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INAHTA

Joint Project

*Prostate Cancer
Screening*

**Evidence Synthesis and Update
Statement of Findings**

Tore Schersten, M. Angeles Baile,
José Asua, Egon Jonsson

January 1999

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Prostate Cancer Screening

Evidence Synthesis and Update Statements of Findings

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The International Network of Agencies for Health Technology Assessment (INAHTA) has been formed to exchange information and undertake collaborative activities in Health Technology Assessment. At the INAHTA Annual Meeting in 1997, prostate cancer screening was identified by a number of agencies as appropriate to consider through an INAHTA project. While the report has been prepared on behalf of INAHTA, the views expressed are those of the authors and do not necessarily reflect the position of INAHTA.

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The Agency for Health Care Policy and Research (AHCPR) is currently supporting an update of screening for prostate cancer and other preventive services through the U.S. Preventive Services Task Force. USA

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Summary

Objective: To summarize scientific evidence regarding the effectiveness and cost-effectiveness of mass screening for prostate cancer.

Methods: Synthesis of the nine eight systematic reviews of scientific evidence on prostate cancer screening undertaken by Health Technology Assessment (HTA) agencies member of INAHTA, and other relevant systematic reviews. High quality primary studies were added to the synthesis to update the information.

Results: Prostate cancer is a significant public health problem with a considerable human burden and high costs for society. The incidence of prostate cancer seems to be increasing in most countries because of better diagnostic test and more frequent use of them, particularly the prostate-specific antigen (PSA) test, an aging of the population, and probably a true increase in incidence.

Prostate cancer usually grows slowly and many men with the disease will never experience problems from it since they will not live long enough for the cancer to achieve clinical significance.

There are no methods available to differentiate between early slow-growing, *benign* cancers and early aggressive, life-threatening cancers.

For localized prostate cancer there are three major types of management: radical prostatectomy, radiotherapy, and watchful waiting. The active treatments, radical prostatectomy and radiotherapy, are both associated with significant side effects.

There is no evidence that mass screening for prostate cancer improve survival. Reported survival improvements for men with early-stage disease might well be explained by length bias or other statistical artifacts rather than by true clinical advances and better outcome.

Conclusion: Mass screening for prostate cancer is not recommended because of lack of evidence regarding the benefits and the considerable risks of adverse effects of subsequent treatment.

Introduction

Prostate cancer is a significant health problem in the Western World and in most countries the incidence rate is increasing.¹ The risk for developing prostate cancer increases with age, beginning to be significant at age 50 with a steep rise after age 65. Because local extension beyond the capsule is rarely associated with symptoms, more than 50 percent of patients already have local extracapsular cancer growth or distant metastases at the time of clinical diagnosis². This fact, together with the substantial morbidity associated with progression of prostate cancer, such as urinary tract obstruction and severe bone pain from metastases, has contributed to stimulate the interest in early detection through screening with the generally available screening tests: *digital rectal examination (DRE)*, serum tumor markers, e.g., *prostate-specific antigen (PSA)*, and *ultrasound (TRUS)*. The reference standard of these tests is histologic confirmation.

However, mass screening asymptomatic men for prostate cancer is controversial in the medical profession. Those who favor screening cite better survival rates in men with early-stage disease treated with radical surgery or radiotherapy, while others point to the lack of either convincing epidemiological data or randomized controlled trials showing improvement in morbidity or mortality. The benefit of treating prostate cancers detected by screening remains to be proven.

Several Health Technology Assessment (HTA) agencies have published systematic reviews of scientific evidence on prostate cancer screening recent years. This paper is a synthesis of these reviews other relevant critical reviews and primary studies identified through additional literature searches.

Methods

This report is a synthesis of systematic reviews of scientific evidence on prostate cancer mass screening undertaken by agencies performing technology assessments (including members of the International Network of Agencies for Health Technology Assessment-INAHTA) and other relevant reviews. The information on screening has been updated by inclusion of high quality primary studies (meeting published inclusion criteria- The Swedish Council on Technology Assessment in Health Care (SBU) *Literature Searching and Evidence Interpretation for Assessing Health Care Practices*. 1993) found by bibliographic search for the period 1996 to November 1998 in: *Medline, HealthStar, and Cochrane Library*.

Analyzed reviews

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Screening

The U.S. Commission on Chronic Illness in 1951 defined screening as “the presumptive identification of an unrecognized disease or defect by application of tests, examinations or other procedures which can be applied rapidly. Screening tests sort out apparently well persons who probably have a disease from those who probably do not. A screening test is not intended to be diagnostic. Persons with positive or suspicious findings must be referred to their physicians for diagnosis and necessary treatment.”

The primary goal of screening is to detect a disease or a defect at an early asymptomatic, pre-clinical stage in order to prevent the outbreak of the disease and to reduce suffering by early morbidity and premature death. Several different types of screening have been described ³.

- **Mass screening:** a comprehensive screening program for an entire segment of the population, e.g., certain age groups or one sex.
- **Selective screening:** involves screening selected, high-risk segments of the population.
- **Opportunistic screening:** testing individual patients using screening instruments. This derives from consultation between patient and physicians.

According to Wilson and Jugner ³, and modified by Cochrane and Holland ⁴, four main principles should be addressed before mass screening can be considered:

Disease severity: Screening should be limited to diseases that are important from a public-health perspective, i.e., those that are common and/or involve severe consequences for individuals in terms of morbidity and risk of death.

Diagnostic method: The screening method must have high sensitivity, i.e., the ability to detect disease when it exists. It must also be capable of detecting disease at a stage prior to the onset of symptoms. In addition to high sensitivity, it requires high specificity, i.e., the capacity to reliably exclude the possibility of disease in healthy individuals.

The method must also be well received by the group invited to screening-not painful, troublesome or otherwise unpleasant.

Treatment opportunities: These must be capable of changing the natural course of the disease in a positive direction. The effects of the treatment should ideally be documented by randomized controlled trials (RCTs).

Costs: The costs of mass screening program, including subsequent diagnosis and treatment, should reasonably correspond to the effects achieved.

Burden of illness

1990 estimates of the worldwide incidence of 17 major cancers found that prostate cancer was the sixth most common cancer among all types of cancers in the total population, and the fourth most common cancer in males, exceeded by lung cancer, stomach cancer and colorectal cancer in that order. The age-standardized incidence was highest in the United States, followed by Western Europe, Australia, and New Zealand. All countries in Asia reported low incidence rates ⁵.

In 1993, the International Agency for Research on Cancer (IARC) described the time trends for prostate cancer incidence and mortality ¹. The incidence varied 7-fold, from 10 per 100,000 among the non-Jewish population in Israel to 70 per 100,000 among men in Sweden. During the observation time both incidence and mortality increased among all populations. The rate of increase, however, was generally slower for mortality than for incidence.

The real prevalence of prostate cancer is impossible to determine. The frequency of autopsy-detected cancers is between 30 and 40 percent in men over the age of 50 and prostate cancer is identified in 10 to 20 percent of men undergoing surgery for benign prostatic hyperplasia.

Table 1: Incidence of prostate cancer using world-standardized rates per 100,000 per year

Country	Crude ratio	World-adjusted standardised rates (ASR)
Australia	70.39	51.51
Canada	86.55	64.73
Denmark	58.30	31.02
France	71.54	46.55
Germany	35.21	25.68
Italy	50.86	24.73
Netherlands	59.49	39.57
Spain	33.98	20.22
Sweden	119.53	55.26
Switzerland	93.90	54.01
USA (white)	142.17	100.79
USA (black)	116.6	136.97

Source: International Agency for Research on Cancer. International Association of Cancer Registries, Cancer Incidence in Five Continents VII- 1988-92

Person-years of life lost to cancer between 1970 and 1984 were analysed by a study in the United States. Life expectancy in men affected with prostate cancer was shortened by 9.1 years in 1970 and by 9.0 years in 1984 ⁶. The least years lost relative to the expectation of life was for those who died of prostate cancer (i.e., prostate cancer reduces a person's life expectancy less than other cancers). This places prostate cancer last among the 21 different types of cancers analysed.

A large proportion of cancers detected by PSA screening may be latent cancers, that are unlikely to produce clinical symptoms or affect survival. Autopsy studies in the U.S. indicate that histological evidence of prostate cancer is present in about 30 percent of men over age 50. The prevalence of prostate cancer in men without previous known prostate cancer during their lifetimes is 10 to 42 percent at age 50 to 59; 17 to 38 percent at age 60 to 69; 25 to 66 percent at age 70 to 79, and 18 to 100 percent at age 80 or older ⁶⁻⁹.

However, fewer than 40,000 men in the U.S. die each year from prostate cancer, suggesting that only a subset of cancers in the population are clinically significant. Because is not yet available, widespread mass screening is likely to detect a large proportion of cancers whose effect on morbidity and mortality is uncertain.

The international variation and time trends in incidence rates can partly be explained by differences in aging of different population and partly by differences in diagnostic intensity and registration of diagnoses. In the 1980s, prostate-specific antigen (PSA) came into wide use as a prostate cancer mass screening method. When an increase in incidence rate is observed following the introduction of a new diagnostic or screening method, a subsequent decrease may be expected as prevalent cases are removed from the population. This has recently been observed in the U.S. State of Utah ⁷. A rapid rise in incidence rates was observed between 1988 and 1991. In 1992 the incidence rates peaked and fell during 1993 and 1994. In the USA, for example, it has been estimated that 88% of the incidence trend could be explained by the increase in transurethral resection of the prostate (TURP) ⁸.

Several studies involving microscopic postmortem examination of the prostate in men who died of other causes than prostate cancer have shown an unexpectedly high occurrence of small carcinomas even in age groups (< 50 years) where symptomatic prostate cancer rarely appears ^{9,10}.

1. Risk factors

There are no epidemiological data that define risk groups sufficiently for a means of distinguishing innocent and progressive, aggressive cancers.

Age is considered an important risk factor with the incidence of both prostate cancer diagnosis and death increasing sharply with age.

Family history is a determinant of risk, with relative risk values of between 2 and 3 reported for men who had a father or brother with prostate cancer. The risk increases to roughly 5-fold with two affected family members. A recently described hereditary clustering of prostate cancer in families may be responsible for about 40 percent of cases in men under age 55 and 10 percent of prostate cancer cases overall ^{11,12}.

Race is a risk factor for prostate cancer. African American men have a 1.3 to 1.6-fold higher risk of getting of prostate cancer than non-African American men. In the 50 to 54 year age group, the risk is 2-fold higher.

There is a possible association between prostate cancer and diet, and especially dietary fat. This assumption is based on case-control studies, but there are various confounding factors, including race, marital status, body mass, physical activity, smoking, alcohol, occupation, vasectomy status, and other non-lipid dietary factors ¹³⁻¹⁸.

- Gene carriers of the recently cloned BRCA-1 gene have a significantly increased risk for prostate cancer, as well as for breast and ovarian cancer ¹⁹.

2. Natural course of prostate cancer

The natural course of a disease refers to the course of disease uninfluenced by treatment. Autopsy findings suggest that prostate cancer often has a prolonged latent course.²⁰ Currently, information on the natural course is obtained from studies where treatment has been introduced only after patients

show symptoms of disease. Treatment has usually been palliative hormonal castration or administration of estrogen.

There are several randomized controlled studies with a primarily untreated control group has been published ^{21, 22, 23, 24}, comparing placebo tablets with radical prostatectomy. Hormonal treatment was given if the disease became symptomatic. No difference in survival rates was observed after 15, 20 and 23 years of followup. Because the small sample size the findings should be interpreted with caution.

In a concurrent analysis ²⁵ of 828 primary untreated cases with clinically localized prostate cancer, including two cohorts from Sweden ²⁶⁻²⁹, two cohorts from the United States ^{30,31}, one from Israel ³², and one from Great Britain ³³, the disease-specific survival after 10 years was 87 percent in 492 patients with grade-1-tumors, 87 percent in 265 patients with grade-2-tumors, and 34 percent in 63 patients with grade-3 tumors. The corresponding figures for estimated metastasis-free survival were 81 percent, 58 percent and 26 percent. Multivariate analysis showed that factors that influenced disease-specific survival were grade-3 tumors and being from Israel.

Most studies reflect relatively low mortality from prostate cancer in localized stages. The grade of differentiation of the cancer appears to be a prognostic indicator for tumor progression, development of metastases, and mortality from the disease.

The natural course of prostate cancer has been studied in patients where incidental cancer was detected by prostate surgery because of benign hyperplasia^{27,34-36}. The risk of tumor progression in small tumors with less than 5 percent cancer in the surgical specimen can be estimated at 5 percent after 5 years, 15 to 20 percent after 10 years, and 25 to 35 percent after 15 years. Fewer than 10 percent of these patients will die from prostate cancer. If the tumor volume is greater than 5 percent in the surgical specimen, the risk of mortality from prostate cancer is substantially higher ²⁷.

The findings from these studies show that prostate cancer usually grows slowly and that many men with this disease will never experience problems from it, since they will not live long enough for the cancer to reach a level of clinical importance.

3. Mortality rates

Mortality data for prostate cancer do not reflect the rise in incidence reported by most countries, but the evidence concerning mortality rates is conflicting. Some authors claim that mortality has increased ³⁷, but others indicate that mortality has not changed appreciably in recent years ^{38,39}.

In the European community a mortality rate of between 12 and 23 per 100,000 men per year has been reported ⁴⁰. The cumulative lifetime risk has been estimated to be 3.9 percent and the cumulative mortality to 1.2 percent⁴¹.

In the United States, the age-adjusted death rate from prostate cancer increased by more than 20 percent between 1973 and 1991. The lifetime risk of dying from prostate cancer is 3.4 percent for American men ².

Mass Screening Methods

The principal mass screening tests for prostate cancer are the digital rectal examination (DRE), transrectal ultrasound (TRUS), and serum tumour markers, e.g., prostate-specific antigen (PSA). The reference standard for these tests is histologic confirmation of cancer. Biopsies are generally not performed on patients with negative test results. Therefore, the incomplete information about the number of true- and false-negative results make it impossible to accurately calculate sensitivity and specificity of these tests. Only the probability of cancer when the test is positive-the positive predictive value (PPV)-can be calculated with any confidence.

1. Digital rectal examination (DRE)

Rectal palpation is normally included in all comprehensive medical examination of men, and is taught to all medical students. It is a subjective method that requires experience and continuous training. The potential of the method to detect cancer is also limited because the examining finger can palpate only the posterior and lateral aspects of the gland. Studies suggest that 20 to 35 percent of tumours occur in portions of the prostate not accessible to the examining finger^{42,43}.

DRE as a mass screening method has been investigated in two randomized studies^{44,45}. Cancer was detected in 1.1 percent and 2.4 percent of the screened population. Different age structures of the screened population was the primary reason for the different results in the studies.

Other non-randomized studies agreed with these results, showing detection rates from 0.2 percent to 2.2 percent⁴⁶⁻⁵¹. These levels are lower than those obtained with other mass screening methods, and DRE's value as a mass screening method must be viewed as being limited. No recent study has recommended DRE as a single detection method. Of the tumors detected after DRE screening and treated surgically, at least one half have already penetrated the prostate capsule, which means a reduced chance of cure.

The relative sensitivity of DRE in detecting prostate cancer has mainly been determined by comparing how many cases of cancer in the same screening study are detected by other methods, independent of the DRE finding. Several studies indicate that 30 to 50 percent of the cancers will go undetected after screening with DRE alone, as compared with screening with TRUS and/or PSA^{45,47,52}.

The positive predictive value of DRE was found to be 28 percent in a randomized study⁴⁴. In other screening studies there are wide variations of PPV, ranging from 5 percent to 69 percent^{44,47,48,53,54}. Poor diagnostic reliability by initial false-positive findings creates major psychological stress and a high cost for secondary diagnostics.

There are no studies showing that DRE screening influences mortality from prostate cancer. DRE is now unacceptable as a sole mass screening method for detecting prostate cancer.

2. Transrectal ultrasound imaging (TRUS)

TRUS imaging of the prostate is performed by inserting an ultrasound transducer into the rectum. It gives a detailed image of the prostate gland's contour, its inner architecture, and adjacent structures. In addition to analysing the echo patterns in the prostate, it also indicates prostate volume, which is used in assessing PSA density.

The TRUS examination of the prostate is relatively resource-intensive, and requires extensive training. Therefore, it has to be performed by specially trained urologists or radiologists. Equipment costs range from U.S. \$40,000 to U.S. \$100,000.

Prostate cancer appears either as low echogenic (black) or isoechogenic areas (indistinguishable from surrounding tissue) ^{55,56}. Benign prostate enlargement, surgical scars, and inflammation also appear as low echogenic changes ^{57,58}, which are therefore not a cancer specific sign. It has been reported that about 95 percent of prostate cancers are hypoechoic, but that not all hypoechoic lesions are malignant and as many as 50 percent may be benign.

TRUS cannot usually detect a cancer that appears in the transitional zone of the prostate, i.e., the area around urethra, from which benign hyperplasia originates⁴⁵. This zone is the primary location for 20 to 30 percent of prostate cancers not detected by TRUS ⁴².

There is a wide variation in reported rates of sensitivity and specificity for TRUS, which reflects the uncertainty of these measurements. In the only referenced study based on a randomly selected population the sensitivity was reported to be 89 percent ⁴⁵.

Because TRUS cannot distinguish between benign and malignant nodules, the positive predictive value is low. Even when cancers are detected, the size of tumors is often underestimated by TRUS.

The low PPV of TRUS leads to high frequency of biopsies, according to reports based on screening studies ^{45,47,59}. A high biopsy rate has unfavorable psychological consequences, due to the large number of false positive test results ⁶⁰ and also to a high frequency of infection from biopsies, ranging from 5 to 6.2 percent ⁶¹⁻⁶³. These complications are important reasons why mass screening strategies should be designed to reduce the biopsy rates substantially without missing clinically significant tumors.

Using TRUS as a primary mass screening instrument would require major resources. No direct evidence shows that use of TRUS as a mass screening test improves disease-specific survival rates. Its main area of application is in secondary diagnostics, combined with histopathology.

3. Prostate-specific antigen (PSA)

Elevation of certain serum markers provides another means of mass screening for prostate cancer. Prostatic acid phosphatase had been used for many years until its role in screening has largely been replaced by prostate-specific antigen (PSA). Prostatic acid phosphatase has a much lower sensitivity (12 to 20 percent) for stage A and B disease and positive predictive value, < 5%, than PSA.

Prostate-specific antigen is a tissue specific glycoprotein, and one of the three proteins that predominate in seminal fluid. It is a serine protease ^{64,65} with structural similarities to the group of proteases called tissue kallikreins ⁶⁵. PSA cleaves the gel-building proteins in the seminal fluid, which leads to dissolution of the gel structure, while at the same time the progressively mobile sperm are set free in the now-fluid semen ⁶⁶.

PSA is normally released in low concentration in blood and circulates about 80 to 90 percent in complex with enzyme inhibitor- *antichymotrypsin (ACT)* and probably- a *macroglobulin*.

PSA is a tissue-specific and not a cancer-specific serum marker and therefore it appears in elevated blood concentrations in morbid prostate conditions other than cancer, e.g., prostatitis and benign hyperplasia. The relationship between benign hyperplasia and the PSA level in blood has been investigated in four major studies⁶⁷⁻⁷⁰. PSA levels above 4 ng/mL. (the diagnostic cutoff) appeared in 30 to 50 percent of examined patients with benign hyperplasia.

Different values have been used to designate normal PSA levels in blood. If normal PSA level in blood is set at 4 ng/mL., 80 percent of tumors that can be detected by current diagnostic technologies will be identified. The PPV for PSA is slightly above 32 percent, which is not substantially higher than for screening with DRE alone (28 percent). If a cutoff level higher than 4 ng/mL. is used, the number of false positives will certainly decline, but more cancers will go undetected by screening; i.e., the sensitivity of the test for early diagnosis of prostate cancer will decline. To disclose more tumors at an early stage a diagnostic cutoff of 2 or 3 ng/mL. has been proposed as the normal PSA level in blood. This would substantially increase false positives and subsequently increase the use of TRUS and biopsy.

Many attempts have been made to improve screening with PSA. They include work on:

- *PSA density*: relating PSA level in blood to gland volume as measured by ultrasound. There is no current information available from trials that gives support for the effectiveness of this strategy.
- *PSA velocity*: measuring PSA level in blood over time. This is based on the assumption that prostate cancer patients should have rapidly increasing PSA levels. However, it has been reported that 25 to 30 percent of men without clinical evidence of prostate cancer show a more than 20 percent increase of the serum PSA concentration over a period of 1 year.
- *PSA with reference to age*: PSA concentrations have been shown to be directly related to age. However, there is no evidence on the usefulness of age-specific reference ranges in screening for prostate cancer.

The reproducibility of these procedures are, however, poor, and therefore of questionable value.

- *Free versus bound PSA*: A more promising technology is the identification of different molecular forms of PSA in blood, which seems to increase the precision of the diagnosis of early prostate cancer.

PSA bonds to ACT (ACT/PSA ratio) in blood from patients with prostate cancer more than in blood from patients with benign hyperplasia (90 percent and 70 percent, respectively)^{67,68}. Accordingly, the proportion of free PSA in relation to the total concentration is less in patients with prostate cancer. Analysis of the proportion of complex-bonded PSA greatly increases the diagnostic specificity of PSA measurement, from 55 percent by conventional methods to 75 percent specificity at sensitivity level of 90 percent⁷¹.

The use of free PSA measurements can reduce unnecessary biopsies in patients with PSA levels of 4.0 to 10.0 ng/mL who are undergoing evaluation for prostate cancer, with a minimal loss of sensitivity in detecting cancer. In men whose prostate size was less 40 cm³ a free PSA cutoff of 13.7% or less would have eliminated 76 percent of the unnecessary biopsies while still detecting at least 90 percent of the cancers. Although for men with larger glands a cut-off of 20.5% would have been required to detect

90% of the cancers, and would have eliminated 38% of the unnecessary biopsies⁷². The 25% free PSA cutoff detected 95% of cancers while avoiding 20% of unnecessary biopsies⁷³.

Treatment

For localized prostate cancer there are three major types of management: radical prostatectomy, radiotherapy, and watchful waiting. Hormone therapies are generally reserved for cases with locally advanced or metastasized disease.

The majority of studies published on treatment have been observational in design, which means that their results need to be interpreted with great caution. These types of studies are biased by a number of factors, such as patient selection. Patients undergoing surgery tend to be younger and have fewer comorbidities than patients treated with radiotherapy. It is also common for surgical patients to have more confined disease than patients undergoing radiotherapy or conservative treatment. There are some randomized controlled trials comparing treatments: Paulson's study⁷⁴, comparing radical surgery versus radiotherapy, and the study made by Veterans Administration Cooperative Urological Research Group (VACURG)^{21, 22, 23, 24} comparing radical prostatectomy versus expectant treatment.

1. Radical prostatectomy

Radical prostatectomy involves the surgical removal of the entire prostate gland and the seminal vesicles. It is considered a curative treatment when the cancer is localized in the prostate gland within the capsule of the prostate. The report *Mass screening for prostate cancer* of SBU relates that the disease-specific survival after 10 to 15 years exceeds 90 percent. The probability of finding metastases in the regional lymph nodes is around 10 percent and finding cancer outside the prostate gland and beyond the tissue resected at surgery is 18 percent. Surgical mortality is less than 1 percent. Total urinary incontinence is relatively uncommon, but permanent impotence rather common.

In a prospective randomized controlled study of radical prostatectomy and placebo versus placebo alone (VACURG)^{21,22, 23,24}, 142 patients with previously untreated prostate cancer were randomly assigned to either prostatectomy followed by daily oral placebo or daily oral placebo without operation. At 15, 20 and 23-year followup, neither stage nor treatment was found to be predictive of outcome. The results of this study must be interpreted with caution. The study did not have the statistical power to detect differences in cancer-specific survival between the groups.

Three other RCTs addressing the question of radical versus conservative management are currently under way. Scandinavian trial⁷⁵ of watchful waiting versus radical prostatectomy, this trial compare mortality rates at 5 and 10 years in men randomized to radical prostatectomy rather than watchful waiting, disease-free survival and metastasis-free survival and measurements of quality of life and economic cost. This trial should reach a definitive conclusion on management of well and moderately well differentiated tumours, it will not provide information on whether the cure rate of poorly differentiated cancers, which are most likely to progress, can be improved by radical surgery⁷⁵.

In the United States, the Department of Veterans Affairs and the National Cancer Institute Cancer Therapy Evaluation Program co-operative study: Prostate Intervention Versus Observation Trial (PIVOT)⁷⁶, compare all cause mortality rates between watchful waiting and radical prostatectomy, it differs from the Scandinavian trial in its greater statistical power and in the fact that all histological grades will be included and other in the U.K., an RCT funded by the Medical Research Council: the PRO6 Trial⁷⁷, compare survival in patients treated by watchful waiting, by radical prostatectomy, or by radical radiotherapy. Quality of life and economic cost will also be compared. The studies have severe recruitment problems and it will take many years before any conclusions are available.

Evidence on radical prostatectomy is based largely on retrospective observational data from American

studies. According to these data the overall 10-year survival of men with confined disease is equivalent to, or better than, that of age-matched men in the population. Tumor histopathologicals differentiation seems to be the best predictor of disease progression following prostatectomy.

The risk of complications increases with age, particularly for men over the age of 75 years⁷⁸. Modelling the effectiveness of treatment following a structured literature review indicates that the expected benefits of surgery decreased rapidly with increasing age, with only men aged 60-65 years likely to achieve benefit. This study also indicated that men with well-differentiated tumours were likely to suffer net harm from radical treatment, as were most sexually active men with moderately differentiated cancer^{78,79}.

a. Patient selection

No signs of metastases should be present and the tumor must be confined within the glandular capsule.

The skeleton is a common site for distant metastases. The primary method for checking for bone metastases is the isotopic bone scan⁸⁰. It is the standard staging method in the United States, but it is not used routinely in all European countries because it is too costly and time consuming. PSA level has been found to be good marker for bone metastases, the sensitivity of PSA in detecting secondary deposits at presentation for levels in excess of 100 microgr/L was 93.75%, the positive predictive value 95.7% and the negative predictive value for levels less than 5 micrograms/L was 90.6%⁸⁰.

The precision of current methods for detection of metastases to the regional lymph nodes, lymphangiography, computed tomography, and MRI, is rather poor. Laparoscopic lymph node dissection has become more widely used in recent years⁸¹ but no scientific evaluation of its safety and efficacy is available. Even here around 95% negative predictive value for PSA as a marker for N₀ (at least in grade I and II).

The size and spread of the local tumor is usually determined by DRE and TRUS. Neither of these methods is particularly precise and neither CT nor MRI is helpful in determining the local extension of the disease^{82,83}.

b. Clinical outcomes

Survival: Comparison of survival between different studies is difficult because the type of survival figures presented varies considerably, and can include overall survival, cause-specific survival, metastases-free survival, progression-free survival, and survival free of local recurrence.

In the United States it is common to operate on patients with small incidental cancers that are detected by routine pathological tissue analysis after surgery for benign prostatic hyperplasia. Cause-specific 10-year survival has been reported at 100 percent for small, focal tumors and 97 percent for larger diffused growing tumors⁸⁴.

In other series, disease-free survival of 62 to 69 percent has been reported at 10-year followup, while cause-specific survival at 10-year followup varies between 88 and 97 percent⁸⁵⁻⁹³. The patient series are to some extent selected since if metastases to the regional lymph nodes or extensive growth of cancer outside the capsule were detected at the beginning of the operation it was usually interrupted. Therefore, these studies are not comparable to survival with radiotherapy or watchful waiting.

Gerber and colleagues⁹⁴ assessed the results of radical prostatectomy in men (2578) with early prostate

cancer. They found that the cancer-specific mortality rate at 10 years in patients with well-differentiated, moderately differentiated, and poorly differentiated adenocarcinoma was 6%, 20%, and 23%, respectively. Distant metastases within 10 years following surgery had been noted in 13%, 32%, and 48% of men with grade 1, 2, and 3 malignancy, respectively.

Surgical mortality: Surgical mortality is now generally below 1 percent⁹³⁻¹⁰¹. The most common cause of death has been cardiopulmonary insufficiency.

Urinary function: Most patients are unable to control urinary flow immediately after the operation. This problem usually subsides during the first 3 months, but permanent problems have been reported in up to 24 percent of patients. Surgical techniques have improved, but incontinence remains a significant long-term problem^{99,102,103}.

Sexual function: Postoperative sexual function is influenced by several factors, such as preoperative potency, age, stage of the disease, and the surgical technique used. Problems in the evaluation of impotence as a consequence of radical prostatectomy are that few studies have assessed preoperative potency levels for comparison, and there are differences in different men's definitions of potency and impotence.

In an interview study of men treated under Medicare who had prostatectomy, 61 percent of those who said they were sexually active before the operation could not have satisfactory erections after the operation, with only 11 percent reporting erections firm enough for intercourse^{100,103,104}.

Quality of life: The quality of life of patients after total prostatectomy has been assessed in only a few studies. Only one prospective study, conducted by Pedersen et al, systematically investigated life quality after surgery found that impotence was the only negative influence on daily life. In that study, the level of incontinence did not cause an increase in distress to patients 3 months post-surgery¹⁰⁵.

Side effects: Early complication rates of radical prostatectomy (within 30 days after surgery) range from 7 to 16 percent, and late complication rates (after 30 days) from 1 to 14 percent.

Treating cases of clinically localized prostate cancer with radical prostatectomy would result in:

- incontinence: about 300 out of every 100,000 men screened
- impotence: about 1,500 out of 100,000 men screened
- incontinence and impotence: 400 to 500 out of 100,000 men screened

2. Radiotherapy

The major technique for radiotherapy is external beam radiation. Other techniques are radioactive seed implants and conformal radiotherapy.

The radiosensitivity of prostate cancer is relatively low. High radiation doses are required to achieve permanent effect. Side effects are therefore also unavoidable, and the demand for optimization calls for the method selected to achieve a reasonable balance between the results of treatment and late side effects. The rectal and vesicle mucosa, small bowel, and femoral heads are the organs at risk. The volume of the prostate and tumor are calculated before CT treatment¹⁰⁶⁻¹⁰⁸.

Dose levels between 50 and 70 Gray are used depending of the tumor volume and stage. Conventional fractionation with target dose of 2 Gy per fraction is most common today¹⁰⁹.

Improvement in dose planning and therapeutic equipment are leading to more refined and individual-specific treatment. The planning target volume dose can be raised, increasing the possibility for cure while minimizing the dose to at-risk organs and thereby reducing side effects.

Most studies of outcomes following radiotherapy are retrospective, observational studies. Studies of external radiotherapy of incidental prostate cancer ¹¹⁰⁻¹¹³ have reported local recurrence rates of 0 to 20 percent and 5-year survival rates of 74 to 100 percent.

In patient series with early-detected cancer confined to the prostate, the corresponding figures were: local recurrence 0 to 23 percent, overall 5-year survival 67 to 93 percent, and 10-year survival 20 to 70 percent ¹¹⁰⁻¹¹².

a. Side effects

Early side effects such as tenesmus, diarrhea, urinary urgency, and general fatigue are usually temporary and possible to control medically.

Late side effects are more serious and difficult to treat. They include intestinal inflammation and bleeding, urethra constriction, urinary incontinence, bone necrosis, and impotence.

In the literature the reported incidence of complications varies between 8 to 95 percent ^{106,109,111-115}. One reason for the high variation is that while some studies report all complications, others report only what are considered serious complications. True comparisons between different studies are not possible.

Available evidence suggests that radiotherapy may be beneficial in lower age groups, 60 to 65 years, but probably harmful in others ⁷⁹.

3. Watchful waiting

Watchful waiting implies no active treatment until patients have symptoms of the disease, e.g., urinary obstruction or pain from bone metastases.

Since the natural course of prostate cancer is poorly understood, evaluation of watchful waiting is difficult. There are several randomized controlled studies with a primarily untreated control group has been published, ^{21,22, 23,24} comparing placebo tablets with radical prostatectomy. There are two articles reporting on pooled analysis from six studies published since 1985 ^{25,116}. One study involved 828 case records of patients treated conservatively. The results indicate that for men with grade I or II localized tumors watchful waiting is a serious option ²⁵, and perhaps for all prostatic cancer patients ¹¹⁶. There is a need for an RCT of watchful waiting versus radical prostatectomy for men with screening-detected prostate cancer.

Cost Analysis

Few studies have investigated the costs of prostate cancer mass screening programs. Further, it is difficult to compare costs of mass screening between countries. This is exemplified by the substantial difference in costs of one Swedish ¹¹⁷ and one British ¹¹⁸ primary care-based screening study. The cost per detected cancer was much higher in Britain than in Sweden.

The benefits of curative treatment for localized prostate cancer are uncertain, which means that cost-effectiveness analysis has to rely heavily on assumptions about treatment effects. Studies of cost-effectiveness that aim to examine whether the total benefit of the program outweighs its total costs are therefore inevitably hampered.

However, cost-effectiveness analysis that aims to examine the program's efficiency in relation to alternatives using endpoints such as cost per detected cancer or cost per patient receiving potentially curative treatment is possible. A comprehensive study examined the costs of different mass screening strategies ¹¹⁹. Researchers studied patient and indirect cost of six mass screening strategies for men aged 55 to 70 years. The total cost per 1,000 individuals screened, cost per cancer detected, cost per small cancer detected, and cost per cancer treated was assessed for each of the strategies. The most costly option per thousand individuals was also the most effective (screening using all three screening methods). The most cost-effective strategy in terms of cost per cancer treated was initial screening with PSA and subsequent TRUS performed for all individuals with PSA level above 4 ng/mL.

Ethical Considerations

Mass screening, which means searching for disease in non-symptomatic individuals, raises many ethical questions. Some of these questions include:

- Are there risks of serious negative consequences for individuals who receive false-positive or false negative results on the mass screening tests?
- Are there treatment methods that are effective in preventing premature death or significant morbidity?
- Are there risks of side effects of treatment that cause more harm than good?
- What are the risks for people who receive unnecessary treatment?
- Do the benefits to some outweigh the risks of harming others?

The World Health Organization has defined criteria to be met by mass screening programs for being medically and ethically acceptable:

The disease can be detected well before it becomes symptomatic. Time is available for diagnosis and treatment before the disease progresses to a dangerous stage.

A practicable and not unreasonably expensive test is available to detect early cancer.

Early detection by mass screening is meaningful for some patients.

Side effects of treatment are acceptable in relation to treatment benefits.

Very few if any mass screening program fully comply with all these criteria as exemplified by these common mass screening programs (Table 2).

Another criterion that could be added to the WHO list is that the cost of a mass screening program should be in a reasonable proportion to the health care costs of the disease itself and to the costs of the medical effects achieved. If early detection makes no difference, it is difficult to defend the cost of mass screening.

Table 2: Correlation between criteria and mass screening

	Detectable before symptomatic?	Reliable test available?	Predictive Positive value	Early treatment meaningful?	Side effects risk for overtreatment
Breast	Yes	Yes	Moderate	Yes	Minor
Cervix	Yes	Yes	Moderate	Yes	Major
Lung	Yes	No?	Poor	No?	Moderate
Prostate	Yes	Yes	Moderate	?	Major

Source: Johansson JE, Abrahamsson PA, Adami HO, Carlsson P, Damber JE, Gustavsson O, et al. *Mass Screening for Prostate Cancer*. Int J Cancer 1996; suppl 9.

The decision to screen or not to screen for prostate cancer, and if so by what means and to what extent, depends on several factors, such as the danger and the treatability of the disease, the reliability of mass screening methods, and, not least, the underlying norms and values. Ethical analysis in this context weighs the probable or expected value of mass screening in the population concerned against the assumed or probable risks of adverse physical or psychological effects for those affected if mass screening is or is not done. What is advantageous to one group may be disadvantageous to another and it is not clear how to balance advantages for one group against disadvantages for another.

It is obvious that prostate cancer mass screening meets few of these ethical criteria, and, most importantly, that mass screening will result in a large number of false-positives and thereby create harm and needless anxiety in many individuals. It can even be questioned if prospective randomized epidemiological trials are ethically justified. They must involve sizeable populations of volunteers without any clinical sign of prostatic cancer to achieve statistical significance of the expected marginal effect. A substantial number of these volunteers will be treated for benign cancers and unnecessarily exposed to significant harmful side effects.

Mass screening for prostate cancer does not currently fulfil the ethical requirements and principles to avoid harm and do good.

Discussion

This paper is a review of current scientific evidence available on the efficacy, safety, effectiveness, and cost-effectiveness of prostate cancer mass screening.

The available information in the medical literature on prostate cancer mass screening is enormous. During the last 5 years more than 1,000 articles have been published, and most of them deal with the accuracy, the positive and negative predictive value, of the diagnostic tests. Studies on the effectiveness of prostate cancer mass screening are scarce, with only one published randomized controlled trial comparing radical prostatectomy with watchful waiting. However, several trials are in progress.

A European multicenter trial with participation from 6 countries (Belgium, the Netherlands, Italy, Portugal, Finland, and Sweden) has recently started^{120,121}. The aim of the trial is to compare prostate cancer mortality in men randomized to be offered screening or to a control group. Because of differences in protocol between the centers, the results may be difficult to interpret as population-based evidence.

In the United States, the National Cancer Institute has financed a randomized trial on prostate cancer mass screening¹²². The men in the study group will be offered four annual screening tests by DRE and PSA. This study has its shortcomings. The method of recruitment, local advertising and through volunteer groups, has created problems of contamination of the control group in the pilot study.

Four trials addressing the question of radical treatment versus conservative management are now under way, two in Scandinavia, one in the U.K., and one in the U.S.A.

Fourteen centers in middle Sweden, Finland, and Iceland, are participating in a trial aimed at comparing mortality rates at 5 and 10 years in men randomized to radical prostatectomy or to watchful waiting.⁷⁵ Inclusion criteria are age < 75 years, clinically stage T1b-T2, Nx, M0, well- or moderately well-differentiated histological grade, and PSA \leq 50 ng/mL. Almost 700 thousand patients have been included in this study.

The USA trial, Prostate Cancer Intervention Versus Observation Trial (PIVOT), is similar, in comparing all cause mortality rates between radical prostatectomy and watchful waiting.⁷⁶ The sample size is larger and therefore the statistical power of this study is greater. In addition, this study includes all histological grades. This study may take many years to complete due to problems with patient accrual.

The U.K. study funded by the Medical Research Council: the PRO6 Trial⁷⁷ compares survival in patients managed by watchful waiting, by radical prostatectomy, or by radical radiotherapy. The recruitment of patients has so far been very slow and it is questionable if it will be possible to complete the trial.

A Scandinavian trial of watchful waiting versus radical radiotherapy with participation of middle Sweden and Denmark has been launched. Hesitation among participating urologists to offer watchful waiting will probably hinder the completion of the study.

These studies have the potential to answer a number of important questions, but many of the most important questions will still be unresolved.

Available mass screening tests, especially PSA in combination with others have the sensitivity to detect early-stage cancers of clinical significance, but also to detect cancers of uncertain clinical importance. Our current knowledge of the natural history of prostate cancer is too poor to determine which cancers

are destined to produce symptoms and affect survival, i.e., grow aggressively, and which will remain latent.

So far there is no evidence that mass screening for prostate cancer improve survival. Reported survival improvement for men with early-stage disease may well be ascribed to length bias and other statistical artefacts rather than true clinical advances with better outcomes.

From relevant studies on prostate cancer mass screening, identified from the *Medline data bases* (1966 to 1985), a cost-effectiveness model for one-time DRE and PSA measurement was constructed to examine possible outcomes¹²³. If a favourable set of assumptions was used, DRE and PSA measurement may increase life expectancy by approximately 2 weeks at a reasonable marginal cost for men who are between 50 and 69 years of age. If less favorable assumptions are used, the estimated net benefit decreases and cost-effectiveness ratio increases dramatically. Even with favourable assumptions the model suggested that mass screening adds only a few days to the average life expectancy of men who are older than 69 years of age. With less favourable assumptions, older men are harmed.

This illustrates the pertinence of the question: *Is cure necessary in those in whom it may be possible, and is cure possible in those in whom it is necessary?*¹²⁴. Mass screening will subject many men to aggressive treatment with risks of death, incontinence, impotence, and other sequelae without clear evidence of benefit. The absence of proof that mass screening reduces mortality from prostate cancer and the relatively high risk of increased treatment-related morbidity are arguments against a policy of mass screening in asymptomatic men.

However, absence of proof is not proof of absence and therefore there are good reasons for further research. Research areas of great interest are the natural history of prostate cancer, factors determining the biologic activity of the cancer, study of the early treatment efficacy and refinement of prognostic tests.

Conclusions

DRE, TRUS, and PSA, used alone or in combination can be used in identifying patients with prostate cancer. In prevalence screening, i.e., the first round of screening, the detection rate may be relatively high. The results of repeated screening (incidence screening) are largely unknown. These tests used alone lack sensitivity and specificity. If they are combined the sensitivity and specificity are raised but remain relatively poor.

Prostate cancer is a significant public health problem in most developed countries (outside of Asia) with a considerable human burden and high costs for society. However, routine population screening for prostate cancer is not recommended because of the lack of evidence regarding the benefits and the considerable risks of adverse effects.

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Appendix

Mass screening for prostate cancer using prostate specific antigen (PSA)

ANAES (Agence Nationale d'Accréditation et d'Evaluation Médicale)

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Date: January 1998

Background: In France, the age-standardized incidence rate of prostate cancer varies from 24.9 to 37.9 per 100 000 according to county (département). Worldwide, it has increased regularly over the last two decades but is currently decreasing maybe because improved early detection has reduced the pool of cancers in asymptomatic men. Age-specific mortality from prostate cancer has also fallen slightly and now stands at 16.7 per 100 000 in France.

Aim: To assess the possible relevance of a systematic mass screening for prostate cancer using PSA.

Method: A critical appraisal of the scientific literature using WHO criteria.

Clinical evidence

- The number of years of life lost to prostate cancer is very much smaller than the number lost to cancer of the lung or gastrointestinal tract.
- The most effective treatment for localized prostate cancer has not been established. Watchful waiting is a fairly common option because of the morbidity of available treatments and their adverse effects on quality of life.
- It is not yet possible to distinguish latent from life-threatening tumors. The best prognostic factor is the degree of tumor differentiation.
- Young men with a family history of prostate cancer (about 9% of patients) may form a high-risk population.
- For the moment, the optimal screening strategy for prostate cancer would seem to be the assay of total prostate specific antigen (PSA) in serum combined with a digital rectal examination. If either of these tests proves to be positive, a biopsy is performed. The strategy cannot be considered a gold standard because (a) PSA levels, and thus threshold levels, depend on the kits used and (b) we do not know the positive predictive value of either test in routine screening.
- Ongoing randomized trials testing the benefits of mass screening in the US and Europe are encountering expected difficulties and it is not certain that their results will be easy to interpret because of the heterogeneity of baseline characteristics, unknown prognostic variables, and the difficulty in ensuring an adequate long-term followup. Clearly, in the absence of adequate prognostic factors and treatments, other types of studies are called for that increase our knowledge-base on the disease but also evaluate the patients' needs and preferences.

Economic viewpoint: The cost of PSA screening *per se* is not prohibitive but, before deciding to allocate any resources, we need more information on how much life expectancy might be increased and also the results of cost-effectiveness studies that take the cost of setting up the screening program into account. For the moment, mass screening using PSA seems premature although individual testing should not be discouraged.

Conclusion: On the basis of current understanding, the ANAES project group does not recommend systematic mass screening for prostate cancer using PSA in asymptomatic men. Moreover, whether the French male population would be ready to accept mass screening is a moot point. Additional studies are required on the information to be given to patients and on when PSA monitoring should be prescribed in an individual patient.