nelson–Aalen method was used to calculate cumulative hazards in both arms. Two sided *P*-values were adjusted to alpha spending in three interim analyses.

In the screening arm, at a median follow-up of 9 years, 5990 prostate cancer cases (8.2%) and 214 prostate cancer deaths were seen. The numbers in the control arm amounted to 4307 prostate cancer cases (4.8%) and 326 prostate cancer deaths. The relative risk of prostate cancer death was 0.8 (95% confidence interval [CI] 0.65–0.98, $P = 0.04$), a 20% relative reduction in prostate cancer mortality. This translated into an absolute risk reduction of 7 per 10,000 men, a number needed to screen exceeding 1000, and a number needed to treat, reflecting the excess of diagnosis in the screening arm with respect to the control group, amounting to 48. With adjustment for contamination, a 27% relative mortality reduction resulted which approaches the benefit which can be expected by men who decide to undergo early detection testing. An exploratory analysis of age groups and a bootstrap analysis of the contribution of each centre were carried out and are reported in [2]. The ERSPC study shows a significant reduction of the relative risk of deaths from prostate cancer of 20% and an approximation of the risk reduction for men who in fact undergo screening of 27%. There was no heterogeneity between centres; the trends seen in the mortality curves suggest a larger effect with longer follow-up. The large number of cases needed to diagnose/treat poses a problem to healthcare providers and at the same time identifies the need for further research in this area.

## The Prostate, Lung, Colon and Ovary Cancer screening trial (PLCO)

The PLCO trial [5] was initiated shortly after the ERSPC trial. It was reported in the same edition of the New England Journal of Medicine. The trial has recruited 76,693 men aged 55–74, randomised to screening or 'usual care' (the control group). PSA testing was applied yearly for a period of 6 years; rectal examination was carried out yearly during years 1–4. A biopsy was recommended to the general healthcare provider if the PSA was equal to or exceeded 4.0 ng/ml and/or if rectal examination was abnormal. 85% of the men were tested. The compliance with biopsy indications, however, was low [6] and amounted to 40% or less on a yearly basis. The overall compliance over the 6-year period is not reported. 2860 cancers (7.4%) were detected in the screening arm, 2322 (6.1%) in the control arm, a rate ratio of 1:22. Fifty deaths from prostate cancer were seen in the screening arm and 44 in the control group. This amounts to a rate ratio of 1:13 with non-significant confidence intervals.

## Why does PLCO not show a difference between screening and control?

First of all, the follow-up of 7 years is too short. Furthermore, extensive screening prior to randomisation has led to a low event rate in both arms. In addition to that, the study reports 52% of screening in the control arm and 85% in the screening arm. The window of 33% is likely to be too small to produce a difference. With the data given in the report it is unlikely that PLCO will contribute to a determination of the value of screening in lowering prostate cancer mortality in the future.

## Preliminary conclusions

The ERSPC study shows a significant reduction in the relative risk of death from prostate cancer in men aged 55–69 of 20% in the intention to screen analysis. Adjustment for non-compliance provides an approximate estimation of the risk reduction for men who are in fact screened of 27%. Trends seen in the mortality curves reported in [2] suggest that a larger effect will emerge with longer follow-up. The large number needed to be diagnosed and treated is likely to prevent the introduction of population based screening around the world at this time. More work is needed to improve the screening procedure to decrease the

number needed to treat to save one prostate cancer death; more favourable numbers are likely to emerge with the pre-planned analysis based on data up to 31.12.2008 (11 year follow-up).

## Advice to men who wish to be screened

With the results of the ERSPC study at hand the message given to men who consider screening for prostate cancer has changed dramatically. Health professionals will have to relate that if a man develops prostate cancer, early detection will decrease the chance of suffering metastatic disease or dying from the disease by at least 27%. The downside of screening remains: there is a considerable chance of being diagnosed and treated for a disease which otherwise may not be harmful. However, indolent disease can be identified with high accuracy [7] and active surveillance can be applied to such men.

## Conflict of interest statement

None declared.

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