REVIEW ARTICLE

Screening for prostate cancer: a controversy or fact

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Abstract

Background: Adenocarcinoma of the prostate is the most frequent malignancy in men and the second leading cause of death in the male population worldwide. The screening for prostate cancer allows early diagnosis of prostate malignancy before the individual presents with symptoms. The early stage of the disease is easier to manage by different therapeutic modalities.

Aim: The aim of this review is to evaluate the reasons and facts for enthusiasm and positive approach towards the clinical decision about whether to screen or not male patients for early detection of prostate cancer.

Methods: We performed a computerized MEDLINE search followed by a manual bibliographic review of cross-references. These reports were analyzed and the important findings were summarized. We analyzed the methods and schedule of screening, as well as advantages and disadvantages of the prostate cancer screening.

Results: There were more than a hundred studies on prostate cancer screening performed but only a few are eligible for a decisive conclusion concerning the prostate cancer screening issue. We reviewed the screening methods, the schedule of screening, the advantages and disadvantages of prostate cancer screening.

Conclusion: The role for prostate cancer screening is not established yet. Definite proof of screening should be assumed as a decrease in the death rate of that cancer due to screening activity. Hippokratia 2010; 14 (3): 170-175

Key words: prostate carcinoma, screening, role, schedule, advantages, disadvantages, review

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Adenocarcinoma of the prostate is the most frequent carcinoma in men and the second leading cause of death in the male population worldwide. The therapy regimen can vary depending on the clinical factors, the stage and the localization of the tumour as well as the degree of its malignant potential. The prostate cancer (PCa) screening seems to be of limited value for diagnosis of an early disease. In contrast, it could be said that even the evidence of its benefit isn't well recognized. The aim of this review is to evaluate the possible reasons for enthusiasm and positive attitude towards the clinical decision about whether to screen or not male patients for early detection of PCa.

Epidemiology of prostate cancer

The estimations for 2006 says, PCa was the most frequently diagnosed cancer in European men, with an estimated 345,900 new cases diagnosed, accounting for 20.3% of the entire cancer load in men[1]. PCa trend worldwide, particularly in the USA were replicated in Europe, with a peak PCa-specific mortality in 1993. This peak of 15.7/100,000 lowered to 14.1/100,000 by 1999[2]. In 2002 only, there are 239,930 new cases of PCa in the United States of America, and 32,447 patients died from PCa[3].

The finding of PSA and its introduction into clinical practice has changed the entire approach to this disease. Essentially it caused an increase in the incidence, diagnosis, and treatment of cases with PCa in the early curable stage, thus leading to a fall in mortality[4-6].

PSA started to be used for screening in the early to mid-1980s. Then, the screening was much simpler matter for both, the patient and the doctor. PSA values above 4.0 ng/mL meant it was abnormal and a biopsy was recommended whereas PSA below 4.0 ng/mL was assumed normal and the patient was told that everything was regular[7,8].

Today, this point of view is wrong since we acknowledged that assessing a man's risk of PCa is definitely more complex. PSA is not abnormal or normal but reflects a range of risks with its variations in value. Different conditions within the prostate, benign or malignant, can influence the rise or fall of PSA. Prostate cancer, acute or chronic prostatitis as well as an intraprostatic abscess or recent endoscopic, transurethral examination can be manifested with elevated PSA while some medications like 5AR inhibitors can decrease the PSA level. When looking to a patient we have to make an individualization of each one taking into regard its medical record, present medical status and familiar cancer history[9]. Hence, a certain PSA value in one patient means something completely different from the same PSA value found in another man who has other risk factors[10-12]. Nevertheless, the fact that PCa is a major health problem with significant associated morbidity and mortality satisfies the first requirement of the criteria for mass screening[13].

Why to screen?

The screening for PCa allows early diagnosis of prostate malignancy before the person has appeared with any symptoms. The early diagnosis of PCa makes the management easier and gives the urologist and the patient more diverse therapeutic modalities. While screening, we search for potential risk groups, environmental, social and economic factors and we evaluate its impact on the cancer incidence and epidemiology. We also need to define and set the starting age for screening of particular risk groups, age limit for screening and to provide a schedule for the investigations[14-16]. The most important concern is how to explain the patient that screening does not mean immediate doubt for a cancer but regular check up and prevention instead.

The basic urological examinations for detection of early PCa consist of digital rectal examination (DRE), measurement of serum total PSA and investigation by transrectal ultrasound (TRUS). This is the so called „diagnostic triad"[17]. When abnormalities are found at any of the examinations mentioned above, a TRUS guided biopsy is indicated[18,19].

In the last ten years there are many controversies concerning the introduction of screening for early PCa as a routine examination for the male population.

Nowadays, there are yet many unanswered questions concerning this particular screening. These dilemmas induced many studies for defining the conditions and the need for screening for PCa. We performed a computerized MEDLINE database search followed by a manual bibliographic review of cross-references. These reports were analyzed and the important findings summarized. We analyzed the methods and schedule of screening, as well as advantages and disadvantages of the PCa screening.

At the moment, there were more than a hundred studies performed but only a few were eligible, based on well defined criteria (randomized studies, large number of analyzed subjects metaanalisis), as being essential for a decisive conclusion concerning the PCa screening issue.

The largest numbers of patients were included in the Canadian study performed in 1988 in the region of Quebec. It consisted of 46,193 man aged from 45 to 80. The follow up period was 11 years[20,21].

The second very important study is the Pilot Randomized Screening Study also known as the Norrkoping Study applied in Sweden. It was initiated in 1987 and considered the organizational, psychological and economic consequences of screening. The study population consisted of 9,026 men, aged 50–69 years from the city of Norrkoping. Every sixth man was randomized to the study group (total 1,494) while the remaining 7,532 men were considered as a control group. DRE was combined with PSA, where abnormal DRE or PSA ≥ 4 ng/mL were assumed as indication for a prostate aspiration biopsy[22]. The clinical consequences of screening after a 15-year follow-up have been reported.

Another study that followed is the Tyrol Prostate Cancer Demonstration Project (Tyrol Study) in 1993. This prospective early PCa detection programme has been carried out in the Austrian state of Tyrol, using PSA testing as a screening tool[23,24]

One of the latest great impact studies is the European Randomized Screening for Prostate Cancer Study (ERSPC). It is a large, multi-centre, randomized controlled screening trial that aspires to show or exclude a decline in PCa mortality of at least 20% in men randomized to a screening arm compared to men in the control arm. It was performed on a huge population of 163,126 men aged from 55 to 69. The follow up period was 9 years[14,15].

The Prostate Cancer Prevention Trial (PCPT) was the first large-scale study to establish PCa status in study participants across the full range of PSA values. Recent reports from the PCPT have challenged the concept of considering a PSA value of 4.0 ng/mL as the upper limit of normal for a prostate biopsy recommendation[25,26]. In an analysis of 2,950 PCPT participants randomized to the study's placebo group and who never had a PSA greater than 4.0 ng/mL or an abnormal DRE, the investigators found that study data suggested that using absolute values for a biopsy indication may not be as important as assessing the PSA velocity[27-29].

Screening methods

The ideal screening test should be minimally invasive, accurate, easily available and performed, acceptable to the general population, with a significant impact on the outcome of the disease, presumably the mortality rate. Currently, there is no diagnostic test for PCa available that would satisfy all of the above mentioned requirements. The methods that have been studied in an European setting and found to be useful as a screening tool are discussed as follows[30].

Screening diagnostic tools

Prostate-Specific Antigen and Its Derivatives

While the PSA test is simple and safe, the dilemma of the precise cut-off levels that trigger biopsy in a screened patient remains unobtainable following the results of the Prostate Cancer Prevention Trial[31].

In the Tyrol Study, initially in 1993, age-referenced PSA values (>2.5 ng/mL for 40–49 years; >3.5 ng/mL for 50–59 years; >4.5 ng/mL for 60–69 years, and >6.6 ng/mL for 70–79 years) were used in combination with percentage-free PSA levels of <22% as criteria for a biopsy recommendation. Since March 1996, the total and free PSA, age, DRE, and TRUS have been set as a standard[32-34]. PSA velocity has also been added to this combination since 2005, with an aim of improving the specificity of the screening tests[35-37].

At the outset of the ERSPC trial, PSA ≥ 4.0 ng/mL and/or an abnormal DRE or TRUS was used as an indication for biopsy. Since February 1997, the PSA threshold of ≥3.0 ng/mL was set as the sole trigger for biopsy[15]. Using a PSA threshold ≥ 4.0 ng/mL, the estimated number needed to screen (NNS) to detect one cancer was 50–77

in men in their fifties; 21–30 for men in their sixties and 11 for men in their seventies[38]. PSA density measurement was also shown a useful tool in the assessment of the degree of aggressiveness in clinically localized PCa. Several studies suggested that PSA density higher than 0.15 ng/ml/cm^3 increases the cancer detection rate[39-41]. In addition, Radwan et al. suggested that value of PSAD higher than 0.2 ng/mL/gr strongly correlated with the extracapsular extension of the cancer[42,43]. Thus, these figures look favorable when compared to the NNS for other malignancies like colorectal and cervical malignancies with their established screening programs. Using the proportional incidence method and studying the interval cancers in the ERSPC, the sensitivity of screening in ERSPC was calculated to be as high as 80% in the screened population[44].

Digital Rectal Examination

Efficacy of DRE findings has been evaluated both as a screening tool and also for determining the screening interval and follow-up in men with an elevated PSA (≥ 3.0 ng/mL) and negative biopsy. After the first screening round of the ERSPC Study, DRE was not used any more because of its low-positive predictive value (PPV), ranging between 4% and 11% in men with PSA levels of <3.0 ng/mL, increasing from 33% to 83% in men with PSA levels of 3.0–9.9 ng/ml[45,46]. When patients with abnormal vs. normal DRE in the first screening round and followed over a period of 8 years with two screening rounds of biopsies were compared, there was no higher incidence/chance for detection of cancer or significant cancer at later screens[47].

Schedule of screening

The screening schedule/interval period is different in various studies, mainly determined by the PCa values particular to each region and the evolving knowledge about natural history and estimated lead time of screen-detected PCa. In the Tyrol and Norrkoping studies it was triennial, in the Goteborg branch of the ERSPC biennial, and in remaining centers of ERSPC every 4 years. The use of a 2-versus 4-year screening schedule in the ERSPC showed higher detection rate in the 2-year interval but found no difference in either the incidence or diagnosis of the aggressive PCa[48]. Finally based upon current evidence from the European trials the use of the PSA cut-off ≥ 3.0 ng/mL as the sole screening tool with a 4-year screening cycle seems to have sensitivity and specificity expected of a screening trial.

Advantages of prostate cancer screening

The efficacy of PCa screening for improvement of the outcome in patients might be confirmed when characteristics of cancers detected in the screened population and controls are compared. Though the main objective of a decrease in cancer-specific mortality with screening has not been sufficiently demonstrated in any randomized study, the pattern of variation in parameters that determine the natural course of the disease was assumed to provide valid information for informed judgments at the present time. Parameters that have been extensively studied as prognostic markers in the management of PCa are PSA at diagnosis, Gleason grade, and clinical stage[49].

Lower PSA at Diagnosis

Comparing the PSA levels at diagnosis in the screened and control population, the ERSPC trial showed a mean (median) PSA of 9.6 ng/mL (5.2 ng/mL) in the screened arm compared to 73.8 ng/mL (11.6 ng/mL) in the control arm. The mean (median) PSA value decreased with each screening round, from 10.5 ng/mL (5.7 ng/mL) to 4.5 ng/mL (4.0 ng/mL) in the third[50].

Migration to lower grade and stage

A favorable shift in the Gleason score patterns was observed in the screened arm which improved further with each screening round. In the first screening round 36.2% of cancers in the screened arm had Gleason score ≥ 7 compared to more than half (55%) in the control arm[50].

There was a significantly favorable stage distribution in the screening compared to control population. In the Norrkoping Study more than half of the cancers (56.5%) have been localized compared to around a quarter (26.7%) in the control group[22].

Decrease in Diagnosis of Metastatic Disease

There was a decrease in the number of cases that were detected with metastasis in the screened compared to the control population in the ERSPC (0.6% vs. 8%). Taking into account the number of men randomized, the incidence of distant metastasis was five times more common in the control arm compared to the screening arm[50]. Similar trends have been reported from the Norrkoping Study and also from the Goteborg branch of ERSPC[22,51].

Disadvantages of screening

Overdiagnosis

In the ERSPC trial the cumulative incidence has been noted to be 7.5% in the screening arm and 2.2% in the control arm[52,53]. It has been well known for many years that a patient with PCa is more likely to die with PCa rather than from it[54]. Draisma et al. estimated that screening at 4 yearly intervals from the age of 55 to 67 would detect 70% of all clinically relevant cancers. Extending the screening to the age of 75 would detect 95% of all clinically relevant cancers but would increase the overdetection rate to >60%[55].

Diagnosis of Indolent Disease (Latent PCa)

Indolent PCa is defined as a pathological organ confined cancer with a tumor volume of ≤0.5 cc without any Gleason grade 4 or 5. It is estimated that up to half of the patients in the ERSPC trial undergoing radical prostatectomy might have indolent disease[56,57]. Still in the Tyrol Study, using the Epstein criteria, the estimated overdiagnosis is reported to be as low as 8.7%, with a finding of

insignificant cancer in radical prostatectomy specimens of only 19.7%[24,58].

Morbidity from Diagnostic Investigations

The morbidity correlated with PCa screening comes from the invasive nature of the TRUS biopsy which has to be performed in about one out of five volunteers (21%)[44]. The introduction of local anesthetic infiltration and prophylactic antibiotics, has improved the morbidity[59]. In the ERSPC Study, haematuria lasting longer than 3 days and haematospermia were present in 22.6% and 50.4% of patients, respectively, and 3.5% of the patients developed a mild fever. The risk of retention of urine and hospitalization were found to be low (0.4%)[59,60].

Morbidity of Treatment

The morbidity of treating PCa with any of the available treatment modalities is significant and is known to be related to the quality of treatment provided[61]. Following radical prostatectomy, in the early postoperative stage, 80–90% of patients report erectile dysfunction and up to half complains of urinary incontinence. These two issues resolve with time up to 95.1% of patients were continent with erectile function maintained in 78.9% of men aged < 65 yrs (Tyrol Study, after 1 year follow up)[24]. The complications associated with radiotherapy are more related with bowel dysfunction (30–35%) and impotence (aprx. 50%).

Conclusion

The role for PCa screening is not established yet. Definite proof of screening is a decrease in the death rate of that cancer due to screening activity. The introduction of screening in few regions of the world showed a big percentage of overdiagnosis and overtreatment in the selected groups of patients due to detection of indolent PCa, as well as higher complication rates from the diagnostic procedures[24,44,52-61]. Earlier stage at diagnosis of PCa and decrease in death rate data indirectly imply a positive effect of PSA in disease detection. Unlike the screening programs for breast and colon cancers, PCa screening has not been shown to be effective in a randomized clinical trial, although recent evidence suggests that for patients with cancer discovered by means other than screening, surgical therapy may decrease PCa mortality compared with watchful waiting. Some professional organizations recommend PCa screening, other recommend it only to offer it and some discourage its use. However, PCa screening has become so popular and common in the United States that there seems to be a discrepancy between the degree of rationality for screening and the quality of the evidence supporting it.

The American Cancer Society, the American Urological Association and the European Urological Association recommends early detection with an annual DRE and PSA beginning at age 50 for all men with a life expectancy greater than 10 years and age 40 for men of African American race or a family history of PCa[62-65]. The 2004 recommendation of a consensus panel for PCa screening recommends a baseline PSA at age 40 for all men. Those men with a serum PSA equal or greater to 0.6 ng/mL (the median PSA for that age group) should undergo yearly screening, whereas those with a value less than 0.6 ng/mL may have another interval PSA at age 45. The same rule applies at age 45.

More cancer is detected with the use of DRE and PSA than with either exam alone. Data suggests normal PSA of 2.5 may be more appropriate in men under the age of 60. Many suggest lowering value for young men and maintaining 4.0 for older patients to minimize "miss rate" in this population.

As we are aware the modern medicine can not obtain sufficient evidence to recommend routine population screening with DRE or PSA. Clinicians caring for men should individualize every patient taking into consideration its race, habits, and family history. They should provide information about potential benefits and risks of PCa screening, and the limitations of current evidence for screening, and make the final decision to screen or not.

Still in absence of right answers for the need and the rational of the PCa screening we must follow the guidelines on this matter. The two most important urological associations in the world, the American (AUA) and the European (EAU) declare that every man over 50 years of age should visit their urologist and perform DRE and PSA at a yearly basis.

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