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## Screening for Prostate Cancer: To Screen or Not To Screen? A Review of The State-of-The-Art

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### Abstract

Prostate cancer is a major public health concern, particularly in the welfare countries, for this reason, screening should be considered to reduce the number of deaths. Screening tests are available, i.e. digital rectal examination; trans-rectal ultrasonography and prostate specific antigen, nevertheless their sensitivity, specificity and positive predictive value are far from being perfect. Evidences from randomized screening trials are still indebted for conclusive evidence. The screening might cause more harm than good due to over diagnosis and overtreatment as a result of limited specificity of the screening tests. According to our point a view, opportunistic screening as part of diagnostics of patients having suspicion for uncertain symptoms of prostatic disorder is fully justified but mass screening of the population of average risk should not be introduced until supportive evidence from randomized controlled trials would be available.

**Keywords:** Prostate Cancer, Opportunistic Screening, Organized Screening.

### Introduction

Prostate cancer is one of the most controversial issues of medical practice, preventive oncology and health care system. Some specialists argue for the necessity of screening, recommend all men aged 50 years and older to regularly undergo screening examination, and the initiative is welcomed by the public at large. Others are reluctant to put the prostate screening on the agenda of public health. The aim of this paper is to overview the currently available evidences and arguments, and tries to find answer to the question: to screen or not to screen.

### The Burden of Prostate Cancer

According to the World Cancer Report 2014, prostate cancer is the second most frequently diagnosed cancer in men [1]. In 2016, there were 1.4 million incident cases of prostate cancer and 381.000 deaths worldwide. Prostate cancer is one of the leading causes of mortality in the global mortality statistics, such as GLOBOCAN database [2], however the relatively high mortality rates might be virtual; in case of those who have been diagnosed with prostate cancer during their lifetime, the death certificate would indicate prostate cancer as cause of death, let the real cause of death be any other inter-current disease.

There are tremendous geographical differences in the incidence among the various regions of the Globe. In the economically developed "welfare countries" such as the Unites States and Nordic and Western countries of Europe, prostate cancer is a major public health problem, and a major burden on the societies, the patients and their relatives. The rates are several times higher in more developed countries compared with less developed ones. A positive correlation was

observed between the standardized incidence rates of prostate cancer and the Human Development Index (HDI), components of which are life expectancy at birth, mean years of schooling, and the gross national income per capita. In addition, there was a negative correlation between standardized mortality rates and HDI [3,4]. The increasing incidence together with an aging and growing population have led to a more than 3-fold increase in prostate cancer cases since 1990. In the same time, the death rates for prostate cancer seems to decrease in the majority of more developed countries attributed mainly to improved treatment and early detection efforts. Prostate cancer incidence rates are still lower in developing countries than in developed countries, but because of a faster increase in rates in developing countries, the gap decreased between 1990 and 2013 from a 4-fold to a 3-fold difference [5]. Prior to Prostate Specific Antigen (PSA) testing it was rare to diagnose before the age 55 years. Since introduction of PSA-test there has been a dramatic increase in the number of men diagnosed with prostate cancer in their late 50's and early 60's [6].

### Risk Factors, Natural History, Pathology

Risk factors for prostate cancer are numerous [7]. The greatest risk factor for prostate cancer is age: this risk increases after the 50 years of age; the majority are diagnosed in men age 65 years of age and older. Family history might have a role to play: men whose relatives have had prostate cancer are considered to be at higher risk; the hereditary form of prostate cancer accounts for just 5% to 10% of all cases. Lifestyle-related factors, such as physical activities, smoking and alcohol consumption are not closely linked to prostate cancer. High dietary fat may be a contributing factor for prostate cancer. Several studies have examined the relationship between prostate cancer and antioxidants; however, the results of these studies are inconsistent [8]. Studies show

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higher incidence among migrants moving from low- to high-risk area [9]. The role of hormone-profile is verified (androgens, androgen-receptors, insulin-like growth) [10]. Prostate cancer has a long natural history, and a long Pre Clinical Period (PCDP) during which it can be detected (Figure 1).

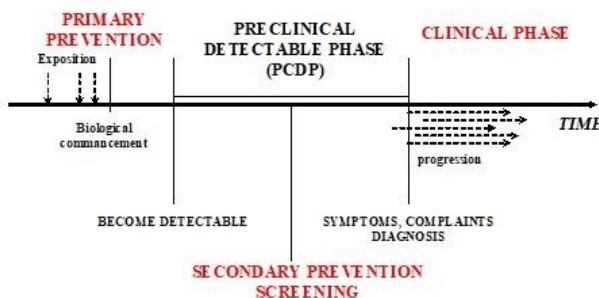


Figure 1: Natural history of disease development.

Cancer of prostate manifests itself in a various ways. Clinical carcinoma includes those cases in which diagnosis of the prostate cancer is made clinically and confirmed histologically. Occult carcinoma is manifested by its metastases before the primary site is detected. Subclinical carcinoma comprises incidental carcinoma which is discovered on microscopic examination of prostate tissue removed surgically for non-malignant disease, and latent carcinoma which is found at autopsy in patient who had had no clinical evidence of prostatic cancer [11].

Most prostate cancers are classified as adenocarcinoma. The primary tumours begin when normal epithelial gland cells mutate into cancer cells. The intraepithelial neoplasia locates in the peripheral zone of the gland, and atypical adenomatous hyperplasia in the transitional zone; these conditions are considered precursors or preclinical conditions, which can be detected by suitable methods. It is very often multi-focal. There is no real evidence for a relationship between Benign Prostatic Hyperplasia (BPH) and cancer [12]. It may spread locally to periprostatic structures, pelvic lymph nodes, and then through the bloodstream to bones, lungs and liver. The rate of progression, thus the prognosis correlates with the degree of cellular differentiation, as reflected in the Gleason's system of grading [13,14].

## Methods of Prostate Screening

For early detection of prostate disorders, for the time being, three methods are at our disposal: Rectal Digital Examination (RDE), Trans Rectal Ultrasonography (TRUS), and measurement of Prostate-Specific Antigen in the serum (PSA).

### Digital Rectal Examination (DRE)

Digital rectal examination is the oldest invasive test. As early as 1905, Hugh Hampton Young suggested that a careful rectal examination could identify changes in prostate gland that could lead to early diagnosis of cancer and early treatment [15]. The sensitivity of rectal examination is limited because its range is no longer than that of the pointing finger of examiner, consequently, it can only palpate rear and lateral surfaces of the gland, but it cannot reach the front and middle surfaces, and the smaller nodules within the gland either. The specificity is also less than optimal because the majority of "positive findings" corresponds to Benign Prostate Hyperplasia (BPH), so too many "false positive" findings occur. The positive predicting value (PPV) of is very low (25-40%) [16]. Given, the considerable lack of evidence supporting its efficacy, the available literature recommend against routine performance of DRE to screen for prostate cancer [17]. However, it should remain a part of routine medical examination.

### Trans Rectal Ultra Sonogray (TRUS)

Transrectal ultrasonography provides more information about the prostate and its environment. The capsule of the gland, seminal vesicle and bladder neck can be visualized. It can detect nodules of 5mm in diameter. It was first developed in the 1970s. TRUS-guided biopsy, under local anaesthetic and prophylactic antibiotics, is now the most widely accepted method to diagnose of prostate cancer [18].

However, the interpretation requires considerable expertise; the test is quite expensive and difficult to perform. The sensitivity and specificity of TRUS in the detection of prostate cancer is low, so it has not been accepted as screening tool. TRUS is useful in guiding fine-needle aspiration.

### Prostate-Specific Antigen (PAS)

Prostate-specific antigen is a glycoprotein produced only by the epithelial cells of prostatic origin. Being present in both benign and malignant epithelial cells, prostate-specific antigen can be detected and quantified in the serum. Those with prostate cancer may have serum PSA level higher than the normal ones. However, it is not specific to carcinoma of prostate, and up to the present, such threshold value could not be established which would definitively indicate the presence of prostate cancer [19].

On the other end, Catalona et al in 1991 published a study in which PAS level was elevated in 25% of prostate cancer cases [20]. The elevated concentration of PSA in the serum is not exclusively characteristic to prostate cancer but a number of other conditions such as inflammation, benign prostate hypertrophy; even ejaculation and digital rectal examination can cause elevated PSA level [21]. Nevertheless, today it is generally accepted that PSA detection in serum is the most sensitive, most appropriate method of detection of prostate cancer.

The "cut-of point" between the benign and malignant samples needs to be clearly defined. The normal range for PSA has been established as less than 4ng/ml. A level over 10ng/ml is most unlikely to be due to prostatitis or benign prostatic hyperplasia, and it most likely indicates prostatic cancer, therefore urologic examination is suggested. The borderline values (4-9.9 ng/ml) need to be interpreted in light of clinical findings. Minimally elevated PSA values need to be repeated before considering prostate ultrasound and biopsy.

A positive PSA-test is not more than expression of suspicion for prostate cancer; therefore, it needs to be histologically confirmed. Though the histopathology should be regarded as "golden standard" of diagnostics of prostate cancer, it is difficult to judge the accuracy of the procedure because the biopsy itself - as a result of the uncertainty of sampling - carries a debt with detection of 10-30% of cancer cases. The sensitivity of PSA-test in the detection of prostate cancer is not more than 20% and only 50% in the advanced cancer. The positive predictive value for a PSA level >4.0ng/ml is approximately 30 percent, meaning that slightly less than one in three men with an elevated PSA will have prostate cancer detected by biopsy [22]. The impact of prostate-specific antigen testing on prostate-cancer mortality PSA screening for prostate cancer is highly controversial. There is considerable controversy regarding the benefits, and risks of population-based screening for prostate cancer.

Evaluating the effect of prostate-specific antigen on the impact of prostate-cancer mortality, up to now, two Randomized Controlled Trials (RCT) were published: the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial, conducted by the National Cancer Institute [23] and the European Randomized Study of Screening for Prostate Cancer (ERSPC) supported by Europe against Cancer, and multiple European agencies and health authorities [24]. Several poor-quality randomized trials and cohort studies have been excluded from the review.



The strength of PLCO trial was a common protocol by ten study centers in the United States. On the other hand, the lack of common design and protocol makes the ERSPC study the more difficult to interpret; it was a collection of seven PSA screening trials employing different study design, screening tests, screening intervals, and different ages of patients at entry and choices of controls. In both studies, in the control groups, they had made efforts to minimalise the most common contaminating factor: namely, the opportunistic screening tests. During 1995 the ERSPC and PLCO study groups explored the possibility of co-operation, specifically the option of a common analysis, as opposed to a meta-analysis, of both trials. Conditions for a common analysis were defined and described in 1996 [25].

The PLCO trial was initiated in 1993, and randomized 76,683 men between 55-74 years of age to an experimental group, and 38,343 subjects as control group. The screening test was annual PSA over 6 years, completed with digital rectal examination. The control group has not been examined PSA, however, some half of the participants had been contaminated with PSA test outside the trial. Considering all PLCO participants, prostate cancer was diagnosed in 4250 men in the screened group and in 3815 men in control group. There was no significant difference in prostate cancer mortality after 13 years of follow-up. Prostate cancer survival was extremely high in both groups. Only 303 of 8065 prostate cancer patients (3.75%) died of prostate cancer after 13 yrs. They have concluded that while PLCO revealed no differences in prostate cancer mortality or survival, the high degree of PSA contamination in control group undoubtedly led to the dramatically favourable outcomes among PLCO participants [26,27].

The European Randomised Study of Screening for Prostate Cancer (ERSPC) was initiated in 1993 to evaluate the effect of screening with Prostate-Specific-Antigen (PSA) testing on death rates from prostate cancer. 182,000 men between the ages of 50 and 74 years were identified through registries in seven European countries for inclusion in the study. Each study had different recruitment and randomization practices. The men were randomly assigned to a group that was offered PSA screening at an average of once every 4 years or to a control group that did not receive such screening. 82% of men accepted at least one offer of screening. During a median follow-up of 9 years, the cumulative incidence of prostate cancer was 8.2% in the screening group and 4.8% in the control group. The absolute risk difference was 0.71 deaths per 1000 men. PSA-based screening reduced the rate of death from prostate cancer by 20% but was associated with a high risk of overdiagnosis [28]. Analyses after 2 and 4 additional years of follow-up consolidated the previous findings. In this update the ERSPC confirms a substantial reduction in prostate cancer mortality attributable to testing of PSA, with a substantially increased absolute effect at 13 years compared with findings after 9 and 11 years. Despite our findings, further quantification of harms and their reduction are still considered a prerequisite for the introduction of population-based screening [29,30].

The ERSPC also investigated how often PSA should be tested. It has been found that in 90% of men, whose PSA value in the first screening round was 1.9ng/ml, 4 years later, in the second round, the PSA value increased to 3ng/ml (at a cutoff point 4ng/ml). From this, they concluded that annual PSA screening is meaningless [31].

The final conclusion of ERSPC is that PSA-based screening significantly reduced mortality from prostate cancer but did not affect all-cause mortality. Unfortunately, the PSA test results in too much over diagnosis. As a result, the healthcare system is overloaded with too many over treated cases, and there are too many avoidable psychological side effects [33]. The solution could be the use of new, more specific biomarkers [33,34].

One can conclude that as per today measurement of prostate specific antigen is the first-line method for screening for prostate cancer. PSA-test may or may not be completed by Digital Rectal Examination

(DRE). However, the sensitivity and specificity of the test are far from being optimal.

## Benefit-To-Harm Ratio

Before a screening programme can be introduced, it must satisfy the requirements that it does more good than harm. No question, the measurement of prostate specific antigen as screening test may help to detect prostate cancer at an earlier stage, but it does not have a significant impact on either overall mortality or death from prostate cancer. ERSPC showed a 20% reduction in prostate cancer mortality after 13 years of follow-up, PLCO showed a non-significant benefit in favor of the control. A meta-analysis by Cochrane review of both trials suggested that screening does not significantly affect prostate cancer mortality [35]. Observational data shows a considerable increase in untreated prostate cancer mortality only 25 years after diagnosis, suggesting that a possible effect of screening would take a comparable time span to become apparent [36].

However, the benefit-to-harm ratio remains uncertain. Because of limited specificity, PSA screening is associated with false-positive results, over diagnosis and overtreatment, including biopsy complications. Over diagnosis is very common. In a meta-analysis of sixty-three studies in 104 publications including 1 904 950 men, over diagnosis was estimated to occur in 20.7% to 50.4% of screen-detected cancers [37].

Due to limited specificity of PSA test, false-positive results, over diagnosis and the consequent overtreatment present a more pressing problem. The screening might bring a number of test-positive cases to the surface which without screening would have been symptomless until the end of their life. As Richard M. Ablin, inventor of the PSA says about “the great prostate hoax”: “Every year, more than a million men undergo painful needle biopsies for prostate cancer, and upward of 100,000 have radical prostatectomies, resulting in incontinence and impotency. But the shocking fact is that most of these men would never have died from this common form of cancer, which frequently grows so slowly that it never even leaves the prostate [38].” The treatment of these cases is unnecessary; it adversely affects the quality of life and may result in avoidable complications [39,40]. Because treatment has potential side effects, it is critical that not all patients with prostate cancer receive aggressive treatment.

Psychological adverse effects need to be mentioned [41,42]. Screening may adversely affect quality of life not only by inducing over diagnosis and overtreatment. Anxiety goes along with waiting for the results, and especially with interpreting them. Three out of four elevated PSA levels were not caused by prostate cancer. That does not only mean that three quarters of men undergoing biopsy are confronted with a false-positive result, and means the start of a long phase of uncertainty and fear of disease. Especially, when an elevated PSA level is not the result of a measuring error, but persists or even increases over time. With a 5- or 10-year history of slowly but continuously increasing PSA levels, uncertainty may grow to such an extent that a prostate cancer diagnosis may come as a relief. Without screening, they would have had up to 10 more years in which they could have felt ‘healthy’ without worsening their prognosis.

## Discussion

Prostate cancer is a major health problem worldwide, particularly in the developed, “welfare countries”, but it is a growing problem in the less developed countries, too. Most of the medical profession argues for making the benefits of screening available for the public at large. On the other side, the public health profession is reluctant to promote the introduction of prostate screening into the healthcare system.



Several trials are published evaluating the effect of prostate screening have shown conflicting results. The European trial (ERSPC) showed a 20% reduction in prostate cancer mortality after 13 years of follow-up. On the other hand, the American trial (PLCO) showed a non-significant benefit in favor of the control. A meta-analysis of both trials suggested that screening does not significantly affect prostate cancer mortality.

The question arises whether screening for prostate cancer does make any sense, or not?

Screening refers to repeated testing of asymptomatic persons applying simple, safe, relatively inexpensive, sensitive and specific methods, suitable for detection of the target condition earlier when it would have been clinically manifested. The overall aim of screening is to favorably modify the course of disease development, to treat it in an early, preclinical stage, when the disease is more responsible to curative treatment, thereby preventing clinically manifest, advanced disease, and fatal outcome.

There are two levels on which screening decisions are made: public health level making health policy decisions followed by implementation of call-and-recall system of screening, based on individual identification of the persons at risk by age in the population, and the individual level: every man making his personal decision whether or not to undergo a screening test. Since the principles of Evidence-Based Medicine (EBM) have been applied in the public health area, there are strict criteria for initiating organized population-based screening in the healthcare system: mortality rates from the target disease are expected to significantly decrease in the target population, attributable to the screening efforts. The evidence can only be obtained from randomized controlled trials (RCT): only reduced mortality in a randomized trial constitutes evidence of the benefit of screening [42]. Screening programmes should be undertaken only when their effectiveness has been demonstrated. All the rest of "evidences" are biased, because the slowly growing tumours are more likely "to stick to the screen" than the fast growing ones, therefore are represented in a larger number ("length bias"), or the diagnosis is advanced in time, thus survival gain is only illusory ("lead bias") [43].

In the healthcare system, screening can be applied in two different ways: opportunistically and in an organized manner. Opportunistic screening is a component of medical/urological practice offering the test whenever opportunity arises, while organized or population screening is a public health measure performed by individual identification, personal invitation of each person on high risk by age [44].

Most of the national and international professional societies published their recommendation for prostate screening. The advice to implement the currently available knowledge is summarized in guidelines. The American Cancer Society, the American Association of Urologists, and the American Society of Family Physicians, the American Society of Clinical Oncologist recommend that each men over 50 years of age who have a life expectancy more than 10 years should be advised to annually undergo prostate screening with prostate specific antigen test wit/without digital rectal examination.

The US Preventive Services Task Force [45], the official forum of disease prevention in the USA recommended against PSA screening in all men saying that there was insufficient evidence advising the public either for or against it. However, more benefit can be expected from screening of men of 55-69 years of age; over 75 years of age the screening is meaningless therefore not recommended at all. As to the age-range to be screened is concerned, the PSA test loses its significance over time because its long natural history the prostate cancer is slowly developing over the years, therefore it is more likely to die from some inter-current disease than from prostate cancer.

The US Preventive Services Task Force (USPSTF) emphasized that prostate cancer should be an individual one and should include informed decision, i.e. discussion of the potential benefits and harms of screening with their patients [46]. Screening offers a small potential benefit of reducing the chance of death from prostate cancer in some men. However, many men will experience potential harms of screening, including false-positive results that require additional testing and possible prostate biopsy, over diagnosis and overtreatment; and treatment complications. In determining whether this service is appropriate in individual cases, patients and clinicians should consider the balance of benefits and harms on the basis of family history, race/ethnicity, comorbid medical conditions, patient values about the benefits and harms of screening and treatment-specific outcomes, and other health needs. Clinicians should not screen men who do not express a preference for screening. The USPSTF recommends against PSA-based screening for prostate cancer in men 70 years and older. The American Society of Clinical Oncology followed by agreeing with this approach only for older men but advising informed decision-making in younger men [47].

These recommendations have been adopted by both Canadian and European professional societies [48,49]. Guidelines on prostate cancers screening summarize the most recent findings and advice for the use in the medical practice. In Northern and Western Europe, the number of men diagnosed with prostate cancer has been on the rise. This may be due to an increase in opportunistic screening, but other factors may also be involved (eg, diet, sexual behavior, etc.).

The 2013 update of the European Association of Urologists Guidelines on Prostate Cancer recommends screening on an individual basis which also implies a baseline measurement of PSA in all men aged 40-45 years to initiate a risk-adapted follow-up approach. The goal should therefore be to maximize the benefits of PSA testing for prostate cancer screening and minimize its harms [50].

Until now, in the public health field, we do not have the kind of convincing evidence, which could provide a solid basis for a decision to introduce organized population-based mass screening for prostate cancer. In the same time, the ongoing opportunistic screening is considered controversial due to the considerable risk of detecting latent cancers.

As a result of the widespread opportunistic screening, much more prostate cancer come to light and treated than it would have been without screening, but mortality does not decrease in the same proportion. The decline in mortality, however, has a huge price. The number of men needed to treat to prevent one death is rather high in prostate cancer screening. According to the ERSPC trial, 1055 screening need to perform to prevent one death; meanwhile 192 false positive results, 37 over diagnosis and overtreatment, 12 cases of impotence and 4 cases of urinary dysfunction may occur [51].

To the question that should mass screening for prostate cancer be introduced at national level, the "Health Evidence Network" program of World Health Organization (WHO) European Regional Office the aim of was the evaluation of the effectiveness of healthcare technologies stated that "Studies in different populations do not provide good evidence that mass screening for prostate cancer does more good than harm [52]."

In Europe, the Advisory Committee on Cancer Prevention explicitly stated that until we have convincing evidence that the PAS test reduces mortality in the target populations, and has a positive impact on quality of life, a screening program for detection of prostate cancer as a public health procedure cannot be recommended [53].



## Conclusion

The organized population screening for cancer is defined as personal invitation of asymptomatic persons at risk by age, and their examination by suitable method in order to determine whether a particular target disease is likely to be established or likely to be excluded. Precondition of introduction of such a screening program is that in randomized controlled trials, after a reasonable period of time the mortality of the target disease decreases in the target population, attributable to the screening. For the time being, there are no evidences available of the effectiveness of screening for cancer of prostate in terms of mortality reduction, therefore – according to the state-of-the-art organized population screening for prostate cancer is not justifiable. However, prostate specific antigen is an indispensable screening tool, which is recommended in those subjects who are clinically suspected of any prostate abnormalities, or, for some reason are classified as high-risk persons for prostate cancer. PSA-test can be performed by urologist or even family physicians on the basis of their medical judgment and “oncology alertness”, having the informed consent of the patient.

It must be kept in mind that due to limited specificity and sensitivity of prostate specific antigen is limited, and it can manifest itself in a high degree of over diagnosis, and this might lead to unavoidable psychological side effects and an avoidable burden on the healthcare system.

Regarding to the lack of prospects for primary prevention, the high incidence and relatively high mortality of prostate cancer, introduction of the large scale screening means a serious dilemma to be solved. It would be desirable to exploit the blessings of secondary prevention for sake of the populations. The long natural history of the disease would make it possible. Unfortunately, at present this is not feasible, the screening test can be applied only on an individual basis, in consultation with a physician [54]. Until the ongoing studies provide evidence of the effectiveness of organized population screening, we have to apply the screening test with self-restraint.

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