2011

HEALTH TECHNOLOGY ASSESSMENT REPORT

MOH/P/PAK/210.10(TR)

MINISTRY OF HEALTH MALAYSIA

PROSTATE CANCER SCREENING

Health Technology Assessment Section (MaHTAS)

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MINISTRY OF HEALTH MALAYSIA

Health Technology Assessment Report

PROSTATE CANCER SCREENING

DISCLAIMER

This Health Technology Assessment has been developed from analysis, interpretation and synthesis of scientific research and/or technology assessment conducted by other organisations. It also incorporates, where available, Malaysian data, and information provided by experts to the Ministry of Health Malaysia. While effort has been made to do so, this document may not fully reflect all scientific research available. Additionally, other relevant scientific findings may have been reported since completion of the review.

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ACKNOWLEDGEMENT

The authors for this Health Technology Assessment Report would like to express their gratitude and appreciation to the following for their contribution and assistance:

- Health Technology Assessment and Clinical Practice Guidelines Council.
- Technical Advisory Committee for Health Technology Assessment.
- Madam Zalina Ahmad and Madam Sin Lian Thye from MaHTAS for their contribution in retrieval of the evidence

DISCLOSURE

The authors of this report have no competing interest in this subject and the preparation of this report is totally funded by the Ministry of Health, Malaysia.

EXECUTIVE SUMMARY

Background

The incidence of prostate cancer is rising worldwide caused mainly by demographic factors and the increase in the number of suspected cases identifies following the introduction of Prostate Specific Antigen (PSA) testing. Prostate cancer is least common in South East Asia, more common in Europe and most common in the United States. The risk factors for prostate cancers are age, family history and race. The natural history of prostate cancer is variable, ranging from indolent to strikingly aggressive with long preclinical phase. While the intention of screening for prostate cancer is to decrease mortality and increase patient's quality of life, the true benefit of screening remains uncertain. This has been highlighted by the conflicting recommendations made by various medical entities.

Technical features

Prostate cancer is classified as an adenocarcinoma, or glandular cancer, that begins when normal semen-secreting prostate gland cells mutate into cancer cells. The PSA test and the digital rectal examination (DRE) are used as primary screening tools in the early detection of prostate cancer. Transrectal ultrasound (TRUS)-guided needle biopsies are perform to confirm diagnosis following PSA and/or DRE testing. The reference standard for these tests is histological confirmation of cancer.

Objective

To assess the effectiveness, safety and economic implications of screening asymptomatic men for prostate cancer compared to no screening or usual care.

Methods

Electronic databases such as MEDLINE, PubMed, EBM Reviews-Cochrane Database of Systematic Reviews, EBM Reviews-Cochrane Central Register of Controlled Trials, EBM Reviews-HTA databases, EBM Reviews-NHS Economic Evaluation Database, EBM Reviews-Cochrane Methodology Register, INAHTA database, HTA database and FDA database were searched. No limits were applied to the search. Additional articles were identified from bibliographies of retrieved articles and hand-searching of journals. All relevant literature was appraised using the Critical Appraisal Skills Programme (CASP) and evidence was graded based on guidelines from U.S./Canadian Preventive Services Task Force.

Results and conclusion

The available evidence on prostate cancer mortality rates from two large randomised controlled trials was conflicting with the European Randomised Study of Screening for prostate cancer (ERSPC) reporting a 20% reduction in prostate cancer mortality but the Prostate, Lung, Colorectal and Ovarian cancer (PLCO) cancer screening study did not. In the ERSPC for every prostate cancer death prevented 1,410 men have to undergo screening, while 48 need to be treated in excess of control population to save one prostate cancer death.

There was good level of evidence to suggest that screening for prostate cancer led to positive stage and grade shift, however, it also led to overdetection and overtreatment. A considerable percentage of screened-detected prostate cancers is indolent and is difficult to differentiate from aggressive cancers. There was no retrievable evidence to determine the long term impact of prostate cancer screening on quality of life or its economic value.

The was good level evidence to suggest that complications associated with PSA test and DRE were mild and infrequent, and major complications associated with TRUS guided needle biopsies were rare. However, false-positive PSA screening test results were associated with adverse psychological effects and prostate cancer treatments were associated with more serious complications which include infection, impotence, incontinence and bowel dysfunction.

There was good level of evidence to suggest that the sensitivity and specificity of PSA test are not ideal leading to high false-positive and false-negative rate and there was no PSA threshold that effectively discriminates between the presence and absence of prostate cancer. Higher PSA level, positive family history of prostate cancer and abnormal DRE result were predictors for prostate cancer.

For mass screening programme to be medically and ethically acceptable, the WHO criteria for mass screening programmes have to be met. Given the uncertainty about the benefits and risks of mass screening for prostate cancer, men should be provided with current information about the benefits and risks of prostate cancer screening (the screening tests, the diagnostic and treatment path) so that each man can make his own decision whether or not to undergo individual screening.

Recommendation

Based on the above review, there was evidence to suggest that prostate cancer screening may reduce the likelihood of men dying from prostate cancer. However, current published data are insufficient to recommend the adoption of population screening for prostate cancer as a public health policy because of the significant overdetection and overtreatment that would result from the screening. Since men with family history of prostate cancer have a significantly higher risk of developing prostate cancer, we therefore recommend selective screening of asymptomatic men with a family history of prostate cancer from the age of 40 years and above.

PSA test may be used for prostate cancer screening. However, there was no PSA threshold that effectively discriminates between the presence and absence of prostate cancer. DRE may be used as an adjunct to PSA test.

Men who expressed an interest in prostate cancer screening need to be properly informed on the potential benefits and harms associated with prostate cancer screening. A standard guideline for prostate cancer screening need to be established.

Organisational issues such as training, manpower, good referral system, treatment and funding need to be addressed at all levels.

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ABBREVIATIONS

HTA	Health Technology Assessment
ASR	Age standardised rate
WHO	World Health Organization
PSA	Prostate-specific antigen
tPSA	Total PSA
fPSA	Free PSA
DRE	Digital rectal examination
TRUS	Transrectal-ultrasound
AUA	American Urological Association
ACS	American Cancer Society
JUA	Japanese Urological Association
CDC	Centre for Disease Control and Prevention
ng/ml	nanogram/millilitre
BPH	Benign prostatic hypertrophy
RR	Relative risk
CI	Confidence interval
PPV	Positive Predictive Value
NPV	Negative predictive Value
AUC	Area under receiver operating characteristic curve
FP	False-positive
ERSPC	European Randomised Study of Screening for Prostate Cancer
PLCO	Prostate, Lung, Colorectal and Ovarian

PROSTATE CANCER SCREENING

1 BACKGROUND

Prostate cancer screening in asymptomatic men remains an area of enormous controversy, with the potential benefits and harms continuing to be debated among healthcare professionals after more than two decades of Prostate Specific Antigen (PSA) screening. The incidence of prostate cancer is rising worldwide. This is caused mainly by demographic factors, particularly the increase in elderly population and more importantly, the increase in the number of suspected cases identified following the introduction of PSA testing.[1] Rates of prostate cancer vary widely across the world. Although the rates vary widely between countries, it is least common in South East Asia, more common in Europe and most common in the United States. According to the International Agency for Research in Cancer, in 2008 prostate cancer was the second most common cancer among men worldwide with age-standardised rate (ASR) of 28.5 cases per 100,000 persons per year. It was the 4th most frequent cause of cancer deaths among men (ASR of 7.5 deaths per 100,000 persons per year). Prostate cancer was most frequently occurring in World Health Organization (WHO) American Region (ASR of 66.7 cases per 100,000 persons per year and ASR of 12.9 deaths per 100,000 persons per year) and WHO Europe Region (ASR of 57.2 cases per 100,000 persons per year and ASR of 11.7 deaths per 100,000 persons per year). In the WHO Western Pacific Region, prostate cancer was the 6th most common cancer among men (ASR of 10.1 per 100,000 persons per year) and the 8th most frequent cancer deaths among men (ASR of 2.9 deaths per 100,000 persons per year). It is the 8th most common cancer among men (ASR of 4.7 per 100,000 persons per year) and the 8th most frequent cancer deaths among men (ASR of 3.2 deaths per 100,000 persons per year) in the WHO South-East Asia Region.[2]

In Peninsular Malaysia, from 2003 to 2005, prostate cancer was the fourth most frequent cancers among males. It accounted for 7.3% (2,150 cases/29,459 cases) of the total cancers in males with ASR of 12 per 100,000 population. Among the ethnic groups in Peninsular Malaysia, the Chinese recorded the highest age adjusted incidence (15.8), followed by Indians (14.8), whereas Malays had half the incidence (7.7) of the other two races. The incidence in Malaysian Chinese (15.8) was higher than the incidence of Chinese in Shanghai (3.0), Hong Kong (8.6), and Taiwan (11.9). Indians in Malaysia (14.8) had higher incidence than their counterparts in Chennai (4.9) and Singapore (9.9). The age specific incidence curve rose exponentially after the age of 50 years old.[3]

In general, the agents that cause the initiation of prostate cancer is unknown. Risk factors for prostate cancers are age, family history and race. The risk for developing prostate cancer increases with age, beginning to be significant at the age of 50 with a steep rise after the age of 65. Men with a family history of prostate cancer have a significantly greater risk of developing prostate cancer than those with no such family history. The pooled relative risk (RR) in first-degree relatives was 2.5. It was highest in relatives of cases diagnosed before 60 years old and the RR declined with age. The risk increases to 3.5-fold with two affected relatives. Relative risk to sons of cases appeared to be lower than in brothers.[4,5,6] African American men have a 1.3 to 1.6-fold higher risk of getting prostate cancer than non-African American men.[7,8]

Although prostate cancer is not rare, it has a variable natural history, ranging from indolent to strikingly aggressive with a long preclinical phase. 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.[7] It is commonly quoted that many more men die with prostate cancer than of it. Autopsy/post-mortem studies showed that while a very high proportion of elderly men had histological evidence of the disease, a much smaller proportion developed clinically apparent cancer.[1] Currently, there are no methods available to differentiate between early slow-growing, benign cancers and early aggressive, life threatening cancers.

The natural history of prostate cancer is poorly understood, but progression appears to be related to the staging and grade of the tumour. For localised 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 metastasised disease. The active treatments (radical prostatectomy and radiotherapy), are both associated with significant risk of sexual, urinary and bowel-related symptoms depending on type of treatment.[7,9,10]

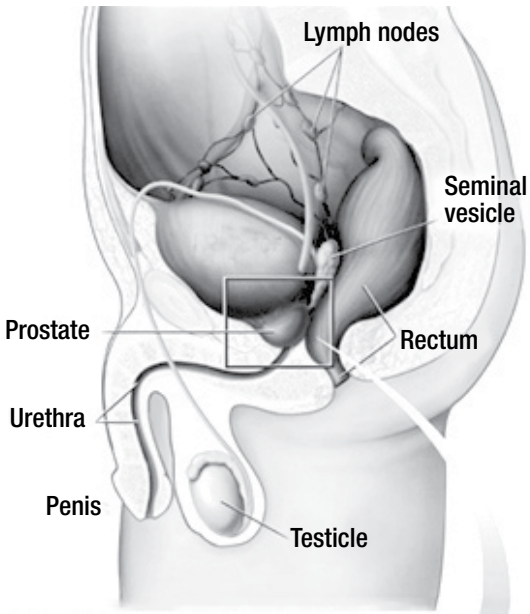
Local extension of prostate cancer beyond the capsule is rarely associated with symptoms. More than 50 percent of patients already have local extracapsular cancer or distant metastases at the time of clinical diagnosis. This fact, together with the substantial morbidity associated with progression of prostate cancer such as urinary tract obstruction and severe bone pain from metastases, has contributed to stimulate the interest in early detection through screening.[7] Screening for any type of cancer aims to increase the chances of successful treatment through early detection of the disease and thus reduce mortality. Screening may be performed in one of the three methods: mass (for example large scale screening for the entire population), selective (for example for high-risk populations) or opportunistic (for example incorporated as part of medical consultation). Testing for, or diagnosing, a disease differs from screening. Diagnostic testing attempts to identify the disease in the presence of symptoms; screening is offered to symptom-free individuals. The PSA test and the digital rectal examination (DRE) are used as primary screening tools in the early detection of prostate cancer. Transrectal ultrasound (TRUS)-guided needle biopsies are perform to confirm diagnosis following PSA and/or DRE testing.[7]

There are guidelines developed by various medical entities for prostate cancer screening. However, their recommendations are conflicting because the true benefit of screening remains uncertain.[11]The American Urological Association (AUA), the American Cancer Society (ACS) and the Japanese Urological Association (JUA) recommends screening of asymptomatic men.[12-14] This is in contrast with the recommendations made by the U.S. Preventive Services Task Force, the Japanese Guideline for Prostate Cancer Screening, and the The United Kingdom National Steering Committee.[15-17]

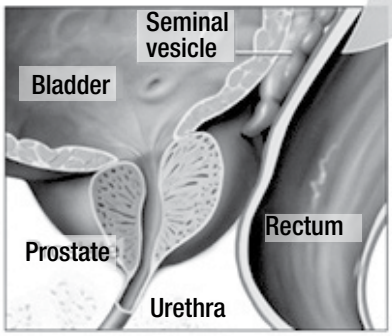
With the significant burden of prostate cancer among males all over the world, one of the strategies for early detection of cancer in the Malaysian National Cancer Management Blueprint 2008-2010 is to provide prostate cancer screening service. Previous Health Technology Assessment (HTA) Reports (1997 and 1999) and Technology Review Report (2007) did not recommend routine population based screening for prostate cancer due to lack of evidence regarding the benefits and cost-effectiveness of screening asymptomatic men for prostate cancer.[1,7,18] Therefore, a HTA is required to look into the most recent available evidence on the effectiveness (especially on the mortality rates from prostate cancer), the safety and the cost-effectiveness of screening asymptomatic men for prostate cancer. This HTA was requested by the Senior Principal Assistant Director of Cancer Unit, Disease Control Division, Ministry of Health, Malaysia.

2 TECHNICAL FEATURES

Prostate cancer is classified as an adenocarcinoma, or glandular cancer, that begins when normal semen-secreting prostate gland cells mutate into cancer cells. The region of prostate gland where the adenocarcinoma is most common is the peripheral zone. The cancer cells may metastasise from the prostate to other parts of the body particularly the bones and the lymph nodes. It may cause pain, difficulty in urinating, problems during sexual intercourse, or erectile dysfunction.[19] The principal mass screening test for prostate cancer are the PSA, DRE and TRUS. The reference standard for these tests is histological confirmation of cancer.[7]



This shows the prostate and nearby organs.



This shows the inside of the prostate, urethra rectum, and bladder.

2.1. Prostate-specific antigen (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 with structural similarities to the group of proteases kallikreins. PSA is normally released in low concentration in blood and circulates about 80 to 90 percent in complex form with enzyme inhibitor - *antichymotrypsin* (*ACT*) and probably - a *macroglobulin*. PSA is tissue-specific and not a cancer-specific serum marker and therefore it can be elevated in men with prostate cancer and with benign prostate diseases such as prostatitis and benign hyperplasia.[7]

PSA assay (test) is used for the measurement of serum PSA in conjunction with DRE as an aid in the detection of prostate cancer in men aged 50 or older. It is also used for serial measurement of PSA to aid in prognosis and management of patients with prostate cancer. It has been approved by FDA since 1986.Several total PSA tests are available such as Access® Hybritech® PSA reagents on the Access Immunoassay Systems (calibrators), bioMerieux VIDAS total PSA assay-P040008 and Dimension RxL Flex PSA Reagent Cartridge –P000021. The presence of amounts above 4.0 ng/ml (nanograms per millilitre) indicates abnormally high concentration of PSA, and possibility of prostate cancer.[20]

Many attempts have been made to improve screening with PSA. They include work on:-[1]

a. PSA density

- Serum PSA density (serum PSA divided by volume of the prostate in millilitres) has been employed in an attempt to increase the specificity of PSA testing to distinguish between patients with BPH and those with small volume organ confined prostate cancer

b. PSA velocity

- Measures the rate of change in serum PSA over time. Determined from consequtive assessments of PSA usually at least 12 months apart.

c. PSA with reference to age

- Serum PSA concentrations have been shown to be directly related to age

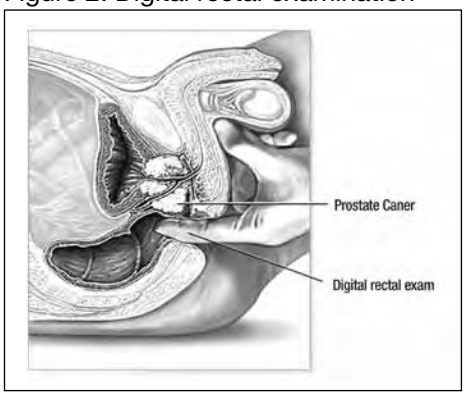
d. Free PSA/Total PSA (fPSA/tPSA)

- Measure the amount of free PSA in the blood. PSA occur in serum in two different molecular forms; free and complexed (or bound).The proportion of complexed PSA is higher in patients with prostate cancer. The amount of free PSA in the sera of men with prostate cancer is lower in men with BPH. If the fPSA/tPSA is less than 0.2, there is a chance that the man has prostate cancer.

2.2. Digital rectal examination (DRE)

DRE is probably the most common examination in urological practice. It requires the insertion of a finger into the rectum to palpate the prostate gland for induration or abnormal masses. Suspected abnormalities can be investigated further by transrectal-ultrasound (TRUS) and biopsy. It was the principal first line method for detecting the presence of prostate cancer prior to the introduction of PSA testing.[1] DRE 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 the lateral aspects of the gland.[7]

Figure 2. Digital rectal examination



2.3. Transrectal-ultrasound imaging (TRUS)

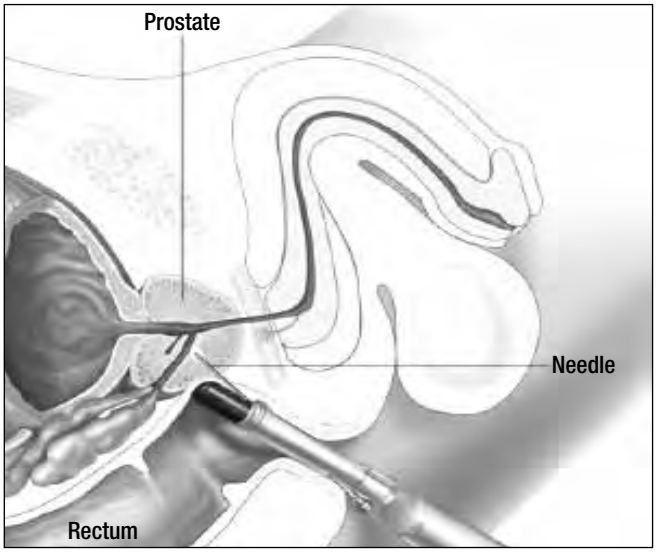
TRUS is currently used in a number of ways; to estimate the size of the prostate, detect prostate cancer, guide needle biopsies, stage the cancers detected and to monitor the disease prior to and after treatment. TRUS is not normally used as a primary screening measure, but to confirm the diagnosis of prostate cancer for those with raised PSA or lesions suspicious on DRE.[1]

TRUS imaging 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. Prostate cancer appears either low echogenic (black) or isoechogenic areas (indistinguishable from surrounding tissue). Benign prostate enlargement, surgical scars, and inflammation also appear as low echogenic changes, which are therefore not a cancer specific sign. It has been reported that about 95 percent of prostate cancers are hypoechoic, but not all hypoechoic lesions are malignant and as many as 50 percent may be benign. TRUS usually cannot detect a cancer that appears in the transitional zone of the prostate; that is the area around the urethra from which benign hyperplasia originates.[7]

2.4. Transrectal-ultrasound guided needle biopsy

Needle biopsy is used to confirm the diagnosis of prostate cancer. Modern transrectal needle biopsies are usually done with ultrasound guidance using a needle mounted in a spring-loaded biopsy 'gun'. Biopsies can be directed towards areas deemed suspicious by DRE or TRUS, or performed systematically to sample the entire prostate; often six biopsies are taken in a sextant pattern from different parts of the prostate gland. It is uncomfortable and can be complicated by infection or bleeding.[21]

Figure 3. Transrectal ultrasound guided needle biopsy



2.5. Treatment

Three major types of treatment are recognised for localised prostate cancer; radical prostatectomy, radiotherapy, and conservative management (watchful waiting). Hormonal therapy and chemotherapy tend to be reserved for cases with advanced or metastasised disease. All treatments can have significant side-effects such as sexuality and reproductive issues. [1,7,19,22]

3 POLICY QUESTION

Should screening for prostate cancer among asymptomatic men be carried out as part of the Malaysia National Cancer Control Programme?

4 OBJECTIVE

To assess the effectiveness, safety and economic implications of screening asymptomatic men for prostate cancer compared to no screening or usual care.

The following research questions were addressed:-

1.1. To undertake a systematic review on the effectiveness, safety and cost-effectiveness of screening asymptomatic men for prostate cancer

1.2. To determine the diagnostic accuracy of the various screening tests used in prostate cancer screening

1.3. To look into the ethical, legal, and organizational aspect related to prostate cancer screening

5 METHODOLOGY

5.1. Literature search strategy

Studies were identified by searching electronic databases. The search was applied to Ovid MEDLINE (1950-Week 1 June 2010), EBM Reviews-Cochrane Database of Systematic Reviews (2005 to March 2010), EBM Reviews-Cochrane Central Register of Controlled Trials (2nd Quarter 2010), EBM Reviews-HTA Databases (2nd Quarter 2010), EBM Reviews-Cochrane Methodology Register (2nd Quarter 2010), EBM Reviews-NHS Economic Evaluation Database (2nd Quarter 2010) via OVID, PubMed, INAHTA database, HTA database and FDA database. The last search was run on 10 August 2010. No limits were applied to the search. Additional articles were identified from reviewing the bibliographies of retrieved articles and hand-searching of journals. General search engine was used to get additional web-based information.

We used the following search terms either singly or in combination; prostate cancer, prostate carcinoma, prostate tumour, prostate tumor, prostate neoplasm, screening, screening programme, prostate-specific antigen, digital rectal examination, transrectal ultrasound, safe*, cost*, adverse events, complication, anxiety, mortality rate, quality of life, QALY, family history, legal, and ethics.

5.2. Study Selection

Based on the policy question the following inclusion and exclusion criteria were used:-

5.2.1. Inclusion criteria:-

a. Study design :
- Systematic Review and Randomised Controlled Trial (RCT) for effectiveness
- Systematic Review, RCT, Cohort and cross-sectional study for safety
- Studies which include economic evaluation

b. Population :
- Men

c. Intervention :
- Prostate cancer screening using the following screening tests individually or in combination:-
  - Prostate-specific antigen (PSA) test (including total, velocity, density and percentage free and complex)
  - Digital rectal examination (DRE)
  - Transrectal ultrasound (TRUS) and TRUS guided biopsy

d. Comparators :
- No screening / usual care

e. Outcome 1. :
- Mortality rate, detection rate, quality of life, quality adjusted life years (QALY) gained
- Adverse events related to prostate cancer screening
- Cost, cost-utility and cost-effectiveness of prostate cancer screening

Outcome 2. :
- Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of DRE and PSA

5.2.2. Exclusion criteria:-

Study conducted in animals

Based on the above inclusion and exclusion criteria, study selection were carried out independently by two reviewers. The titles and abstracts of all studies were assessed for the above eligibility criteria. If it is absolutely clear from the title and / or the abstract that the study was not relevant, it was excluded. If it was unclear from the abstract and / or the title the full text article was retrieved. Two reviewers assessed the content of the full text articles. Disagreement was resolved by discussion.

5.3. Quality assessment strategy

The methodological quality of all the relevant full text articles retrieved was assessed using the Critical Appraisal Skills Programme (CASP) tool depending on the type of study design.[23] Quality assessment was conducted by two reviewers. Disagreements were resolved by discussion. All full text articles were graded based on guidelines from the U.S./Canadian Preventive Services Task Force (Appendix 1)[24]

5.4. Data extraction strategy

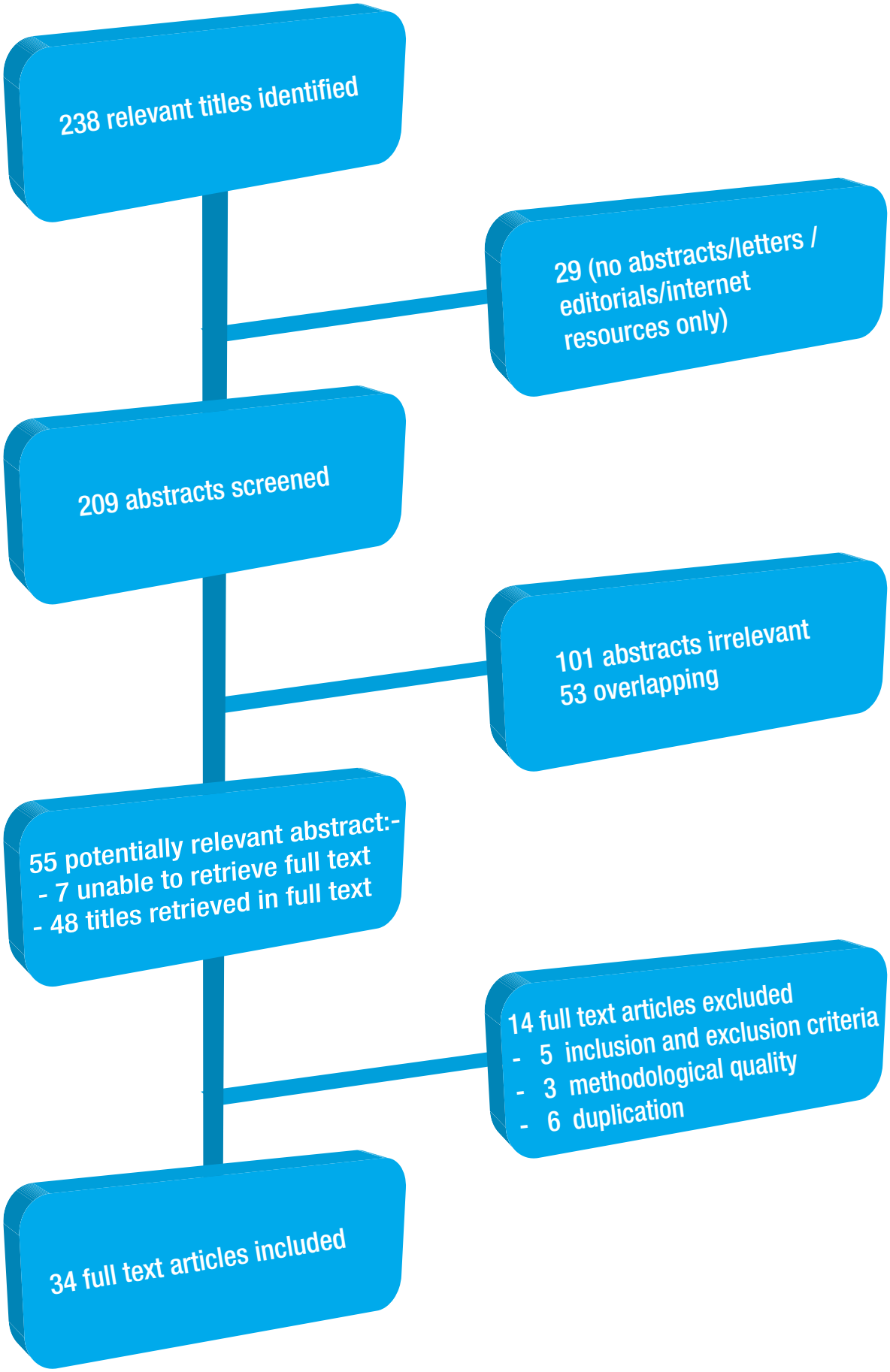
Data were extracted from included studies by a reviewer using a pre-designed data extraction form (evidence table as shown in Appendix 5) and checked by another reviewer. Disagreements were resolved by discussion. Details on: (1) methods including study design; (2) study population characteristics including age, trial inclusion and exclusion criteria; (3) types of intervention including screening using PSA (total, velocity, density and percentage free and complex), DRE, TRUS and TRUS guided biopsy; versus no screening or usual care; (4) type of outcome measures including mortality rate, detection rate, quality of life, quality adjusted life years (QALY) gained, adverse events related to screening and treatment, cost, cost-utility and cost-effectiveness of prostate cancer screening, diagnostic accuracy of screening tests used (sensitivity, specificity, PPV, NPV), and (5) any information on ethical, legal and organizational aspect related to prostate cancer screening were extracted. The extracted data were presented and discussed with the expert committee.

6 RESULTS

Search strategies yielded many published articles related to prostate cancer screening. A total of 238 relevant titles were identified and 209 abstracts were screened using the inclusion and exclusion criteria. Of these, 101 abstracts were found to be irrelevant and 53 abstracts overlapping. Fifty-five potentially relevant abstracts were attempted for retrieval. Of these, 48 potentially relevant articles were retrieved in full text, and full text for seven abstracts cannot be retrieved. After reading and appraising the full text articles, 34 full text articles were included as shown in Figure 4. Fourteen full text articles were excluded based on inclusion and exclusion criteria, quality of the studies and duplication and are listed in Appendix 6.

The articles comprised three HTA reports, two systematic review, 16 RCTs, 4 RCTs (post hoc analysis), two cohort studies, five cross sectional studies and two economic evaluation papers. We also included one article by the World Health Organization (WHO) and one article by the Centres for Disease Control and Prevention (CDC).

Figure 4. Flow chart of retrieval of articles used in the results



6.1. EFFECTIVENESS OF PROSTATE CANCER SCREENING PROGRAMME

6.1.1. Prostate cancer mortality

Any form of screening aims to reduce the mortality and increase person's quality of life. The information on prostate cancer mortality associated with prostate cancer screening was reported by a systematic review and two large RCTs. The Cochrane Systematic review by Ilic *et al.* included one RCT (Quebec study) and one quasi-randomised controlled trial (Norrkoping study) with a total of 55,512 participants comparing mass screening for prostate cancer with PSA, DRE and TRUS guided biopsy with no screening. Patients were followed-up for 11 years in the Quebec study and for 15 years in the Norrkoping study. However, the authors acknowledged that both trials had methodological weaknesses. The authors re-analysed the results from the two studies using intention-to-screen principle and meta-analysis. They found that there were no statistically significant differences in prostate cancer mortality between men randomised for prostate cancer screening and control (relative risk, 1.01; 95% confidence interval [CI], 0.80 to 1.29). The systematic review concluded that given that only two RCTs were included, and the high risk of bias of both trials, there is insufficient evidence to either support or refute the routine use of mass, selective or opportunistic screening compared to no screening for reducing prostate cancer mortality.[25 level 1]

Recently in 2009, the long awaited results of two large RCTs of prostate cancer screening with PSA testing and DRE had been published and reported different conclusions regarding the efficacy of screening.[26,27] The Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening study is United States (U.S.) based study which was conducted at 10 U.S. study centres involving men aged 55 to 74 years. From 1993 through 2001, 38,343 men were randomly assigned to annual screening with PSA testing and DRE (screening group) and 38,350 men were assigned to the usual care. Usual care sometimes included screening, as some organizations have recommended. In the screening group, rates of compliance were 85% for the PSA testing and 86% for DRE. Rates of screening in the control group increased from 40% in the first year to 52% in the sixth year for PSA testing and ranged from 41% to 46% for DRE. After seven years of follow-up, the incidence of death per 10,000 person-years was 2.0 (50 deaths) in the screening group and 1.7 (44 deaths) in the control group (rate ratio, 1.13; 95% CI, 0.75 to 1.70). At ten years of follow-up, at which time 67% of the data were complete, the incidence of death per 10,000 person-years was 2.7 (92 deaths) in the screening group and 2.4 (82 deaths) in the control group (rate ratio, 1.11; 95% CI, 0.83 to 1.50). The authors concluded that after seven to ten years of follow-up, the rate of death from prostate cancer was very low and did not differ significantly between the two study groups. Follow-up in the PLCO cancer screening study is planned to continue until all subjects reach at least 13 years. A final report will be presented once the planned duration of follow-up is completed.[26 level 1]

In contrast, the European Randomised Study of Screening for Prostate Cancer (ERSPC) which was initiated in 1990's in seven European countries (Netherlands, Belgium, Sweden, Finland, Italy, Spain and Switzerland) demonstrated a 20% reduction in prostate cancer mortality (rate ratio, 0.80; 95% CI, 0.65 to 0.98; adjusted P=0.04). The study involved 182,160 men between the ages of 54 to 74 years which were randomly assigned to a group that was offered PSA screening at an average of every 4 years or to a group that did not receive such screening. The predefined core age group for the study included 162,243 men between the ages of 55 and 69 years. The mortality follow-up was identical for the two groups and ended on December 31, 2006. In the screening group, 82% of men accepted at least one offer of screening. The median follow-up was 8.8 years in the screening group and 9.0 years in the control group. The study found that 1,410 men would need to be screened and 48 additional cases of prostate cancer would need to be treated to prevent one death from prostate cancer. The authors concluded that PSA-based screening reduced the rate of death from prostate cancer by 20% but was associated with a high risk of overdiagnosis.[27 level 1] Several possible explanations were given for the lack of reduction in mortality in the PLCO cancer screening study such as threshold of 4 ng/ml and DRE to trigger diagnostic evaluation may not be effective, whereas, in the ERSPC, a PSA of 3 ng/ml generally was used to trigger a biopsy. Second, the level of screening in the

control group could have been substantial to dilute any modest effect of annual screening in the screening group (40% in the first year and increased to 52%) in the sixth year, whereas it is only 6% in the ERSPC. Thirdly, in the PLCO screening study, 44% of men in each study group had undergone one or more PSA tests at baseline, which would have eliminated some cancers detectable on screening from the randomised population. The cumulative death rate from prostate cancer at 10 years in the two groups combined was 25% lower in those who had undergone two or more PSA tests at baseline than those who had not been tested. There was virtually no screening at baseline in the ERSPC population. Fourth, is the improvement in therapy for prostate cancer during the course of the trial probably resulted in fewer prostate-cancer deaths in the two study groups, which blunted any potential benefit of screening.[26,13]

6.1.2. Detection of prostate cancer

a. Detection rate

Several studies have demonstrated an increased detection of prostate cancer in the screened arm compared with the control arm. The Norrkoping study demonstrated that the rate of diagnosis of prostate cancer in the screening group was 47% higher compared to the control group (relative risk, 1.47; 95% CI, 1.16 to 1.86) [25 level 1.] In the PLCO cancer screening study, at seven years, prostate cancer had been diagnosed in more subjects in the screening group (2,820) than in the control group (2,322) (rate ratio, 1.22; 95% CI, 1.16 to 1.29) and at 10 years the excess in the screening group persisted (rate ratio, 1.17; 95% CI, 1.11 to 1.22).[26 kevel 1] Similarly in the ERSPC, they detected 5,990 prostate cancers in the screening group and 4,307 in the control group, with a cumulative incidence of 8.2% and 4.8% respectively.[27 level 1.]

Andriole *et al*. found that the detection rate of prostate cancer among the screening group in the initial screening round of the PLCO cancer screening study was 1.4% whereas Grubb *et al.* found that the detection rate of prostate cancer in the first four rounds of the PLCO cancer screening study was 4.9%.[28-29 level 1] The detection rate of prostate cancer in the six centres of the ERSPC involving 58,710 men during the first screening visit and during the second screening visit did not show much difference (331/10,000 men) versus (335/10,000 men).[30 level 1]

b. Stage and grade shift

Screening for prostate cancer using PSA test has led to stage and grade shift manifested by a reduction in detection rate of aggressive cancers during subsequent screening. This was demonstrated by findings from the centres of the ERSPC and also PLCO cancer screening study.[28-31 level]. In the PLCO cancer screening study, 12% of cancer detected at the initial screening round had Gleason score 8-10, whereas only 7% of cancer detected at subsequent 4 rounds had Gleason score 8-10.[28-29 level 1] van der Kwast *et al.* reported that in the six centres of the ERSPC, the overall detection rate of high-grade (Gleason score 8-10) cancers showed a reduction during the second screening visit from 26.0/10,000 men to 12.6/10,000 men.[30 level 1.] Hoedemaker *et al.* in his study on prostate cancer characteristics in a cohort of 4,491men aged 55 to 75 assigned to the screening group of the Rotterdam section of the ERSPC, noted that 36% of adenocarcinomas detected in the first screening round had Gleason score of 7 or higher but only 16% of those detected in the second round had Gleason score of 7 or higher (mean difference = 20; 95% CI, 10% to 30%, $P < 0.001$). He also noted that 25% of the adenocarcinomas detected in the first screening round had adverse prognostic features compared to only 6% of those detected in the second round (mean difference =19; 95% CI, 11% to 26%, $P < 0.001$).[31 level 1]

The percentage of localised tumours were higher in the screening group compared to the control group as demonstrated by the Norrkoping study (84% versus 27%) and the ERSPC.[25,27 level 1] In the PLCO cancer screening study, the percentage of prostate cancer with Gleason score 8-10 was lower in the screening group compared to the control group (8.4% versus 11.5%) and in the ERSPC the percentage of prostate cancer with Gleason score ≥ 7, was lower in the screening group compared to the control group as shown (27.8% versus 45.2%).[26-27 level 1]

c. Interval cancer

There are variations in the screening protocol, particularly in the interval between different screening rounds. The rate of interval cancers (those clinically diagnosed within a screening interval) gives an indication of the sensitivity of the screening program and the appropriateness of the length of the screening interval.

Roobol *et al.* conducted a study to compare the number and characteristics of interval cancers among men in the Rotterdam section of the ERSPC and among men in the Gothenburg section of the ERSPC. Men were screened at four yearly intervals in the Rotterdam section and at 2 yearly intervals at the Gothenburg section. They found that the 10-year cumulative incidence of all prostate cancers were higher in the Gothenburg section (13.14%) compared to Rotterdam section (8.41%), P<0.001. The cumulative incidence of interval cancer was also higher in the Gothenburg section (0.74%) compared to the Rotterdam section, (0.43%), P=0.51. There was no significant difference in the cumulative incidence of aggressive interval cancer (0.12%) in the Gothenburg section and (0.11%) in the Rotterdam section, (P=0.72). The authors concluded that the 2-year screening interval had higher detection rates than the 4-year interval but did not lead to lower rates of interval and aggressive interval prostate cancers.[32 level 1]

d. Lead time and overdetection

Screening for prostate cancer advances the time of diagnosis (lead time) and detects cancers that would have not been diagnosed in the absence of screening (overdetection). Overdetection and the consequent overtreatment of prostate cancer are contributors to the harms and costs associated with PSA screening.

The mean lead time and overdetection rate is described by Draisma *et al.* They estimated mean lead time and overdetection rates associated with several PSA screening programs with the simulation program MIcrosimulation Screening ANalysis (MISCAN). MISCAN models were validated against data from the Rotterdam section of the ERSPC. For a single screening test at the age of 55 years, the mean lead time was 12.3 years and the overdetection rate was 27%; 95% CI, 24% to 37% whereas at the age of 75 years, the mean lead time was 6.0 years and the overdetection rate was 56%; 95% CI, 53% to 61%. For a screening program with 4-yearly screening interval from age 55 to 67, the mean lead time was 11.2 years and the overdetection rate was 48%; 95% CI, 44% to 55% whereas for a screening program with yearly screening interval from age 55 to 67, the overdetection rate was 50%; 95% CI, 46% to 57%. Extending annual or 4-yearly screening interval to the age of 75, would result in at least two cases of overdetection for every relevant cancer detected. The model based lead time estimates support a prostate cancer screening interval of more than 1 year.[33]

Draisma *et al*. in another study estimated the mean lead time and overdetection for PSA testing of U.S. men aged 54 to 80 years in 1985-2000 using three models of prostate cancer progression and detection calibrated to the Surveillance, Epidemiology, and End Results (SEER) programme. Estimates of lead times using different definitions were compared across models. The estimates of overdetection produced by the three models ranged from 23% to 42% of all prostate cancers detected by PSA. Also highlighted that precise definition and population used to estimate lead time and overdetection can be important drivers of study results and should be clearly specified.[34]

e. Indolent prostate cancer

Screening for prostate cancer has resulted in an increased incidence. However, not all cancers deserve immediate treatment. It has therefore become more important to be able to identify those screened-detected prostate cancers most likely to show indolent behaviour. Roemeling *et al.* used the Kattan-nomogram which was validated and recalibrated for use in a screening setting to calculate the number of men who were predicted to have indolent cancer in a screen-detected cohort from Rotterdam Section of the ERSPC. They found that of 1,629 cancers detected in two subsequent rounds, 825 were suitable for nomogram use and the remainder were unlikely to have indolent cancer. A total of 485 of 825 men (59%) were predicted to have indolent cancer, which was 485 of 1,629 (30%) of all screened-detected cases. They also found that cancers found at repeated screening after four years had a higher probability of indolent cancer than cases from the prevalence screening (44% versus 23%, P<0.001).[35]

6.1.3. Quality of life

The short-term effects of population-based screening for prostate cancer on health related quality of life (health status) were reported by Essink-Bot *et al*.

They conducted a longitudinal study of 626 attenders to the Rotterdam prostate cancer screening programme and of 500 nonparticipants. Attenders of the screening programme and nonparticipants completed self-assessment questionnaires (SF-36 that is Medical Outcomes Study 36-Item Short-Form Health Survey) and (EQ-5D that is EuroQol measure for health-related quality of life health surveys) to measure generic health status as well as an additional questionnaire for anxiety items related to prostate cancer screening.

They found that physical discomfort during DRE and during TRUS were reported by 181/491(37%) of men and 139/487 (29%) of men respectively and discomfort during prostate biopsy were reported by 64/116 (55%) of the men. The mean scores for health status and anxiety indicated that participants did not experience relevant changes in physical, psychological, and social functioning during the screening procedure. However, high levels of anxiety were observed throughout the screening process among men with high predisposition to anxiety. Similar scores for anxiety predisposition were observed among attenders and nonparticipants. The authors concluded that at group level, they did not find evidence that prostate cancer screening induced important short-term health-status effects, despite the short-lasting side effects related to biopsy procedures. However, subgroups may experience high levels of anxiety. [36 level 1]

The study on long term effect of population-based screening for prostate cancer on health related quality of life (health status) is now being carried out in the PLCO cancer screening study and the ERSPC.[26-27 level 1]

6.2. SAFETY

Risk incurred from a screening process can result from the screening itself or from down-stream diagnostic or treatment interventions.

6.2.1. Complications of PSA test and DRE

Andriole *et al.* reported the complications associated with screening in the screening group of the PLCO cancer screening study. They described that the complications associated with screening were mild and infrequent. PSA testing led to complications at the rate of 26.2 per 10,000 screenings, primarily dizziness, bruising and hematoma and included three fainting episodes per 10,000 screenings. [26 level 1]

The most frequent complication of DRE in men is discomfort and pain. Essink-Bot *et al.* reported 181/491 (37%) of men in the Rotterdam screening trial for prostate cancer had discomfort during DRE.[36 level 1] Romeo *et al.* evaluated patients' perception of pain and discomfort during DRE among 100 patients. They reported that 73% reported moderate, severe or unbearable pain for at least one domain (61% complained of pain, 22% complained of urinary urgency and 22% complained of bowel urgency). They also reported that emptying the bladder immediately before examination did not reduce the incidence of moderate, severe or unbearable pain. However, it does not affect the intention of having a prostate examination in the future.[37 level III] Andriole *et al.* reported few episodes of bleeding or pain at a rate of 0.3 per 10,000 screening. [26 level 1]

6.2.2. Complications of TRUS guided needle biopsy

The two main risks of TRUS guided needle biopsy are bleeding and infection. Andriole *et al*. in their PLCO cancer screening study, reported that complications occurred in 68 of 10,000 diagnostic evaluations after positive results on screening. These complications were primarily infection, bleeding, clot formation, and urinary difficulties.[26 level 1] Complications of TRUS guided systematic sextant prostate biopsies performed in the Rotterdam section of the ERSPC were reported by Rietbergen *et al*. and Raaijmakers *et al.*[38-39 level 1] From June 1994 to July 1996, 1,687 TRUS guided systematic sextant prostate biopsies were performed and mild complications such as haematospermia (45.3%) and haematuria (23.6%) were reported. Major complications were less frequently seen. Fever were seen in 4.2% of biopsies whereby 3.1% requiring antibiotic therapy and 0.4% requiring admission. Urinary retention was seen in 0.4% of biopsies.[38 level 1]

Similar complications rates were reported by Raaijmakers *et al.* involving 5,802 biopsies. The most frequent minor complications were haematospermia (50.4%) and haematuria (22.6%). Major complications were seen far less frequently. Two hundred men (3.5%) developed fever after biopsies and 27 men (0.5%) were admitted to hospitals because of signs of prostatitis and/or urosepsis. Urinary retention was seen in 0.4% of biopsies. Risk factor analysis revealed that an earlier episodes of prostatitis was significantly associated with pain after biopsy ($P = 0.024$) and hospital admission ($P = 0.014$). Prostate volume and transition zone volume/total volume were predictors for urinary retention.[39 level 1] Lee *et al*. in their study to determine risk factors for patients who suffered major complications and hospitalisation after TRUS guided prostate biopsies among 1,529 consecutive patients found that urinary tract infection and rectal preparation might affect complication rate.[40 level III]

6.2.3. Psychological effects of prostate cancer screening

Psychological implications of participants who had false-positive screening results for prostate cancer compared with participants not undergoing prostate biopsy following a normal PSA test were reported by McNaughton-Collins *et al*., Fowler *et al.*, and Katz *et al.* McNaughton-Collins *et al.* compared 167 men who had abnormal screening results but a benign prostate biopsy results with 233 men who had a normal PSA (defined as < 2.5 ng/ml). After six weeks, 81/167 (49%) of men in the biopsy group reported thinking about prostate cancer either "a lot" or "some of time" compared with 18% of the control group, $P < 0.001$. In addition, 67/167 (40%) of the biopsy group worried "a lot" or "some of the time" about developing prostate cancer compared with 18% in the control group, $P < 0.001$. One year later, Fowler *et al.* demonstrated that men who underwent prostate biopsy were more often reported worrying about prostate cancer. Twenty-six percent (32/121) of men in the biopsy group reported having worried "a lot" or "some of the time" that they may develop prostate cancer compared with 10/164 (6%) in the control group, $P < 0.001$. Moreover, 46% of the biopsy group reported thinking their wife or significant other was concerned about them developing prostate cancer versus 14% in the control group, $P < 0.001$. The study also found that more men in the biopsy group than in the control group had at least one additional PSA test (73% versus 42%, $P < 0.001$) and another biopsy (15% versus 1%, $P < 0.001$) and more likely to visit urologist (71% versus 13%, $P < 0.001$). [41-42 level II-2]

Katz *et al.* conducted a cross sectional telephone survey of two groups of men at two months after prostate cancer screening. Group 1 included 109 men with abnormal PSA test or DRE but negative biopsies for prostate cancer (false-positive screening results) and group 2 (control) included 101 age-matched primary care patients with PSA screening test in the reference range (< 4 ng/ml). They found that men with false-positive screening results (group 1) were more likely than control group to worry about getting prostate cancer, have a higher perceived risk of prostate cancer ($P < 0.001$) and reported at least moderate problem with sexual function.[43 level III]

6.2.4. Treatment related complications

In the PLCO cancer screening study, Andriole *et al.* reported that treatment related complications were generally more serious which include infection, incontinence, impotence and other disorders. Such complications are now being catalogued in the quality-of-life study and are particularly pertinent in cases of overdetection.[26 level 1] Two HTA reports conducted in 2002 and 2006 reported that prostate cancer treatment causes clinically significant harms, including erectile dysfunction, bowel dysfunction and incontinence.[44-45] Reported complication rates varies between studies. The HTA report by Bunting *et al.* reported erectile dysfunction rates between 32% to 79.6%, and incontinence rates between 3.5% to 9.6%.[44] Mambourg *et al.* reported erectile dysfunction rates of 39.6% to 80.0%, incontinence rates of 10% to 22%, and bowel dysfunction rates of 8% to 43%.[45]

6.3. COST/ COST-EFECTIVENESS

No robust Cost-effectiveness analysis (CEA) or Cost utility analysis (CUA) based on large RCTs, regarding the economic value of PSA screening, is available. However, two full text articles on economic evaluation related to prostate cancer screening were included in the report. Holmberg *et al.* evaluated the clinical and economic consequences of prostate cancer screening based on a limited screening trial in a Swedish community and a decision tree model. In 1987, 1,492 men (50-69 years) were selected randomly and were invited to repeat screening. They were examined every third year and followed-up up for 10 years (total of four screening rounds). The other 7,679 men in the population acted as control. They found that the total incremental health care costs for prostate cancer will increase by 179 million Swedish krona (SEK) per year with screening compared to no screening. The incremental cost with screening compared to no-screening is as shown in table 1. The authors concluded that general screening for prostate cancer can be performed with a reasonable cost per detected localised cancer,[46]

Table 1. Incremental cost with screening compared to no screening

	Cost (SEK) 1996
Cost per detected cancer	158,000
Cost per detected localised cancer	167,000
Cost per potentially curative cancer	249,000

Ekwuewe *et al.* conducted a systematic review to examine the resource costs (included the direct and indirect costs) for prostate cancer screening, diagnostic tests and staging in the United States compared with other industrialised countries. Electronic databases such as MEDLINE, EMBASE and CINAHL were searched from January 1980 through December 2008. From 262 studies examined, 28 met the inclusion criteria (15 studies conducted in the U.S. and 13 studies conducted in other industrialised countries). The pooled baseline resource cost for studies conducted in the U.S and other industrialised countries were shown in table 2.[47]

Table 2. Pooled baseline resource cost for screening test, diagnostic test and staging of prostate cancer according to studies conducted in the United States and other industrialised countries

Test	Cost (in 2003, U.S. dollar)
Studies conducted in U.S.	
Screening with PSA	$ 37.23 (13.11-77.18)
Screening with DRE	$ 31.77 (4.20-61.48)
Diagnostic (urology consultation)	$ 76.91 (39.60-156.04)
Diagnostic (TRUS)	$ 237.18 (71.38-488.84)
Diagnostic (Biopsy)	$ 393.08 (105.04-1,923.72)
Staging (pathologic or histologic)	$ 94.14 (45.77- 145.46)
Clinical staging	$ 736.52 (197.86-1097.53)
Studies conducted in other industrialised countries	
Screening with PSA	$ 30.92 (15.56 -69.00)
Screening with DRE	$ 33.54 (16.13 -66.66)
Diagnostic (urology consult)	$ 97.04 (55.61-147.84)
Diagnostic (TRUS)	$ 103.77(38.91-185.04)
Diagnostic (Biopsy)	$ 164.96 (31.64-298.51)
Staging (pathologic or histologic)	$ 131.23 (59.83-241.13)
Clinical staging	$ 306.40 (146.74-603.67)

In the Malaysian context, the cost for tPSA test is RM 17.00 and the cost of fPSA test is RM 30.00. fPSA will be done only for sample with tPSA between 4.0 to 10.0 ng/ml. This will help to differentiate high PSA level associated with benign prostatic hypertrophy (BPH) or prostate cancer.(verbal communication with pathologist in Kuala Lumpur General Hospital)

6.4 DIAGNOSTIC ACCURACY OF SCREENING TESTS

6.4.1. Prostate-specific antigen (PSA) test

Most of the diagnostic accuracy studies on PSA suffer from differential verification bias. Patients with abnormal PSA levels were verified with biopsy, which is the reference test while patients with normal PSA levels were verified with clinical follow-up because of the invasiveness of prostate biopsy procedure. Because of this, many studies reported only the PPV of prostate cancer screening.

The Prostate Cancer Prevention Trial (PCPT) which was conducted from 1993 to 2003 at 221 U.S. centres is the only large scale screening trial that conducted prostate biopsy for all participants at the end of the trial period and allows the reporting of true sensitivity and specificity. The study randomised 18,882 men aged 55 years or older with a normal DRE and PSA level less than or equal to 3 ng/ml to receive either finasteride or placebo for seven years. Measurement of DRE and PSA were performed annually. A prostate biopsy was recommended if PSA level exceeded 4.0 ng/ml or the DRE results were suspicious of cancer. At the end of seven years all participants not previously diagnosed with prostate cancer were requested to undergo and end-of-study biopsy within 90 days of the randomisation anniversary. Of 8,575 men in the placebo group with at least one PSA measurement and DRE in the same year, 5,567 (65.2%) had at least one biopsy. The study demonstrated that for detecting any prostate cancer, PSA cut off values of 1.1, 2.1, 3.1, and 4.1 ng/ml yielded sensitivity of 83.5%, 52.6%, 32.2%, and 20.5%, and specificity of 38.9%, 72.5%, 86.7%, and 93.8% respectively. The sensitivity and specificity of PSA for aggressive prostate cancer; Gleason score 8 or higher

was greater (50.9% and 89.1%) for PSA value ≥ 4 ng/ml and (68.4% and 81.0%) for PSA value ≥ 3ng/ml, respectively. Age-stratified analysis showed slightly better performance of PSA in men younger than 70 years versus those 70 years or older with the area under operating characteristic curve (AUC) values of 0.699 (standard deviation [SD], 0.013) versus 0.663 (SD, 0.013), P = 0.03. The AUC for PSA to discriminate ; any prostate cancer versus no cancer was 0.678 (95% CI, 0.666-0.689), Gleason grade 7 or greater cancer versus no cancer was 0.782 (95% CI, 0.748-0.816) and Gleason grade 8 or greater cancer versus no cancer was 0.827 (95% CI, 0.761-0.893).The authors concluded that there was no cut point of PSA with simultaneous high sensitivity and high specificity for monitoring healthy men for prostate cancer, but rather a continuum of prostate cancer risk at all values of PSA.[48 level 1]

Schroder *et al.* found that in the ERSPC, with most centres using PSA cut off value of 3.0 ng/ml for prostate biopsy, the PPV was 24.1% (range, 18.6% to 26.9%).[27 level 1]

Maattanen *et al*. estimated the specificity of PSA in prostate cancer screening using data from a RCT conducted in Finland (one of the ERSPC centre) with 32,000 men in the screening arm. They calculated specificity as the proportion of men with screen negative findings (screen negatives, SN) relative to those with screen negative and False Positive (FP) results (SN/SN+FP). A SN finding was defined as either PSA ≤ 4 ng/ml or PSA 3.0 to 3.9 ng/ml combined with negative ancillary test (DRE and f/tPSA). In the first screening round specificity was estimated at 0.93; 95% CI, 0.92 to 0.93. In the second screening round specificity was estimated at 0.91; 95% CI, 0.90 to 0.91.[49 level 1]

In the PLCO cancer screening study, Grubb *et al.* found that the PPV value of a PSA level of > 4 ng/ml decreased from 17.9% at T0 (initial screening round) to 10.4% at T1 (first screening round) and to 12.3% at T3 (third screening round). The PPV for DRE in the absence of positive PSA was constant over time (2.9% to 3.6%). For men with a positive PSA and DRE screen, the PPV were higher than for either test alone, 37% at T0 and 18-23% at T1-T3.[29 level 1]

The proportion of false-positive (FP) screening results indicates one aspect of adverse effect of screening, in addition to overdetection and overtreatment. The FP results are related to the specificity of the screening test, and are common in prostate cancer screening. Kilpelainen *et al*. reported the FP screening results of the Finnish prostate cancer screening trial which is the largest centre in the ERSPC. They completed three screening rounds with a 4-yearly screening interval (mean follow-up time of 9.2 years). They used a PSA cut off level of 4 ng/ml, in addition men with PSA 3.0 to 3.9 ng/ml and a positive auxillary test (DRE of f/tPSA ratio) for referral to biopsy. They found that the proportion of FP screening results varied from 3.3% to 12.1% per round. Of the screened men, 12.5% had at least one FP during the three screening rounds. The risk of next round prostate cancer following a FP result was 12.3% to 19.7% versus 1.3% to 3.7% following a screen negative result (depending on the screening round), risk ratio, 3.6 to 9.9. More than half of the men with one FP result had another FP result at a subsequent screening round. Men with a FP result were 1.5 to 2.0 times more likely not to participate in subsequent rounds compared with men with normal screening result (21.6% to 29.6% versus 14.0% to 16.7%) respectively.[50 level 1.]

Schroder *et al*. reported that in the ERSPC, of 13,308 men who underwent prostate biopsy for an elevated PSA value, (75.9%) had a false-positive result.[27 level 1]

It has become increasingly clear that there is no PSA threshold that effectively discriminates between the presence and absence of prostate cancer. Early large-scale prostate cancer screening studies used 4.0 ng/ml PSA as the threshold value to prompt a recommendation for prostate biopsy and a PSA level at or below 4.0 ng/ml had been considered 'normal", with no action necessary. However, PCPT study found that prostate cancer could be found at all levels of PSA and that in this group of men with normal PSA levels, 15% had prostate cancer.[51 level 1] If the threshold were lowered uniformly from 4.0 ng/ml, higher prostate cancer detection rate, together with reduced specificity that would occur would translate into significant increase in false-positive screen results, prostate biopsies, and diagnosis of cancers that would have never become important clinically if they were left undetected (overdetection and overtreatment).

The situation has lead to the development of predictive model of prostate cancer. Thompson *et al.* included 5,519 men from the placebo group of the PCPT who underwent prostate biopsy, had at least one PSA measurement and a DRE performed during the year before the biopsy, and has at least two PSA measurements performed during the three years before the biopsy. Logistic regression was used to model the risk of prostate cancer and high-grade disease associated with age at biopsy, race, family history of prostate cancer, PSA level, PSA velocity, DRE result, and previous prostate biopsy. They found that variables that predicted prostate cancer included higher PSA level, positive family history of prostate cancer, and abnormal DRE results whereas a previous negative prostate biopsy was associated with reduce risk. Neither age at biopsy nor PSA velocity contributed independent prognostic information. Higher PSA level, abnormal DRE result, older age at biopsy, and African American race were predictive for high-grade disease (Gleason score ≥ 7) whereas previous negative prostate biopsy reduce the risk.[51 level 1]

6.4.2 Digital rectal examination (DRE)

The value of DRE in primary care screening for prostate cancer was analysed by Hoogerdam *et al.* in their systematic review and meta-analysis. Fourteen studies were eligible for selection and of which five studies complied with the predetermined list of 'good quality requirements'. The pooled results of the meta-analysis of the five "good-quality studies' showed a sensitivity of 0.64 (0.47 to 0.80), specificity of 0.97 (0.95 to 0.99), PPV of 0.47 (0.29 to 0.64) and NPV of 0.99 (0.98 to 0.99).[52 level 1]

Schroder *et al.* evaluated the usefulness of DRE as a stand-alone screening test and in conjunction with measured PSA levels. The study was part of the ERSPC, Rotterdam section involving 10,523 men aged 54 to 76 years who were randomly assigned to the screening arm. The underlying prevalence of detectable prostate cancer was estimated by logistic regression analysis and used for calculating the sensitivity of DRE. PPV of DRE ranged from 4% to 11% in men with PSA level of 0 to 2.9 ng/ml and from 33% to 83% for men with PSA levels of 3.0 to 9.9 ng/ml or more. Most tumours detected by DRE in men with PSA levels < 4 ng/ml were small (mean volumes = 0.24 to 0.83ml) and Gleason score of 6 or less. Overall sensitivity of DRE was 37% and increases with increasing PSA levels. Overall specificity of DRE was 91% and remains greater than 83% over the total range of PSA values. The authors concluded that for PSA values of 0 to 3.9 ng/ml, the PPV and sensitivity of DRE, tumour volume and tumor grade were strongly dependant on PSA level. DRE has poor performance in low PSA ranges.[53 level 1]

Gosselar *et al.* evaluated the additional value of a suspicious DRE for the detection of prostate cancer in men with an elevated PSA level in subsequent screenings and the tumour characteristics of prostate cancer detected in men with suspicious DRE. Throughout the three screenings of the ERSPC, Rotterdam section, 5,040 biopsy sessions were evaluated. A PSA level of ≥ 3.0 ng/ml was used as a cut off for biopsy indication. In the initial screening, the PPV of suspicious DRE in conjunction with elevated PSA level, to detect prostate cancer was 48.6% compared 22.4% for men with normal DRE. Both PPVs decreased in consecutive screens; 29.9% versus 17.1% in the second screening and 21.2% versus 18.2% in the third screening respectively. Statistically significant prostate cancers with Gleason score > 7 were detected in men with suspicious DRE compared to normal DRE; in the first screening (71% versus 29%, P < 0.001), in the second screening (68.8% versus 31.2%, P < 0.001) and in the third screening (85.7% versus 14.3%, P < 0.002) respectively.[54 level I]

It has been suggested that the results of DRE are subjective, difficult to record accurately and it is believed that the degree of accuracy depend on the examiner experience. Two studies described the inter-examiner variability in the assessment of the prostate using DRE.[49-50] Varenhorst *et al.* describe the agreement between observations made by the general practitioner and urologist. Two urologists and seven general practitioners were involved. The two physicians performed independent assessment of the prostate in 933 men aged between 50 to 69 years at a primary care centre with regards to nine variables as part of a prostate cancer screening programme.

Complete agreement for all observations was reached in 46.5% (95% CI, 43.3% to 49.7%) of the men. Kappa (K) values between 0.485 and 0.682 were obtained for six variables (fair agreement); these were size, tenderness, midline furrow, symmetry, induration and nodularity. Agreement regarding fixation, lateral sulci and seminal vesicles was poor (K = 0.001 and 0.022).[55 level III]

In a cross sectional study, Smith and Catalona demonstrated the variability of DRE findings for faculty and resident urologists working within the context of a prostate screening program at a university medical centre (Washington school of medicine). The faculty or post-residency fellows had a weighted mean of 23 years experience, while resident urologists had weighted mean of 3 years experience. DRE examinations were performed in 116 consecutive volunteers twice on the same day, with different urologist performing the examinations. They were blinded to the results of the other examinations and to the volunteers serum PSA level.DRE results were coded as being benign or sufficiently suspicious for cancer to warrant a prostatic biopsy. They found that the inter-examiner agreement among urologists was only fair (K = 0.22, P = 0.009). Inter-examiner variability was greater between faculty and resident urologists (K = 0.13, P = 0.13) than among faculty urologists (K = 0.63, P = 0.004).[56 level III]

6.4.3. Screening intervals

The yield of screening in terms of cancer cases detected declines rapidly with repeated screening. If screening were to reduce deaths, PSA screening as infrequently as 4 years could yield as much benefit as annual screening as demonstrated by the ERSPC, which had a screening interval of four years.[27 level 1] This is supported by findings by Hoedemaker *et al.* and Roobol *et al.* [31-32 level 1]

6.5 OTHER CONSIDERATIONS

6.5.1. Organizational

The WHO advocates that it is necessary to establish the effectiveness of screening programmes for prostate cancer by performing well-designed RCTs, before making any recommendation for public health policy.[57]

In Malaysia, currently there is no national prostate cancer screening programme. However, PSA test and DRE are being performed when the need arises. There is a Prostate Awareness Campaign organised yearly with the aim of creating awareness among the public regarding the various conditions related to the prostate such as BPH, erectile dysfunction and prostate cancer.

Training is a very important component in detection of prostate cancer since DRE is a subjective method that requires experience and continuous training as shown by Varenhorst *et al*., Smith and Catalona.[7,55-56 level III] Similarly, 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.[7]

6.5.2. Ethical and legal consideration

Mass screening, which means searching for disease in asymptomatic individuals raises many ethical questions. Some of these questions include:-[7]

- Are there risks of serious negative consequences for individuals who receive false-positive and 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 received unnecessary treatment?
- Do the benefits outweigh the risks of harming others?

In 1968, Wilson and Jungner authored a WHO document entitled "Principles and Practice of Screening for disease (Public Health Papers, No. 34)" has defined ten criteria to be met by mass screening programmes for it to be medically and ethically acceptable. This criteria has been reviewed in 2003 as in Appendix 4.

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.[7]

It is obvious that mass screening for prostate cancer meets few of the ethical criteria, and most importantly mass screening will result in a large number of false-positive and thereby create harm and needless anxiety in many individuals.[27 level 1,50 level 1]

Given the uncertainty about the benefit of mass screening, Centres for Disease Control and Prevention (CDC) mentioned that the principal public health approach is to support informed decision making about screening. Public health agencies and related organizations are attempting to provide men with current information about the benefits and risks about prostate cancer screening so that each men can make his own decision, given his own values and preferences. Informed decision making occurs when a man:-[58]

- Understand the nature risks of prostate cancer
- Understands the risks, benefits, and alternatives to prostate cancer screening
- Participates in decision making at a level he desires
- Makes a decision consistent with the preferences and values, or defers the decision to a later time

Shared decision making is the process carried out between a patient and his health care professional in a clinical setting where both parties share information, and the man makes an informed decision about prostate cancer screening.[45,58]

A commentary by Merenstein published by JAMA in January 2004 sparked a considerable debate. He recalled his experience as a family medicine resident, when he was sued for letting a patient decide whether to be screened for prostate cancer after engaging him in a shared decision making, as recommended by current guidelines. The patient declined screening and was later found to have prostate cancer. The patient successfully sued the practice for encouraging shared decision making to decide whether to screen for prostate cancer.[59 level 1] Following the incident, Krist *et al.* conducted a study at the practice that was sued to evaluate whether physicians changed their prostate cancer screening behaviour after the lawsuit. The study was conducted as part of a RCT on Web-based and paper-based decisions aid for prostate cancer conducted between January 2002 and November 2004. Patients and physicians completed exit-questionnaires about prostate cancer screening discussions after health maintenance examinations. The questionnaires were designed to measure the quality of the decision-making process. They compared the responses before, during and after physicians became aware of the lawsuit. A total of 432 of 497 (87.0%) of patients completed questionnaires. Comparing patients response over the three time periods, there were no changes in the average locus of decision-making control, time spent discussing screening, number of screening topics discussed, knowledge scores, or decisional conflict. The frequency with which physicians reported performing PSA testing increased (84% before versus 90% after; P = 0.03), and physicians were more likely to report that they made the decision alone, rather than the patients had made the screening decisions (3.3% before versus 11.1% after; P = 0.003). The authors concluded that the physicians in closest proximity to this well-known legal case continued to engage patients in shared decision making and to let patients decide whether to be screened.[59 level 1]

7 DISCUSSION

Screening for prostate cancer has long been a controversial issue. This review identified one systematic review and the interim results of two large RCTs (the ERSPC and PLCO cancer screening trial) on prostate cancer mortality which is lacking in the previous HTAs.[1,18,44,45] The ERSPC reported a relative prostate cancer reduction of at least 20% by PSA based population screening in 162,000 asymptomatic men aged 55 to 69 years. For every prostate cancer death prevented, 1,410 men have to undergo screening, while 48 need to be treated in excess of control group population to save one prostate cancer death.[26 level 1] In contrast, results of the randomised PLCO cancer screening study in the U.S. showed no significant effect of screening on mortality, but the study suffered from a significant level of contamination in the control arm.[27 level 1] Similarly, a systematic review and meta-analysis by Cochrane Collaboration based on the Norrkoping and Quebec studies indicated no statistically significant difference in prostate cancer mortality between men randomised for prostate cancer screening and those randomised to control.[25 level 1]

Early evidence from prostate screening studies also suggests positive stage and grade shift, however, the serious risks incurred by overdetection and overtreatment, particularly the risk of treating many men for screened-detected prostate cancer who would not have experienced ill effects from their disease if it had been left undetected are contributors to harms and costs associated with prostate cancer screening.[25-31,33-34] Another concern is that a considerable percentage (30%) of screened-detected cancers is indolent and probably does not need to be detected at all or can still be detected later in a curable stage.[35] These findings are similar to findings by Bunting *et al.*[44]

Screening for prostate cancer is primarily performed using DRE and PSA test. However, the specificity and sensitivity of both these modalities are not ideal (low) leading to high false-positive and false-negative rate. False-positive men constitute a special group that receives unnecessary interventions but may harbour missed cancers.[27,50] The consequences of false-positive screening results include psychological effects (more often worried about prostate cancer) and further examinations such as biopsies.[41-43] These findings were also highlighted by the U.S. Preventive Services Task Force in 2008.[11] The side effects associated with biopsies and various prostate cancer treatments need to be appreciated.[26,38-40,44-45]

Evidence suggests that there is no PSA threshold that effectively discriminates between the presence and absence of prostate cancer which leads to the development of predictive model for prostate cancer risk. Variables that predicted prostate cancer included higher PSA level, positive family history for prostate cancer, and abnormal DRE results.[51]

The evidence regarding the long term effect on quality of life and robust cost-effectiveness data using large RCTs to show the economic value of prostate cancer screening is still lacking. Further publications on quality of life and cost-effectiveness analysis from the ERSPC and PLCO cancer screening study are essential to provide more concrete evidence on mass prostate cancer screening.

The uncertainty about the benefits of mass screening, including the uncertain balance between benefits and risks, highlights the importance of involving men in the screening decision to discuss the potential benefits or harms associated with prostate cancer screening.

Limitations

Our study has several limitations. Although we only included RCTs for effectiveness, we also included cohort and cross sectional studies for adverse events. Most of the diagnostic accuracy studies on PSA suffer from differential verification bias since not all men undergoing PSA testing was subjected to biopsies. Although there was no restriction in language during the search but only English full text articles were included in the report. Although every effort has been made to retrieve full text articles, there were seven abstracts which the authors failed to retrieve full text.

8 CONCLUSION

8.1. Effectiveness of prostate cancer screening programme

i. Conflicting evidence from the preliminary findings of two large randomised controlled trials on prostate cancer mortality:-

   a. The ERSPC reported a 20% reduction in prostate cancer mortality (rate ratio, 0.80; 95% CI, 0.65 to 0.98; adjusted P = 0.04). For every prostate cancer death prevented, 1,410 men have to undergo screening, while 48 need to be treated in excess of control population to save one prostate cancer death.

   b. The PLCO cancer screening study did not show significant reduction in prostate cancer mortality (rate ratio, 1.13; 95% CI, 0.75 to 1.70).

ii. Good level of evidence to suggest screening for prostate cancer led to:-

   a. Increased detection of prostate cancer in the screened population compared with the non screened population.

   b. Positive stage and grade shift.

   c. Overdetection and overtreatment.

iii. There was evidence to suggest a considerable percentage of screened-detected prostate cancers is indolent and is difficult to differentiate from aggressive cancers.

iv. There was no retrievable evidence to determine the long term impact of prostate cancer screening on quality of life.

8.2. Safety

i. Good level of evidence to suggest that:-

   a. Complications associated with PSA test and DRE were mild and infrequent (dizziness, bruising, haematoma, fainting, pain and discomfort).

   b. Minor complications associated with TRUS guided needle biopsies were frequent but major complications were rare.

ii. Fair level of evidence to suggest that false-positive PSA screening test results were associated with adverse psychological effects.

iii. There was evidence to show that prostate cancer treatments were associated with more serious complications which include infection, impotence, incontinence and bowel dysfunction.

8.3. Cost/cost-effectiveness

There was no robust evidence retrieved to determine its economic value.

8.4. Diagnostic accuracy of screening tests

i. Good level of evidence to suggest that:-

   a. The sensitivity and specificity of PSA test varies with PSA cut off values. The sensitivity of serum PSA at 4 ng/ml is around 20% and the specificity is around 93%. Lower threshold values improves sensitivity at the expense of false-positive results.[48]

   b. There was no PSA threshold that effectively discriminates between the presence and absence of prostate cancer.

c. Screening of prostate cancer using PSA test was associated with high false-positive rate (75.9% in the ERSPC).[27]

d. DRE may be useful in more selective screening procedures to decrease unnecessary biopsies.

e. Higher PSA level, positive family history of prostate cancer and abnormal DRE result were predictors for prostate cancer.

f. PSA screening as infrequently as 4 years could yield as much benefit as annual screening.

8.5. Other considerations

i. Proper training of staff involved in the screening programme is essential since DRE and TRUS examinations require experience as well as continuous training.

ii. For a mass screening programme to be medically and ethically acceptable, the WHO criteria for mass screening programmes as shown in Appendix 4 have to be met.

iii. Given the uncertainty about the benefits and risks of mass screening for prostate cancer, men should be provided with current information about the benefits and risks of prostate cancer screening (the screening tests, the diagnostic and treatment path) so that each man can make his own decision whether or not to undergo individual screening.

9 RECOMMENDATION

i. Based on the above review there was evidence to suggest that prostate cancer screening may reduce the likelihood of men dying from prostate cancer. However, current published data are insufficient to recommend the adoption of population screening for prostate cancer as a public health policy because of the significant overdetection and overtreatment that would result from the screening. Population based screening for prostate cancer is also not recommended by the U.S. Preventive Services Task Force, the UK National Steering Committee, and the Cancer Council Australia.[11,17,60] Since men with family history of prostate cancer have a significantly higher risk of developing prostate cancer, we therefore recommend selective screening of asymptomatic men with a family history of prostate cancer from the age of 40 years and above.

ii. PSA test may be used for prostate cancer screening. However, there was no PSA threshold that effectively discriminates between the presence and absence of prostate cancer.

iii. DRE may be used as an adjunct to PSA test.

iv. Men who expressed an interest in prostate cancer screening need to be properly informed on the potential benefits and harms associated with prostate cancer screening.

v. A standard guideline for prostate cancer screening need to be established.

vi. Organisational issues such as training, manpower, good referral system, treatment and funding need to be addressed at all levels.

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APPENDICES

Appendix 1

HIERARCHY OF EVIDENCE FOR EFFECTIVENESS STUDIES
DESIGNATION OF LEVELS OF EVIDENCE

I Evidence obtained from at least one properly designed randomized controlled trial.

II-I Evidence obtained from well-designed controlled trials without randomization.

II-2 Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group.

II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.

III Opinions or respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.

SOURCE: US/CANADIAN PREVENTIVE SERVICES TASK FORCE (Harris 2001)

Appendix 2

HEALTH TECHNOLOGY ASSESSEEMENT (HTA) PROTOCOL PROSTATE CANCER SCREENING

1. BACKGROUND INFORMATION

The incidence of prostate cancer is rising worldwide. This is caused mainly by demographic factors, particularly the increase in elderly population and more importantly, the increase in the number of suspected cases identified following the introduction of prostate specific antigen (PSA) testing.[1] In general, the agents which cause the initiation of prostate cancer is unknown. Age is considered an important risk factor. The risk for developing prostate cancer increases with age, beginning to be significant at the age of 50 with a steep rise after the age of 65. Family history is a determinant of risk, with relative risk values between two and three for men who had a father or brother with prostate cancer. The risk increases to five-fold with two affected family members. Race is a risk factor for prostate cancer. African American men have a 1.3 to 1.6-fold higher risk of getting prostate cancer than non-African American men. In the 50 to 54 year old the risk is two-fold higher. There is a possible association between prostate cancer and diet.[2]

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.[2] It is commonly quoted that many more men die with prostate cancer than of it. Autopsy/post-mortem studies showed that while a very high proportion of elderly men had histological evidence of the disease, a much smaller proportion developed clinically apparent cancer.[1] There are no methods available to differentiate between early slow-growing, benign cancers and early aggressive, life threatening cancers. The natural history of prostate cancer is poorly understood, but progression appears to be related to the staging and grade of the tumour. For localised 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 metastasised disease. The active treatments (radical prostatectomy and radiotherapy), are both associated with significant risk of sexual, urinary and bowel-related symptoms depending on type of treatment.[2]

In the 1990s, prostate cancer was reported as the sixth most common cancer among all types of cancers in the total population, and the forth most common cancer in males. The age-standardized incidence was highest in the United States, followed by Western Europe, Australia and New Zealand. All countries in Asia had reported low incidence rates.[2] In Peninsular Malaysia, from 2003 to 2005, prostate cancer was the fourth most frequent cancers among the males and accounted for 7.3% of the total cancers in males. Among the ethnic groups in Peninsular Malaysia, the Chinese recorded the highest age adjusted incidence (15.8), followed by Indians (14.8), whereas Malays had half the incidence (7.7) of the other two races. The incidence in Malaysian Chinese (15.8) was higher than the incidence of Chinese in Shanghai (3.0), Hong Kong (8.6), and Taiwan (11.9). Indians in Malaysia (14.8) had higher incidence than their counterparts in Chennai (4.9) and Singapore (9.9).[3] Mortality rates appear to vary between countries. Among developed countries, the age-adjusted death rate for prostate cancer is highest in Sweden, with an estimated rate of 27.7 per 100,000 men, and lowest in Japan, with an estimated rate of 5.7 per 100,000 men. The United States of America falls between these two extremes, with an estimated rate of 15.8 per 100,000 men.[4]

Local extension of prostate cancer beyond the capsule is rarely associated with symptoms. More than 50 percent of patients already have local extracapsular cancer or distant metastases at the time of clinical diagnosis. This fact, together with the substantial morbidity associated with progression of prostate cancer such as urinary tract obstruction and severe bone pain from metastasis, has contributed to stimulate the interest in early detection through screening.[2] Screening for any type of cancer aims to increase the chances of successful treatment through early detection of the disease. Screening may be performed in one of the three methods: mass (for example large scale screening for the entire population), selective (for example for high-risk populations) or opportunistic (for example incorporated as part of medical consultation). Testing for, or diagnosing, a disease differs from screening. Diagnostic testing attempts to identify the disease in the presence of symptoms; screening is offered to symptom-free individuals. The PSA test and the digital rectal examination (DRE) are used as primary screening tools in the early detection of prostate cancer. Transrectal ultrasound-guided needle biopsies (TRUS) are perform to confirm diagnosis following PSA and/or DRE testing.[5]

While the intention of screening for prostate cancer is to decrease mortality and increase patient's quality of life, the true benefit of screening remains uncertain. Use of the DRE as a screening tool is limited due to the inability to palpate the entire prostate gland, while the PSA test produces high false-negative and false-positive results. Additional causes of concern include the cost of follow-up tests, the potentially invasive nature of these tests, the potentially false sense of security following false negative test results, and the use of harmful treatment regime that may not provide any improvement in health outcomes.[5] The uncertainty about the value of prostate cancer screening has been further highlighted by the conflicting recommendations by various medical entities.[6,7]

With the significant burden of prostate cancer among males all over the world and in Malaysia, one of the strategies for early detection of cancer in the Malaysian National Cancer Management Blueprint 2008-2010 is to provide prostate cancer screening service. Therefore, a Health Technology Assessment (HTA) is required to look into the effectiveness and cost-effectiveness of screening asymptomatic men for prostate cancer. This HTA was requested by the Senior Principal Assistant Director of Cancer Unit, Disease Control Division, Ministry of Health, Malaysia.

2. POLICY QUESTION

2.1. Should screening for prostate cancer among asymptomatic men be carried out as part of the Malaysian National Cancer Control Programme?

3. OBJECTIVE

3.1. To determine the effectiveness, safety and cost-effectiveness of screening asymptomatic men for prostate cancer.

3.2. To determine the diagnostic accuracy of the various screening tests used in prostate cancer screening.

3.3. To look into the ethical, legal, and organizational aspect related to prostate cancer screening

4. METHODOLOGY

4.1. Search Strategy

Electronic database will be searched for published literatures pertaining to screening for prostate cancer.

4.1.1 Databases as follows; MEDLINE, PubMed, EBM Reviews-Cochrane Database of Systematic Review, EBM-Reviews-Cochrane Central Register of Controlled Trials, EBM Reviews-Health Technology Assessment, EBM Reviews-Cochrane Methodology Register, EBM Reviews-HNS Economic Evaluation Database, INAHTA Database, HTA database and FDA database.

4.1.2 Additional literatures will be identified from the bibliographies of the related articles.

4.1.3 General search engine will be used to get additional web-based information.

4.1.4 There will be no limitation applied in the search.

4.1.5 The following search terms will be used either singly or in various combinations:-
prostate cancer, prostate carcinoma, prostate tumour, prostate tumor, prostate neoplasm, screening, screening programme, prostate -specific antigen, digital rectal examination, transrectal ultrasound, safe*, cost*, adverse events, complication, anxiety, mortality rate, quality of life, QALY, family history, legal and ethics.

4.2. Inclusion and exclusion criteria

4.2.1. Inclusion criteria

a. Study design :			Systematic Review and Randomised Controlled Trials (RCT) for effectiveness, Systematic review, RCT, Cohort and Cross-sectional study for safety, and studies which include economic evaluation
b. Population:			Men
c. Intervention :			Prostate cancer screening using the following screening tests individually or in combination:-
		i.	digital rectal examination (DRE)
		ii.	prostate specific antigen (PSA) test (including total, velocity, density and percentage free and complex)
		iii.	transrectal ultrasound (TRUS) biopsy
d. Comparators :			No screening / usual care
e. Outcome 1. :		i.	Mortality rate, detection rate, quality of life, quality adjusted life years (QALY) gained
		ii.	Adverse events related to prostate cancer screening programme
		iii.	Cost, cost-utility and cost-effectiveness of prostate cancer screening programme
Outcome 2. :			Sensitivity, specificity, positive predictive value and negative predictive value of DRE and PSA

4.2.2 Exclusion criteria

Animal study

Based on the above inclusion criteria, study selection will be carried out independently by two reviewers. Disagreement will be resolved by discussion.

4.3 Data extraction strategy

The following data will be extracted:

4.3.1 Details of methods and study population characteristics

4.3.2 Details of intervention and comparator

4.3.3 Details of individual outcomes for effectiveness, safety and cost associated with screening programme

4.3.4 Details on diagnostic accuracy of screening tests used in prostate cancer screening

4.3.5 Information on ethical, legal and organization

Data will be extracted from selected studies by two reviewers using a pre-designed data extraction form. Disagreements will be resolved by discussion.

4.4 Quality assessment strategy

The methodology quality of all retrieved literatures will be assessed using the relevant checklist of Critical Appraisal Skill Programme (CASP) by two reviewers depending on the type of the study design.

4.5 Methods of analysis/synthesis

Data on the effectiveness, safety and cost-effectiveness of prostate cancer screening will be presented in tabulated format with narrative summaries. Data on screening tests used will also be presented in tabulated format with narrative summary. No meta-analysis will be conducted for this Health Technology Assessment.

5 REPORT WRITING

Appendix 3

SEARCH STRATEGY

1. MEDLINE (OVID) 1950 to June week 1 2010

01. prostate carcinoma
02. screening programme
03. prostate cancer
04. 1 and 2
05. 3 and 2
06. prostate specific antigen
07. screening
08. complication
09. adverse events
10. anxiety
11. Digital rectal examination
12. Transrectal ultrasound
13. 06 and 07 and 08
14. 06 and 08
15. 06 and 09
16. 06 and 10
17. 11 and 08
18. 11 and 09
19. 11 and 10
20. 12 and 08
21. 12 and 09
22. 12 and 10
23. family history
24. prostate cancer
25. prostate cancer screening
26. 23 and 24
27. 23 and 25

2. EBM Reviews-Cochrane Database of Systematic Review (OVID)

01. prostate carcinoma
02. screening programme
03. prostate cancer
04. prostate tumour
05. prostate tumor
06. prostate neoplasm
07. 1 and 2
08. 3 and 2
09. 4 and 2
10. 5 and 2
11. 6 and 2
12. screening
13. safe
14. cost*
15. adverse events
16. mortality rate
17. quality of life
18. QALY
19. prostate specific antigen
20. digital rectal examination
21. transrectal ultrasound
22. 3 and 12 and 13
23. 3 and 12 and 14
24. 3 and 12 and 15
25. 3 and 12 and 16
26. 3 and 12 and 17
27. 3 and 12 and 18
28. 3 and 12 and 19
29. 3 and 12 and 20
30. 3 and 12 and 21
31. family history
32. prostate cancer screening
33. 31 and 3
34. 31 and 32
35. complication
35. 19 and 12 and 35
36. 19 and 12 and 15
37. 20 and 12 and 35
38. 20 and 12 and 15
39. 21 and 12 and 35
40. 21 and 12 and 15

Appendix 4

SCREENING CRITERIA

The Wilson-Jungner criteria for appraising the validity of a screening programme

1. The condition being screened for should be an important health problem
2. The natural history of the condition should be well understood
3. There should be a detectable early stage
4. Treatment at an early stage should be of more benefit than at a later stage
5. A suitable test should be devised for the early stage
6. The test should be acceptable
7. Intervals for repeating the test should be determined
8. Adequate health service provision should be made for the extra clinical workload resulting from screening
9. The risks, both physical and psychological, should be less than the benefits
10. The costs should be balanced against the benefits

World Health Organisation 1968

Criteria for appraising the viability, effectiveness and appropriateness of a screening programme 2003

The condition

1. The condition should be an important health problem.
2. The epidemiology and natural history of the condition, including development from latent to declared disease, should be adequately understood and there should be a detectable risk factor, disease marker, latent period or early symptomatic stage.
3. All the cost-effective primary prevention interventions should have been implemented as far as practicable.
4. If the carriers of a mutation are identified as a result of screening the natural history of people with this status should be understood, including the psychological implications.

The test

5. There should be a simple, safe, precise and validated screening test.
6. The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed.
7. The test should be acceptable to the population.
8. There should be an agreed policy on the further diagnostic investigation of individuals with a positive test result and on the choices available to those individuals.
9. If the test is for mutations the criteria used to select the subset of mutations to be covered by screening, if all possible mutations are not being tested for, should be clearly set out.

The treatment

10. There should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment.
11. There should be agreed evidence-based policies covering which individuals should be offered treatment and the appropriate treatment to be offered.
12. Clinical management of the condition and patient outcomes should be optimised in all healthcare providers prior to participation in a screening programme.

The screening programme

13. There should be evidence from high-quality randomised controlled trials that the screening programme is effective in reducing mortality or morbidity. Where screening is aimed solely at providing information to allow the person being screened to make an 'informed choice' (for example, Down's syndrome and cystic fibrosis carrier screening), there must be evidence from high-quality trials that the test accurately measures risk. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened.
14. There should be evidence that the complete screening programme (test, diagnostic procedures, treatment/intervention) is clinically, socially. and ethically acceptable to health professionals and the public.
15. The benefit from the screening programme should outweigh the physical and psychological harm (caused by the test, diagnostic procedures and treatment).
16. The opportunity cost of the screening programme (including testing, diagnosis and treatment, administration, training and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole (ie value for money).
17. There should be a plan for managing and monitoring the screening programme and an agreed set of quality assurance standards.
18. Adequate staffing and facilities for testing, diagnosis, treatment, and programme management should be available prior to the commencement of the screening programme.
19. All other options for managing the condition should have been considered (for example, improving treatment and providing other services), to ensure that no more cost-effective intervention could be introduced or current interventions increased within the resources available.
20. Evidence-based information, explaining the consequences of testing, investigation, and treatment, should be made available to potential participants to assist them in making an informed choice.
21. Public pressure for widening the eligibility criteria for reducing the screening interval, and for increasing the sensitivity of the testing process, should be anticipated. Decisions about these parameters should be scientifically justifiable to the public.
22. If screening is for a mutation, the programme should be acceptable to people identified as carriers and to other family members.

http://www.gp-training.net/training/tutorials/management/audit/screen.htm.

Appendix 5

Evidence Table : Effectiveness
Question : Is prostate cancer screening effective in detecting and reducing mortality due to prostate cancer?

Bibliographic citation	1. Ilic D, O'Connor D, Green S, Wilt T. Screening for prostate cancer. Cochrane Database of Systematic Reviews 2006, Issue 3.
Study Type / Methodology	Systematic Review and meta-analysis of 2 randomised controlled trials. The primary objective of this review was to determine the efficacy of screening asymptomatic men for prostate cancer in reducing all cause and prostate cancer-specific mortality. Electronic searches of the PROSTATE register, the Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, CANCERLIT and NHS EED. PROSTATE register was searched in November 2004, and the rest for studies published between 1966 and January 2006. Hand searching for reviews and technical reports and grey literature was conducted. There was no restriction to language. Studies were selected by two of the authors based on inclusion criteria. Two authors independently assessed the selected trials. Data was extracted using data extraction form. Statistical analysis was conducted based on intention to screen analysis.
LE	I
Number of patients and patient characteristics	2 RCTs; Quebec and Norrkoping trials Quebec trial:- - commenced in 1988, recruited men aged 45 to 80 years registered on the 1985 electoral rolls of Quebec City, Canada. - A total of 46,193 men were randomised 2:1 to annual prostate screening and no screening or usual care. - Screening group = 31,133 - Control group = 15,353 - Exclusion:- Men with previous diagnosis of prostate cancer, or previously been screened for prostate cancer and referred to the study's clinic for consultation were excluded. Norrkoping trial:- • commenced in 1987. Recruited men from Norrkoping, Sweden, aged 50 to 69 years registered on the 1987 national population register. • A total of 9026 men were identified with every sixth man "randomised" to screening every 3 years. • Screening group=1,494 • Control group=7,532
Intervention	Mass screening for prostate cancer using Digital rectal examination (DRE), Prostate specific antigen (PSA) and transrectal ultrasound (TRUS) biopsy individually or in combination. Biopsy if PSA > 3 ng/ml or abnormal DRE. First 2 rounds DRE alone, final two rounds DRE AND PSA. TRUS biopsy if abnormal DRE or PSA > 4ng/ml.
Comparison	No screening/usual care No screening
Length of follow up (if applicable)	11 years 15 years

Outcome measures/ Effect size	According to intention to screen analysis Primary outcome a. Prostate cancer specific mortality i. Quebec study - Rate Ratio (RR) 1.01; 95% CI: 0.76 to1.33 ii. Norrkoping study - RR 1.04; 95% CI: 0.64 to 1.68 iii. Pooled analysis • RR 1.01; 95% CI: 0.80 to 1.29 b. Detection rate i. Quebec study - prevalence 3.0% (244/8,137 first screening visits) ii. Norrkoping study • 85 prostate cancer diagnosed in screening group (85/1494) • 292 prostate cancer diagnosed in control group (292/7532) • RR 1.47; 95% CI: 1.16 to 1.86 Secondary outcome a. Clinical stage distribution i. Quebec (Jewett Staging System) - 244 detected in 1st screening - 123 at follow up 70% in stage B in 1st screening round, 86% at follow-up Secondary outcome b. Clinical stage distribution ii. Norrkoping (TNM Staging System) - 292 cancers in control group - 85 cancers in intervention group Localised tumours:- - 84% in intervention group - 27% in control group c. Quality of life - Neither study assessed the impact of screening upon quality of life d. Cost - Neither study reported cost assessment e. Harms of screening - Neither study reported the impact of any associated harms of screening Authors conclusion Given that only two randomised controlled trials were included, and the high risk of bias in both trials, there is insufficient evidence to either support or refute the routine use of mass selective or opportunistic screening compared to no screening for reducing prostate cancer mortality. Note Quebec Study Only 7,348 /31,133 in the screening group were screened. 1,122/15,353 in the control group were also screened.
General comments	Quality assessment (CASP) 1. Yes 2. Yes 3. Yes 4. Yes 5. Yes 6. RR,95% CI 7. CI is wide, and not significant

Evidence Table : Effectiveness
Question : Is prostate cancer screening effective in detecting and reducing mortality due to prostate cancer?

Bibliographic citation	2. Andriole GL, Crawford ED, Grubb RL, Buys SS, Chia D, Church TR *et al.* Mortality results from a Randomized Prostate-Cancer Screening Trial. N Engl J Med. 2009;360(13):1310-1319
Study Type / Methodology	Randomised Controlled Trial. Aim of the report was to provide information on prostate cancer incidence, staging, and mortality in both study groups during the first 7 to 10 years of the study. From 1993 through 2001, 76,693 men at 10 U.S. study centres were randomly assigned to receive either annual screening or usual care. Men in the screening group were offered PSA testing for 6 years and digital rectal examination for 4 years. All PSA test were performed at a single laboratory. DRE was performed by physicians, qualified nurses or physicians assistants. At study entry subjects completed a baseline questionnaire that inquired about demographic characteristics, medical and screening histories. A biorepository for the collection and storage of blood and tissue samples was an integral component of the trial. The subjects and healthcare providers received the results and decided on the type of follow-up evaluation. Screening outside the trial protocol in the control group was assessed through random surveys. The numbers of all cancers and deaths and cause of deaths were ascertained.
LE	I
Number of patients and patient characteristics	Men, aged between 55 and 74 years. Screening group (38,343) Control group (38,350) Exclusion criteria - history of PLCO cancer - current cancer treatment - starting in 1995, having had more than one PSA blood test in the previous 3 years
Intervention	Annual PSA testing for 6 years and annual digital rectal examination (DRE) for 4 years. PSA level of 4 ng/ml was considered to be positive for cancer.
Comparison	No screening / usual care Usual care sometimes included screening, as some organizations have recommended Note: In the control group, rate of PSA testing was 40% in the first year and increased to 52% in the sixth year
Length of follow up (if applicable)	To be followed- up for 13 years. At 7 years vital status was known for 98% of the men in the two groups. At 10 years vital status was known for 67% of the subjects. Median duration of follow-up was 11.5 years (range, 7.2 to 14.8 in the two groups)

Outcome measures/ Effect size	According to intention to screen analysis **Primary outcome** **a. Prostate cancer specific mortality** **i. At 7 years** **Screening group** - Death rate =2 per 10,000 persons years (50 deaths) **Control group** - Death rate =1.7 per 10,000 persons years (47 deaths) - **Rate ratio (RR)** 1.13; 95% CI: 0.75 to1.70 **i. At 10 years** **Screening group** - Death rate =2.7 per 10,000 persons years (92 deaths) **Control group** - Death rate =2.4 per 10,000 persons years (82 deaths) - **Rate ratio (RR)** 1.11; 95% CI: 0.83 to1.50 **b. Proportion of death according to tumour stage.** - little difference Screening group: -60% (stage 1or II tumours), 2% (stage III) and 36% (stage IV) Control group: -52% (stage 1or II tumours), 4% (stage III) and 39% (stage IV) **Secondary outcome** **a. Detection rate** **i. At 7 years** **Screening group** - 2820 prostate cancer cases **Control group** - 2322 prostate cancer cases - **Rate ratio (RR)** 1.22; 95% CI: 1.16 to1.29 **ii. At 10 years** **Screening group** - 3452 prostate cancer cases **Control group** - 2974 prostate cancer cases - **Rate ratio (RR)** 1.17; 95% CI: 1.11 to1.22 **b. Tumour characteristics (10 years)** - majority stage II at diagnosis - nearly all adenocarcinomas - > 50% had Gleason score of 5 to 6 - Number of subjects with stage III and IV tumours were similar (122 in screening group and 135 in control group) - Gleason score of 8 to 10 :- control group (341 subjects) screening group (298 subjects) Authors conclusion After 7 to 10 years of follow-up, the rate of death from prostate cancer was very low and did not differ significantly between the two groups.
General comments	Quality assessment (CASP) 1. Yes 2. Yes 3. Yes 4. Yes 5. Yes 6. Yes 7. Yes 8.Yes, RR, CI 9.Wide CI, not very precise

Evidence Table : Effectiveness
Question : Is prostate cancer screening effective in detecting and reducing mortality due to prostate cancer?

Bibliographic citation	3. Schroder FH, Hugosson J, Roobol MJ, Tammmela TLJ, Ciatto S, Nelen V *et al.* Screening and prostate cancer mortality in a randomized European study. N Engl J Med.2009;360: 1320-1328
Study Type / Methodology	Randomised Controlled Trial (multicentre). Initiated in early 1990s. Aim of the study was to evaluate the effect of screening with prostate-specific antigen (PSA) testing on the 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. The seven countries are Netherlands, Belgium, Sweden, Finland, Italy, Spain and Switzerland. 182,160 subjects 50-74 years old underwent randomization whereby 162,387 subjects were in the core age group (55 to 69 years). The men were randomly assigned to the screening and control group. Recruitment and randomisation procedures differ among countries and were developed in accordance with national regulations. All centres except Finland, subjects were assigned in a 1:1 ratio to the screening or the control group. In Finland 1:1.5. Each centre reported data on recruitment, screening and mortality twice a year to a central data centre. Treatment policies performed according to local policies and guidelines.
LE	I
Number of patients and patient characteristics	162,387 men were in the core age group (55-69 year old) • 144 died between identification and randomisation Screening group (72,890 men) Control group (89,353 men) Age at randomisation:- Screening group:- Mean age = 60.9 years Median age = 60.3 years Control group:- Mean age = 60.7 years Median age = 59.9 years
Intervention	PSA screening once every 4 years except Belgium 4-7 years and Sweden every 2 years. Most centres:- PSA cut off value of 3.0 ng/ml as an indication for biopsy. Finland:- PSA value of 4 ng/ml as positive for biopsy, PSA value 3 to 3.9 ng/ml DRE or f/tPSA Italy:- PSA value of 4 ng/ml as positive for biopsy, PSA 2.5 to 3.9 DRE and TRUS Netherland and Belgium until 1997, combination of DRE, TRUS and PSA value of 4 ng/ml. After that PSA testing only.

Comparison	No screening
Length of follow up (if applicable)	Begin at randomisation and ended at death, emigration, or uniform censoring date (December 31, 2006) Median follow-up 8.8 years in the screening group and 9 years in the control group.
Outcome measures/ Effect size	According to intention to screen analysis for the core age group (55 to 69 year old) **Primary outcome** **a. Prostate cancer specific mortality** **Screening group** - 214 deaths **Control group** - 326 deaths **Rate ratio (RR)** - 0.80; 95% CI: 0.65 to 0.98, P = 0.04 (adjusted) **Absolute risk difference** - 0.71 deaths per 1000 men • **To prevent one death:-** **Number needed to screen** - 1,410 men, - additional 48 cases needed to be treated **Secondary outcome:-** **a. Detection rate** **Screening group** - 5,990 prostate cancer cases - cumulative incidence 8.2% **Control group** - 4,307 prostate cancer cases - cumulative incidence 4.8% **Secondary outcome** **b. Tumour characteristics** **i. Gleason score < 6** - 72.2% screening group - 54.8% control group **ii. Gleason score >7** • 27.8% screening group • 45.2% control group **iii.** The cumulative incidence of local prostate cancer was higher in the screening group than in the control group **c. Adverse events** - no deaths were reported as direct complication (for example due to septicaemia or bleeding) associated with a biopsy procedure **Authors conclusion** PSA-based screening reduced the rate of death from prostate cancer by 20% but was associated with high risk of overdiagnosis. **Note:** 82.2% of men in the screening group were screened at least once.
General comments	Quality assessment (CASP) 1. Yes 2. Yes 3. Yes 4. Yes 5. Yes 6. Yes 7. Yes 8. Yes, RR, CI 9. Narrow CI, precise

Evidence Table : Effectiveness
Question : Is prostate cancer screening effective in detecting and reducing mortality due to prostate cancer?

Bibliographic citation	4. Andriole GL, Levin DL, Crawford ED, Gelmann EP, Pinsky PF, Kramer BS *et al.* Prostate cancer screening in the Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening trial: Findings from the initial screening round of a randomized Trial. J Natl Cancer Inst. 2005;397:433-481
Study Type / Methodology	Randomised Controlled Trial. The aim is to describe the population enrolled in the PLCO trial, their baseline PSA and DRE screening results and diagnostic follow-up results during the first year of follow-up. From 1993 through 2001, 76,693 men at 10 U.S. study centres were randomly assigned to receive either annual screening or usual care. Men in the screening group received PSA and DRE tests. All PSA test were performed at a single laboratory. DRE was performed by physicians, qualified nurses or physicians assistants. At study entry subjects completed a baseline questionnaire that inquired about demographic characteristics, medical and screening histories. Men with positive PSA and DRE were notified and advised to see their primary care provider for diagnostic follow-up. Primary care providers were also notified. PLCO trial staff obtained medical records related to diagnostic follow-up of positive screens. Certified tumour registrars ascertained the stage, Gleason grade, and type of all diagnosed cases of prostate cancer.
LE	I
Number of patients and patient characteristics	Men, aged between 55 and 74 years. Screening group (38,350) Control group (38,355) Exclusion criteria - history of PLCO cancer - current cancer treatment - starting in 1995, having had more than one PSA blood test in the previous 3 years
Intervention	Annual PSA and annual digital rectal examination (DRE) PSA level of > 4 ng/ml was considered suspicious for cancer.

Comparison	No screening / usual care
Length of follow up (if applicable)	1 year
Outcome measures/ Effect size	**Primary outcome** **a. Compliance with screening test** • DRE (89.1%) • PSA (89.4%) **b. Positive results (suspicious of cancer)** - DRE (7.5%) - PSA (7.9%) - Positive for both DRE and PSA (1.2%) - Rates of positive DRE increased with age (4.9% for 55 to 59 years) increased to 11.5% for 70 to 74 years (P_{trend}<0.001) - Probability of positive PSA increased with age (4.1% for 55 to 59 years) increased to 14.0% for 70 to 74 years (P_{trend}<0.001) **c. Detection rate** **Screening group** - 1.4% **d. Tumour characteristics (1 year)** - 10% Gleason score 2-4 - 45% Gleason score 5-6 - 31% Gleason score 7 - 12% Gleason score 8-10 - 2% Unknown - 83% clinical T1 or T2 cancers (stage 1 or II) - 6% T3 cancers (stage III) - 4% T4 or evidence of nodal or metastatic disease (stage IV)
General comments	Quality assessment (CASP) 1. Yes 2. Yes 3. Yes 4. Yes 5. Yes 6. Yes 7. Yes 8. Percentage 9. CI Not mentioned

Evidence Table : Effectiveness
Question : Is prostate cancer screening effective in detecting and reducing mortality due to prostate cancer?

Bibliographic citation	5. Grubb RL III, Pinsky PF, Greenle RT, Izmirlian G, Miller AB, Hickey TP *et al.* Prostate cancer screening in the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial: update on findings from the initial four rounds of screening in a randomized trial. BJU Int 2008; 102:1524-1530
Study Type / Methodology	Randomised Controlled Trial. The aim was to describe the results of the first four rounds (T0-T3) of prostate cancer screening in the PLCO cancer screening trial. From 1993 through 2001, 76,693 men at 10 U.S. study centres were randomly assigned to receive either annual screening or usual care. Men in the screening group received PSA and DRE tests. DRE was performed by physicians, qualified nurses or physicians assistants. Men with positive PSA and DRE were notified and advised to seek further diagnostic evaluation through their primary care providers who were also notified of the test results. PLCO trial staff obtained medical records related to diagnostic follow-up of positive screens. Certified tumour registrars ascertained the stage, Gleason grade, and type of all diagnosed cases of prostate cancer.
LE	I
Number of patients and patient characteristics	Men, aged between 55 and 74 years. Screening group (38,349) Study population:- • Non-Hispanic white (86%) • 60% < 65 years old at enrolment • 25% had a history of an enlarged or inflamed prostate or problems with prostate • 7.1% had a family history of prostate cancer • 34.6% had 1 PSA test in the 3 years before the study entry and 9.4% had more than one **Exclusion criteria** - previous prostate cancer or surgical removal of the prostate - use of finasteride during previous 6 months
Intervention	Annual PSA for 5 years and annual digital rectal examination (DRE) for 3 years PSA level of > 4 ng/ml was considered positive.

Comparison	No screening / usual care
Length of follow up (if applicable)	4 years
Outcome measures/ Effect size	**Primary outcome** **a. Compliance with either screening test** • Decreased slightly 89.4% at baseline (T0) to 85.1% at T3 **b. Positive results** - DRE (range 6.8% to 7.6% at T0-T3) - PSA (range 7.7% to 8.8% at T0-T3) **c. Detection rate among 38,349 men in intervention arm** - 1,902 (4.9%) • 1,603(84.2%) screen detected • 204 (10.7%) interval • 95 (5.0%) never had PLCO screen **d. Tumour characteristics (4 years)** - 69% Gleason score 2-6 - 21.1% Gleason score 7 - 7% Gleason score 8-10 - 2.9% Unknown - 96.2% (stage 1 to II) - 1.6 % (stage III) - 2.1% (stage IV)
General comments	Quality assessment (CASP) 1. Yes 2. Yes 3. Yes 4. Yes 5. Yes 6. Yes 7. Yes 8. Percentage, CI for PPV 9. Precise (CI narrow)

Evidence Table : Effectiveness
Question : Is prostate cancer screening effective in detecting and reducing mortality due to prostate cancer?

Bibliographic citation	6. van der Kwast TH, Ciatto S, Martikainen PM, Hoedemaeker R, Laurila M, Pihl CG *et al.* Detection rates of high-grade prostate cancer during subsequent screening visits. Results of the European Randomized Screening Study for Prostate Cancer. Int. J. Cancer.2006; 118:2538-2542
Study Type / Methodology	Randomised Controlled Trial. The aim of the study was to compare Gleason scores attributed to prostate cancers detected on prostate needle biopsies and the cancer detection rates during subsequent screening rounds in 6 centres of the ERSPC. Men from 8 different European countries participated in the screening programs offered by the ERSPC centres. Toulous (France) and Aarau (Switzerland) were not included in the study because second screening visit data are not yet available. Data from the remaining 6 countries were included:- - Goteborg (Sweden) - Helsinki, Tampere (Finland) - Rotterdam (Netherlands) - Florence (Italy) - Getafe (Spain) - Antwerp (Belgium) Screening centres differs with regards to age range, screening intervals and biopsy indications. Data was provided by the central database of the ERSPC coordinator. Pathology committee was established to promote the comparability of needle biopsy reporting between the individual ERSPC centres. Training sessions to reduce inter-observer variation in Gleason grading were organized for the reference pathologists of the participating pathology laboratories at 2 yearly intervals. Gleason scores were compressed into 3 categories, according to international guidelines; Gleason scores 2-6, Gleason score 7 and Gleason scores 8-10.
LE	I
Number of patients and patient characteristics	Screened 58,710 men during 1st visit 40,425 men during 2nd visit Age range: - Goteborg (Sweden); 51-66 years - Helsinki, Tampere (Finland); 55/59/63/67 years - Rotterdam (Netherlands); 55-75years - Florence (Italy); 55-70 years - Getafe (Spain); 45-70 years - Antwerp (Belgium); 55-74 year

Intervention	PSA, DRE or TRUS at 2 yearly or 4 yearly interval **Biopsy indication:-** - Sweden PSA ≥ 3.0 ng/ml) - Finland PSA ≥ 4 ng/ml or positive DRE (1996-1998) or proportion of free PSA ≤ 0.16 (since 1999) at PSA ≥ 3 ng/ml - Netherlands PSA ≥ 4 ng/ml or positive DRE or TRUS at PSA ≥ 3 ng/ml; since 1997 PSA ≥ 3 ng/ml - Italy PSA ≥ 4 ng/ml or positive DRE or TRUS at PSA ≥ 2.5 ng/ml - Spain PSA ≥ 4 ng/ml until May 1998 then PSA ≥ 2.9 ng/ml - Belgium PSA 4 ng/ml or positive DRE or TRUS
Comparison	No screening
Length of follow up (if applicable)	2 to 4 years
Outcome measures/ Effect size	**Primary outcome** **a. Gleason scores:-** - Increased proportion of Gleason score 6 cancers from 62.5% in the 1st screening visit to 75% in the second screening visit (P< 0.001) - Decrease proportion of Gleason score 7 cancers in Goteborg, Finland and Rotterdam. - High-grade (Gleason score 8-10) cancer varied per screening centre:- • 1st screening visit from 5.1 to 41.1/10,000 men • second screening visit from 6.4 to 29.3/10,000 men - Overall detection rate of high- grade cancer:- • 1st screening visit - 26.0/10,000 men • 2nd screening visit - 12.6/10,000 men **b. Cancer detection rate** 1st screening visit • 331/10,000 men 2nd screening visit • 335/10,000 men **Secondary outcome** **a. Positive Predictive value (PPV) during 1st screening** - 17% to 27%
General comments	Quality assessment (CASP) 1. Yes 2. Yes 3. Yes 4. Can't tell 5. Yes 6. Yes 7. Yes 8. Percentage, and rate 9. CI not mentioned

Evidence Table : Effectiveness
Question : Is prostate cancer screening effective in detecting and reducing mortality due to prostate cancer?

Bibliographic citation	7. Hoedemaker RF, van der Kwast TH, Boer R, de Koning HJ, Roobol M, Vis AN *et al.* Pathologic features of prostate cancer found at population-based screening with a four-year interval. J Natl Cancer Inst. 2001;93:1153-1158
Study Type / Methodology	Randomised Controlled Trial. The aim of the study was to determine whether a longer interval between screening rounds would compromise the detection of curable prostate cancer. Studied prostate cancer characteristics in a cohort of men during two rounds of population-based screening. A cohort of 4,491 men aged 55-75 years, all of whom had been randomly assigned to the screening group in the Rotterdam section of ERSPC from June 1994 to March 1996 were invited to participate in the initial PSA screening. Men who received that screening were invited for a second screening 4 years later. In participants who complied with the recommendation for biopsy, systematic sextant biopsies were obtained during longitudinal ultrasonographic scanning of the prostate. Pathology findings from needle biopsy cores were compared for men in both rounds.
LE	I
Number of patients and patient characteristics	First round of screening, 4,133 men aged 55-75 years. Second round of screening, 2,385 participants.
Intervention	Screening using PSA, DRE and TRUS First screening round from June 1994 to March 1996. Biopsy were recommended for men with serum PSA ≥ 4 ng/ml or abnormal DRE or abnormal TRUS Second screening round from June 1998 to March 2000. Biopsies were recommended to all men with serum PSA ≥ 3 ng/ml regardless of the outcome of DRE or TRUS.
Comparison	No screening
Length of follow up (if applicable)	4 years
Outcome measures/ Effect size	**Primary outcome** **Detection of prostate cancer:-** **a. Median amount of cancer in biopsy set** • First screening round - 7.0 mm ,95% CI: 5.4 mm to 8.6 mm • Second screening round - 4.1 mm, 95% CI: 2.6 mm to 5.6 mm (P=0.001) **b. Adenocarcinoma detected with Gleason score of 7 or higher** • First screening round - 36 % • Second screening round - 16% (Mean difference = 20%, 95% CI: 10% to 30% , P<0.001) **c. Adenocarcinoma detected with adverse prognostic features** • First screening round - 25 % • Second screening round - 6% (Mean difference = 19%, 95% CI: 11% to 26% , P<0.001) Baseline PSA values were predictive for the amount of tumour in biopsies in men with cancer in the first round but not for that in the second round. Conclusion Most large prostate cancers with high serum PSA were effectively detected in a prevalence screen. In this population, a screening interval of 4 years appears to be short enough to constrain the development of large tumours, although it is inconclusive whether this will result in a survival benefit,
General comments	Quality assessment (CASP) 1. Yes 2. Yes 3. Yes 4. Yes 5. Yes 6. Yes 7. Yes 8. Percentage 9. CI wide, not precise

Evidence Table : Effectiveness
Question : Is prostate cancer screening effective in detecting and reducing mortality due to prostate cancer?

Bibliographic citation	8. Roobol MJ, Grenabo A, Schroder FH, Hugosson J. Interval cancers in Prostate Cancer Screening: Comparing 2-and 4- year screening intervals in the European Randomized Study of Screening for Prostate Prostate Cancer, Gothenburg and Rotterdam. J Natl Cancer Inst. 2007;99:1296-1303
Study Type / Methodology	Randomised Controlled Trial. The aim of the study was to compare the number and characteristics of interval cancers, defined as those diagnosed during the screening interval but not detected by screening. Involved men in the screening arm of the ERSPC participating through two centres; Gothenburg (2-year screening interval) and Rotterdam (4 year screening interval) All participants who were diagnosed with prostate were ascertained by linkage with national registries. A potentionally life-threatening (aggressive) interval cancer was defined as one with at least one of the following characteristics at diagnosis:- • Stage M1 or N1 • Plasma PSA concentration greater than 20.0 ng/ml • Gleason score > 7
LE	I
Number of patients and patient characteristics	Men aged 55 to 65 years at the time of the first screening. **Rotterdam** Screening group, n=13,301 Control group, n= 13,309 **Gothenburg** Screening group, n= 4,202 Control group, n= 5,951
Intervention	Screening using PSA, DRE or TRUS **Rotterdam:-** screening at 4 yearly interval (screened 2 or 3 times up to December 31, 2005 or maximum 10 years after initial screening) **Gothenburg:-** screening at 2 yearly interval (screened 5 or 6 times up to December 31, 2005 or maximum 10 years after initial screening)
Comparison	No screening

Length of follow up (if applicable)	10 years
Outcome measures/ Effect size	**Primary outcome** **Detection rate:-** • **Rotterdam (screening at 4 yearly interval** • **Gothenburg (screening at 2 yearly interval** **a. Screen detected prostate caner** • Rotterdam; 1,061 (7.98%) • Gothenburg; 521 (12.40% **b. Interval cancer** • Rotterdam; 57 (0.43%) • Gothenburg; 31 (0.74%) (P<0.51) **c. All prostate cancer** • Rotterdam; 1,118 (8.41%) • Gothenburg; 552 (13.14%) (P<0.001) **d. Aggressive interval cancer** • Rotterdam; 15 (0.11%) • Gothenburg; 5 (0.12%) (P<0.72) **e. Prostate cancer in control group** • Rotterdam; 317 (2.38%) • Gothenburg; 402 (6.76%) Conclusion The rate of interval cancer, especially aggressive interval cancer, was low in this study. The 2-year screening interval had higher detection rates than the 4-year interval but did not lead to lower rates of interval and aggressive interval prostate cancers.
General comments	Quality assessment (CASP) 1. Yes 2. Yes 3. Yes 4. Yes 5. Yes 6. Yes 7. Yes 8. Percentage, and rate 9. CI not mentioned

Evidence Table : Effectiveness
Question : Is prostate cancer screening effective in detecting and reducing mortality due to prostate cancer?

Bibliographic citation	9. Draisma G, Boer R, Otto SJ, van der Cruijsen IW, Damhuis RAM, Schroder FH *et al*.. Lead times and overdetection due to prostate-specific antigen screening: Estimates from the European Randomized Study of Screening for Prostate Cancer. J Natl Cancer Inst. 2003;95:868-878
Study Type / Methodology	Randomised controlled trial (post hoc analysis) The aim of the study was to estimate the mean lead times and overdetection rates associated with several different PSA programs with simulation program MISCAN an acronym for MIcrosimulation Screening ANalysis. MISCAN models were validated against data from the Rotterdam section of the ERSPC trial which enrolled 21,166 men in the control arm and 21,210 men screened in the screened arm in which 1,498 prostate cancers were diagnosed. MISCAN models are designed to evaluate cancer screening programs. MISCAN models use a Markov process of states and transitions to simulate and compare individual life histories in the presence and absence of a cancer screening program. Information about the epidemiology and natural history of the studies cancer, population characteristics, and screening modalities were used to set the key parameters of the model. Definition:- Lead time is the time by which PSA screening advances prostate cancer diagnosis. Overdetection is when screening detects cancers that would not have been diagnosed in the absence of screening.
LE	1
Number of patients and patient characteristics	Men age 55 to 74 years old Screening arm;- n=21,210 Control arm:- n=21,166
Intervention	Screening using PSA, DRE and TRUS First 9,766 men assigned to the screening arm received a DRE, TRUS and a PSA test. Biopsy were recommended for men with serum PSA ≥ 4 ng/ml or abnormal DRE or abnormal TRUS The remaining 10,204 men invited for the first round and all men invited for the second round received a PSA test. Biopsy were recommended to all men with serum PSA ≥ 3 ng/ml.
Comparison	No screening
Length of follow up (if applicable)	4 years
Outcome measures/ Effect size	**Primary outcome** **Mean lead times and rates of overdetection** • - **Depended on man's age at screening** **a. For a single screening test at age 55** • Mean lead time:- - 12.3 yeas, 95% CI:11.6 to 14.1 years • Overdetection rate - 27%, 95% CI:24% to 37% **b. For a single screening test at age 75** • Mean lead time:- - 6.0 yeas, 95% CI:5.8 to 6.3 years • Overdetection rate - 56%, 95% CI:53% to 61% **c. For a screening program with a 4-yearly screening interval from age 55 to 67** • Mean lead time:- - 11.2 yeas; 95% CI: 110.8 to 12.1 years • Overdetection rate - 48%; 95% CI: 44% to55% • Lifetime risk of cancer diagnosis - Increased from 6.4% to 10.6%, relative increase of 65%; 95% CI: 56% to 87% **d. For a screening program with a yearly screening interval from age 55 to 67** • Overdetection rate = 50% (46% to57%) • Lifetime risk of cancer diagnosis - Relative increase of 80%; 95% CI: 69% to 116% Extending annual or 4 yearly screening to the age of 75 would result in at least two cases of overdetection for every clinically relevant cancer detected. Conclusion; support a prostate cancer screening interval of more than 1 year.
General comments	

Evidence Table : Effectiveness
Question : Is prostate cancer screening effective in detecting and reducing mortality due to prostate cancer?

Bibliographic citation	10. Draisma G, Etzioni R, Tsodikov A, Mariotto A, Wever E, Gulati R *et al*.. Lead times and overdetection in prostate-specific antigen screening: Importance of methods and context. J Natl Cancer Inst. 2009;101:374-383
Study Type / Methodology	Randomised Controlled Trial (post hoc analysis). To investigate why different studies have yielded different results and to explore the three factors associated with it:- i. Context of estimates, including population, epidemiology of the disease, and the way screening was practised ii. Definitions of lead time and overdiagnosis used iii. Method used to calculate the estimate Lead times and fractions of overdiagnosis for PSA testing of US men aged 54 to 80 years in 1985-2000 were estimated using three models of prostate cancer progression and detection calibrated to the Surveillance, Epidemiology, and End Results program (SEER) program. Estimates of lead times using different definitions were compared across models. The three models are Fred Hutchinson Cancer Research Center (FHCRC) model, University of Michigan (UMich) model and microsimulation screening analysis (MISCAN) model. Lead times were estimated by use of three definitions (non-overdiagnosed, censored and uncensored). Also compared US and earlier estimates from Rotterdam section of the ERSPC that were calculated by use of MISCAN model.
LE	I
Number of patients and patient characteristics	US male population 50-84 years in 1985 to 2000.
Intervention	Screening using PSA, DRE and TRUS
Comparison	No screening /usual care
Length of follow up (if applicable)	
Outcome measures/ Effect size	**Primary outcome** **Mean lead times and rates of overdetection:-** **a. Estimated mean lead time** • 5.4 years to 6.9 years • Similar across model but different according to definition used **b. Overdiagnosis** • 23% to 42% of all prostate cancers detected by PSA **c. MISCAN model for ERSPC Rotterdam** • Mean lead time:- - 7.9 years • Overdetection rate - 66% **d. MISCAN model for SEER (US data)** • Mean lead time:- - 6.9 years • Overdetection rate - 42% Conclusion The precise definition and the population used to estimate lead time and overdiagnosis can be important drivers of study results and should be clearly specified.
General comments	

Evidence Table : Effectiveness
Question : Is prostate cancer screening effective in detecting and reducing mortality due to prostate cancer?

Bibliographic citation	11. Roomeling S, Robbol MJ, Kattan MW, van cer Kwast TH, Steyerberg EW , Schroder FH. Normogram Use for the Preduction of Indolent Prostate Cancer.2007;110 (10):2218-2221
Study Type / Methodology	Randomised Controlled Trial (post hoc analysis) The aim of the study was to apply Kattan-nomogram to estimate the proportion of indolent cancers. The Kattan-nomogram for prediction of indolent prostate cancer was validated and calibrated for use in the screening setting. The calibrated nomogram was used to calculate the number of men who were predicted to have indolent cancer in screen-detected cohort from ERSPC study, Rotterdam section. The nomogram was applied to men identified with screen detected prostate cancer comprising the following features:- i Clinical stage T1c or T2 i. PSA 20 ng/ml or less ii. Primary and secondary Gleason Grade 3 or less iii. Positive cores 50% or less iv. Total cancer in biopsy cores 20 mm or less v. Benign tissue in all cores of 40 mm or more Indolent cancer was defined by a total tumour volume less than 0.5 ml, confined to the prostate (no focal or established extracapsular extension) with no Gleason pattern 4 or 5.
LE	
Number of patients and patient characteristics	1,629 cancers (men) detected in 2 subsequent screening rounds.
Intervention	Screening using PSA, DRE and TRUS and biopsy PSA cutoff for biopsy indication ≥ 3 ng/ml. Screening conducted every 4 years (completed 2 screening rounds)
Comparison	No screening
Length of follow up (if applicable)	4 years
Outcome measures/ Effect size	**Primary outcome** **a. Proportion of Indolent cancer:-** • 825/1,629 (51%) of cancers detected in 2 subsequent screening rounds were suitable for nomogram use according to the given criteria. • 485/825 (59%) men were predicted to have indolent cancer. • Assuming none of the cases excluded for nomogram use were indolent (n=804), an estimated 485/1629 (30%) of all screen-detected men were predicted to have indolent disease. • Cancers found at repeated screening after 4 years had a higher probability of indolent cancers than cases from the prevalence screening (44% versus 23%, P <0.001) Conclusion The current nomogram can identify substantial groups of screen-detected cancers that are likely indolent and can therefore be considered for active surveillance.
General comments	

Evidence Table : Effectiveness
Question : Is prostate cancer screening effective in detecting and reducing mortality due to prostate cancer?

Bibliographic citation	12. Essink-Bot ML, de Koning HJ, Nijis HGT, Kirkels WJ, van der Maas PJ, Schroder FH. Short-term effects of population-based screening for prostate cancer on Health-Related Quality of Life. J Natl Cancer Inst.1998;90:925-931
Study Type / Methodology	Randomised controlled trial (post hoc subset analysis) To examine health-related quality of life (or health status) among men screened for prostate cancer. Involved participants in the Rotterdam screening trial for prostate cancer (attenders) and non participants. Nonparticipants consisted of a random selection of 500 nonparticipants who had been invited to the screening trial during the period of September 1995 through March 1996. Participants of the screening program (attenders) and nonparticipants completed self-assessment questionnaires (SF-36 that is Medical Outcomes Study 36-Item Short-Form Health Survey) and (EQ-5D that is EuroQol measure for health-related quality of life health surveys) to measure generic health status as well as an additional questionnaire for anxiety items related to prostate cancer screening. The attenders completed questionnaires at T1 (baseline) and T2 (waiting room) and either at T3 (when nothing suspicious was found in the initial screening tests) or at T4 (during the waiting period for the biopsy result) and T5 (after being inform that the biopsy result did not confirm a prostate cancer diagnosis).
LE	1
Number of patients and patient characteristics	625 participants on the Rotterdam (Netherlands) prostate cancer screening programme - mean age of 63.2 years 500 non participants - mean age of 64.8 years
Intervention	Survey using self administered questionnaire at T1, T2, T3, T4, T5
Comparison	Survey using self administered questionnaire at T1
Length of follow up (if applicable)	
Outcome measures/ Effect size	**Primary outcome** **a. Physical discomfort during DRE, TRUS and biopsy** - 181/491 (37%) had physical discomfort during DRE - 139/487 (29%) had discomfort during TRUS - 64/116 (55%) had discomfort during prostate biopsy **b. Mean scores for health status and anxiety** • Participants did not experience relevant changes in physical, psychological, and social functioning during the screening procedure • High levels of anxiety were observed throughout the screening process among men with high predisposition to anxiety • Similar scores for anxiety predisposition were observed among attenders and nonparticipants Conclusion At group level, we did not find evidence that prostate cancer screening induced important short-term health-status effects, despite the short-lasting side effects related to biopsy procedures. However, subgroups may experience high levels of anxiety.
General comments	

Evidence Table : Safety
Question : Is prostate cancer screening using PSA/DRE/TRUS guided biopsy safe?

Bibliographic citation	1. Andriole GL, Crawford ED, Grubb RL, Buys SS, Chia D, Church TR *et al.* Mortality results from a Randomized Prostate-Cancer Screening Trial. N Engl J Med. 2009;360(13): 1310-1319
Study Type / Methodology	Randomised Controlled Trial. Aim of the report was to provide information on prostate cancer incidence, staging, and mortality in both study groups during the first 7 to 10 years of the study. From 1993 through 2001, 76,693 men at 10 U.S. study centres were randomly assigned to receive either annual screening or usual care. Men in the screening group were offered PSA testing for 6 years and digital rectal examination for 4 years. All PSA test were performed at a single laboratory. DRE was performed by physicians, qualified nurses or physicians assistants. At study entry subjects completed a baseline questionnaire that inquired about demographic characteristics, medical and screening histories. A biorepository for the collection and storage of blood and tissue samples was an integral component of the trial. The subjects and healthcare providers received the results and decided on the type of follow-up evaluation. Screening outside the trial protocol in the control group was assessed through random surveys. The numbers of all cancers and deaths and cause of deaths were ascertained
LE	I
Number of patients and patient characteristics	Men, aged between 55 and 74 years. Screening group n= 38,343 Control group n=38,350 Exclusion criteria:- - history of PLCO cancer - current cancer treatment - starting in 1995, having had more than one PSA blood test in the previous 3 years

Intervention	Annual PSA testing for 6 years and annual digital rectal examination (DRE) for 4 years. PSA level of 4 ng/ml was considered to be positive for cancer.
Comparison	No screening / usual care Usual care sometimes included screening, as some organizations have recommended Note: In the control group, rate of PSA testing was 40% in the first year and increased to 52% in the sixth year
Length of follow up (if applicable)	To be followed- up for 13 years. At 7 years vital status was known for 98% of the men in the two groups. At 10 years vital status was known for 67% of the subjects. Median duration of follow-up was 11.5 years (range, 7.2 to 14.8 in the two groups)
Outcome measures/ Effect size	**Outcome on safety** **Screening Related Risks** **a. Complications of DRE** - 0.3 per 10,000 screenings (bleeding or pain) **b. Complications of PSA test** - 26.2 per 10,000 screenings (dizziness, bruising and hematoma) • 3 fainting episodes per 10,000 screenings **c. Medical complications from diagnostic process** - 68 per 10,000 diagnostic evaluation after a positive results on screening (primarily infection, bleeding, clot formation, and urinary difficulties) **d. Treatment related complications** - generally more serious, include infection, incontinence, impotence and other disorders. Such complications are now being catalogued in quality of life study and particularly pertinent to overdiagnosis.
General comments	Quality assessment (CASP) 1. Yes 2. Yes 3. Yes 4. Yes 5. Yes 6. Yes 7. Yes 8.Yes, RR, CI 9.Wide CI, not very precise

Evidence Table : Safety
Question : Is prostate cancer screening using PSA/DRE/TRUS guided biopsy safe?

Bibliographic citation	2. Romero FR, Romero AW, Filho TB, Bark NM, Yamazaki DS, de Oliveira junior FC. Patient' perceptions of pain and discomfort during digital rectal exam for prostate cancer screening.Arch. Esp. Urol. 2008 ;61(&):850-854
Study Type / Methodology	Cross sectional and RCT To evaluate patients' perception of pain and discomfort during rectal exam for prostate cancer screening. In the first part of the study, during a prostate cancer screening program at an Institution in Brazil, 100 patients voluntarily undergoing DRE for prostate cancer screening were included. Patients answered an anonymous questionnaire regarding pain, urinary urgency and bowel urgency during DRE and its potential impact on future examination. Exclusion:-illiterate patients, without consent, clinical or laboratory evidence of urinary tract infection or prostatitis. In the second part of the study, another group with 100 patients were randomly divided into two subgroups to analyze if emptying the bladder immediately before DRE reduces patient discomfort. 50 patients were asked to urinate immediately before examination (intervention group) and 50 patients underwent DRE without urinating (control group). Patients were matched by age, education, AUA prostate symptom score, PSA < 4.0 ng/ml. Exclusion:- - current history of pain or bleeding with bowel movement - prior history of anal surgery - DRE suspicious of cancer Randomisation stratified to the day of the week DRE was performed.
LE	III
Number of patients and patient characteristics	First part of study:- - 100 patients, median age was 50 years (range 40-66) Second part of the study:- - 100 patients, median age was 52 years (range 50-59)
Intervention	Survey using self administered questionnaire, immediately after examination Urinate immediately before DRE examination
Comparison	Without urinating before DRE examination
Length of follow up (if applicable)	1 year
Outcome measures/ Effect size	**Primary outcome** **Discomfort related to pain, urinary urgency and bowel urgency** **a. First part:-** • 73% reported moderate, ssevere or unbearable discomfort for at least one domain - 61% complained of pain - 22% complained of urinary urgency - 22% complained of bowel urgency • 94% patients will repeat the prostate examination next year **b. Second part:-** • Emptying the bladder immediately before examination did not reduce the incidence of moderate, severe or unbearable pain - 58% versus 50%, P=0.115 • Urinary urgency - 22% versus 16%, P=0.151 • Bowel urgency - 16% versus 14%, P=0.264 No difference in the number of patients that will repeat the prostate examination (96% versus 90%, P=0.162) Conclusion Pain and discomfort during DRE are not negligible but do not affect intention to have a prostate examination in the future.
General comments	

Evidence Table : Safety
Question : Is prostate cancer screening using PSA/DRE/TRUS guided biopsy safe?

Bibliographic citation	3. Rietbergen JBW, Kruger AEB, Kranse R, Schroder FH. Complications of transrectal ultrasound-guided systematic sextant biopsies of the prostate: Evaluation of complication rates and risk factors within a population-based screening program. UROLOGY. 1997;49(6):875-880
Study Type / Methodology	Randomised Controlled Trial The aim is to study the complications and the risk factors for complications within the screened population of the European Randomized Study of Screening for Prostate Cancer (ERSPC), Rotterdam section. Between June 1994 and July 1996, 1,687 ultrasound guided systematic sextant biopsies were performed after screening 6,198 men using prostate specific antigen level (cut off vale of 4 ng/ml), digital rectal examination, and transrectal ultrasonography. All biopsies were performed by resident urologist in an outpatient setting. Neither prebiopsy bowel preparations nor cleansing enemas were used. Procedure was performed without anaesthesia. After 2 to 3 weeks, all patients were seen by one of the staff urologist and were informed about the biopsy results. At that time, a questionnaire relating to complications following the biopsy was filled. Three possible risk factors for complications were evaluated:- - a positive biopsy outcome - a prior history of diabetes mellitus - a history of prostatitis
LE	I
Number of patients and patient characteristics	1,687 procedures to obtain biopsy specimen
Intervention	Ultrasound guided systematic sextant biopsies
Comparison	No screening
Length of follow up (if applicable)	
Outcome measures/ Effect size	**Primary outcome** **a. Complications rate** • Minor complications defined as expected side effects of the biopsy procedure causing minimal or no discomfort and requiring no additional treatment:- - haematospermia [765 (45.3%)] - haematuria [398 (23.6%)] - rectal bleeding [29 (1.7%)] Did not require hospitalisation • Major complications defined as adverse effects causing significant discomfort, disability, or requiring additional treatment:- - Pain [126 (7.5%), but only 0.4% used analgesics] - Nausea or sickness [15 (1%)] - Urinary retention [7 (0.4%)] - Fever > 38.5°C [71 (4.2%)] • Antibiotic therapy [52 (3.1%)] • Hospital admission [7 (0.4%)] • Sepsis [3 (0.2%)] **b. Possible risk factors for complications after biopsy:-** Risk factors for complications could not be identified
General comments	Quality assessment (CASP) 1. Yes 2. Yes 3. Yes 4. Yes 5. Yes 6. Yes 7. Yes 8. Percentage (%), P value 9. No CI

Evidence Table : Safety
Question : Is prostate cancer screening using PSA/DRE/TRUS guided biopsy safe?

Bibliographic citation	4. Raaijmakers R, Kirkels WJ, Roobol MJ, Wildhagen MF, Schroder FH. Complication rates and risk factors of 5,802 transrectal ultrasound-guided systematic sextant biopsies of the prostate within a population-based screening program. UROLOGY. 2002;60(5):826-830
Study Type / Methodology	Randomised Controlled Trial The aim is to evaluate the complication rates and possible risk factors of biopsy of the prostate with the aim of improving patient counselling and the safety of the procedures. Within the biopsy protocol of the Rotterdam section of the ERSPC, 5,802 transrectal ultrasound-guided systematic sextant biopsies were evaluated between June 1994 and August 2001. All biopsies were performed by resident urologist in an outpatient setting. Neither prebiopsy bowel preparations nor cleansing enemas were used. Procedure was performed without anaesthesia. All participants receive prophylactic antibiotic therapy. After 2 to 3 weeks, all patients were seen by one of the staff urologist and were informed about the biopsy results. At that time, a questionnaire relating to complications following the biopsy was filled.
LE	I
Number of patients and patient characteristics	5,802 procedures to obtain biopsy specimen
Intervention	Ultrasound guided systematic sextant biopsies
Comparison	No screening
Length of follow up (if applicable)	
Outcome measures/ Effect size	**Primary outcome** **a. Complications rate** Of the 5,802 biopsy procedures, 5,676 (97.8%) post-biopsy questionnaire were filled by staff urologist • Minor complications defined as expected side effects of the biopsy procedure causing minimal or no discomfort and requiring no additional treatment:- - haematospermia [2,858 (50.4%)] - haematuria lasting longer than 3 days [1,280 (22.6%)] • Major complications defined as adverse effects causing significant discomfort, disability, or requiring additional treatment:- - Urinary retention [20 (0.4%)] - Fever > 38.5°C [200 (3.5%)] Hospital admission - 27 men (0.5%) • 25(92.%) because of signs of prostatistis and / or urosepsis • One of them admitted to ICU because of septic shock
General comments	Quality assessment (CASP) 1. Yes 2. Yes 3. Yes 4. Yes 5. Yes 6. Yes 7. Yes 8. Percentage (%), correlation coefficient (R), P value 9. No CI

Evidence Table : Safety
Question : Is prostate cancer screening using PSA/DRE/TRUS guided biopsy safe?

Bibliographic citation	5. Lee SH, Chen SM, Ho CR, Chnag PL, Chen CL, Tsui KH. Risk factors associated with Transrectal Ultrasound Guided Prostate Needle Biopsy in Patients with Prostate Cancer. Chang Gung Med J.2009;32(6):623-627
Study Type / Methodology	Cross sectional study To determine associated risk factors for patients who suffered major complications and hospitalisation after TRUS-guided prostate biopsy in a large screening population. Study was performed between January 2003 and July 2006 in Taiwan. 1,529 consecutive patients suspected of having prostate cancer were involved All biopsies were performed with a spring loaded biopsy gun and 18-gauge Tru-Cut needle. A 2012 Bruel and Kjaer 7.0 MHZ biplanar ultrasound probe was used for diagnostic ultrasonography and sextant biopsy, under local nasethesia All biopsies were six-core biopsy. Complications rates were recorded.
LE	III
Number of patients and patient characteristics	1,529 consecutive patients suspected of having prostate cancer. Indicators included:- -high PSA > 4 ng/ml - hypoechoic lesions on transrectal sonography - abnormal DRE Mean age 67.6 ± 9.81 years (SD).
Intervention	TRUS-guided prostate biopsy
Comparison	
Length of follow up (if applicable)	
Outcome measures/ Effect size	**Primary outcome** **a. Complications rate:-** - 147/1,529 (9.6%) patients had complications - some patients may have more than one complication - 1/3 required hospital admission and antibiotic therapy - all patients fully recovered - 62 patients (4.1%) had gross haematuria - 26 patients (1.7%) had acute urinary retention - 21 patients (1.4%) had urinary tract infections - 17 (1.1%) had haematospermia - 14 (0.9%) had anal bleeding - 7 (0.5%) had anal pain **b. Associated risk factors:-** • Urinary tract infection • Rectal preparation Significantly associated with complication, P<0.01
General comments	

Evidence Table : Safety
Question : Is prostate cancer screening using PSA/DRE/TRUS guided biopsy safe?

Bibliographic citation	6. McNaughton -Collins M, Fowler FJ, Caubet JF, Bates DW, Lee JM, Hauser A *et al.*. Psychological effects of a suspicious prostate cancer screening test followed by a benign biopsy result. Am J Med.2004;117: 719-725
Study Type / Methodology	Cohort study To evaluate the short term psychological implications of an apparently false-positive screening result for prostate cancer. 400 consecutive men were assembled between August 2001 and September 2002 from primary care practices of Masachusetts General Hospital and Boston Medical Centre. Men were identified for biopsy and control groups through weekly review of pathology reports and PSA test results. The patients were recruited based on inclusion and exclusion criteria. Participants were mailed a brief (< 10 minutes), self administered, pretested questionnaire about 6 weeks after benign biopsy result (biopsy group) or normal PSA screening PSA test result (PSA <2.5 ng/ml), control group. Overall 471 eligible men were sent a survey and 400 (85%) responded. - 167/191 (87%) in the biopsy group - 233/280 (83%) in the control group
LE	II-2
Number of patients and patient characteristics	167 men in the biopsy group and 233 men in the control group. The mean (± SD) age of the men surveyed was 60 ± 9 years (range, 40 to 88 years)
Intervention	Survey among participants with benign prostate biopsy results which was performed because of a suspicious screening test results. (After 6 weeks of the results).
Comparison	Survey among participants not undergoing prostate biopsy following a normal PSA test
Length of follow up (if applicable)	
Outcome measures/ Effect size	**Primary outcome** **Psychological effects** **a. Having thought about prostate cancer either "a lot" or "some of time"** **Biopsy group** - 81/167 (49%) **Control group** - 42/230 (18%), P<0.001 **b. Having worried "a lot" or "some of the time" that they may develop prostate cancer** **Biopsy group** - 67/167 (40%) **Control group** - 18/231 (8%), P<0.001 **Secondary outcome:-** **a. Prostate cancer knowledge** **-** More men in biopsy group than in the control group answered questions about prostate cancer and biopsy correctly. However only 4/165 (2%) in the biopsy group answered all three knowledge questions correctly. **b**. Prostate biopsy experience - 42/163 (26%) reported moderate- to-severe pain (grade 7 or greater) - 39/163 (24%) reported minimal or no pain (grade 2 or lower)
General comments	

Evidence Table : Safety
Question : Is prostate cancer screening using PSA/DRE/TRUS guided biopsy safe?

Bibliographic citation	7. Fowler FJ, Barry MJ, Walker-Corkery B, Caubet JF, Bates DW, Bates DW, Lee JM *et al.*. The impact of a suspicious prostate biopsy on patients psychological, socio-behavioural, and medical care outcomes. J Gen Intern Med.2006;21: 715-721
Study Type / Methodology	Cohort study To evaluate the psychological, sociobehavioural, and medical implications of apparently false positive prostate cancer screening result. 400 consecutive men were assembled between August 2001 and September 2002 from primary care practices of Masachusetts General Hospital and Boston Medical Centre. Men were identified for biopsy and control groups through weekly review of pathology reports and PSA test results. The patients were recruited based on inclusion and exclusion criteria. Participants were mailed a brief (< 10 minutes), self administered, pretested questionnaire about 6 weeks after benign biopsy result (biopsy group) or normal PSA screening PSA test result (PSA <2.5 ng/ml), control group. Patients who returned the 6-week questionnaire, were surveyed again at 6 months, and those who responded at 6 months were sent questionnaires at 12 months. Patients who did not return any questionnaire were not sent further surveys. Overall 471 eligible men were sent a survey and 400 (85%) responded (6 week). - 167/191 (87%) in the biopsy group - 233/280 (83%) in the control group At 6 months, 333/399 (83%) responded - 139/167 (83%) in the biopsy group - 194/232 (84%) in the control group At 12 months, 285/331 (86%) responded - 121/138 (88%) in the biopsy group - 164/193 (85%) in the control group
LE	II-2
Number of patients and patient characteristics	167 men in the biopsy group and 233 men in the control group. Mean age for biopsy group, 61.1 years Mean age for normal PSA group, 59.8 years.
Intervention	Survey among participants with benign result from prostate biopsy performed because of a suspicious screening test results at 6 months and 12 months.
Comparison	Survey among participants not undergoing prostate biopsy following a normal PSA test 6 months and 12 months.
Length of follow up (if applicable)	1 year
Outcome measures/ Effect size	**Primary outcome** **a. Psychological effects (at 12 months)** • **% of men having worried "a lot" or "some of the time" that they may develop prostate cancer** **Biopsy group** - 32/121 (26%) **Control group** - 10/164 (6%), P<0.001 **b. Sociobehavioural impact (at 12 months)** • **% of men reported thinking their wife or significant other was concerned about them developing prostate cancer "a lot" or "some of the time".** **Biopsy group** - 46% **Control group** - 14%, P<0.001 **c. Medical care at 12 months** - Biopsy men more likely than those in the control group to have had at least 1 follow-up PSA test over the year (73% versus 42%, P<0.001) - more likely to have another biopsy (15% versus 1%, P <0.001) - more likely to visit urologist (71% versus 13%, P <0.001)
General comments	

Evidence Table : Safety
Question : Is prostate cancer screening using PSA/DRE/TRUS guided biopsy safe?

Bibliographic citation	8. Katz DA, Jarrad DF, McHorney CA, Hillis SL, Wiebe DA, Fryback DG. Health perceptions in patients who undergo screening and workup for prostate cancer. Urology.2007;69(2):215-220
Study Type / Methodology	Cross-sectional study Aim of the study was to determine whether positive screening test (abnormal PSA or digital rectal examination) in men with a negative biopsy for prostate cancer is associated with worsened mental health and increased cancer-related worry during the short-term follow-up. Also to determine the relationship between a positive screening test and self-reported sexual function. Conducted cross sectional survey 2 months after prostate cancer screening and work-up of two comparison group:- - among biopsy recipients who showed no evidence of prostate cancer on microscopic examination following a suspicious screening test (group 1) - Primary care patients with a PSA test < 4ng/ml Group 1- recruited from one university hospital and one-university affiliated community teaching hospital (University of Iowa, Iowa city) Group 2-recruited from six university-affiliated primary care practices Exclusion criteria:- - history of prostate cancer - prostate intraepithelial neoplasia or intermediate results on prostate biopsy Approximately one month following the index test (biopsy or PSA) all potentially eligible patients received a letter of invitation which was sign by the urologist or primary care physician
LE	III
Number of patients and patient characteristics	Group 1 Biopsy recipients who showed no evidence of prostate cancer on microscopic examination following a suspicious screening test -130 eligible, 109 (84%) completed the survey (21 refused or unreachable) - Mean age , 62 years Group 2 Primary care patients with a PSA test < 4ng/ml - 139 eligible, 101 (73%) completed the survey (38 refused or unreachable - Mean age , 60 years
Intervention	Brief 15 minute survey using telephone or mailed questionnaire **Outcomes included**:- - SF-36 mental health, role emotional, social, vitality, and role physical scales - Sate Anxiety Index, short-form version of (SAI-6) - two items on sexual function - questions related to cancer related worry
Comparison	
Length of follow up (if applicable)	
Outcome measures/ Effect size	**Primary outcome** **a. Anxiety and prostate cancer related worry** - Group 1 patients were more worried than group 2 patients about getting prostate cancer • Mean worry = 3.9 versus 4.5, P = 0.001 (5-point scale, where 1 = extreme and 5 = none) - Group 1 also perceived their risk of prostate cancer to be significantly greater than control (P=0.001) **Secondary outcome** **a. SF-36 subscales and sexual function items** • No significant differences across state anxiety or SF-36 subscales • Sexual bother was greater for group 1 patients - 19% group 1 patients reporting that sexual function was a moderate-big problem compared to 10% of group 2 patients Conclusion Men with abnormal prostate cancer screening tests report increased cancer-related worry and more problems with sexual function, despite having a negative biopsy result. Effective counselling interventions are needed prior to prostate cancer screening and during follow-up.
General comments	

Evidence Table : Safety
Question : Is prostate cancer screening using PSA/DRE/TRUS guided biopsy safe?

Bibliographic citation	9. Bunting P, Brundage M, Geol V, Klotz L, Iscoe Neill, Morash C, Paszat L, Rosser W, Shapiro J. Prostate-specific Antigen (PSA) Screening in Asymptomatic Men. ICES Institute for Evaluative Sciences.2002
Study Type / Methodology	HTA (Systematic review). To update the 1997/98 HTA report. Sytematic search was conducted using the following databases:- • Medline • Embase • CANCERLIT Search was limited to more recent years (1995-2001). Clearly defined search strategy was used. Also additional web based literature from learned societies, health technology assessment agencies, advocacy groups and disease foundation. Include back-referencing and also grey literature. Studies were appraised by two readers.
LE	
Number of patients and patient characteristics	76 articles met inclusion criteria. case series, cohort, case control and RCT
Intervention	Screening for prostate cancer using Prostate Specific Antigen (PSA) 278 patients with localised prostate cancer either diagnosed by screening (59%) or clinical detection (41%)
Comparison	No screening
Length of follow up (if applicable)	
Outcome measures/ Effect size	**Secondary outcome** i. Prostatectomy (Potosky *et al.* 1998) Death = 0.1 to 0.2 % Erectile dysfunction = 79.6% Incontinence = 9.6% ii. Radiotherapy Death< 1.0 % Erectile dysfunction = 61.5% Incontinence = 3.5% j. iii. Prostatectomy (Stanford *et al.* 1998) Erectile dysfunction = 59.9% Incontinence = 8.4% k. iv. Prostatectomy (Catalona *et al.* 1998) Erectile dysfunction = 32-53% Incontinence = 8% v. Health related quality of life after treatment with radical prostatectomy or external-beam radiation in screened detected and clinically detected populations. (Maladinska 2001) • did not differ in terms of post-treatment urinary, bowel and sexual function despite smaller and more favourable tumours
General comments	INAHTA Checklist:- - No contact details - Policy questions not clear

Evidence Table : Safety
Question : Is prostate cancer screening using PSA/DRE/TRUS guided biopsy safe?

Bibliographic citation	10. Mambourg F, Van den Bruel A, Devriese A, Leys M, Vinck I, Lona M, Neyt M, Ramaekers D. Health Technology Assessment prostate-specific antigen (PSA) voor prostaatkanker screening. Bruxelles:Centre Federal d'Expertise des Soins de Sante (KCE); April 2006. KCE Reports vol. 31A.
Study Type / Methodology	HTA (Systematic review). The aim of the HTA was to describe the clinical effectiveness, cost-effectiveness, organizational issues and ethical patient issues on the use of PSA-tests in prostate cancer screening. Sytematic search was conducted using the following databases:- • Medline (Ovid) • Cochrane Library • Camphell library • CRD, ACP Journal club, DARE • Embase • INAHTA, GIN, ANAES, SSMG Search reports published between 2000 and 2005 for HTA and until January 2006 for original studies. For economic evaluation; published from 1990 to 2005. Abstract in English, Dutch or French. Clearly defined search strategy was used. Reports were critically appraised for quality.
LE	
Number of patients and patient characteristics	HTA reports, systematic reviews, guidelines, cohort studies, case control studies and RCT
Intervention	Screening for prostate cancer using Prostate Specific Antigen (PSA)
Comparison	No screening /usual care
Length of follow up (if applicable)	
Outcome measures/ Effect size	**Outcome on safety** **Complications of curative treatments:-** i. Erectile dysfunction after radical prostatectomy Risk = 76% to 80% (Hu 2004,Potosky 2004,2000) ii. Erectile dysfunction after external radiotherapy Risk = 39.6% to 63% (Hamilton 2001, Potosky 2000, 2004) iii. Bowel dysfunction after radical prostatectomy Risk = 9.2% to 23.9% (Potosky 2000) iv. Bowel dysfunction after external radiotherapy Risk = 8% to 43% (Hamilton 2001, Potosky 2000, 2004, Talcott 2003, Little 2003) v. Incidence of incontinence at 3 months after radical prostatectomy - 10% to 22.2% Quality of life after treatment with radical prostatectomy - 64% of patients <65 years reported very dissatisfied with the change in their sexual life (Malindaska, 2001)
General comments	INAHTA Checklist:- - Short summary in not technical term not in English language

Evidence Table : Economic evaluation
Question : What is the cost / cost effectiveness of prostate cancer screening ?

Bibliographic citation	1. Holmberg H, Carlsson P, Lofman O, Varenhorst E. Economic evaluation of screening for prostate cancer: a randomized population based programme during a 10-year period in Sweden. Health Policy. 1998; 45: 133-147
Study Type / Methodology	Economic evaluation Aim to evaluate the clinical and economic consequences of prostate cancer screening based on a limited screening trial in a Swedish community and a decision tree model. In 1987, 1,492 men (50-69 years) in central Norrkoping were selected randomly and were invited to repeat screening. They were examined every third year and followed-up up for 10 years (total of four screening rounds). The other 7,679 men in the population acted as control
LE	
Number of patients and patient characteristics	1,492 men (50-69 years) Control, 7,679 men in the population acted as control
Intervention	DRE and PSA
Comparison	No screening
Length of follow up (if applicable)	10 years
Outcome measures/ Effect size	a. **Primary outcome** Incremental cost with screening compared with non-screening (SEK, 1996):- - Cost per detected cancer= 158,000 - Cost per detected localised cancer = 167,000 - Cost per potentially curative treatment = 249,000
General comments	

Evidence Table : Economic evaluation
Question : What is the cost / cost effectiveness of prostate cancer screening ?

Bibliographic citation	2. Ekwueme DU, Stroud LA, Chen Y. Cost analysis of screening for, diagnosing, and staging prostate cancer based on a systematic review of published studies. Prev Chronic Dis. 2007;4(4). http://www.cdc.gov/pcd/06_0051.htm
Study Type / Methodology	Economic evaluation. The objective of the study was to examine the resource costs for prostate cancer screening, the diagnostic tests and staging and to examine how these costs differ in the United States from costs in other industrialized countries. Measurement of resource costs used include;- - direct costs included resources used in early detection of prostate cancer such as physicians's consultation time, other medical staff time, medical supplies, office or room space, equipment and patient recruitment. - indirect costs included patients's loss of income from time off from work, loss of leisure time, transportation cost, and travel time. Electronic databases MEDLINE, EMBASE, and CINAHL were searched, for published articles or reports on prostate cancer published from January 1980 through December 2003 Studies selected according to criteria and use Monte Carlo simulation methods to pool and analyse data.
LE	
Number of patients and patient characteristics	Identified 262 studies, of which 28 met all inclusion criteria. • 15 studies from United States 13 from other industrialized countries
Intervention	Screening for prostate cancer
Comparison	No screening /usual care
Length of follow up (if applicable)	
Outcome measures/ Effect size	**Primary outcome** **a. Pooled baseline resource cost (in 2003, U.S. Dollar):-** **vi. Studies conducted in United States** - screening with PSA = $ 37.23 (13.11-77.18) - screening with DRE = $ 31.77 (4.20-61.48) - Diagnostic (urology consultation) = $76.91 (39.60-156.04) - Diagnostic (TRUS) = $237.18 (71.38-488.84) - Diagnostic (Biopsy) = $393.08 (105.04-1,923.72) - Staging (pathologic or histologic) = $ 94.14 (45.77- 145.46) - Clinical staging = $ 736.52 (197.86-1097.53) **ii. Studies conducted in other industrialized countries** - screening with PSA = $ 30.92 (15.56 -69.00) - screening with DRE = $ 33.54 (16.13 -66.66) - Diagnostic (urology consult) = $97.04 (55.61-147.84) - Diagnostic (TRUS) = $103.77(38.91-185.04) - Diagnostic (Biopsy) = $164.96 (31.64-298.51) - Staging (pathologic or histologic) = $ 131.23 (59.83-241.13) - Clinical staging = $ 306.40 (146.74-603.67)
General comments	

Evidence Table : Diagnostic accuracy of screening tests.
Question : What is the diagnostic accuracy of PSA/DRE/TRUS in detecting prostate cancer ?

Bibliographic citation	1. Thompson IM, Ankerst DP, Chi C, Lucia MS, Goodman PJ, Crowley JJ *et al.* Operating characteristics of Prostate-Specific Antigen in Men with an initial PSA level of 3.0 ng/ml or lower. JAMA. 2005; 294(1): 66-70
Study Type / Methodology	Randomised controlled trial The aim is to estimate the Receiver Operating Characteristic (ROC) curve for PSA Calculation of PSA ROC curves (AUC) in the placebo group of the Prostate Cancer Prevention Trial (a RCT from 1993 to 2003 in 221 U.S. centres). 18,882 men aged 55 years or older with a normal DRE and PSA level less than or equal to 3 ng/ml were randomised to receive either finasteride or placebo for seven years.
LE	I
Number of patients and patient characteristics	8,575 men in placebo group
Intervention	Finasteride DRE and PSA were performed annually A prostate biopsy was recommended if PSA level exceeded 4.0 ng/ml or the DRE results were suspicious of cancer At the end of seven years all participants not previously diagnosed with prostate cancer were requested to undergo and end-of-study biopsy within 90 days of the randomisation anniversary
Comparison	Placebo DRE and PSA were performed annually A prostate biopsy was recommended if PSA level exceeded 4.0 ng/ml or the DRE results were suspicious of cancer At the end of seven years all participants not previously diagnosed with prostate cancer were requested to undergo and end-of-study biopsy within 90 days of the randomisation anniversary
Length of follow up (if applicable)	7 years
Outcome measures/ Effect size	**Primary outcome** **Detection of any prostate cancer with PSA cut-off values of:-** - 1.1 ng/ml (sen = 83.5%, spec = 38,9%) - 2.1 ng/ml (sen = 52.6%, spec = 2.5%) - 3.1 ng/ml (sen = 32.2%, spec = 86.7%) - 4.1ng/ml (sen = 20.5%, spec = 93.8%) The sensitivity and specificity of PSA for aggressive prostate cancer; Gleason score 8 or higher was greater:- - (50.9% and 89.1%) for PSA value ≥ 4 ng/ml - (68.4% and 81.0%) for PSA value ≥ 3ng/ml To discriminate any prostate cancer versus no cancer ROC curve (AUC) :- - 0.678 (95% CI, 0.666-0.689) To discriminate Gleason grade 7 or greater cancer versus no cancer ROC curve (AUC) :- - 0.782 (95% CI, 0.748-0.816) To discriminate Gleason grade 8 or greater cancer versus no cancer ROC curve (AUC) :- - 0.827 (95% CI, 0.761-0.893)
General comments	

Evidence Table : Diagnostic accuracy of screening tests.
Question : What is the diagnostic accuracy of PSA/DRE/TRUS in detecting prostate cancer ?

Bibliographic citation	2. Schroder FH, Hugosson J, Roobol MJ, Tammmela TLJ, Ciatto S, Nelen V *et al.* Screening and prostate cancer mortality in a randomized European study. N Engl J Med.2009;360:1320-1328
Study Type / Methodology	Randomised Controlled Trial (multicentre). Initiated in early 1990s. Aim of the study was to evaluate the effect of screening with prostate-specific antigen (PSA) testing on the 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. The seven countries are Netherlands, Belgium, Sweden, Finland, Italy, Spain and Switzerland. 182,160 subjects 50-74 years old underwent randomization whereby 162,387 subjects were in the core age group (55 to 69 years). The men were randomly assigned to the screening and control group. Recruitment and randomisation procedures differ among countries and were developed in accordance with national regulations. In all centres except Finland, subjects were assigned in a 1:1 ratio to the screening or the control group. In Finland 1:1.5. Each centre reported data on recruitment, screening and mortality twice a year to a central data centre. Treatment policies performed according to local policies and guidelines.
LE	I
Number of patients and patient characteristics	162,387 men were in the core age group (55-69 year old) • 144 died between identification and randomisation Screening group (72,890 men) Control group (89,353 men) Age at randomisation:- Screening group:- Mean age = 60.9 years Median age = 60.3 years Control group:- Mean age = 60.7 years Median age = 59.9 years
Intervention	PSA screening once every 4 years except Belgium 4-7 years and Sweden every 2 years. Most centres:- PSA cut off value of 3.0 ng/ml as an indication for biopsy. Finland:- PSA value of 4 ng/ml as positif for biopsy, PSA value 3 to 3.9 ng/ml DRE or f/tPSA Italy:- PSA value of 4 ng/ml as positif for biopsy, PSA 2.5 to 3.9 DRE and TRUS Netherland and Belgium until 1997, combination of DRE, TRUS and PSA value of 4 ng/ml. After that PSA testing only.
Comparison	No screening
Length of follow up (if applicable)	Begin at randomisation and ended at death, emigration, or uniform censoring date (December 31, 2006) Median follow-up 8.8 years in the screening group and 9 years in the control group.
Outcome measures/ Effect size	**Secondary outcome** **a. Positive predictive value (PPV) of a biopsy (the number of cancers detected on screening divided by the number of biopsies)** - 24.1% (range, 18.6% to 29.6%) - 75.9% had false positive results
General comments	Quality assessment (CASP) 1. Yes 2. Yes 3. Yes 4. Yes 5. Yes 6. Yes 7. Yes 8. Yes, RR, CI 9. Narrow CI, precise Verification bias

Evidence Table : Diagnostic accuracy of screening tests.
Question : What is the diagnostic accuracy of PSA/DRE/TRUS in detecting prostate cancer ?

Bibliographic citation	3. Maattanen L, Hakama M, Tammela TLJ, Ruutu M, Ala-Opas M, Juusela H *et al*. Specificity of serum prostate-specific antigen determination in the Finnish prostate cancer screening trial. British Journal of Cancer.2007;96(1):56-60
Study Type / Methodology	Randomised Controlled Trial. The aim of the study was to estimate the specificity of the PSA test in the Finish prostate cancer screening trial. Part of the European Randomized Study of Screening for Prostate Cancer (Finnish) section. Study population of 80,458 men at ages 55-67 years were indentified form the Population Register Centre Finland. Started in 1996. From 1996-1999, 8000 men were annually allocated to the screening arm using computer algorithm based on random numbers and were invited for the first screening round. The second screening round was carried out carried out after 4 year interval between 2000-2003. Specificity was calculated as the proportion of men with screen negative findings (screen negatives, SN) relative to those with screen negative and False Positive (FP) results (SN/SN+FP)
LE	I
Number of patients and patient characteristics	20,794 men were screened in the first screening round 18,612 men were screened in the second screening round.
Intervention	Screening for prostate cancer using Prostate Specific Antigen (PSA). Men with PSA ≥ 4 ng/ml were referred for DRE, TRUS and prostate biosy Men with PSA 3.0 to 3.9 ng/ml were referred for supplementary test; DRE or proportion of free PSA (f/TPSA) with cut-off 0.16 . Those with positive DRE or F/TPSA were referred for prostate biopsy
Comparison	No screening
Length of follow up (if applicable)	
Outcome measures/ Effect size	**Primary outcome** **Diagnostic accuracy of PSA** a. Specificity of first screening round:- - 0.933; 95%CI: 0.929 to 0.936 b. Specificity of second screening round**:-** - 0.912; 95%CI: 0.908 to 0.916 Specificity decreased with age. **Secondary outcome** **a. Detection rate** i. First screening round - 2.4% ii. Second screening round - 3.1%
General comments	Study is an RCT, part of ERSPC study, Finnish section. Specificity calculated using this formula; SN/SN+FP. Differential verification bias

Evidence Table : Diagnostic accuracy of screening tests.
Question : What is the diagnostic accuracy of PSA/DRE/TRUS in detecting prostate cancer ?

Bibliographic citation	4. Grubb RL III, Pinsky PF, Greenle RT, Izmirlian G, Miller AB, Hickey TP *et al.* Prostate cancer screening in the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial: update on findings from the initial four rounds of screening in a randomized trial. BJU Int 2008; 102:1524-1530
Study Type / Methodology	Randomised Controlled Trial. The aim was to describe the results of the first four rounds (T0-T3) of prostate cancer screening in the PLCO cancer screening trial. From 1993 through 2001, 76,693 men at 10 U.S. study centres were randomly assigned to receive either annual screening or usual care. Men in the screening group received PSA and DRE tests. DRE was performed by physicians, qualified nurses or physicians assistants. Men with positive PSA and DRE were notified and advised to seek further diagnostic evaluation through their primary care providers who were also notified of the test results. PLCO trial staff obtained medical records related to diagnostic follow-up of positive screens. Certified tumour registrars ascertained the stage, Gleason grade, and type of all diagnosed cases of prostate cancer.
LE	I
Number of patients and patient characteristics	Men, aged between 55 and 74 years. Screening group (38,349) Study population:- • Non-Hispanic white (86%) • 60% < 65 years old at enrolment • 25% had a history of an enlarged or inflamed prostate or problems with prostate • 7.1% had a family history of prostate cancer • 34.6% had 1 PSA test in the 3 years before the study entry and 9.4% had more than one Exclusion criteria - previous prostate cancer or surgical removal of the prostate - use of finasteride during previous 6 months
Intervention	Annual PSA and for 5 years annual digital rectal examination (DRE) for 3 years PSA level of > 4 ng/ml was considered positive.
Comparison	No screening / usual care
Length of follow up (if applicable)	4 years
Outcome measures/ Effect size	**Secondary outcome** **a. Positive Predictive value (PPV)** - **PSA > 4 ng/ml** (decreased from 17.9% at T0 to 10.4% to 12.3% at T1 to T3) - **DRE positive but PSA < 4ng/ml** (constant over time, 2.9% to 3.6%) - **PSA positive and DRE positive** (37.7% at T0 and 18 to 23% at T1 to T3)
General comments	Quality assessment (CASP) 1. Yes 2. Yes 3. Yes 4. Yes 5. Yes 6. Yes 7. Yes 8. Percentage, CI for PPV 9. Precise (CI narrow) Verification bias

Evidence Table : Diagnostic accuracy of screening tests.
Question : What is the diagnostic accuracy of PSA/DRE/TRUS in detecting prostate cancer ?

Bibliographic citation	5. Kilpelainen TP, Tammela TLJ, Maattanen L, Kujala P, Stenman UH, Ala-Opas M *et al.* False-positive screening results in the Finnish prostate cancer screening trial. British Journal of Cancer. 2010;102 (3);469-474
Study Type / Methodology	Randomised Controlled Trial The aim of the study was to assess the proportion of False Positive (FP) results in a population based RCT in Finland during the three screening rounds. Evaluated whether men with a FP result are at a greater risk of decreased screening compliance, subsequent prostate cancer (PC), or repeated FP results. Also investigated how many biopsies men with FP results undergo and whether the use of medication for BPH affects FP rates. Finnish Prostate Cancer Screening Study is the largest component of the ERSPC. Finish trial comprises 80,255 men born during 1929-1944 (aged 55, 59, 63 or 67 years at entry). Subjects identified from the Finnish Population Registry. 8000 men was allocated to the screening arm annually during 1996-1999 and the remaining men formed the control group. A FP result was defined as a positive screening result without cancer in biopsy within 1 year from the screening test.
LE	I
Number of patients and patient characteristics	30,195 in the screening arm
Intervention	Screening using PSA, DRE and TRUS and biopsy, free to total PSA ratio (F/T PSA) PSA cutoff for biopsy indication ≥ 4 ng/ml. In addition men with PSA 3.0 to 3.9 ng/ml and a positive auxiliary test were referred. Screening conducted every 4 years(completed 3 screening rounds)
Comparison	No screening
Length of follow up (if applicable)	Mean follow-up time 9.2 years
Outcome measures/ Effect size	**Primary outcome** **a. Risk of False Positive (FP) results:-** • 1,611 cancers were detected - 543 in first round [Detection rate (DR) = 2.6%] - 613 in the second round (DR = 3.3%) - 455 in the third round (DR = 3.6%) • Proportion of FP screening results varied from 3.3 to 12.1% per round • Among screen positive result:- - First round, = FP 67.3%, 27.5% diagnosed PC, 5.2% not biopsied - Second round, = FP 64.6%, 26.6% diagnosed PC - Third round, = FP 60.7%, 27.7% diagnosed PC • Of 23,771 men who participate at least once during the three rounds, (12.5%; 95% CI: 12.1 to 12.9) had at least one FP • Proportion of men with at least one FP result increased consistently with age from 9.0% in the youngest age cohort to 15.7% in the oldest age cohort (with only two screening rounds) • The risk of next round PC following a FP result was 12.3% to 19.7% versus 1.3% to 3.7% following a screen negative result, risk ratio 3.6 to 9.9 • More than half of the men with one FP result had another FP at a subsequent screening round • Men with a FP result were 1.5 to 2.0 times more likely not to participate in subsequent rounds compared with men with normal screening result (21.6% to 29.6% versus 14.0% to 16.7%) Conclusion FP result is a common adverse effect of prostate cancer screening and affects every eight men screened repeatedly, even when using a relatively high cutoff level. FP men constitute a special group that receive unnecessary interventions but may harbour missed cancers. New strategies are needed for risk stratification in PC screening to minimise the proportion of FP men.
General comments	Study is an RCT, part of ERSPC study, Finnish section. Verification bias.

Evidence Table : Diagnostic accuracy of screening tests.
Question : What is the diagnostic accuracy of PSA/DRE/TRUS in detecting prostate cancer ?

Bibliographic citation	6. Thompson IM, Ankerst DP, Chi C, Goodman PJ, Tangen CM, Lucia MS *et al.* Assessing prostate cancer risk: Results from the prostate cancer prevention trial. J Natl Cancer Inst. 2006; 98:529-534
Study Type / Methodology	RCT (post hoc analysis) Used prostate biopsy data from men who participated in the Prostate Cancer Prevention Trial (PCPT) to develop a predictive model of prostate cancer. Logistic regression was used to model the risk of prostate cancer and high-grade disease associated with age at biopsy, race, family history of prostate cancer, PSA level, PSA velocity, DRE result, and previous prostate biopsy.
LE	I
Number of patients and patient characteristics	5,519 men from the placebo group of the PCPT who underwent prostate biopsy, had at least one PSA measurement and a DRE performed during the year before the biopsy, and has at least two PSA measurements performed during the three years before the biopsy
Intervention	Predictive model based on PCPT data
Comparison	
Length of follow up (if applicable)	
Outcome measures/ Effect size	Primary outcome **Variables that predicted prostate cancer included**:- - higher PSA level - positive family history of prostate cancer, - abnormal DRE results - A previous negative prostate biopsy was associated with reduce risk. - Neither age at biopsy nor PSA velocity contributed independent prognostic information. Predictive for high-grade disease (Gleason score ≥ 7) - Higher PSA level - Abnormal DRE result - Older age at biopsy - African American race - Previous negative prostate biopsy reduce the risk.
General comments	

Evidence Table : Diagnostic accuracy of screening tests.
Question : What is the diagnostic accuracy of PSA/DRE/TRUS in detecting prostate cancer ?

Bibliographic citation	7. Hoogendam A, Buntinx F, de Vet CW. The diagnostic value of digital rectal examination in primary care screening for prostate cancer: a meta-analysis. Family Practice. 1999; 16: 621-626
Study Type / Methodology	Systematic review and meta-analysis Only studies relating to unselected populations and using either biopsy or surgery as the reference standard were included. MEDLINE search from 1983 to 1995 Methodological aspects of all the studies were assessed using a list of criteria proposed by the Cochrane Methods Working group on meta-analysis of diagnostic and screening tests.
LE	I
Number of patients and patient characteristics	22,000 patients (from 14 studies)
Intervention	Predictive model based on PCPT data
Comparison	
Length of follow up (if applicable)	
Outcome measures/ Effect size	**Primary outcome** 14 studies were eligible for selection of which five studies complied with the predetermined list of 'good quality requirements'. Pooled results of the meta-analysis of the five "good-quality studies':- - Sensitivity of 0.64 (0.47 to 0.80) - Specificity of 0.97 (0.95 to 0.99) - PPV of 0.47 (0.29 to 0.64) - NPV of 0.99 (0.98 to 0.99)
General comments	

Evidence Table : Diagnostic accuracy of screening tests.
Question : What is the diagnostic accuracy of PSA/DRE/TRUS in detecting prostate cancer ?

Bibliographic citation	8. Schroder FH, van der Maas P, Beemsterboer P, Kruger AB, Hoedemaker R, Rietbergen *J et al.* Evaluation of the Digital Rectal Examination as a screening test for prostate cancer. J Natl Cancer Inst. 1998; 90(23):1817-1823
Study Type / Methodology	Randomised Controlled Trial. The aim of the study is to assess the usefulness of DRE as a stand-alone screening test and in conjunction with PSA levels. Part of the European Randomized Study of Screening for Prostate Cancer, Rotterdam section. Data was collected for 33 month-period starting on July 1, 1994 (1994-1997). Participants were recruited from the population registry of Rotterdam and from surrounding communities. Men, ages 54 to 70 years were randomly assigned to the screening or no screening. DRE, TRUS were carried out by trained personnel. Training periods lasted for 4-6 weeks and their normal and abnormal findings were randomly counterchecked by experienced staff. **Statistical evaluation**. Parameter APPA, is an estimate of underlying prevalence prostate cancer as a function of PSA level. The APPA is based on logistic regression analysis that considers DRE, TRUS, PSA and prostatic volume and used to calculate sensitivity and specificity.
LE	I
Number of patients and patient characteristics	11500 were randomly assigned to the screening arm of whom 10,523 were (92%) were screened.
Intervention	Screening for prostate cancer using Prostate Specific Antigen (PSA), DRE and TRUS Biopsy in all men who had at least one of the following results:- - abnormal DRE - abnormal TRUS - PSA ≥ 4ng/ml.
Comparison	No screening
Length of follow up (if applicable)	33 months
Outcome measures/ Effect size	**Primary outcome** **a. Detection rate** i. **PSA, DRE and TRUS** - 4.5% ii. **DRE alone** - 2.5% b. **Diagnostic accuracy of DRE** **Positive Predictive Value (PPV):-** - 4% to 11% (PSA levels 0-2.9 ng/ml) - 33% to 83% (PSA levels of 3.0 to 9.9 ng/ml or more) **Overall sensitivity:-** - 37% Sensitivity of DRE increases with increasing PSA levels **Overall specificity:-** - 91% Specificity remains greater than 83% over the total range of PSA values **Secondary outcome** **a. Tumour characteristics** • Most tumours detected by DRE in men with PSA levels < 4 ng/ml were small (mean volumes = 0.24 to 0.83ml) Authors conclusion For PSA values of 0 to 3.9 ng/ml. the PPV and sensitivity of DRE, tumour volume and tumor grade were strongly dependant on PSA level. DRE has poor performance in low PSA ranges
General comments	Study is an RCT, part of ERSPC study, Rotterdam section. Used the parameter APPA to calculate the sensitivity and specificity of DRE. Verifiaction bias

Evidence Table : Diagnostic accuracy of screening tests.
Question : What is the diagnostic accuracy of PSA/DRE/TRUS in detecting prostate cancer ?

Bibliographic citation	9. Gosselaar C, Roobol MJ, Roemeling S, Schroder FH. The role of the digital rectal examination in subsequent screening visits in the European Randomized Study of Screening for Prostate Cancer (ERSPC), Rotterdam. European Urology. 2008;54:581-588
Study Type / Methodology	Randomised Controlled Trial The aim of the study was to determine the additional value of a suspicious DRE for the detection of prostate cancer (PC) in men with an elevated PSA level in subsequent screenings and the tumour characteristics of PCs detected in men with suspicious DRE. In the screening arm of the ERSPC, Rotterdam, men aged 55 to 75 years were invited for every 4-year PSA determination, and a PSA level ≥ 3.0 ng/ml prompted a transrectal ultrasound (TRUS)-guided lateralized sextant biopsy (May 1997 to October 2006). All men underwent DRE prior to biopsy. When biopsy results are benign, participants were re-invited for 4 year later. 5,040 biopsy sessions throughout the three screens were evaluated for the presence of PC in relation to the DRE result. The overall positive predictive value (PPV) of this screening procedure was a combination of PPV_{nDRE} and PPV_{sDRE}.
LE	I
Number of patients and patient characteristics	Men aged 55 to 75 years old 5,040 biopsy sessions
Intervention	Screening using PSA, DRE and TRUS and biopsy PSA cutoff for biopsy indication ≥ 3 ng/ml. Screening conducted every 4 years (completed 3 screening rounds)
Comparison	No screening
Length of follow up (if applicable)	9 years
Outcome measures/ Effect size	**Primary outcome** **b. Positive Predictive Value (PPV) of abnormal (suspicious) and normal DRE in conjunction with elevated PSA level to detect prostate cancer:-** • PPV for screening visit 1 - PPV for suspicious DRE (PPV_{sDRE}) = 48.6% - PPV for normal DRE (PPV_{nDRE}) = 22.4% • PPV for screening visit 2 - PPV for suspicious DRE (PPV_{sDRE}) = 29.9% - PPV for normal DRE (PPV_{nDRE}) = 17.1% • PPV for screening visit 3 - PPV for suspicious DRE (PPV_{sDRE}) = 21.2% - PPV for normal DRE (PPV_{nDRE}) = 18.2% **c. Biopsy Gleason score of detected prostate cancers in men with abnormal (suspicious) versus normal DRE (Biopsy Gleason score > 7);-** • Screening visit 1 - 71% versus 29%, P<0.001 • Screening visit 2 - 68.8% versus 31.2%, P<0.001 • Screening visit 3 - 85.7% versus 14.3%, P<0.002 Conclusion At initial and subsequent screenings, the chance of having cancer at biopsy was higher in men with a suspicious (abnormal) DRE than in men with a normal DRE, and the combination of a PSA level ≥3.0 ng/ml with a suspicious DRE resulted in detecting significantly more PCs with Gleason score >7. DRE may be useful in more selective screening procedures to decrease unnecessary biopsies and overdiagnosis.
General comments	Study is an RCT, part of ERSPC study, Rotterdam section. Verification bias.

Evidence Table : Diagnostic accuracy of screening tests.
Question : What is the diagnostic accuracy of PSA/DRE/TRUS in detecting prostate cancer ?

Bibliographic citation	10. Varenhorst E, Berglund K, Lofman O, Pedersen K. Inter-observer variation in assessment of the prostate by digital rectal examination. British Journal of Urology.1993;72 :173-176
Study Type / Methodology	Cross sectional study The aim of the study was to evaluate the variability of the results from duplicate DRE performed by a urologist or a general practitioner. A group of 1,494 men in Norrkoping were randomly selected from a population of 9,026 men aged 50 to 69 years and invited to participate in a screening programme for carcinoma of the prostate by dual DRE. The examinations were performed independently by a urologist and a general practitioner at a primary health care centre according to a standardised method. Performance of the first of the two examinations alternate between the two physicians. Physicians performed independent assessment of the prostate with regards to 9 variables as part of the screening programme for carcinoma of the prostate. Agreement between observations made by the general practitioner and urologist was analysed using kappa (K) statistics. Kappa of:- - >0.75 (excellent agreement) - 0.40 to 0.75 (fairly good agreement) - <0.40 poor agreement
LE	III
Number of patients and patient characteristics	933 men aged between 50 to 69 years.
Intervention	Screening using DRE
Comparison	No screening
Length of follow up (if applicable)	
Outcome measures/ Effect size	**Primary outcome** **a. Inter-observer variation between Urologist and General Practitioner concerning variables in DRE of the prostate:-** - complete agreement for all observations was reached in 46.5%; 95% CI: 43.3% to 49.7%) - Kappa (K) = 0.485 and 0.682 was obtained for six variables (fair agreement):- • Size • Tenderness • Midline furrow • Symmetry • Induration • Nodularity - K= 0.001 and 0.022 was obtained for three variables (poor greement):- • Fixation • Lateral sulci • Seminal vesicles **Secondary outcome** **a. Detection rate** i. - Malignancy suspected in 37/933 men (4.0%) - Malignancy confirmed in 12/933 men (1.3%)
General comments	

Evidence Table : Diagnostic accuracy of screening tests.
Question : What is the diagnostic accuracy of PSA/DRE/TRUS in detecting prostate cancer ?

Bibliographic citation	11. Smith DS, Catalona WJ. Inter-examiner variability of digital rectal examination in detecting prostate cancer. UROLOGY.1995; 45(1): 70-74
Study Type / Methodology	Cross sectional The aim of the study was to assess the inter-examiner variability of DRE for faculty and resident urologists working within the context of a prostate screening program at a university medical centre. Study was conducted between November 1991 and January 1992 in Washington University school of Medicine, St. Louis, Missouri. All volunteers were recruited through a press release asking healthy men to participate in a study of PSA measurement as a screening test for prostate cancer. Blood samples were obtained before DRE or at least 1 week after. All 116 had a second DRE performed by a different examiner on the same visit as the first. Examiners were blinded to results of the other DRE and to the subject's PSA concentration. All DRE results were coded as either benign or suspicious for cancer. 8 different examiners, representing a range of experience [4 faculty or post-residency fellows (weighted mean of 23 years experience) and 4 were residents (weighted mean of 3 years experience)] Kappa (K) statistics was used to evaluate the inter-examiner variability of DRE. Kappa of:- - < 0.20 (poor or slight agreement) - 0.21 to 0.40 (fairly agreement) - 0.41 to 0.60 (moderate agreement) - 0.61 to 0.80 (substantial agreement) - > 0.80 (almost perfect agreement)
LE	III
Number of patients and patient characteristics	116 consecutive male volunteers. Mean age, 61.6 years; SD = ± 6.9 years, range: 50 to 80 years
Intervention	Screening using DRE and PSA
Comparison	No screening
Length of follow up (if applicable)	
Outcome measures/ Effect size	**Primary outcome** **a. Inter-observer variation among urologists whether or not the DRE was suspicious of cancer:-** - complete agreement on whether or not DRE was suspicious of cancer in 84% of subjects - Kappa = 0.22, P =0.09 (fair agreement) **b. Inter-observer agreement by level of examiner experience:-** • Both faculty urologist K= 0.63, P = 0.004 (substantial agreement) • Faculty urologist and resident urologist K= 0.13, P = 0.13 (poor agreement) • Both resident urologist K= 0.25, P = 0.09 (fair agreement) Conclusion The reproducibility of DRE for detecting prostate cancer is only fair among urologist. Further studies are indicated to evaluate inter-examiner variability between primary care physicians and urologist.
General comments	

Evidence Table : Ethical and legal consideration.
Question : What is the ethical and legal consideration in PSA screening ?

Bibliographic citation	1. Krist AH, Woolf SH, Johnson RE. How physicians approach prostate cancer screening before and losing a lawsuit. Ann Fam Med. 2007; 2007: 5(2): 120-125
Study Type / Methodology	RCT To evaluate whether physicians changed their prostate screening behaviour after a lawsuit. The study was conducted as part of a RCT on Web-based and paper-based decisions aid for prostate cancer conducted between January 2002 and November 2004. Patients and physicians completed exit-questionnaires about prostate cancer screening discussions after health maintenance examinations. The questionnaires were designed to measure the quality of the decision-making process. Compared the responses before, during and after physicians became aware of the lawsuit..
LE	I
Number of patients and patient characteristics	497 patients
Intervention	Exit questionnaires
Comparison	
Length of follow up (if applicable)	
Outcome measures/ Effect size	**Primary outcome** 32 of 497 (87.0%) of patients completed questionnaires. Comparing patients response over the three time periods:- - no changes in the average locus of decision- making control - time spent discussing screening, - number of screening topics discussed - knowledge scores, or decisional conflict. - Frequency with which physicians reported performing PSA testing increased (84% before versus 90% after; P = 0.03), - physicians were more likely to report that they made the decision alone, rather than the patients had made the screening decisions (3.3% before versus 11.1% after; P = 0.003). Conclusion Authors concluded that the physicians in closest proximity to this well-known legal case continued to engage patients in shared decision making and to let patients decide whether to be screened.
General comments	

Appendix 6

LIST OF EXCLUDED STUDIES

1. Brindle LA, Oliver SE, Dedman D *et al*. Measuring the psychological impact of population-based prostate-specific antigen testing for prostate cancer in the UK. *BJU International*. 2006;98:777-782
2. Taylor KL, Shelby R, Kerner J *et al*. Impact of undergoing prostate carcinoma screening on prostate carcinoma-related knowledge and distress. *CANCER*. 2002;85(2):1037-1043
3. Chiang IN, Chang SJ, Pu YS et al. Major complications and associated risk factors of transrectal ultrasound guided needle biopsy: A retrospective study of 1875 cases in Taiwan. *J Formos Med Assoc*. 2007;106(11):929-934
4. Grubb III RL, Black A, Izmirlian G et al. Serum prostate-specific antigen hemodilution among obese men undergoing screening in the Prostate, Lung, Colorectal and Ovarian Cancer Screening trial. *Cancer Epideniol Biomakers P*rev. 2009; 18(3):748-751
5. Mistry K, Cable G. Meta-analysis of prostate-specific antigen and digital rectal examination as screening tests for prostate carcinoma. J *Am Board Fam Pract*. 2003;16:95-101
6. Ross KS, Carter B, Pearson JD *et al*. Comparative efficiency of prostate-specific antigen screening strategies for prostate detection. *JAMA*. 2000; 284:1399-1405
7. Postma Rense, Schroder FH, van Leenders GJLH *et al*. Cancer detection and cancer characteristics in the European Randomized Study of screening for prostate cancer (ERSPC)-Section Rotterdam. A comparison of two rounds of screening. *European Urology*. 2007;52:89-97
8. Makinen T, Tammela TLJ, Stenman UH *et al*. Second Round results of the Finnish population-based prostate cancer screening trial. *Clinical Cancer Research*. 2004;10:2231-2236
9. Maattanen L, Auvinen A, Stenman UH *et al*. European randomized study of prostate cancer screening: first –year results of the Finnish trial. *British Journal of Cancer*. 1999; 79(7/8):1210-1214
10. Kwiatkowski M, Huber A, Moschopulos M *et al*. Screening for prostate cancer: Results of a prospective trial in Canton Aargau, Switzerland. *Swiss Med Wkly*. 2004;134;580-585
11. Makinen T, Tammela TLJ, Hakama M *et al*.Tumor characteristics in a population-based prostate cancer screening trial with prostate-specific antigen. *Clinical Cancer Research*. 2003;9:2435-2439
12. Sandblom G, Varenhorst E, Lofman O *et al*. Clinical consequences of screening for prostate cancer: 15 years follow-up of a Randomised Controlled Trial in Sweden. *European Urology*. 2004;46:717-724
13. Ford M, Havstad SL, Demers R *et al*. Effects of false-positive prostate cancer screening results on subsequent prostate cancer screening behaviour. *Cancer Epidemiol Biomarkers Prev*. 2005;14(1):190-194
14. McLernon DJ, Donnan PT, Gray M *et al*. Receiver operating characteristic of prostate specific antigen test in an unselected population. *Journal of Medical Screening*. 2006;13(2):102-107