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ICES Institute for Clinical Evaluative Sciences

Prostate-specific Antigen (PSA) Screening in Asymptomatic Men

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Prostate-Specific Antigen (PSA) Screening in Asymptomatic Men

Executive Summary

Purpose of the Report

The early detection of cancer has long been a targeted message to the general public. Consequently, it is not surprising that men are interested in prostate cancer screening strategies as part of the imperative for cancer-free health. However, prostate cancer screening in asymptomatic men remains an area of significant controversy, with the potential benefits and harms continuing to be debated among health professionals and the public after more than a decade of use. The purpose of this report is to review the current evidence about the effectiveness of screening for prostate cancer in asymptomatic men, using a blood test called prostate-specific antigen (PSA).

Prostate Cancer

Prostate cancer has surpassed lung cancer as the most frequently diagnosed cancer and is the second most frequently reported cause of cancer death in Canadian men. The risk of prostate cancer and death from this cancer increases with age. The disease is rare in Canadian males under 45 years of age, but the incidence increases faster with age than that of any other major cancer. Currently in Canada, one in eight (1/8) men will have the disease during their lifetime and approximately one in 30 (1/30) men will die of the disease.

Most, but not all, prostate cancers are slow-growing tumours. The literature suggests that screening detects both aggressive, malignant tumours as well as indolent, non-aggressive tumours. Retrospective analyses of pathological features of tumours found in screened men with prostate cancer who underwent radical prostatectomy are helping to clarify the issue of "indolent" tumours, defined as small, well-differentiated, organ-confined tumours undetected during the life of the patient, and usually identifiable only on postmortem. There is little high quality evidence available to help determine what proportion of tumours detected by PSA screening are not indolent, and how many of those tumours are cured with early therapy. Some studies suggest that the pathological features of most prostate cancers detected using PSA screening do not resemble autopsy-detected cancers and are more likely to be clinically important. However, these studies do not definitively answer the question about whether patients are helped by the detection of these tumours.

The treatment of prostate cancers with radiation or radical prostatectomy can result in significant morbidity, including urinary incontinence (about 3-8% of patients) and erectile dysfunction (about 30-60% of patients). The frequency of complications appears

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to be the same, whether the cancer was detected by screening or presented clinically. The complication rates appear to be dropping when compared to data reported in the early-to-mid 1990s. It has been reported that better results are achieved in younger men with organ-confined cancer and with increasing surgeon experience using nerve-sparing and other surgical techniques.

Definition and goals of PSA Screening

Because there are currently no effective measures for disease prevention, attention has shifted to screening as an approach to controlling prostate cancer. *Screening* is an organized activity in which a test is applied to a whole population in order to identify a subset of the population with an increased risk of having the disease of interest. Screening activities are usually the result of an established health policy that should be based on high quality evidence. Cancer screening programs have as their principal goal the reduction of mortality. If mortality is not reduced, patients live with the disease for a longer time without the benefit of survival gains. To be truly successful, a screening test must be accurate, and there must be evidence that the benefits of early detection outweigh the potential harms. A screening test is considered accurate when it can detect a large number of people in a population with early stage disease without generating a large number of false-positive results (these patients without cancer undergo the anxieties and risks of investigation without any chance of benefit). The test must have good *sensitivity* (the proportion of persons with a disease who test positive) and *specificity* (the proportion of persons without a disease who test negative). A test that has poor sensitivity leads to a high proportion of false-negative results, while a test with poor specificity leads to a high proportion of false-positive results.

For PSA, the sensitivity ranges between 72-90% and the specificity ranges between 59-98% (depending on age group and prevalence). This means that out of 100 asymptomatic men screened with PSA, ten will have a positive test. Of these, three will have prostate cancer, but seven will undergo investigations (likely including biopsy) and will be found not to have prostate cancer. Of the 90 men with a normal PSA, one or two will be found to have prostate cancer during the next several years (a false-negative test).

Because screening may detect relatively small, slowly growing tumours, and because treatment does not always cure patients in whom cancer is detected, the best method for clearly demonstrating the effectiveness of a screening program is a randomized trial comparing screening with no screening.

Clinical studies of PSA screening

Unfortunately, no randomized trials have been reported comparing PSA screening with the absence of PSA screening in asymptomatic men. Two large, high quality randomized trials evaluating the effect of PSA screening upon mortality are currently underway, one in Europe (The European Study of Screening for Prostate Cancer) and one in the United

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States (The Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial). However, they are only due for completion in 2008 and 2014 respectively. One study from Quebec has been reported as a randomized controlled trial, but is clearly not, making its interpretation difficult.

In the absence of evidence from randomized trials, researchers have studied trends in mortality from prostate cancer. These trends are encouraging, with declines in the proportion of clinically or pathologically advanced prostate cancer in regions where PSA screening has been introduced. There have been concomitant decreases in prostate cancer mortality rates in the United States, Canada and Tyrol, Austria among others. For example, in Canada, age-standardized mortality ratios for prostate cancer increased by 1.5% annually between 1976 and 1991, while between 1991 and 1995, the rates decreased slightly. Although these decreases may be due to PSA screening, they occurred sooner after the introduction of screening than expected, and may be affected by other factors such as improved treatment of prostate cancer.

Recommendations of Professional Organizations

Numerous professional organizations and health technology agencies have made recommendations about PSA screening. Although their recommendations vary, a considerable majority recommend ***against*** population-based PSA screening. The majority suggest that PSA screening should be offered on an individual basis to men who wish to have the test, provided they are fully informed of the potential benefits and risks.

Recommendations and Policy Options

The potential for over-treatment of some prostate cancers not destined to cause future mortality, the uncertainty about the benefits of aggressive treatment of screen-detected cancers, the lack of evidence from randomized trials of the effectiveness of PSA screening, and the relatively high costs of prostate cancer screening programs combine to suggest that a program of PSA screening of asymptomatic men should not be introduced at this time. This decision should be constantly revisited as new information becomes available, especially that from the ongoing randomized trials. Prostate cancer mortality statistics should be carefully monitored as well, because this data may provide useful information to guide decision-making and policy development.

Presently, the Ministry of Health and Long-Term Care (MOHLTC) in Ontario does not pay for a PSA test if it is performed in an asymptomatic man for purposes of screening (although any investigation of an elevated PSA and subsequent treatment is paid for). Two options regarding this policy seem reasonable (the three authors could not unanimously agree about the preferred option):

- **Continue the Status Quo:** Health care resources are limited, and many believe that resources should be preferentially directed to tests and therapies that have been shown to be effective and cost-effective. Continuing the policy of not covering PSA

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screening for asymptomatic men is consistent with this evidence-based approach, and with other MOHLTC policies such as only paying for drugs that have been demonstrated to be cost-effective.

- **Provide PSA Testing on Request, with informed consent:** The lack of evidence about the effectiveness of PSA screening is not the same as knowing that PSA screening is ineffective. The biological rationale for PSA screening is reasonably strong, and the decrease in prostate cancer mortality shortly after PSA screening was introduced is intriguing. Many tests and therapies are paid for by the MOHLTC without definitive proof of benefit, and it could be argued that a PSA screening test should be paid for if men are fully informed about its potential benefits and risks. Men should be given a decision aid describing the options and their consequences, and should indicate that they have fully understood the information provided.

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Prostate-Specific Antigen (PSA) Screening in Asymptomatic Men

I. Introduction

The Institute for Clinical Evaluative Sciences (ICES) staff were asked by the Ontario Ministry of Health and Long-Term Care (MOHLTC) to update the evidence from the existing literature on the diagnostic accuracy, effect on patient outcomes and utility of screening programs for asymptomatic men using serum prostate-specific antigen (PSA) testing.

Prostate cancer screening in asymptomatic men remains an area of enormous controversy, with the potential benefits and harms continuing to be debated among health professionals after more than a decade of PSA screening. Early detection of all cancers has been a targeted message to the general public for decades, and it is reasonable to expect that men would want to embrace prostate cancer screening strategies as part of the imperative for cancer-free health. A decrease in prostate cancer mortality has been seen in some areas recently, and it is plausible that PSA screening has contributed to this decrease. Some non-randomized studies suggest that PSA screening may have an effect. Conversely, concerns about PSA screening include: the possibility that early detection/screening will not have an impact on prostate cancer-related deaths; the exposure of men without symptoms to substantial risk of significant morbidity related to treatment; over-detection and over-treatment of cancers which are difficult to categorize into aggressive and non-aggressive tumours; and the significant cost to society of a screening strategy for which the sensitivity and specificity is not ideal. Probably the greatest concern is that no randomized trial has yet demonstrated an effect of PSA screening upon mortality. This report endeavours to discuss these issues using the best available evidence.

II. Epidemiology and Clinical Picture of Prostate Cancer

a. Epidemiology of Prostate Cancer

Cancer of the prostate has surpassed lung cancer to become the most frequently diagnosed cancer in Canadian men (excluding non-melanoma skin cancer), and the second most frequently reported cause of cancer death. The risk of prostate cancer or death from this cancer increases with age. Although the disease is rare in Canadian males less than 45 years of age, the incidence increases faster with age than that of any other major cancer. The probability of clinical prostate cancer developing is about 1% by 60 years of age, but increases to 9% by age 80. Currently in Canada, one in eight men will have the disease during their lifetime, and 1 in approximately 30 men will die of the disease.[1]

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Family history is consistently associated with risk of prostate cancer in epidemiologic studies, but this may be influenced by detection bias. Androgens significantly alter growth rates, and progression of prostate cancer from pre-clinical to clinically significant forms may result, in part, from altered androgen metabolism. The highest incidence rates for prostate cancer in the world are found among African-American men. Differences in risk by race may reflect three factors: exposure differences, differences in detection, and biological differences. Consumption of polyunsaturated fat, supplements with beta-carotene, and Vitamin D deficiency are being studied in relation to prostate cancer risk, as is the relation with dietary zinc and selenium. Cadmium is a significant environmental contaminant that has been linked to prostatic cancer in some, but not all, epidemiologic studies.[1]

Many industrial and occupational exposures have been studied in relation to prostate cancer risk, but the findings are inconclusive. Interest has focused on farming and, to a lesser extent, the rubber industry. Numerous other factors, including cigarette smoking, energy intake, obesity and physical activity, have been investigated, with mixed findings.

b) Treatment of Prostate Cancer

Prostate cancer can be treated with watchful waiting, surgery, radiotherapy or chemotherapy. It is beyond the scope of this report to discuss the various treatment modalities. However, it is important to recognize that regardless of tumour-type, the treatment of prostate cancer with radiation or radical prostatectomy can result in significant morbidity, including urinary incontinence and erectile dysfunction. The effect of these side-effects upon quality of life must be considered when contemplating a PSA screening strategy. These potential complications, some of which occur frequently (*Tables 1a & Ib*), are associated with treatment of prostate cancers, whether they are detected by screening or found on clinical presentation. It is encouraging that the rates of these complications appear to be falling, with better results reported in younger men with organ-confined cancers and with increasing surgeon experience using nerve-sparing and other surgical techniques.[2-8] Whether these results can be achieved by the majority of surgeons performing prostatectomy is not known.

Table 1a Risk of Complications Following Prostatectomy or Radiotherapy

Risk	Surgery (%)	Radiotherapy (%)
Death	0.1-0.2	< 1
Erectile Dysfunction ~24 months postop	79.6	61.5
Incontinence	9.6	3.5

Source: Potosky AL et al. *J Natl Cancer Inst* 2000;92(19):1582-92 and Talcott JA et al. *J Clin Oncol* 1998;16(1) :275-83.

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Table 1b. Risk of Complications Following Prostatectomy

Risk	Stanford et al	Catalona et a l
Erectile Dysfunction ≥18 months postop	59.9%	32-53%*
Incontinence	8.4%	8%

Source: Stanford JL et al. *JAMA* 2000;283(3):354-60 and Catalona WJ et al. *J Urol* 1999 ;162(2) :433-8
* NOTE: in pre-operatively potent men with bilateral nerve-sparing surgery (32%) versus unilateral nerve-sparing procedures (53%)

Clearly, a screening program will only be worthwhile if the treatment of prostate cancer is effective and the beneficial outcomes justify the anxiety, morbidity and mortality induced by screening, and the investigation of false positive results. Controversy continues about the optimal treatment of prostate cancer that is identified using screening programs. "Expectant management" or "watchful waiting" with selective delayed interventions can be a management strategy used in patients with favourable natural history and clinical parameters.[9] Both urologists and radiation oncologists advocate active treatment of most sub-groups of patients, but the treatment recommended is often that which their specialty delivers.[10] Both agree, however, that standard treatments which include radical prostatectomy, external beam radiation, and brachytherapy can have significant side effects, including incontinence and sexual dysfunction. If these treatments had less worrisome morbidity, the debate about the value of the early detection of prostate cancer would likely be significantly diminished.[11]

The concern with significant morbidity associated with surgical intervention on potentially indolent prostate cancers is well-founded, as almost 90% of men have histologic evidence of latent prostate cancers by age 90 – in other words, most men, if they live long enough, develop prostate cancer which may have no clinical significance nor influence mortality.[12] Even in men with known prostate cancers, reports have shown that more than 60% of these men die of other causes as their tumours are slow-growing.[13]However, emerging evidence suggests that a number of the cancers detected by screening *are* clinically important, and not simply indolent, incidentally detected cancers. Observational studies suggest that advanced tumour grade, stage and volume increase the probability of progression.[14] Experts' improved ability to stratify patients according to risk of death and progression of disease during their expected lifetime is permitting a more selective approach to therapy. Men with Gleason scores (a grading system for tumour aggressiveness with values from 2-10) ranging between 2 and 4 have a probability of dying from prostate cancer within 15 years of 4-7% when treated conservatively, while the probability increases substantially to 60-87% in men whose scores are 8 to 10 (*Table 2*).[15]

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Table 2 Chance of dying from Prostate Cancer within 15 years of Diagnosis by Gleason Score

Gleason Score	Risk (%)
2 - 4	4 - 7
5	6 - 11
6	18 - 30
7	42 - 70
8 - 10	60 - 87

Source: Albertsen PC et al. *JAMA* 1998;280:975-80 [15]

There is a suggestion that tumours detected using PSA testing may be more "clinically important", particularly in younger men, than latent cancers detected on autopsy, as the pathological staging of PSA detected-cancers treated with radical prostatectomy reveals poorly differentiated cell types, extension beyond the prostate capsule, large gland volumes and metastases in 31-41% of patients.[16-18]

Finally, an important analysis of the health-related quality of life outcomes in 278 patients with localized prostate cancer diagnosed either by screening (59%) or clinical detection (41%) was reported by Madalinska in 2001.[19] This prospective study compared patients undergoing primary treatment of their prostate cancer with radical prostatectomy or external-beam radiation, and examined the changes in health-related quality of life that occurred as a result of either treatment in both screen-detected and clinically-detected populations. Patients were followed for twelve months. These important points emerged: a) screened patients did not differ demographically from the clinical detection group, but had more favorable tumour stage/grade; and b) the screen-detected patients did not differ from the clinically-detected patients in terms of post-treatment urinary, bowel and sexual function. The importance of this study is the accurate assessment of outcomes that are meaningful to men as they consider their treatment options. The most important new finding, discussed in an accompanying editorial by Ganz and Litwin [20]is that screen-detected patients experienced the same quality of life changes, the same increased "symptoms" after prostatectomy or radiotherapy, despite smaller and "more favourable" tumours. They suggest that for men whose prostate cancers are screen-detected, the decrements in quality of life "should only be justified if and when screening is shown to reduce mortality".[20] Once the results of the ongoing European and American screening trials are released, screening-related survival gains must be adjusted to reflect the quality of life changes induced by curative treatment. They also suggest that these should include estimations of impairments in urinary, bowel and sexual function, as well as the decreased anxiety levels of individuals who have been "cured" of prostate cancer – quality-adjusted survival must be improved if screening is to be judged effective.

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c) The Epidemiology of Screening for Prostate Cancer

Attention has shifted to early detection as an approach to controlling prostate cancer because there are currently no effective measures for disease prevention. However, because most, but not all, prostate cancers are slow-growing tumours, screening often detects both indolent, non-aggressive prostate cancers as well as aggressive malignant tumours.

Prostate cancer fits poorly into conventional screening models because of the uncertain effectiveness of aggressive treatment for prostate cancer and a reservoir of men with unsuspected indolent cancers. This proportion of men with unsuspected prostate cancers that may not cause morbidity or mortality and who are unlikely to benefit from aggressive treatment will decrease the effectiveness of a screening program. In epidemiologic terms, there are several "biases" which exert influence as well. For example, indolent, unsuspected prostate cancers found in the screened population accentuate the detrimental effects of *length bias* on studies evaluating the effectiveness of prostate cancer screening (because screening may detect more slow-growing tumours with relatively good prognoses than faster-growing tumours with poorer prognoses, screened patients appear to have less advanced disease and concomitant improved survival – called *length bias*). Persons who are "screened" have cancers diagnosed earlier than individuals who are "unscreened", and those who have cancers detected by screening maneuvers often have earlier-stage disease and appear to live longer – known as *lead time bias*. The presence of *lead time* and *length bias* mean that survival data that is not derived from randomized trials may not provide compelling evidence about the effectiveness of a screening test or program.

d) Changes in Mortality of Prostate Cancer

There are encouraging reports of prostate cancer mortality rates steadily declining in the United States and Canada [21-23] with the introduction of PSA screening, a pattern which has also been observed in Tyrol, Austria.[24] In Canada, between 1976 and 1991, age-standardized mortality ratios (SMRs) for prostate cancer increased 1.54% per year. However, between 1991 and 1995 rates decreased slightly.[23] Meyer reported that the overall decline in prostate cancer mortality between 1991-1997 was important for both older (20%) and younger men (29%).[23] A more recent paper from Quebec by Meyer found no inverse relationship between prostate cancer incidence and mortality, suggesting that the decrease in mortality was not due to an increase in PSA screening.[25,26] In the US, prostate cancer mortality declined 6.6% between 1990-1995.[27] Reports of increasing proportions of patients with curable disease at the time of diagnosis have steadily increased.[24,28,29]

The decline in prostate cancer mortality rates shortly after the introduction of PSA screening is encouraging, but cannot be considered as definitive evidence that screening caused all or most of this decline. Such a sudden decline so soon after the introduction of a screening test for a *cancer known for its long latency* is unexpected, and is unusual

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when one considers that the test was in use in the context of controlled clinical trials rather than among the general public until the late 1980s. One cannot exclude the potential contribution of the lead-time and length biases mentioned above, increased awareness of prostate cancer, increased awareness of screening for prostate cancer, and improved surgical, radiation and medical treatment for prostate cancer (for example, between 1982 and 1992 the percentage of American men treated with radical prostatectomy increased from 7 to 32%, [30] and the emergence of androgen deprivation therapy may have delayed disease progression for men with advanced/recurrent disease for several years);[31] or, from an epidemiologic perspective, misclassification of deaths.[30]

e) *The Cost-effectiveness of Screening*

The potential for over-treatment of prostate cancers not destined to cause future mortality, the uncertainty about the benefits of aggressive treatment of screen-detected cancers, and the relatively high costs of prostate cancer screening programs are all areas of concern.[29,32,33] Krahn and colleagues estimate the cost of screening all men between the ages of 50 and 74 in Canada in 1995 would cost $317 million dollars or the equivalent of $121 per man screened (first year direct cost).[32] Although this investment may turn out to be good value for money if future studies clearly document a benefit of PSA screening, the magnitude of these costs underline the importance of having high quality evidence of effectiveness before embarking on a population-based screening program.

III. The Goals of Screening

a) *What is the difference between symptomatic and asymptomatic disease?*

The most common reason for PSA testing of men "with symptoms" is prostatism; men with symptoms of prostatism are not at greater risk for prostate cancer that those without. Prostatism is often the reason that men are screened – both the patient and his physician consider this "diagnostic testing" because there are "symptoms". However, screening asymptomatic men is a different manoeuver.

b) *Screening - all men, with or without symptoms*

Screening is usually defined as an organized activity in which a test is applied to a whole population in order to identify a subset of the population who may have the disease of interest. Conversely, when screening tests are applied simply upon request or in an *ad hoc* fashion in asymptomatic patients in whom there is no clinical suspicion of disease, the process is called *case-finding*. A screening test, to be truly successful, must not just be accurate, but there must be evidence that using it for early detection is beneficial, and outweighs the potential harms. Screening activities are usually the result of an established health policy which should be based on high quality evidence. A screening test is considered accurate when it can detect a large number of people in a population with early stage disease without generating a large number of false-positive results. The test must have good *sensitivity* (the proportion of persons with a disease who test positive)

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and *specificity* (the proportion of persons without a disease who test negative). A test that has poor sensitivity leads to a high proportion of false-negative results, while one with poor specificity leads to a high proportion of false-positive results. A common measure of the accuracy of a screening test is the *positive predictive value* (PPV) – the probability that the target condition is present if the test is positive. If a test has a PPV of 25%, it means that three out of four of the abnormal test results will be falsely positive. One caveat, however: PPVs can vary markedly depending on local prevalence rates.

Cancer screening programs have as a principal goal the reduction of mortality. If mortality is not reduced, patients not only live with the disease for a longer time but also lack the benefit of survival gains. As a general principle, when any cancer-screening strategy is implemented, rapid *downstaging*) is generally seen (earlier detection causes a shift in "stage of disease"; tumour is likely to be smaller, more localized, with less chance of metastases) in association with its introduction and uptake (as has happened with prostate cancer) – or, the strategy decreases significantly the number of invasive cancers that are diagnosed (inferring that the screening test is making a difference). This is what occurred with the introduction of Papanicolou (Pap) smears in the decline in cervical cancers. An RCT of PAP testing was never performed; rather, the significant shift in cervical cancer mortality formed the basis of its widespread adoption.

Screening as a population-based manoeuver may not always be successful, either because of the relative insensitivity of the tests or because of the biology of the disease. In the case of prostate cancer, a difficult problem must be addressed. Prostate cancer has a high prevalence in older men. Autopsy studies have shown that by the age of 90, most men (90%) have latent or microscopic prostate cancer, which has *not* been the cause of death.[12] This is explained by the usually slow doubling time of the tumor and the age of men when the cancer first develops.

Some of the discussion about PSA screening is reminiscent of earlier arguments in favor of lung cancer screening using chest x-ray and sputum cytology among male smokers aged 45 and older – a practice ultimately demonstrated to be ineffective in clinical trials.[34] Physicians, as well as the American Cancer Society, endorsed screening, pending the evidence. Preliminary reports of stage shifting in patients with lung cancer were enthusiastically received, but despite the stage shift, subsequent trial reports did not show a reduction in lung cancer mortality among those who had been screened. Estimates of the sensitivity and specificity of the screening strategies (lung and prostate cancer) are similar (roughly 50-75% sensitivity and 90-95% specificity for early-stage disease). Moreover, the shift to post-surgical stage I disease noted in the early years of lung cancer screening trials (roughly 50% with screening versus 20% among controls), is similar in magnitude to the shift to pathologic stage T1-2 disease in prostate cancer screening studies (roughly 70 - 85% with screening versus 30-40%). The analogies between the current prostate cancer screening debate and the older lung cancer screening debate should provoke caution regarding widespread dissemination of prostate cancer screening, pending experimental evidence that such screening does more good than harm.[34] As previously mentioned, stage shift is a common consequence of screening, and does not

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mean outcomes will be better in screened individuals as compared to those who have not undergone screening – this has yet to be demonstrated for prostate cancer in controlled trials. Other parallels can be found as well; early-stage curability was not adequately tested in lung cancer trials and has not been adequately tested in prostate cancer trials as yet.

It is important to point out that PSA screening advocates have dismissed this comparison, arguing the incomparability of the respective tumour growth rates. The asymptomatic detectable interval in lung cancer screening may have been so short that cancers, thought localized, were in fact already metastasized – making the trial result negative. Advocates suggest that PSA screening may detect the disease at a point in time which is amenable to curative therapy, whereas lung cancer is much more aggressive by nature. They argue that because prostate cancer is relatively slow-growing compared to lung cancer, screening should have a positive effect. However, this is not necessarily so. Prostate screening may have no effect upon mortality because the asymptomatic detectable period may be so long that many cancers will be found that are not destined to cause significant morbidity and mortality in the patients' lifetimes. The difficulty in distinguishing rapidly-growing cancers destined to cause future morbidity and mortality from indolent tumours which will not (but feature a significant rate of treatment complications), will continue to provoke controversy until the RCTs are completed successfully.

c) Characteristics of PSA as a Screening Tool

PSA as a screening tool was described in pioneering work by Catalona [35] and other investigators who demonstrated that the early detection of prostate cancer is possible through the use of serum determination of PSA. However, the relatively poor sensitivity and specificity of the test in differentiating benign prostatic hyperplasia (BPH), indolent cancers and those tumours which are aggressive has been partially responsible for the controversy about its usefulness for screening asymptomatic men.

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Table 3 What is the accuracy of the PSA test?

For every 100 men over the age of 50 who have the PSA test:

About 90 will have a normal PSA level (≤ 4.0 ug/L), and about 10 will have a higher than normal level.

- These 10 men will then need to go through other tests and examinations. At the end of these tests:
  - Three men (3/10) will be found to have significant prostate cancer after the first biopsy; i.e., seven men (7/10) will be found not to have prostate cancer at this time (false positives);
  - Over the next several years, another two of these men (2/10) will have significant prostate cancer detected during follow-up;
  - Over an extended period of time, five of the ten men will be found not to have prostate cancer despite further investigation (false positives).
- One or two of the 90 men who had a normal PSA test will actually have prostate cancer that is clinically significant and will cause symptoms at a later date (false negatives).

Source: Ontario Prostate Specific Antigen (PSA) Clinical Guidelines: The PSA Clinical Guideline Expert Committee for the Laboratory Proficiency Testing Program (LPTP), 97.09.30. Physician Reference Document. ICES 1998.[12]

PSA testing does have several clear advantages. The test result *may* be abnormal when cancer is present and digital rectal examination (DRE) is normal. Secondly, the test detects a higher percentage of patients with potentially curable cancer than any other detection test. The test also has some weaknesses, such as a high false positive rate and a significant false negative rate (*Table 3*).

The best estimate of the sensitivity of PSA for the detection of cancer ranges between 72-90% with a specificity range between 59-98% (depending on age group and prevalence.[16,36] In asymptomatic men, the positive predictive value of a PSA level >4.0 ug/L is 28-35% – therefore, about two thirds of positive tests will be false positives. There is a large literature concerning the effect of varying the definition of an abnormal test (if one lowers the value, the number of detected cancers will increase, but so will the already high false positive rate; if one raises the value, the false positive rate will decrease but the number of detected cancers will also decrease).

There is interest in using age-specific reference ranges, since the PSA level increases normally with age, and of using free- and total PSA levels. New methods for enhancing the specificity of PSA screening using additional and "refining" tests are currently under evaluation. One is the fractionation of "bound" and "unbound" amounts of PSA in the blood (PSA circulates both "free" and in "complexes" with micromolecules); other methods include the use of PSA density to distinguish high- and low-risk patients, and PSA velocity. These issues are discussed in greater detail in *Appendix 1*. However, at the present time, most information about the impact of PSA screening uses a normal range of ≤4.0 ug/L.

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IV. Effectiveness/Harm of PSA Screening

a) Choosing the literature: the search strategy

We reviewed the available evidence by conducting an electronic search of the medical literature and the websites of professional organizations, learned societies, advocacy groups and foundations.

First, clinical trials, guidelines, evidence-based statements and summaries and major review articles were identified using bibliographic databases such as Medline, Embase, the Cochrane Library, HealthSTAR, and CANCERLIT. For the most part, the searches for relevant literature were limited to more recent years (1995-2001). A clearly defined search strategy was used (*Appendix 2*).

Second, the project team conducted a search for relevant literature on the Internet. A broad-based review of web-based literature from learned societies, health technology assessment agencies, advocacy groups, and disease foundations (i.e., Canadian Cancer Society) was performed to understand the basis of public education around prostate cancer, screening technologies and techniques, and interpretive stances.

Third, back-referencing was performed to identify reports not found in the electronic search, as well as available grey literature (reports published by relevant private or public agencies) missed in indexed sources, but which were cited by other authors.

Critical appraisal techniques were employed to delineate those articles which came closest to standards of "best evidence".[37] These articles were appraised by two independent readers, and were included in the review if there was agreement that the articles met these standards (*Table 4*). We caution readers that this was *not a formal systematic review* but rather *an update* on previous work done in 1997/98 on PSA testing in asymptomatic men.[12]

Table 4 Retrieval of Articles

Medline, Embase, HealthSTAR, CancerLIT 1995 – 2001	1239 abstracts
Met criteria for preliminary review	109 articles
Met criteria for inclusion	76 articles
Guidelines/Reports/Policy and Position Statements	26
Web-based policy/position	18

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b) The Important Clinical Studies

A large summary table of findings is included in *Appendix 3* with commentary on all articles deemed "best evidence" or "best available evidence". We urge readers to review this Appendix for details about the various studies. However, in this section we will only summarize the four studies that have, or are likely to, provide important evidence about the benefits and harms of PSA screening.

i) European Study of Screening for Prostate Cancer (ERSPC)

This is one of the most important randomized trials of PSA screening. The centers in the European study include the Netherlands, Belgium, Finland, Italy, Portugal, Spain, Sweden, France, Norway and Switzerland. The goal of this large trial is to determine whether a significant reduction of mortality from prostate cancer can be achieved by screening.

The study was planned to recruit 190,000 men in total, roughly aged 55-70 years. The trial is powered to detect a 20% relative difference in prostate cancer mortality ten years after the start of the trial. The methods of recruitment, the age of the participants, and the choice of "normal PSA" varies somewhat between the centers. Upon completion, this trial is anticipated to provide level I evidence[37] about the benefits of PSA screening. Although many papers have already been published from this trial, none of them present data about the rates of morbidity and mortality in the screened and unscreened populations.

ii) Prostate, Lung, Colorectal & Ovarian Cancer Screening Trial (PLCO)

This large American study of volunteers was started in 1993, and has a sample of 74,000 men aged 55-74 years. Results of long term follow-up are expected in 2014. The primary endpoint of the trial is overall mortality. Secondary endpoints include: assessment of screening variables including sensitivity, specificity, and positive predictive value; incidence, stage and survival experience of cancer cases; and the mortality predicative value of biologic and/or prognostic characteristics of tumor tissue as intermediate endpoints. (see *Appendix 3*).

The researchers have planned this trial to have sufficient power (90%) to detect a 20% relative risk reduction in prostate cancer mortality at ten years. Half of the men will be randomized to "usual care" in the community, and half will be screened annually with PSA and DRE for five years. The PSA cutpoint is > 4.0 ug/L. In late 1998, the protocol was modified to extend follow-up to a minimum of 13 years for all participants.

On completion, this trial is anticipated to provide us with level I evidence about the effectiveness of PSA screening,[37] but the final results of long-term follow-up are not expected to be available for another 12 years.

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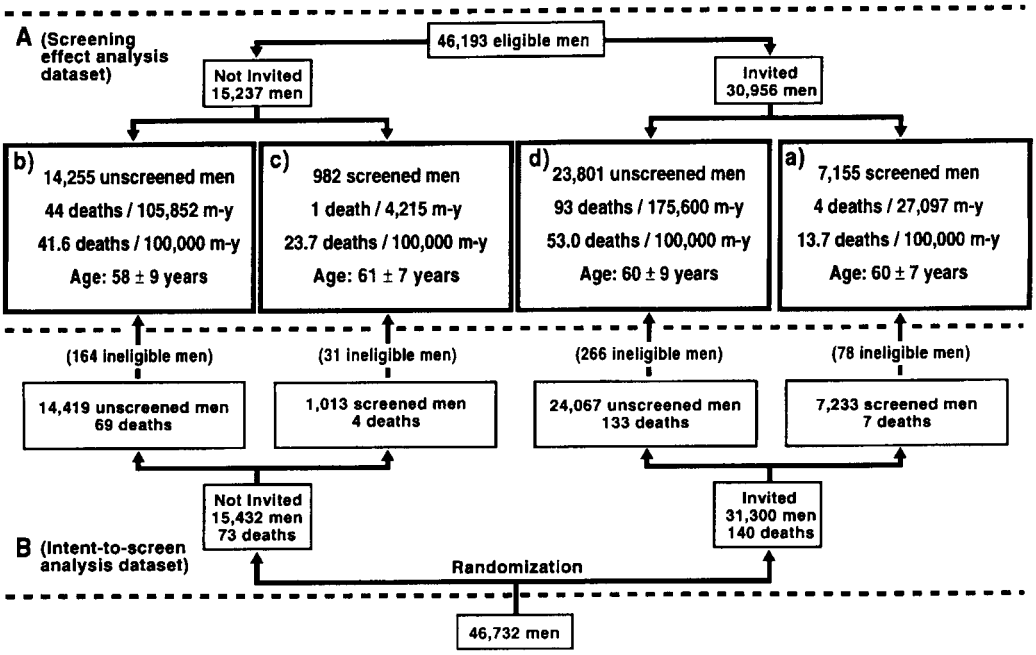
iii) Canada: the 1988 Quebec Trial of Screening for Prostate Cancer (Laval)

This study was begun in Quebec in 1988.[22] The design is complicated (please see Figure below). Using electoral lists, a total of 46,193 men aged 45-80 years residing in the area of Quebec City were identified. Of these 30,956 were "randomized" out of the sample to "be invited to be screened", while the remaining 15,237 men from the electoral list were to be "controls". 7,155 men accepted the invitation and were screened, as were 982 men in the control arm who were unaware that they were part of a study. A total of 8,137 (23%) men were therefore screened, and those who refused/non-responders/and planned controls from electoral sample constituted the control group (n=38,056). These men were followed from 15 November 1988 to 31 December 1996 (see *Appendix 3*).



Prostate cancer mortality rates reported during the eight-year study period were 15 and 48.7 per 100,000 man-years respectively, in the screened and unscreened groups (3.25 odds ratio favouring screening /early treatment).

Of the 8,137 screened men from both arms of the study, 367 in total were diagnosed with prostate cancer (4.5%), of whom five died. In the unscreened control group (38,056), there were 137 deaths attributed to prostate cancer between 1989 and 1996. First, among the 367 cancers identified by screening, 91.6% were at clinical stage M0 at diagnosis (not metastasized – localized to the prostate capsule) and 78% of these presumably had localized disease treated with either radical prostatectomy or radiation therapy.

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This striking difference in mortality between PSA-screened (0.06%) and unscreened (0.36%) men needs cautious interpretation because this may have resulted from factors other than screening. This study has been described as a randomized controlled trial (RCT). However the study does not meet the criteria of a RCT, because there was considerable crossover between the control and screened groups, and the trial was not analyzed according to the intention-to-treat principal. Nine hundred and eighty two (982) men from the control arm were combined with the 7,155 men in the screening arm for the "screening results", and the unscreened arm combined men who were not invited to participate with those who did not accept the invitation to be screened.

When an intention-to-treat analysis was conducted comparing mortality between the two groups, there was no prostate cancer mortality advantage seen for men randomized to screening (Relative Risk 1.06; 97/30956 deaths [0.313] in unscreened men versus 45/15237 deaths [0.295] in screened men).[38]

iv) *The Tyrol Study*

This study evaluates a free, comprehensive PSA screening program initiated in the Tyrol, Austria in 1993, described as an "unique natural experiment" which compares prostate cancer mortality in the Tyrol, (where PSA screening was made available at no cost), with the rest of Austria (where it was not). Although this is not “best evidence” – a randomized controlled trial – it nonetheless deserves careful attention because it is often cited as “definitive” and its mortality results are striking. The study was performed collaboratively by family physicians, medical officers, urologists and the Tyrolean Blood Bank of the Red Cross. PSA screening was made freely available to all men ages 45-75 years in the Tyrol region of Austria. Of the 307,249 males in Tyrol, ~65,000 fell into this age group. All men in this age group were invited to undergo PSA screening. Men with abnormal PSA levels were referred to physicians for further evaluation, while men whose PSA was normal were invited to repeat the PSA test a year later; if the PSA was elevated, men were then invited to undergo DRE and TRUS.

The interim results of the comparison of prostate cancer mortality rates between Tyrol and the rest of Austria were recently published.[24] By 1998, 66% (>76,000) men in Tyrol had been screened at least once. Of these, 7,100 were aged 45-49 and 2,900 were 40-44 years of age, and are included in the analyses of incidence and mortality rates. The number of Tyrolean men who died of prostate cancer between the ages of 40-79 stayed constant from 1970-1993. The mortality rate then declined, even though the number of men who died of prostate cancer in the other regions of Austria did not decline. Based on the age-specific rates in Tyrol between 1986 and 1990, there was a 32% decrease in prostate cancer mortality in 1997, 42% decrease in 1998, and 33% decrease in 1999 compared to expected mortality.

In addition to a significant decline in prostate cancer mortality in Tyrol, there was also a significant increase in the number of organ-confined, potentially curable cancers detected. These results are impressive, and have been interpreted by some as evidence for

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the efficacy of PSA screening. Others have been more cautious, pointing out that this is not a randomized trial, and that some or all of the difference between the Tyrol and the rest of Austria could be due to several differences. The decline in mortality may be due to aggressive downstaging; some have argued that one would not expect such a rapid decline in death so shortly after the institution of screening, since many prostate tumours are relatively slow-growing. It should also be noted that the Tyrol has a very sophisticated screening and treatment program (heightened public awareness, the availability of high-quality urologic care and appropriate treatment facilities) that may not be easily replicable elsewhere. The study investigators themselves suggest that improvement in treatment modalities as well as earlier detection may be influencing the mortality rate. Thus, the Tyrol study cannot be considered definitive evidence of the efficacy of PSA screening.

v) Summary of studies to date

When completed, the screening studies mentioned above (especially the two randomized trials) should provide high quality evidence about the effectiveness of PSA screening. However, the trials use different definitions of an abnormal PSA (which have sometimes changed during the conduct of the trial), and there is some contamination of the control group with PSA testing (which will decrease the likelihood of finding an effect of PSA testing). Thus, the interpretation of even these studies may not be straightforward (see *Appendix 4*).

c) A Summary of the positions of professional societies and health technology assessment agencies

Our review identified a number of position statements about PSA screening from professional organizations, as well as a number of health technology assessments. Given the lack of definitive evidence, it is not surprising that there is some difference of opinion among the groups. However, the majority *do not recommend* a formal screening program; some suggest that PSA testing should be offered to men who are fully informed about its potential benefits and risks. A number of groups in Canada, USA and UK have articulated positions concerning use of PSA as a screening test in the general population, and these are collected and summarized in *Appendix 5*.

- The American Urological Association (AUA) and the American Cancer Society (ACS) were the first large organizations to recommend the use of PSA screening on a grand scale. However, a task force of the AUA recently published a “best practice policy” on the use of PSA testing, stating that “the decision to use PSA for the early detection of prostate cancer should be individualized. Patients should be informed of the known risks and the potential benefits.”[39]

- In Canada, a number of bodies have presented recommendations on screening and early detection. The Canadian Urological Association's (CUA) current guidelines for early detection of prostate cancer as of June 1996, are as follows: "The digital rectal examination (DRE) and prostate specific antigen (PSA) measurements increase the

early detection of clinically significant prostate cancer. Men should be made aware of the potential benefits and risks of early detection so that they can make an informed decision as to whether to have this test performed."

- The position of the National Cancer Institute (NCI) of Canada and the Canadian Cancer Society (CCS) has been shaped by the recommendations from the 1997 National Prostate Cancer Forum Report. Their recommendations state “that all men over the age of 50 years should discuss with their doctor the potential benefits and risks of early detection using Prostate Specific Antigen (PSA) and Digital Rectal Examinations so they can make informed decisions about the use of these tests. Men at high risk because of family history, or those of African Canadian ancestry may wish to discuss the need for testing at a younger age”.

- Until research resolves the question, many organizations including the U.S. Preventive Services Task Force (USPSTF), Canadian Task Force on Preventative Health (CTFPH), and the NCI do not recommend routine PSA screening. And even organizations that do recommend it, such as the AUA and the American Cancer Society advise doctors and patients to make the decision only after full discussion of the uncertain benefits and known risks.

An abbreviated listing of the positions taken by various organizations appears in *Table 5*.

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Table 5 Positions Taken by Professional Organizations and Learned Societies*

Recommendation for screening in asymptomatic men with informed consent after education concerning risks and benefits	**Canadian Cancer Society** http://www.cancer.ca (accessed 2.1.02) **Alberta Cancer Agency** http://www.cancer.ab.ca/site/prostate/pscreen.htm (accessed 2.1.02) **Canadian Urologic Association** http://www.cua.org/ (accessed 28.12.01) **American Cancer Society** Web site references: (American Cancer Society, Prostate Cancer Screening Guideline, Jan Feb 2001 Issue of CA – A Cancer Journal for Clinicians) **American Urologic Association** http://www.auanet.org/media_press/press_releases/prostate.cfm (accessed 31.12.01)
Recommendation against screening in asymptomatic men	**Canadian Task Force on Preventive Health** http://www.ctfphc.org/ (accessed 28.12.01) Reviews in Progress (Aug 2001) **Health Services Utilization and Research Commission (HSURC) – Saskatchewan** Guideline re-certified – February 2001. http://www.hsurc.sk.ca/research_studies/research.php3?rid=11&rstatus=3 (accessed 2.1.02) **American College of Preventive Medicine** http://www.acpm.org/prostate.htm (accessed 30.12.01) **American Medical Association** http://www.ama-assn.org/ama/pub/article/2036-2928.html (accessed 31.12.01) **US Preventive Services Task Force** http://www.aafp.org/fpr/971000fr/12.html (accessed 2.1.02) **British Association of Urologists** http://www.nelh.nhs.uk/guidelinesdb/html/Prostate-ft.htm (accessed 2.1.02) **European Union** *European Journal of Cancer* 2000;36:1473-1478 **Urologic Society of Australia** http://www.urosoc.org.au/info/psa.html (accessed 2.1.02) Reviewed March 1999
Can be interpreted as recommending against screening in asymptomatic men (report similarly to other agencies but no concrete statement)	**National Cancer Institute** http://search.nci.nih.gov/search97cgi/s97_cgi CANCER FACTS National Cancer Institute ° National Institutes of Health fact sheet was reviewed on 1.11. 01 **BC Cancer Agency** http://www.bccancer.bc.ca/pg_g_04.asp?PageID=2749&ParentID=4 (accessed 2.1.02) **American Academy of Family Physicians** http://www.aafp.org/afp/20000815/practice.html (accessed 31.12.01)
Recommend against screening in asymptomatic men, but test performance will be provided upon patient demand and informed consent after risk/benefit education	**National Health Service in UK** http://www.nelc.org.uk/docs/psa/psa_frame.htm (31 Dec 2001) 4th July 2001 – launch of informed choice project for prostate cancer
Recommend against screening in asymptomatic men, but test performance should be provided upon patient demand on documented informed consent after risk/benefit education	**American College of Physicians** http://www.acponline.org/vas2000/sessions/cancer.htm (2 January, 2002)

* Please see *Appendix 5* for complete table and quotation of recommendations.

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The most recent health technology assessments of PSA testing as a population-based screening tool in asymptomatic men in other countries was published in August, 2001 in the *International Journal of Health Technology Assessment* (*Appendix 6*).[16,40-50] The entire issue reported on screening policies and practices in Switzerland, Austria, Belgium, Germany, Greece, Italy, the Netherlands, the United Kingdom and Sweden. None of these countries recommend population-based PSA screening because of a lack of scientific evidence of the effectiveness of screening. Most have an explicit statement confirming a decision not to consider implementing comprehensive population-based PSA screening until results from long-term RCTs demonstrate that screening has an important impact on morbidity and mortality.

V. Overall Conclusions

Earlier in this document we discussed the lack of high-quality evidence supporting the use of PSA testing in asymptomatic men until the large European and American randomized trials are completed. Less convincing evidence that might support PSA screening suggests that when men have localized tumours at diagnosis they appear to live longer, have higher 5-year survival rates than men with advanced disease, and are more likely to have early-stage tumours (stage shift). Data indicate that in men diagnosed at a younger age, the disease seems more aggressive.[51] However, many prostate cancers are slow-growing tumours and never threaten the life of the individual;[52] it is difficult to differentiate tumours that grow rapidly from those that do not; the sensitivity and specificity of the PSA test is not ideal so many men without cancer undergo unnecessary investigations and anxiety; biopsies miss approximately ten percent of cancers; and the treatment of prostate cancer has considerable morbidity (urinary incontinence and erectile dysfunction).

In the absence of evidence from randomized trials, researchers have studied trends in mortality from prostate cancer. These trends are encouraging, with declines in the proportion of clinically or pathologically advanced prostate cancer in regions where PSA screening has been introduced. There have been concomitant decreases in prostate cancer mortality rates in the United States, Canada and Tyrol, Austria among others. For example, in Canada, age-standardized mortality ratios for prostate cancer increased by 1.5% annually between 1976 and 1991, while between 1991 and 1995, the rates decreased slightly. Although these decreases may be due to PSA screening, they occurred sooner after the introduction of screening than expected, and may be affected by other factors such as improved treatment of prostate cancer.

The potential for over-treatment of some prostate cancers not destined to cause future mortality, uncertainty about the benefits of aggressive treatment of screen-detected cancers, the lack of evidence from randomized trials of the effectiveness of PSA screening, and the relatively high costs of prostate cancer screening programs combine to suggest that *a program of PSA screening of asymptomatic men should not be introduced at this time*. This decision should be constantly revisited as new information becomes available, especially that from the on going randomized trials. Prostate cancer mortality

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statistics should be carefully monitored as well, because this data may provide useful information to guide decision-making and policy development.

Presently, the Ministry of Health and Long-Term Care (MOHLTC) in Ontario does not pay for a PSA test if it is performed in an asymptomatic man for purposes of screening (although any investigation of an elevated PSA and subsequent treatment is paid for). Two options regarding this policy seem reasonable (the three authors could not unanimously agree about the preferred option):

- **Continue the Status Quo:** Health care resources are limited, and many believe that resources should be preferentially directed to tests and therapies that have been shown to be effective and cost-effective. Continuing the policy of not covering PSA screening for asymptomatic men is consistent with this evidence-based approach, and with other MOHLTC policies such as only paying for drugs that have been demonstrated to be cost-effective.

- **Provide PSA Testing on Request, with informed consent:** The lack of evidence about the effectiveness of PSA screening is not the same as knowing that PSA screening is ineffective. The biological rationale for PSA screening is reasonably strong, and the decrease in prostate cancer mortality shortly after PSA screening was introduced is intriguing. Many tests and therapies are paid for by the MOHLTC without definitive proof of benefit, and it could be argued that a PSA screening test should be paid for if men are fully informed about its potential benefits and risks. Men should be given a decision aid describing the options and their consequences, and should indicate that they have fully understood the information provided. The United Kingdom's policy regarding PSA screening is provided below, as an example of what might be contemplated in Ontario.

On the 4th of July, 2001, the following policy was officially introduced by the Public Health Minister of the National Health Service (NHS), UK:

"If a patient requests a PSA test:
He should first be provided with information about the advantages and disadvantages of PSA testing.
He should be offered the opportunity to discuss his interpretation of the information, using the more detailed information contained in: one of the leaflets that are available; Frequently Asked Questions about Prostatic Cancer and the PSA Test; the National Electronic Library for Prostate Cancer (part of the National electronic Library for Cancers)

If the patient wishes to have the PSA test, it should only be arranged with a laboratory participating in the National External Quality Assurance Scheme (NEQAS) scheme;
The patient whose test result indicates the need for further investigation should be referred to a urologist; he should be given more information about treatment options, including the opportunities to enter randomized controlled trials.
The NHS will not be inviting men for Prostatic Specific Antigen (PSA) testing and does not expect GPs to raise the subject of PSA testing with asymptomatic male patients."

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Appendix 1

Other Evolving Research Refining the PSA test and its Use

There is no question that the information which is starting to flow from large screening trials is of enormous importance in resolving the questions and dilemmas arising from the use of this test. Nor is there debate over the utility of the PSA test in monitoring those with previously diagnosed prostate cancer, or in helping to establish the diagnosis in those with clinical suspicion of the disease on the basis of DRE. One difficult issue remains the use of PSA as a screening instrument in asymptomatic men with no clinical suspicion nor heightened risk of prostatic disease. Much of the "latest" research still acknowledges the suboptimal specificity of the PSA test, and suggests other tests to support the use of the PSA test as a screening manoeuver – which raises even more questions. The value of 4.0 ug/mL has traditionally been used as the upper limit of normal in testing, but there are two variations in findings worth mentioning: up to 20% of men with prostate cancer have a value less than 4 ug/mL, and additionally, only 25% of men with a PSA between 4-10 ug/mL will have a positive biopsy. Because of these limitations, attempts are being made to refine the accuracy of PSA in prostate cancer detection. In the interim, as we await the results of these large studies, the available indirect evidence must be carefully considered.

Causes of PSA elevation other than cancer

Traditionally recognized causes of elevated PSA levels ($\geq$ 4.0 ug/L) include recent prostatic biopsy, recent transurethral resection of the prostate (TURP), acute urinary retention, acute prostatitis, or benign prostatic hyperplasia (BPH).

Kits for measuring PSA made by different manufacturers can produce clinically important variations in levels of prostate-specific antigen.[53,54] A change from one test kit to another should be considered as the cause of a relatively small change in the PSA level. There appears to be even greater variability in the results of kits that measure free PSA than in those that measure total PSA.[53,55]

NOTE: There is further information available in Section IV-Table IVa of the 1998 Physician Reference Document [12] about factors which have an effect on PSA levels.[56]

Sensitivity, specificity, positive predictive value (PPV) of PSA using "original" cutpoint of < 4.0 ug/L, and the effect of age upon PSA levels

A PSA concentration greater than 4 ug/L has a sensitivity of 80-85% in detecting prostate cancer. Analyses of archived blood samples suggest that PSA elevations and low free-to-total PSA ratios precede the development of prostate cancers by up to a decade.

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PSA also has limited specificity, producing false-positive results in patients with benign prostatic disease (between 25-46% of men with BPH have elevated PSA values). The specificity of PSA is also age-related: for example, based on population data for one American region, PSA specificity is 98%, 87% and 81% for men aged 50-59, 60-69 and 70-79 respectively.[16] In asymptomatic men, the positive predictive value (PPV) of a PSA value > 4.0 ug/L is 28-35% – therefore, about two of three positive tests are false-positive.[35,57] In comparison, the reported positive predicted value when digital rectal examination (DRE) is negative is 20%.[16]

Sensitivity and specificity of the PSA test and the "best" cut-point at which an elevated result should prompt a prostatic biopsy are unclear. Biopsies, the "gold standard", are usually only performed when PSA test results or DRE of the prostate cause the treating physician concern. This potential "workup bias" was assessed in male subjects in the Physicians' Health Study, in which Gann [58] assessed the relationship between baseline serum PSA levels at the start of the study and the subsequent clinical diagnosis of prostate cancer. Their finding was that a PSA normal of <4.0 ug/L at baseline had a sensitivity of 46% in identifying cases of prostate cancer within the next decade. The specificity in the study population (mean age of 63 years) was 91% – but the specificity varied with the age of the patient and the possibility of that individual having BPH.

The specificity of the test may be as low as 54% in older men with BPH using the same cutpoint.[59] In a screening study in which the probability of an elevated PSA level increased from 5% in ~50 year old men to ~25% in men in their 70s using the same cut point of 4.0 ug/L, the probability of prostate cancer remained about 30% because as prevalence increases with age, the specificity of the PSA test decreases.[60] Interestingly, in this study 45% more cases of cancer were detected by PSA testing than DRE alone, but DRE detected 18% more cases of cancer than PSA alone – in other words, each test picked up cancers missed by the other.

Using lower cutpoints of PSA for "normal" PSA levels

Revisiting the decision to use the traditional cutpoint of 4.0 ug/L as the upper limit of a "normal" PSA level has brought some interesting results as well. In studies by Catalona and Babaian,[61,62] men with normal DRE and PSA levels of 2.5-4.0 ug/L underwent transrectal prostatic biopsy; 12-23% of the men were found to have prostate cancer, which has prompted many experts to recommend that the threshold for biopsy be lowered. However, the difficulty with redefining the "normal range" for PSA is the lack of knowledge about the true prevalence rate, which varies between countries.

In the European Randomized Study of Screening for Prostate Cancer (ERSPC) - Rotterdam section,[63] the normal range for the study was reduced from ≥ 4.0 ug/L (used in 8,612 initial subjects recruited in 1996, of whom 430 men had prostate cancer) to ≥ 3.0 ug/L in an additional 7,943 men screened in 1997. The tumour characteristics from the "first" protocol were re-studied with the new screening regimen. Prostate cancers

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detected with the lower cutpoint had a similar distribution of Gleason Scores but a larger proportion of patients with confined disease were found. Tumour volumes were smaller in patients with even lower PSA levels (< 2.9 ug/L); the proportion of minimal disease in that group was 50% compared to 28% in the group with PSA levels between 3.0-3.9 ug/L. Overall, the characteristics of cases of prostate cancer detected with the lower cutpoint differed very little from those detected in the original regimen. The comparison revealed a detection rate (proportion of subjects in whom cancer was found) to be similar (5.0% at 4.0 ug/L and 4.7% at 3.0 ug/L respectively). This similarity was thought to be due to the fact that more prostate cancers were found in the lower range group than was anticipated.

The authors report that although the avoidance of digital rectal examination and transrectal ultrasound in about 80% of the cases could be considered "advantageous" in the context of population-based screening, it does not work as well for clinical practice where DRE is often performed before a PSA level is obtained. They also conclude that the characteristics of prostate cancer with PSA levels between 3.0-3.9 ug/L can be expected to be similar to those found at the traditional cutpoint of $\geq$ 4.0 ug/L, and that the need to diagnose cancers at PSA values less than 3.0 ug/L is debatable.

Prostatic biopsy techniques

There has been research which has changed prostatic biopsy techniques as well. Transrectal ultrasound-guided biopsy is the traditional standard of prostate cancer. Biopsy of areas identified as potentially abnormal by DRE or hypoechoic lesions identified on transrectal ultrasound are usually obtained. As these methods are well known to be less sensitive than desired, biopsies are also systematically obtained from areas of the prostate that are considered "normal" by these examinations. The usual strategy has been to obtain six biopsy specimens in a sextant pattern, but recent studies have revealed that this approach results in a residual probability of undetected cancer of at least 10%. The net result is that the number of times a biopsy should be performed is also under debate. The fact that biopsy cannot detect all prostate cancers can, in the words of researchers, lead to a “chronic state of anxiety” in patients labeled as "PSAdynia".[10,20,64] As approximately 75% of men who undergo prostatic biopsy have PSA levels of 4.0-10.0 ug/L and do not have prostate cancer, a great challenge to researchers is to find something which does a much better job of discriminating BPH from prostate cancer.

Sensitivity, specificity, positive predictive value (PPV) of PSA using age-specific reference ranges of PSA

There is interest in the use of age-specific reference ranges (*See Table below*). PSA values generally increase with age and are also higher in certain racial groups.[65,66] Using this strategy, the suggested cutpoints for prostate biopsy in younger men aged 40-49 years would be 2.5 ug/L, 3.5 ug/L in men age 50-59 years, 4.5 ug/L in men 60-69 years,

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and 6.5 ug/L in men 70-79 years. However, this approach to care in older men has been criticized because of the low sensitivity of the test.[16]

Age-related "normal" PSA cut-points

Age Range (years)	Serum PSA Concentration (ug/L)
40 - 49	< 2.5
50 - 59	< 3.5
60 - 69	< 4.5
70 - 79	< 6.5

Source: Oesterling JE et al JAMA 1993; 270:860-64 [65]

The main factors that increase the likelihood of having a prostate cancer diagnosis (other than PSA testing) include:

- Older age (autopsy series have demonstrated that 90% of men have prostate cancer by age 90),
- Black race (which increases the risk by a factor of 1.5 approximately),
- A family history of prostate cancer in a first-degree relative which, at least, doubles the risk.

Survey work done by Fowler [67] demonstrated that although family practitioners in the US generally feel that there is little benefit to screening men whose life expectancy is less than ten years or who are 75 years of age and older, many urologists do not, although this too is being tested in studies currently underway.

A 1999 study [68] tested the diagnostic efficiency of PSA and DRE when using either the 4.0 ug/L cutpoint or an age-specific reference range as an abnormal PSA cutpoint. In a study of 116,000 volunteers (non-randomized) cumulatively screened during Prostate Cancer Awareness Week in 1992-95, a total of 22,014 men (18.9%) were found to have an abnormal PSA, abnormal DRE, or both. When using age-specific reference ranges, 17,561 (15.1%) had an abnormal PSA, abnormal DRE, or both. Significantly higher PPVs indicated that PSA + DRE is most effective in screening for early detection of prostate cancer. Using the age-specific reference range, PSA values had higher PPVs suggesting fewer unnecessary prostatic biopsies. Lower sensitivities result in fewer cancers being detected.

Prostate volume or density

Studies have been done to investigate adjusting the PSA level to account for prostate volume or density by using ultrasound. The standard reference ranges for PSA don't account for age-related volume changes in the prostate (primarily due to growth of BPH tissue), so the proposal of age-related PSA reference ranges to improve PSA sensitivity in

younger men and specificity in older men is an attractive one. The PSA level is divided by the gland volume as determined by ultrasound. A value greater than 0.15 ug/L is the suggested cutpoint and may be predictive of cancer.[69] This approach would ostensibly increase detection of cancers in younger men with early, organ-confined disease who could benefit from local definitive therapy, while avoiding the local treatment of clinically insignificant tumours in older men.[65] However, the methodology is unlikely to be useful for mass screening because of its logistical difficulty, the highly specialized expertise required, and the inaccuracy of the measurements which are often obtained.

PSA Velocity

Another suggested approach is to track "PSA velocity". An increase of at least 0.75 ug/mL (or a 20% increase) within one year has a reported specificity of 90% in those with relatively low PSA levels. The hypothesis is that this rate of change is more suggestive of prostate cancer than BPH, but this type of tracking should be done three times – at least a year apart – to achieve reasonable precision,[11] although there is no consensus on that recommendation. Results should also be considered in the context of within-group variability, which has been reported to be anywhere from 5-40% in different groups of patients.[14] Some patients also seem to be "hypervariable" while others are not.

Free PSA

Because PSA circulates both "free" and in "complexes" with micromolecules, measurement of free PSA and PSA complexes can stratify the risk of prostate cancer for men with total PSA ranges from 4.0-10.0 ug/L (or 2.5 -10.0 ug/L),[61,65,70] because prostate cancer is associated with a lower percentage of circulating free PSA (fPSA) than is BPH (for reasons which are still unclear). Patients with total PSA (tPSA) of 3-10 ug/L are the most difficult to diagnose, and comprise the group most frequently biopsied to rule out/confirm cancer. If the DRE and transrectal ultrasound (TRUS) are negative and there is an isolated elevation of PSA, many of the biopsies in this group prove to be negative. If the free-to-total (F/T) ratio is > 0.25, the risk of prostate cancer is only five percent, suggesting that biopsy can be avoided. The type of cancer in that 5% is usually indolent.[12]

Experts suggest the potential usefulness of free-to- total PSA ratio testing (F/T PSA) for those patients with an abnormal total PSA result to help distinguish between BPH and prostate cancer, and to decrease the need for biopsy. Current evidence suggests that the specificity of the PSA test may be enhanced by the use of this measurement (see Table below).

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PSA Specificity Measurement

F/T PSA < 0.10	Probability of prostate cancer is > 90%	probabilities change depending on age, race, and family history
F/T PSA > 0.20	Probability of prostate cancer is < 10%	

Source: Urology 1996;48(6a):1-3. note - in men with PSA values of 3-10 ug/L [71]

In Catalona's widely-read trial,[61] the probability of prostate cancer at biopsy in men with PSA levels of 4.0-10.0 ug/L plus normal DRE ranged from 56% in men that had a free-to-total PSA ratio of up to ten percent, to 8% for men with a free-to-total ratio of >25%. It was suggested that men with ratios more than 25% do not need to be biopsied, but only 20% of the men in this study had this ratio – and they still had a cancer probability of eight percent. This percentage probability would still lead many physicians and their patients to proceed with biopsy. In an article the following year, Catalona suggested fPSA use in men with tPSA values of 2.51- 4.0 ug/L to optimize cancer detection and minimize unnecessary biopsies.[70] Assays for the specific micromolecules to which PSA binds offer promise in further reducing false-positive rates. Concern about greater variability in fPSA kit results than in the kits that measure tPSA remains worrisome for some researchers, but according to lab experts this concern about greater variability between fPSA measurements compared to tPSA measurements is probably related more to specimen handling than anything else. fPSA is much less stable than tPSA. Measurement of complexed PSA has equivalent diagnostic "power" to the fPSA ratio and the specimen is much more stable on storage [72]

In late 1999, the World Health Organization (WHO) designated two calibration standards (also known as the Stamey standard) developed at Stanford University as international standards to be used to improve the reliability of serum PSA testing. These calibrators are standardized samples of purified PSA that can be used to calibrate the assays – 10% free and 90% complexed – used to determine PSA levels. There are significant improvements in laboratory methods agreement after calibration with the WHO calibrator (which reduces result variability between labs), well born out in reported improvements in Ontario laboratories (QMP-LS reports).

Screening intervals

Annual PSA screening may not be the most effective strategy, given the slow growth rate of early prostate cancers. Longer screening intervals, such as every two years, may be more appropriate and have been supported in recent decision analyses.[73] These researchers have also suggested the possible benefit of starting testing at 40 or 45 years, and stopping testing at an earlier age (75, or even 65 years of age) in men with PSA levels which are persistently low (0.5-1.0 ug/L). Hoedemaeker suggested intervals of up to 4 years in those with low PSA levels (also see PSA velocity).[74]

No single approach – PSA density, PSA velocity, age-/race-specific reference ranges, or free PSA – has been shown to be more accurate than the others.[75,76]

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Appendix 2 Search Strategies

The primary search on Medline was the most specific utilizing controlled vocabulary and textwords. The $ sign indicates truncation. Due to low retrieval in some sets and in an effort to be as comprehensive as possible, some sets appear duplicated. Where possible, duplication between databases was removed. The searches were re-run as the databases were updated. All searches were limited to the years 1995-2001. The EMBASE search was limited to age groups in order to reduce the number of retrievals and in the knowledge that there is a large overlap between EMBASE and Medline.

Medline 1995-September 2001 (OVID)

1. prostatic neoplasms/pc
2. prostatic neoplasms/
3. mass screening
4. prostate-specific antigen/
5. 2 and (3 or screen$.tw.)
6. 4 and (3 or screen$.tw.)
7. exp population surveillance/
8. 7 and 2
9. limit 6 to (controlled clinical trial or meta analysis or randomized controlled trial)
10. 6 and (randomi$ or control$).tw.
11. limit 5 to (consensus development conference or consensus development conference, nih or controlled clinical trial or evaluation studies or guideline or meta analysis or multicenter study or practice guideline or randomized controlled trial or technical report or validation studies)
12. 5 and (randomi$ or control$).tw.
13. 1 or 5 or 8 or 9 or 10 or 11 or 12
14. . l/13 lg=en
15. 14 not animal

HealthStar/Ovid Healthstar ≤1975 to September 2001≥

1. prostatic neoplasms/ and screen$.tw.
2. limit 1 to nonmedline
3. limit 2 to (yr=1995-2001)

Cancerlit ≤1975 to September 2001≥ (OVID)

1. prostatic neoplasms/ and screen$.tw.
2. limit 1 to (nonmedline and yr=1995-2001)

Embase ≤1980 to 2001 Week 46≥ (OVID)

1. exp *PROSTATE TUMOR/ or exp *PROSTATE SPECIFIC ANTIGEN/ or exp *PROSTATE CANCER/ or exp *PROSTATE CARCINOMA/
2. 7 and screen$.tw.
3. limit 2 to (english language and yr=1995-2001)
4. limit 3 to (yr=1995-2001 and (adult ≤18 to 64 years≥ or aged ≤65+ years≥))

Cochrane Library Issue 4 2001

1. Prostatic-Neoplasms* :ME
2. Prostate-Specific-Antigen* :ME
3. Screen :KY
4. (#1 or #2) and 3.

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Appendix 3 Summary Table of PSA Screening Studies

European Study of Screening for Prostate Cancer (ERSPC)

Study	Country	Study Design	Screening Protocol	Results	Comments
The International Prostate Screening Trial Evaluation Group **European J Cancer 1999** [77]	**European Study of Screening for Prostate Cancer (ERSPC)** Centres in Belgium, Sweden, Portugal, Spain, Finland, The Netherlands, Italy. In 1999, additional centres in France, Norway and Switzerland were under consideration.	RCT	➢ Initiated 1994 ➢ Men age 55 to 70 years ➢ Planned with sample size of 190,000 men ➢ DRE not to be used for screening when PSA is normal (≤ 3.0 ng/ml) ➢ Trial expected to attain 90% power to detect a statistically significant reduction in prostate cancer mortality of the order of 20% **at 10 years** ➢ Method of recruitment, age of the enrollees, PSA cut-offs vary somewhat among centres	➢ Ongoing ➢ Objective: to determine whether a significant reduction of mortality from prostate cancer can be achieved by screening, through detection of cancer at earlier stages, followed by effective treatment. ➢ **Outcomes from volunteer studies**: will provide estimates of screening efficacy, i.e. the degree of benefit in those who agree to be screened ➢ **Outcomes from population-based studies**: will provide estimates of screening effectiveness, i.e. the degree of benefit in a population invited to be screened, taking into consideration the extent that those invited agree to attend for screening.	➢ Several differences among countries: ➢ Randomized invitations vs volunteer trials ➢ Major differences in baseline mortality from prostate cancer. ➢ Analyses will have to stratify by country and trial in order not to affect the validity of the studies ➢ Different policies *vis-a-vis* application of radical therapy or watchful waiting of confirmed disease and immediate or delayed hormone therapy for more advanced disease ➢ Differences in the trials in the frequency of rescreening, ranging from annual PSA tests in Portugal to every 4 years in The Netherlands, Belgium, Finland and Italy. ➢ In Finland and Sweden, larger numbers of control subjects than in the intervention arms, a process which increases power with minimal increases in costs ➢ Likely to be differences in compliance and contamination rates. ➢ Other potential differences the collaborators hope to overcome (by agreeing upon common/uniform criteria) include differences in pathology classification and potential differences in cause of death classification.

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Study	Country	Study Design	Screening Protocol	Results	Comments
Schroder et al **Urology 2001** [63]	ERSPC Rotterdam, The Netherlands	➢ RCT – Volunteer trial – written informed consent required. ➢ Men identified by means of population registry received letter asking them to participate. Men who responded to the intake questionnaire and who provided informed consent were randomized ➢ Controls followed-up through Cancer Registry	➢ *Original screening protocol* (1994 to 1997): Biopsy if PSA ≥ 4.0, DRE+ or TRUS+; and rescreening after 4 years to a total of two screens ➢ ***Revised screening protocol (Feb 1997 to May 1999):* Biopsy if PSA ≥ 3.0 ng/mL; DRE or TRUS not included; rescreening after 4 years to a total of 2 screens; 1-year screen after benign biopsy omitted**	➢ Ongoing	➢ This paper describes the modification of the original protocol ➢ Several papers reporting interim results have been published to date
Schroder et al **J Urology 2000** [78]	ERSPC Rotterdam, The Netherlands	RCT – see above	➢ See above ➢ 1994 to 1997 ➢ to evaluate the diagnostic value of PSA, DRE, TRUS and tumour characteristics at low PSA, (0 to 4.0 ng/mL) ➢ among men with PSA < 4.0 ng/mL, biopsy performed only if abnormal DRE or TRUS	➢ (results of initial screening using original screening protocol only) ➢ 11,500 randomized to screening, 10,523 actually screened ➢ 9,211/10,523 (87.5%) had PSA < 4.0 ng/mL (12.5% had PSA ≥ 4.0 ng/mL) ➢ 1,315/9,211 had biopsy ➢ 127/1,315 men had prostate cancer ➢ Overall, PPV of DRE and TRUS at PSA 0 to 3.9 ng/mL = 9.7% ➢ PPV = 2.2% if PSA 0 - 0.9 ➢ PPV = 8.5% if PSA 1.0 - 1.9 ➢ PPV = 13.4% if PSA 2.0 - 2.9 ➢ PPV = 25.4% if PSA 3.0 - 3.9 ➢ PPV = 24.1% if PSA 4.0 - 9.9 (similar to PPV if PSA 3.0 to 3.9) ➢ Overall, cancer detection rate was 1.4%	➢ Sensitivity and PPV of DRE and TRUS increased as PSA ranges were closer to 4.0 ➢ PPV and detection rates unacceptably low if PSA 0 – 0.9 ng/mL ➢ Distribution of Gleason scores 2-6, 7 and 8-10 did not seem to be associated with PSA except for men with PSA < 2.0.; however, Gleason scores were 8 – 10 only when PSA > 4.0 ng/mL

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Study	Country	Study Design	Screening Protocol	Results	Comments
Hoedemaeker et al **JNCI 2001** [74]	ERSPC Rotterdam, The Netherlands	RCT – see above	➢ Original for Prevalence Screen ➢ Men 55 to 75 years of age, Biopsy if PSA ≥ 4.0, DRE+ or TRUS+; and rescreening after 4 years to a total of two screens ➢ Men who refused biopsy were excluded from further evaluation ➢ 2nd round ➢ Biopsy if PSA ≥ 3.0 ng/mL; DRE or TRUS not included; 1-year screen after benign biopsy omitted ➢ pathologic features of prostate cancer detected at prevalence screen compared to those detected in second round in a sub-sample of men assigned to the screening arm between June 1994 and March 1996.	➢ Prevalence screen ➢ 4491 randomized to screening; 4133 (92%) actually screened on first round (prevalence screen) ➢ 1129 had biopsy recommended; 1027 (24.8%) agreed to undergo biopsy ➢ 177 (17.2%) had prostate cancer ➢ Overall detection rate = 4.3% ➢ Detection rate among men 59 – 75 years was 4.9% ➢ 2nd round ➢ After various exclusions, 3,023 invited for second screen ➢ 2,385 accepted ➢ 481 (20.2%) had biopsy recommend; 440 (18.4%) agreed to undergo biopsy ➢ 94 (21.4%) had prostate cancer ➢ Detection rate = 3.9% (not statistically different from rates in first round, using Pearson chi-squared test, 2-tailed)	➢ Goal of study was to determine if an interval of four years between PSA screening tests could compromise the detection of curable cancer. ➢ Prostate cancer detection rates similar in both rounds (Note: lower attendance at second round) ➢ Median PSA levels for men diagnosed with prostate cancer were lower in second round ➢ At prevalence screen, PSA levels at biopsy were higher in men with adenocarcinoma than in men with benign disease; at the second round, PSA levels did not differ significantly between men with prostate cancer and those with benign disease. ➢ Amount of adenocarcinoma from sextant biopsy was significantly lower at second round than in those detected at initial round. ➢ Prostate cancers detected at second round were better differentiated ➢ In summary, the number of cancers with adverse prognostic factors at second round were significantly lower (lower volume and grade), and baseline PSA levels did not predict prostate cancer in second round. ➢ Findings suggest that large prostate cancers and those with high grade are detected at the prevalence screen and that even an interval of 4 years is not long enough for large tumours to develop. ➢ Findings do not prove that screening has a beneficial effect on prostate cancer mortality.

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Study	Country	Study Design	Screening Protocol	Results	Comments
Vis et al **Prostate 2001** [79]	ERSPC Rotterdam, The Netherlands	RCT – see above	➢ To compare tumour characteristics in men screened for prostate cancer with and without DRE as an initial screening test at low PSA (0.0 to 3.9 ng/mL) ➢ 10,226 men who underwent screening using initial protocol which included biopsy with PSA ≥ 4.0 ng/mL and DRE and TRUS ➢ 10,753 who participated in revised screening protocol which included biopsy with PSA ≥ 3.0 ng/mL and did not include DRE.	➢ At low PSA, 26.6% (117/440) of screen-detected cancers were detected after evaluation of a suspicious DRE ➢ The number of cancers and tumor aggressiveness features were highly associated with serum-PSA level. ➢ The proportion of possibly harmless disease steadily declined from 100% (PSA 0.0 – 0.9 ng/mL) to 15.4% (PSA 3.0-3.9 ng/mL) ➢ DRE performed unnecessarily in 94.7 – 100% of cases, when detection of clinically significant disease was aimed for. ➢ Using PSA (and a cut-off of 3.0 ng/mL) as the only screening tool, 24.3% (121/498) of screen-detected cancers were in the PSA range 3.0 – 3.9 ng/mL, and 60.0% were assessed as clinically significant.	➢ Authors conclude: ➢ DRE as initial screening test for prostate cancer at low PSA values (0.0 – 3.9 ng/mL) may be replaced by screening using serum-PSA only. ➢ At PSA levels below 3.0 ng/mL, 289 rectal exams are required to find one case of clinically significant disease, and 96 rectal exams are needed to diagnose prostate cancer of any size, grade, or stage.
The International Prostate Screening Trial Evaluation Group **European J Cancer 1999** [77]	ERSPC Antwerp, Belgium	➢ RCT – Volunteer trial ➢ Men aged 55 to 74 years of age selected from population registries with a target of 30,000 men.	➢ Original ➢ Used PSA level ≥ 4.0 ng/mL ➢ Rescreening every 4 years to a total of 2 screens ➢ Revised ➢ Used PSA level ≥ 3.0 ng/mL ➢ Rescreening every 4 years to a total of 2 screens	➢ Ongoing	

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Study	Country	Study Design	Screening Protocol	Results	Comments
The International Prostate Screening Trial Evaluation Group **European J Cancer 1999** [77]	Florence, Italy	➢ RCT - Randomized invitations ➢ Men aged 50-69 years selected from population registries with a target of 15,000; screening started October 1996	➢ Biopsy if PSA level ≥ 4.0 ng/mL ➢ Biopsy will also be performed for suspicious abnormalities found at DRE/TRUS which is routinely performed in subjects with PSA between 2.5 and 4 ng/mL ➢ Rescreening every 4 years to a total of three to four screens	➢ Ongoing	
Maattanen et al **Brit J Cancer 1999** [80]	ERSPC Finland	➢ RCT - Randomized invitations ➢ N= 20,398 men aged 55-67 years from Helsinki and Tampere ➢ Population registries are bases for randomized invitations (in a ratio of 1invited: 2 controls; informed consent not obtained from controls. ➢ Enrolment over 4 years with a total study population of 80,000 planned. ➢ First year of enrolment was 1996.	➢ Biopsy if PSA ≥ 4.0 ng/mL or DRE+ ➢ If PSA 3.0 – 3.9 ng/mL, DRE offered ➢ Initially, 119 men with PSA 2.0 – 2.9 were also offered DRE ➢ Rescreening every 4 years to a total of 3 screens, except for those enrolled at 67 years of age who will have 2 screens. ➢ Primary end point is mortality from prostate cancer, which will be reported based on 10 years of follow-up, with quality of life and cost-effectiveness as the secondary end points.	➢ *First year results* ➢ 7,337 randomized to screening arm ➢ 5,053 (69%) agreed to be screened ➢ Of participants, 3773 (75%) had PSA < 2.0 ng/mL; 852 (17%) between 2.0 and 3.9 ng/mL, and 428 (8.5%) ≥ 4.0 ng/mL ➢ Of men with PSA between 2.0 and 2.9, 119 were offered DRE; 110 / 119 (92%) underwent DRE; 8/110 (7%) were suspicious; 3 / 8 (38%) had prostate cancer ➢ Of men with PSA between 3.0 and 3.9, 272 were offered DRE and 257 (94%) accepted; 39/272 (39%) had suspicious DRE; 9/39 (23.1%) had prostate cancer ➢ PPV was 23% and detection rate was 3.3% for DRE among men with PSA 3.0 to 3.9 ng/mL. ➢ Of men with PSA ≥ 4.0 ng/mL, all (100%) were referred to diagnostic examinations; ➢ 401/428 had biopsy ➢ 106/401 diagnosed with prostate cancer	➢ Preliminary results suggest that a good participation rate can be achieved in a population-based trial. ➢ Cancers detected with screening have characteristics associated with more favourable prognosis compared with tumours detected otherwise.

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Study	Country	Study Design	Screening Protocol	Results	Comments
				➢ PPV was 26% when PSA ≥ 4.0 and 54 % for PSA of 10 ng/mL or higher ➢ PPV if PSA ≥ 4.0 decreased from 31% among men < 60 years of age to 22% among men older than 60 years ➢ Cancer detection rate was 2.1% when PSA ≥ 4.0 ng/mL ➢ > 80% of cancers were localized and well or moderately differentiated ➢ PSA concentrations increased with age	
The International Prostate Screening Trial Evaluation Group **European J Cancer 1999** [77]	ERSPC Portugal	➢ RCT - Randomized invitation ➢ Men aged 50 to 74 years of age, recruited through general practitioners ➢ Target is 15,000 men.	➢ Screening Protocol ➢ Rescreening annually is planned to a total of 4 screens	➢ Ongoing	
The International Prostate Screening Trial Evaluation Group **European J Cancer 1999** [77]	ERSPC Sweden	RCT – Randomized invitation	➢ Population registries in Malmo and Gothenburg are the bases for randomization, at a ratio of 1 invited:2 control. ➢ Target is 32,400 men aged 50 to 66 years ➢ Rescreening every 2 years to a total of 3 screens.	➢ Ongoing	

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The American PLCO Study

Study	Country	Study Design	Screening Protocol	Results	Comments
PLCO (Prostate, Lung, Colorectal & Ovarian Cancer Screening Trial) **NCI Press Office 1996 & 2001** [81,82]	USA	➢ RCT - Volunteer trial ➢ Volunteers who sign a consent to be randomized ➢ Recruitment started in 1993. ➢ Enrollment complete July 2001.	➢ 10 PLCO Screening Centres ➢ planned sample size of 74,000 men aged 55-74 years, half randomised to receive annual PSA and DRE screening to a total of six screens and half to "usual care" in the community ➢ Planned on the assumption that it would have 90% power to show a statistically significant 20% reduction in prostate cancer mortality at 10 years. ➢ PSA cut-off is $\geq$ 4.0 ng/mL ➢ 13-years of follow-up	➢ Ongoing ➢ Primary endpoint is mortality ➢ Secondary objectives of the trial include assessment of: screening variables for each intervention including sensitivity, specificity, and positive predictive value; incidence, stage and survival experience of cancer cases; and the mortality predictive value of biologic and/or prognostic characteristics of tumor tissue as intermediate endpoints.	➢ In winter 1998, changes were made to the protocol. Follow-up was extended for three years so that all participants will be followed at least 13 years. PSA tests were added during the 4th and 5th years.

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Quebec, Canada Study

Study	Country	Study Design	Screening Protocol	Results	Comments
Labrie et al **The Prostate 1999** [22]	Quebec, Canada	➢ Randomized, population-based trial ➢ 46,193 men aged 45-80 years, identified through electoral lists as residing in the area of Quebec City ➢ 15 Nov 1988 to 31 Dec 1996 i.e., follow-up of 8 years	➢ PSA and DRE at initial exam ➢ 3.0 ng/mL upper limit of normal. ➢ Annual screening; PSA alone used at follow-up visits ➢ TRUS and Biopsy performed only if PSA or DRE abnormal	➢ 30,956 were randomized to be invited to be screened, of whom 7,155 (23%) accepted and were screened ➢ 38,056 unscreened men ➢ In control group, 982 men were screened ➢ *Initial analysis and results* ➢ (982 screened men in control group were combined with 7,155 men who accepted to be screened; the unscreened arm combined those men who were not invited to participate (n=15,237) with those who did not accept the invitation to be screened. ➢ Of 8,137 screened men, 367 diagnosed with prostate cancer ➢ Between 1989 and 1996, a total of 142 deaths due to prostate cancer were observed; 5 deaths among 8,137 screened men (4/5 diagnosed at initial visit); 137 deaths among 38,056 unscreened men ➢ Prostate cancer mortality rates during 8-year period were 48.7 and 15 per 100,000 man-years in the unscreened and screened groups, respectively, for a 3.25 odds ratio in favor of screening and early treatment	➢ Letter of invitation for screening resulted in potential imbalance between groups i.e., significant risk of *selection bias / volunteer bias* in screening arm as only 23% of those randomized to be screened actually had screening ➢ The low response rate raises questions regarding the magnitude of benefit of a population-based PSA screening programme (although in late 80s, prostate cancer awareness was lower than it is today). ➢ Substantial crossover occurred between groups; although this study was meant to be conducted as a randomized trial, men in the control group were unaware that they were part of a study; 982 men in control arm were screened. ➢ *Intention-to-treat analysis* ➢ No reduction in mortality was found i.e., no reduction in prostate cancer mortality when those who were randomised to be invited to be screened were compared with the control group not invited

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Study	Country	Study Design	Screening Protocol	Results	Comments
				➢ At first visit, where both PSA and DRE were used, 14% of cancers were found by DRE in men having normal PSA; at follow-up visit, only 3% of cancers were found by DRE in men having normal PSA ➢ PSA was > 3.0 ng/mL in 16.6% and 15.6% of men at initial and follow-up visit ➢ 90.5% and 90.0% of cancers at first and follow-up visits were detected with PSA alone compared to 41.1% and 25% by DRE alone ➢ A 67% decrease in prostate cancer mortality reported in screened group.	

Tyrol Studies

Study	Country	Study Design	Screening Protocol	Results	Comments
Horninger et al **Eur J Cancer 2000**[83]	Tyrol, Austria	➢ Overall study: Prospective cohort ➢ (This study reports results on initial screen only)	➢ October 1993 to September 1994 ➢ 65,000 men, ages 45 to 75 invited ➢ Men with abnormal PSA were invited to undergo further evaluation with DRE and TRUS, while men whose PSA was normal were invited to repeat test within 1 year	➢ *Results of mass-screening with PSA as the initial test* ➢ *Results – Age-referenced* ➢ 21,078/65,000 screened (32%); 1618/21,078 (8%) had increased PSA; 778 (48%) had biopsy ➢ 197/778 (25%) had prostate cancer ➢ 95/135 (70%) who underwent radical prostatectomy had organ-confined cancer; of these 70% were missed by DRE and detected by PSA only; 82 % missed by TRUS	➢ Overall: ➢ 8% with elevated PSA when age-referenced ➢ 9% with elevated PSA when cutoff is $\geq$ 4.0 ng/mL ➢ 983/21,078 biopsies when using both age-referenced cutoffs and PSA $\geq$ 4.0 ng/mL as a cutoff ➢ 205/983 biopsies represents 20.8 % of biopsies performed in study ➢ 23 patients whose cancers would not have been detected using age-referenced cutoffs represent 0.1% of all study participants and 10% of all cancers detected ➢ number of biopsies in younger age groups (45 – 59 years) did not increase significantly

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Study	Country	Study Design	Screening Protocol	Results	Comments
			➢ 3 separate analyses planned: ➢ *1. Age-referenced cut-offs*: ➢ Ages 45 – 49 PSA ≥ 2.5 ➢ Ages 50 – 59 PSA ≥ 3.5 ➢ Ages 60 – 69 PSA ≥ 4.5 ➢ Ages 70 – 75 PSA ≥ 6.5 ➢ If PSA elevated, invited to undergo DRE and TRUS ➢ *2.Comparison of men with elevated PSA according to age-referenced levels to men with PSA levels > 2.5 ng/mL and < 4.0 ng/mL* ➢ *3. Comparison of men with normal PSA according to age-referenced levels to all men ages 50 to 75 years with PSA levels ≥ 4.0 and < 6.5 ng/mL*	➢ 130/135 (97%) were judged to be clinically important with regard to stage, grade and volume ➢ Overall cancer detection rate was 1.2% ➢ *Results – Comparing men with elevated PSA according to age-referenced levels to men with PSA > 2.5 ng/mL to < 4.0 ng/mL,* ➢ 66/1618 men with elevated PSA ➢ 66/66 (100%) had –ve DRE ➢ 66/66 (100%) had biopsy ➢ 16/66 (24%) had prostate cancer ➢ 16/16 (100%) cancers were organ confined and clinically significant ➢ *Results – Comparing men with normal PSA according to age-referenced levels to men with PSA levels ≥ 4.0 ng/mL and < 6.5 ng/mL* ➢ 1872/21,078 (9%) had increased PSA ➢ 320/1872 (17.1%) underwent DRE and TRUS ➢ 205/320 (64%) underwent biopsy ➢ 23/205 (11%) had prostate cancer ➢ 7/23 (30%) had a suspicious DRE ➢ 23/23 (100%) had radical prostatectomy ➢ 8/23 (35%) had organ-confined disease ➢ 5/23 considered to be clinically important with respect to stage, grade and volume	➢ 16/66 (24.2%) carcinomas detected in younger age groups (45 – 59 years); all were organ-confined and clinically insignificant; in older group > 59 years only 5 (21.7%) considered to be of clinical importance ➢ Authors conclude: ➢ By using age-reference ranges, compared with cut-off ≥ 4.0 ng/mL, numerous biopsies can be avoided ➢ However, 0.1% of all men in study or 12 of prostate cancers would not have been detected ➢ If cut-off increased to 4.5 in men 60 – 69 and to 6.5 in men 70 – 79, 23 (11%) of cancers not detected ➢ Of 23 prostate cancers, 7 (30%) would have been detected by DRE ➢ Results support usefulness of age-specific reference ranges for serum PSA

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Study	Country	Study Design	Screening Protocol	Results	Comments
Reissigl et al **Prostate 1997** [84]	Tyrol, Austria	Case series	➢ All male blood donors aged 40 to 65 years on whom PSA testing was routinely performed beginning January 1991 for a period of 3 years ➢ 2272 asymptomatic blood donors divided into 2 groups. ➢ Group 1 included men between 40 and 49 years, DRE if PSA > 4.0 ng/mL; biopsy if suspicious DRE; if DRE normal then no further evaluation but encouraged to return for annual PSA test; at one year, biopsy if a 20% increase in PSA ➢ *Group 2* included men aged 50 – 65 years, TRUS if PSA > 4.0 ng/mL; biopsy if TRUS suspicious	➢ *Among men 40 – 49 years (n = 568)* ➢ 44 of 568 men (8%) presented with PSA > 4.0 and 100% were evaluated by DRE ➢ 2 /44 men (5%) who had suspicious finding on DRE underwent biopsy; both were negative for cancer ➢ 42 men with PSA > 4.0 but negative DRE encouraged to return annually for PSA ➢ 12/42 (29%) showed a 20% increase one year later. ➢ 4/12 (33%) men biopsied had prostate cancer ➢ 2 men with suspicious findings on DRE and negative biopsy at initial screening presented with increase in PSA in second year and both had prostate cancer when biopsied ➢ Cancer detection rate 1.1%; 5 of 6 (83.3%) cancers were organ-confined; Gleason scores ranged from 4 to 8 (mean 5.2) ➢ *Among men 50 – 65 years (n = 1704)* ➢ 240 (14%) had PSA > 4.0 ng/mL; 9% had suspicious findings from DRE; 240 (100%) had biopsy ➢ 58/240 (24%) had prostate cancer; all underwent radical prostatectomy; 42/58 (73%) of cancers missed by DRE ➢ Cancer detection rate 3.4%; 50/58 (86.2) cancers were organ-confined; Gleason scores ranged from 4 to 9 (mean 5.5); only 2 turmours microscopically focal and well differentiated and therefore possibly insignificant	➢ Authors conclude: ➢ PSA measurement in blood donors is a useful method for recruiting volunteers and represents an additional possibility for early detection of prostate cancer in asymptomatic younger males. ➢ However, blood donors may represent unique sub-population and results are not generalizable ➢ A well designed and conducted clinical trial that compares the screened and unscreened population is needed to determine if screening prolongs survival

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Study	Country	Study Design	Screening Protocol	Results	Comments
				➢ PPV for PSA = 18%; PPV for DRE = 5% ➢ *Overall* ➢ Overall cancer detection rate was 2.8% ➢ 42 (72%) of cancers missed on DRE and detected solely by PSA ➢ 50 of 58 pathologically staged cancers (86%) were found to be organ confined ➢ 44/50 (88%) of the organ-confined cancers were missed by DRE and detected solely by PSA.	
Bartsch et al **Urology 2001** [24]	Tyrol, Austria	➢ Population-based study	➢ Cancer incidence data from the Cancer Registry and cancer mortality data from the Central Statistics Office from 1970 to 1999 was used to compare prostate cancer mortality in Tyrol, where PSA screening was made available in 1993 at no cost, to the rest of Austria, where it was not ➢ By 1998, approximately 66% of men in Tyrol aged 45 - 75 had been tested at least once ➢ Initially only total PSA was done but free PSA was added in 1995 ➢ DRE was not part of the initial screening program	➢ The number of 40 – 79-year old Tyrolean men who died of prostate cancer remained constant from 1970 to 1993, it then declined, while the number of other Austrian men who died of prostate cancer did not. ➢ Based on the age-specific rates in Tyrol between 1986 and 1990 there was a 32% decrease in prostate cancer deaths in 1997, a 42% decrease in 1998 and a 33% decrease in 1999 compared to expected. ➢ In addition to a significant decline in prostate cancer mortality in Tyrol, there was also a significant increase in the number of organ-confined, potentially curable cancers detected.	➢ Authors conclude: ➢ The policy of making PSA testing freely available and the wide acceptance by men in the population is associated with a decrease in prostate cancer mortality in an area in which urology services and radiotherapy are available freely to all patients ➢ It is unclear how much of the survival benefit can be attributed to screening and how much can be attributed to treatment which included radical prostatectomy and hormonal therapy for early disease ➢ Any contribution from early detection and treatment will only become apparent in years to come ➢ Results are less conclusive than a randomized controlled trial.

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Study	Country	Study Design	Screening Protocol	Results	Comments
			➢ Since October 1995, bisected PSA levels together with percent free PSA levels < 18% used		

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Other Research Studies in PSA Screening

Study	Country	Study Design	Screening Protocol	Results	Comments
Babaian et al **J Urology 2001** [62]	USA	Case series	➢ 3,172 men ages 40 – 75 years who participated in a free early detection program at the University of Texas between September 1998 and September 1999. ➢ Biopsy if PSA levels ≥2.5 and ≤ 4.0 ng/mL ➢ An 11-core multisite directed biopsy scheme was used to obtain all biopsies ➢ All biopsy cores were colour coded for location specificity and examined by one pathologist	➢ 322 men (10.2%) has PSA between 2.5 and 4.0 ng/mL ➢ 268 of 322 were eligible to participate in study based on eligibility criteria; all were asked to undergo a biopsy ➢ 151 (56%) agreed to participate and underwent DRE and TRUS prior to biopsy; prostate volume was also determined ➢ 37/151 (24.5%) had prostate cancer; cancer incidence was 26% among white men; 23% among black men; and, 7% Hispanic ➢ Comparison of the conventional systematic sextant biopsy strategy and an 11-core multisite directed scheme revealed cancer detection rates of 17.9% and 24.5%, respectively; an alternate biopsy site only was positive in only 10 patients. ➢ 27/37 (67.6%) classified as having clinically significant disease (based on definition proposed by Terry et al, i.e., > 1 positive core, Gleason score ≥ 7 or a cancer focus in 1 core > 3 mm). ➢ Results of DRE were abnormal in 11 (7.3%) men, including 6 (5.5%) of those who had negative and 5 of those (13.5%) who had positive biopsy results; results of TRUS were abnormal in 31(20.5%) men, including 18 (15.8%) with negative and 13 (35.1%) with positive biopsy results.	➢ A significant number of men with PSA in the range of 2.5 to 4.0 ng/mL had prostate cancer and the majority of cancers were clinically significant ➢ Authors recommend a decrease in the threshold for biopsy; if this recommendation were accepted, they suggest that conventional systematic sextant technique may be preferable to an extended strategy.

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Study	Country	Study Design	Screening Protocol	Results	Comments
Carter et al **JAMA 1997** [73]	USA	Retrospective cohort study	➢ Part 1 ➢ Serial PSA measurements at 2- and 4-year intervals from frozen serum samples ➢ Serum samples from men who were participants in a prospective aging study (Baltimore Longitudinal Study of Aging) ➢ 40 men who eventually developed prostate cancer (cases) ➢ 272 men who did not develop prostate cancer (controls) ➢ Part 2 ➢ Case series of 389 consecutive men treated surgically for nonpalpable prostate cancer ➢ Outcome measures ➢ Probability of a PSA conversion to 4.1 – 5.0 ng/mL and to > 5.0 ng/mL at 2 and 4 years ➢ Probability of detecting curable prostate cancer by age and pretreatment PSA level	➢ When pretreatment PSA ≤ 4.0 ng/mL nonpalpable PCs were highly likely (34/36, 94%) to be curable (organ-confined and Gleason score < 7 and negative margins) and the majority (25/36, 69%) were small cancers. ➢ When pretreatment PSA > 4.0 ng/mL and ≤ 5.0 ng/mL, cancers were highly likely to be curable (32/36, 89%) and a minority were small tumours (12/36, 33%). ➢ When pretreatment PSA > 5.0 ng/mL, 96/317 (30%) of cancers were noncurable. ➢ PSA conversion (for cancer cases) to a level at which cure is less likely (>5.0 ng/mL) is rare (0%) after 2 or 4 years when the initial PSA is < 2.0 ng/mL ➢ PSA conversion to a range at which cancers are likely to be curable and less likely to be small (4.1 – 5.0 ng/mL) is rare after 2 years (0% - 4%) when the baseline PSA level is < 2.0 ng/mL but common when the baseline PSA is between 2.1 and 3.0 ng/mL (27%) or 3.1 and 4.0 ng/mL (36%)	➢ Data suggest that for men with no cancer suspected on DRE, a PSA level of 4.0 to 5.0 ng/mL is an acceptable range for maintaining the detection of curable prostate cancer ➢ Suggests that 2-year PSA testing interval is not likely to miss curable prostate cancer among men with no palpable suspicion of cancer on DRE and a PSA level less that 2.0 ng/mL

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Study	Country	Study Design	Screening Protocol	Results	Comments
Carvalhal et al **J Urology 1999** [85]	USA	Longitudinal, community-based study of serial screening	➢ To evaluate the detection rate of prostate cancer in men with suspicious digital rectal examination findings and PSA levels ≤ 4.0 ng/mL ➢ 22,513 community volunteers enrolled from May 1991 to December 1997 in PSA-2 and PSA-3 prostate cancer screening protocols (see Smith et al 1997) ➢ PSA and DRE at 6 month intervals ➢ Biopsy if suspicious findings on DRE and PSA ≤ 4.0ng/mL ➢ Until May 1995, quadrant biopsies, from May 1995 sextant biopsies	➢ N = 2703 with a suspicious DRE and PSA ≤4.0 ng/mL ➢ 1905 (70.4%) men underwent biopsy ➢ 244/1905 (12.8%) had cancer ➢ 1672/1905 (87.8%) underwent quadrant biopsies with 201 (12%) cancers detected; 233 underwent sextant biopsies with 43 (18.4%) cancers detected (increase associated with sextant biopsies was significant, p=0.0001) ➢ 12.8% detection rate correlated with age, race, and PSA (p=0.03) ➢ PPV of a suspicious DRE was 5, 14 and 30% in men with PSA 0-1.0, 1.1-2.5 and 2.6 to 4.0 ng/mL, respectively ➢ Of the cases that were surgically staged 82% were organ confined and 78% were moderately differentiated	➢ Authors concluded: ➢ Majority of cancer cases detected by DRE had features of clinically important and potentially curable disease ➢ PPVs in study are strong argument for performing DRE in prostate cancer screening programs even when PSA is low ➢ Compliance did not differ according to age, race, or PSA level ➢ Cancer detection increased after sextant biopsies were performed
Crawford et al **Prostate 1999** [68]	USA	Retrospective cohort study	➢ Of 142,111 records of men screened from 1992 to 1995, 116,000 met the following criteria: ages 40 to 79; had valid PSA (≥ 0 ng/mL) and had DRE results ➢ Purpose of study was to examine the diagnostic efficiency of PSA and DRE testing when using either 4.0 ng/mL or an age-specific reference range (ASRR) as an	➢ *When using a 4.0 ng/mL cutoff PSA* value, the PPVs of abnormal PSA alone, abnormal DRE alone, and combined abnormal PSA and DRE tests were 27.7%, 17.7%, and 56.0%, respectively. ➢ Sensitivities were 34.9%, 27.1% and 38.0%, respectively ➢ Specificities were 63.1%, 49.0% and 87.92%, respectively ➢ The PPVs of combined tests were highest when using a 4.0 ng/mL cutoff PSA value or an ASRR cutoff PSA value (all P <0.001) ➢ When using age-specific reference ranges, the PPVs of PSA, DRE,	➢ Significantly higher PPVs indicated that utilizing both a PSA test and a DRE is most effective in screening for the early detection of prostate cancer ➢ Although higher PPVs when using an ASRR cutoff PSA value suggested fewer unnecessary biopsies, lower sensitivities resulted in fewer cancers detected. ➢ Authors recommend that the combination of a PSA test with a cutoff value of 4.0 ng/mL and a DRE should continue to be utilized in the screening programs.

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Study	Country	Study Design	Screening Protocol	Results	Comments
			abnormal cutoff PSA value ➢ Using 4.0 ng/mL as cutoff, 22,014 (18.9%) had elevated PSA, abnormal DRE or both ➢ Using age-specified ranges, 17,561 (15.1%) had elevated PSA, abnormal DRE or both ➢ These men were classified into 3 categories: men with abnormal PSA but normal DRE; men with normal PSA but abnormal DRE; and men with abnormal PSA and DRE ➢ The positive predictive value (PPV), sensitivity and specificity of PSA, DRE, and combined PSA and DRE were evaluated.	and combined tests were higher than those when using a 4.0 ng/mL but without statistical significance (all P > 0.05). ➢ Sensitivity of PSA when using an ASRR was lower than when using 4.0 ng/mL.	
Gann et al **JAMA 1995** [58]	USA	Nested case control study of men providing plasma samples before a 10-year follow-up	➢ 366 men (cases) diagnosed with prostate cancer and 1098 men (3 controls per case), matched by age, were randomly selected from all cohort members (from the Physicians' Health Study, an ongoing RCT that enrolled 22,071 men aged 40 to 84 years in 1982)	➢ Using a single serum sample collected 10 years before disease ascertainment, authors demonstrated: ➢ 2-fold risk of a prostate cancer diagnosis in men with PSA levels of 1.01 to 1.50 ng/mL ➢ 5-fold risk in men with PSA levels of 2.01 to 3.00 ng/mL compared with men with PSA levels < 1.0 ng/mL.	➢ Authors concluded that "PSA has the highest validity of any circulating cancer screening marker discovered thus far" and recommend "that cost-effective screening strategies incorporating PSA testing are warranted." ➢ The use of archived plasma allowed them to develop a direct estimate of lead time i.e., 5.4 years for aggressive tumours ➢ PSA with cutoff of 4.0 had a sensitivity of 46% in identifying cases of prostate cancer in next decade, specificity was 91%. ➢ Serum PSA level is a strong predictor of a future diagnosis of prostate cancer – even when serum levels are below "normal".

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Study	Country	Study Design	Screening Protocol	Results	Comments
Carvalhal et al **J Urology 1999** [85]	USA	Longitudinal, community-based study of serial screening	➢ To evaluate the detection rate of prostate cancer in men with suspicious digital rectal examination findings and PSA levels ≤ 4.0 ng/mL ➢ 22,513 community volunteers enrolled from May 1991 to December 1997 in PSA-2 and PSA-3 prostate cancer screening protocols (see Smith et al 1997) ➢ PSA and DRE at 6 month intervals ➢ Biopsy if suspicious findings on DRE and PSA ≤ 4.0ng/mL ➢ Until May 1995, quadrant biopsies, from May 1995 sextant biopsies	➢ N = 2703 with a suspicious DRE and PSA ≤4.0 ng/mL ➢ 1905 (70.4%) men underwent biopsy ➢ 244/1905 (12.8%) had cancer ➢ 1672/1905 (87.8%) underwent quadrant biopsies with 201 (12%) cancers detected; 233 underwent sextant biopsies with 43 (18.4%) cancers detected (increase associated with sextant biopsies was significant, p=0.0001) ➢ 12.8% detection rate correlated with age, race, and PSA (p=0.03) ➢ PPV of a suspicious DRE was 5, 14 and 30% in men with PSA 0-1.0, 1.1-2.5 and 2.6 to 4.0 ng/mL, respectively ➢ Of the cases that were surgically staged 82% were organ confined and 78% were moderately differentiated	➢ Authors concluded: ➢ Majority of cancer cases detected by DRE had features of clinically important and potentially curable disease ➢ PPVs in study are strong argument for performing DRE in prostate cancer screening programs even when PSA is low ➢ Compliance did not differ according to age, race, or PSA level ➢ Cancer detection increased after sextant biopsies were performed
Crawford et al **Prostate 1999** [68]	USA	Retrospective cohort study	➢ Of 142,111 records of men screened from 1992 to 1995, 116,000 met the following criteria: ages 40 to 79; had valid PSA (≥ 0 ng/mL) and had DRE results ➢	➢ *When using a 4.0 ng/mL cutoff PSA* value, the PPVs of abnormal PSA alone, abnormal DRE alone, and combined abnormal PSA and DRE tests were 27.7%, 17.7%, and 56.0%, respectively. ➢ Sensitivities were 34.9%, 27.1% and 38.0%, respectively ➢ Specificities were 63.1%, 49.0% and 87.92%, respectively	➢ Significantly higher PPVs indicated that utilizing both a PSA test and a DRE is most effective in screening for the early detection of prostate cancer ➢ Although higher PPVs when using an ASRR cutoff PSA value suggested fewer unnecessary biopsies, lower sensitivities resulted in fewer cancers detected. ➢ Authors recommend that the combination of a PSA test with a cutoff value of 4.0 ng/mL and a DRE should continue to be utilized in the screening programs.

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Study	Country	Study Design	Screening Protocol	Results	Comments
			➢ Purpose of study was to examine the diagnostic efficiency of PSA and DRE testing when using either 4.0 ng/mL or an age-specific reference range (ASRR) as an abnormal cutoff PSA value ➢ Using 4.0 ng/mL as cutoff, 22,014 (18.9%) had elevated PSA, abnormal DRE or both ➢ Using age-specified ranges, 17,561 (15.1%) had elevated PSA, abnormal DRE or both ➢ These men were classified into 3 categories: men with abnormal PSA but normal DRE; men with normal PSA but abnormal DRE; and men with abnormal PSA and DRE ➢ The positive predictive value (PPV), sensitivity and specificity of PSA, DRE, and combined PSA and DRE were evaluated.	➢ The PPVs of combined tests were highest when using a 4.0 ng/mL cutoff PSA value or an ASRR cutoff PSA value (all P <0.001) ➢ When using age-specific reference ranges, the PPVs of PSA, DRE, and combined tests were higher than those when using a 4.0 ng/mL but without statistical significance (all P > 0.05). ➢ Sensitivity of PSA when using an ASRR was lower than when using 4.0 ng/mL.	

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Study	Country	Study Design	Screening Protocol	Results	Comments
Gann et al **JAMA 1995** [58]	USA	Nested case control study of men providing plasma samples before a 10-year follow-up	➢ 366 men (cases) diagnosed with prostate cancer and 1098 men (3 controls per case), matched by age, were randomly selected from all cohort members (from the Physicians' Health Study, an ongoing RCT that enrolled 22,071 men aged 40 to 84 years in 1982) ➢ PSA testing was evaluated by measuring levels in stored blood at the start of follow-up in a cohort of men who later were or were not diagnosed with prostate cancer ➢ A baseline risk of prostate cancer of 1.0 if PSA $\leq$ 1.0 was arbitrarily selected.	➢ Using a single serum sample collected 10 years before disease ascertainment, authors demonstrated: ➢ 2-fold risk of a prostate cancer diagnosis in men with PSA levels of 1.01 to 1.50 ng/mL ➢ 5-fold risk in men with PSA levels of 2.01 to 3.00 ng/mL compared with men with PSA levels < 1.0 ng/mL. ➢ A single elevated PSA level detected 80% of all aggressive cancer diagnosed within 5 years and about 50% of aggressive cancers as early as 9-10 years before diagnosis. ➢ Only 96 of 1098 men who remained free of prostate cancer diagnosis over a 10 year period had an elevated PSA, therefore, the number of false positives remained low over this period of time. ➢ The mean lead time using PSA testing was estimated to be 5.4 years ➢ Mean age at baseline was 62.9 years ➢ Mean age at prostate cancer diagnosis was 68.7 years	➢ Authors concluded that "PSA has the highest validity of any circulating cancer screening marker discovered thus far" and recommend "that cost-effective screening strategies incorporating PSA testing are warranted." ➢ The use of archived plasma allowed them to develop a direct estimate of lead time i.e., 5.4 years for aggressive tumours ➢ PSA with cutoff of 4.0 had a sensitivity of 46% in identifying cases of prostate cancer in next decade, specificity was 91%. ➢ Serum PSA level is a strong predictor of a future diagnosis of prostate cancer – even when serum levels are below "normal".
Ito et al **Urology 2000** [86]	Japan	Retrospective cohort	➢ 6744 men who had undergone mass screening for prostate cancer in Gunma Prefecture from 1994 to 1998 ➢ Biopsy if abnormal PSA, DRE or TRUS	➢ The diagnostic efficiency of the age-specific PSA reference range was optimal with cutoff values of 3.0, 3.5, 4.0, 4.0, and 7.0 mg/mL in subjects 60 – 64, 65 – 69, 70 – 74, 75 – 79, and > 80 years of age, respectively.	➢ Authors conclude: ➢ The age-specific PSA reference range cutoff value in this setting demonstrated better diagnostic efficiency that the standard cutoff value of PSA and the age-specific PSA reference range determined by the 95% confidence interval.

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Study	Country	Study Design	Screening Protocol	Results	Comments
			➢ Men > 60 years were grouped according to their age at 5-year intervals ➢ Cutoff value of the age-specific PSA reference range was calculated for each group by analyzing the ROC curve	➢ By using the age-specific PSA reference range as determined by the ROC curve, the sensitivity, specificity, and efficiency increased to 92.4%, 91.2% and 84.3%, respectively. ➢ When the standard PSA reference range was used for the diagnosis, the sensitivity, specificity, and efficiency was 89.1%, 92.4%, and 82.3%, respectively ➢ All of the cases of prostate cancer detected by using the age-specific PSA reference range with the cutoff point based on the ROC curves were clinically significant.	➢ Likely to be a useful diagnostic index for the first step of mass screening in Japanese men.
Ito et al **Cancer 2001** [87]	Japan	➢ Prospective cohort – informed consent for mass screening for prostate cancer had been received from all subjects	➢ N = 8595 men , ages ≥ 50 years ➢ Initial PSA level ≤ 4.0 ng/mL ➢ Biopsy if abnormal PSA, DRE or TRUS ➢ If biopsy negative, men were followed with repeated PSA, DRE and TRUS examination every 6 months and underwent biopsies up to 3 times if their PSA level increased or abnormal DRE and TRUS were highly suspicious. ➢ Cases were divided into 3 groups: PSA levels <1.0, 1.0 to 1.9 ng/mL and 2.0 to 4.0 ng/mL	➢ Prostate cancer detected in 0.18% (8 of 4526), 1.0% (27 of 2724), and 3.6% (49 of 1345) of men whose initial PSA levels were lower than 1.0, 1.0 to 1.9, and 2.0 to 4.0 ng/mL respectively ➢ Among the prostate cancer cases, 25% (6 of 8), 56% (15 of 27), and 63% (31 of 49) were detected by abnormal PSA in patients with initial PSA levels lower than 1.0, 1.0 to 1.9, and 2.0 to 4.0 ng/mL, respectively. ➢ The detection rates of prostate cancer within 3 years after the initial visit were 0.07%, 0.24%, and 1.2% in cases with initial PSA levels lower than 1.0, 1.0 to 1.9, and 2.0 to 4.0 ng/mL, respectively.	➢ In individuals with initial PSA levels lower than 1.0 ng/mL, it is recommended that DRE and PSA screening be done every 3 years, and DRE is more useful than PSA ➢ In individuals with initial PSA levels of 1.0 to 4.0 ng/mL, annual measurement of PSA was more useful than DRE, and it is recommended that PSA screening should be performed once each year. ➢ The prostate cancer detection rate of screening increased during the 10 years after the initial visit with little fluctuation , especially in cases with initial PSA levels of 2.0 – 4.0 ng/mL. ➢ Cases with PSA levels of 2.0 to 4.0 ng/mL are at high risk of developing prostate cancer in the future ➢ Overall, authors recommend that DRE and PSA measurements be performed every year for individuals with initial PSA level of 1.0 to 4.0 ng/mL

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Study	Country	Study Design	Screening Protocol	Results	Comments
			➢ The prostate cancer detection rate, the clinicopathologic features of the prostate cancer and the clinical usefulness of PSA velocity were investigated.		
Smith et al **JAMA 1996** [28]	USA	➢ Longitudinal, community-based study of serial screening ➢ July 1989 – Sept 1991	➢ N=10,248 men ≥ 50 years ➢ Screened at 6 month intervals for a minimum of 48 months ➢ DRE not performed at time of PSA testing	➢ 79% returned for screening at 48 months ➢ Compliance 50% in subsets that started with elevated PSA level (> 4.0ng/mL) ➢ 2.5% had died by end of 4-yr screening ➢ 38% with initial PSA, 4.1 to 9.9 had cancer detected ➢ 70% with initial PSA ≥ 10 ng/mL had cancer detected ➢ Percent with clinically advanced cancer was significantly lower in cancers detected through serial screening; 6% of cancers were clinically advanced when detected at initial screening vs 2% of those cancers detected during serial screening ➢ 85% of all prostate cancers were detected during the first 2 yrs of screening ➢ In men who underwent surgery, the proportion with high-grade cancer decreased from 11% to 6%, and the proportion with pathologically advanced cancer was proportionately reduced but not significantly reduced (from 33% to 27%). ➢ 3% of total cohort had cancer detected at time of initial screening	➢ The authors examined the first 4 years of serial PSA-based screening trends to determine compliance, the prevalence of abnormal screening test results, cancer detection rates, and the stage and grade of cancers detected, and they concluded that the proportion of men with abnormal test results decreased, and the prostate cancer detection rate decreased to near the reported population-based incidence rates. ➢ However, follow-up was short, only 3 – 4 years (Ito 2001) ➢ Results may not be generalizable due to: 1) low rate of participation by Afro-American (99% white); and 2) selection bias, i.e., all participants were community volunteers

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Study	Country	Study Design	Screening Protocol	Results	Comments
				➢ The rate of conversion to a PSA value > 4.0 ng/mL was very low (< 1% each year) for those subjects entering the trial with PSA < 2.5 ng/mL ➢ In the entry range of 2.5 – 4.0 ng/mL, the conversion rate was 5 – 6% each year ➢ Data demonstrate that after 4 years of testing 8662 men at 6-month intervals, the rate of PSA conversion to > 4.0 ng/mL was 4% when the baseline PSA was less than 2.5 ng/mL and 48% when the baseline PSA level was 2.6 to 4.0 ng/mL	
Smith et al **American Cancer Society 1997** [88]	USA	➢ Longitudinal study (this paper reports results of initial screen only)	➢ ~30,000 community volunteers enrolled in one of three screening protocols (PSA-1, PSA-2, and PSA-3) ➢ Inclusion criteria include: age > 50 years and no history of prostate cancer or prostatitis ➢ *PSA-1:* ➢ N = 10,248 men enrolled from July 1989 to September 1991 ➢ If PSA > 4.0 ng/mL, then DRE and TRUS ➢ Biopsy if either DRE or TRUS suspicious ➢ *PSA-2:*	➢ Initial PSA levels similar across studies *and* cancer detection rates across studies within each PSA stratum were similar ➢ 9% (938/10,248), 17% (3114/18608) and 20% (486/2478) of volunteers recommended for biopsy in the PSA-1, PSA-2 and PSA-3 studies, respectively ➢ Proportion of men who complied with biopsy recommendations differed among 3 studies; 8% (866/10248), 13% (2466/18608), and 8% (198/2478) of the volunteers underwent biopsy in the PSA-1, PSA-2 and PSA-3 studies, respectively ➢ Cancer was detected in 33% (284/866), 25% (606/2466) and 31% (62/198) of men who underwent biopsy in the PSA-1, PSA-2 and PSA-3 studies, respectively	➢ The authors conclude: ➢ Although the study population was not population-based, the results demonstrate that, at least in men who self-select to be screened, the tests have reasonable PPV and they detect carcinomas at an earlier stage ➢ The majority of screen-detected tumors had the pathologic characteristics of medically significant carcinoma

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Study	Country	Study Design	Screening Protocol	Results	Comments
			➢ N = 18,608 men enrolled from May 1991 to April 1995 ➢ PSA and DRE every 6 months ➢ Biopsy if PSA > 4.0 ng/mL and / or DRE +ve (quadrant biopsy until April 1995, then sextant biopsy) ➢ *PSA-3:* ➢ N = 2,478 men enrolled from May 1995 to December 1996 ➢ PSA and DRE every 6 months ➢ Biopsy if PSA > 2.5 ng/mL (sextant biopsy and histopathologic protocol)	➢ PPV for cancer detection was 33% for PSA-1, 25% for PSA-2 and 31% for PSA-3 groups ➢ The overall cancer detection rate was 3.0% (952/31,334) ➢ In subset of 108 men from whom completely embedded surgical specimens were obtained, only 10 (9%) were categorized as having possibly harmless cancer	
Yao et al **J Urology 2001** [89]	USA	➢ Retrospective cohort study ➢ From a population of 1.1 million men, SEER and Medicare data were linked together for 36,422 patients diagnosed with prostate cancer between 1989 and 1993.	➢ Men ≥ 65 years with newly diagnosed prostate cancer during 1989 and 1993 ➢ Residing in 9 geographic areas ➢ Relationship of the interval of 3-12, 13-24, 25-36 and 37-64 months, corresponding to testing once every 1 to 3 and greater than 3 years, respectively, after a negative PSA test and the diagnosis of nonlocalized disease or death for	➢ Among men who would be diagnosed with prostate cancer the risk of non-localized cancer did not differ in those tested 2 or 3 years compared with the risk in those tested 1 year before diagnosis (RR=1.0, 95% CI 0.84 – 1.20 or RR = 1.02, 95% CI 0.74-1.40 respectively). ➢ Prostate cancer specific mortality in the biennial and annual groups was also similar (RR=0.96, 95% CI 0.64 – 1.44). ➢ Risk of prostate biopsy in these men was directly related to the number of PSA tests performed	➢ Patients who choose to undergo PSA testing may be tested on a biennial instead of annual basis without an increased risk of nonlocalized cancer ➢ Decreasing the frequency of PSA testing may lead to fewer prostate biopsies ➢ Large population based nature of database allowed authors to address many methodological constraints observed in previous studies, including restricted sample size, failure to account for several confounding factors and lack of generalizability to the population at large ➢ However, nature of the database does not permit detailed analysis of the potential influence of various PSA cutoffs, density, velocity, fractions as well as other potential factors.

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Study	Country	Study Design	Screening Protocol	Results	Comments
			➢ cancer specific survival was considered the measure of an acceptable PSA testing interval ➢ Risks of non-localized cancer and cancer specific survival were determined by logistic regression ➢ Age, geographic region, year of diagnosis and race were included as covariates.		➢ It also is conceivable that patients at lower risk for cancer may have been tested less often. This scenario would result in the appearance that longer testing intervals are acceptable when in fact such intervals would be acceptable only in low risk cases.

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Appendix 4

Some methodological comments on the screening trials

The interim results from European studies in particular are highly quoted as proof that PSA is an effective screening tool which should be widely used on a population-wide basis to reduce prostate cancer mortality. The interim results show promise, but while final results are eagerly anticipated, there are several important problems to consider. There are significant methodological differences among trials which will have to be taken into consideration "if and when any heterogeneity in the findings is eventually identified".[52] Some of the potential problems that the authors highlight are listed below:

- Different ways of recruiting participants are used: volunteer trials with enrollment after informed consent (the Netherlands, Canada, USA) versus population-based randomization followed by invitation to participate (Finland, Italy, Portugal, Sweden.
- There are major differences in baseline mortality from prostate cancer. Countries with highest mortality are Sweden, Finland, The Netherlands, Belgium and the U.K. Those with the lowest mortality rates are Portugal, Spain and Italy. Canada and USA are intermediate. These differences will have an impact on the power of the studies.
- Analyses will have to be stratified by country and trial in order not to affect the validity of the studies.
- A difference in outcome could relate to different policies about provision of radical therapy or watchful waiting of confirmed disease and immediate or delayed hormone therapy for more advanced disease.
- There are also differences in the trials in the frequency of re-screening, ranging from annual PSA tests in the US, Canada and Portugal to every four years in the Netherlands, Belgium, Finland and Italy.
- There are likely to be differences in compliance and contamination rates. We mentioned earlier in this document that there are concerns about the amount of PSA screening being done in an ad lib fashion in the control arm of the trial.
- Other potential differences the investigators/collaborators hope to overcome by agreeing upon common/uniform criteria include differences in pathology classification and potential differences in cause of death classification.
- Outcomes in volunteer studies will provide estimates of screening efficacy (i.e. the degree of benefit in those who agree to be screened). The PLCO trial will also permit analysis of whether benefit is concentrated in certain risk groups (e.g. those with a positive family history). Outcomes in population-based studies will provide estimates of screening effectiveness, i.e. the degree of benefit in a population invited to be

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screened, taking into consideration the extent that those invited agree to attend for screening.

- **Tyrol study**: since screening was introduced in the Tyrol in 1993, the study parameters have changed markedly: initially, age-referenced levels in combination with percent free PSA of less than 22% were used as the biopsy criteria; incrementally, age-referenced PSA levels in combination with percent free PSA of less than 18% were then added.[24,83,84] Since October 1995, bisected PSA levels together with percent free PSA levels of less than 18% were used, and finally, since March 1996, PSA transition zone density has been introduced as an additional diagnostic parameter in selecting patients for biopsy to decrease the number of unnecessary biopsies. It may be difficult to draw conclusions about specific characteristics of the screening program because of the change of parameters.

- **The Tyrol study** authors conclude that decline in mortality is likely to be due to aggressive downstaging and successful treatment – and that *any contribution made by detecting and treating early cancers will only become apparent in the years to come*.

- **The Tyrol study** will be difficult to reproduce. The geographic region, the significantly heightened public awareness, the availability of high-quality urologic care and appropriate treatment facilities, all of which are available to the whole population, influenced the success of the study.

- **The Tyrol study** investigators suggest that disease prevention strategies, improvement in treatment modalities as well as earlier detection may be influencing the mortality rate.

Appendix 5 Recommendations for PSA Screening by Organization

Organization	Recommendation	Source / Date
Canada		
Canadian Cancer Society [90]	Recommends that all men over the age of 50 years should discuss with their doctor the potential benefits and risks of early detection using Prostate Specific Antigen (PSA) and Digital Rectal Examinations so they can make informed decisions about the use of these tests. Men at high risk because of family history, or those of African Canadian ancestry may wish to discuss the need for testing at a younger age.	http://www.cancer.ca (28 February 2002)
Alberta Cancer Society [91]	All men should have the opportunity to undergo a DRE and PSA test if, after assessing the benefits and risks of early detection, they choose to be screened. The Canadian Cancer Society therefore recommends that men should be made aware of the benefits and risks of early detection using DRE and the PSA test, so they can make informed decisions. In combination, PSA and DRE offer the best possibility of detecting prostate cancer, since each can signal the presence of the disease that the other might miss.	http://www.cancer.ab.ca/site/prostate/pscreen.htm (2 January 2002)
British Columbia Cancer Agency [92]	Serum PSA is of unknown value as a population screening test. Although there is good evidence that it increases the detection rate of early stage clinically significant prostate cancers, there is little evidence to date that such early detection leads to reduced mortality; the "gold standard" for evaluating screening tests. Fit men (men with at least 10 years life expectancy) between the ages of 50 and 70 should be made aware of the availability of PSA as a detection test for prostate cancer. They should be aware of the potential benefits and risks of early detection so they can make an informed decision as to whether to have the test performed."	Revised July 2000 by the Genitourinary Tumour Group Http://www.bccancer.bc.ca/pg_g_04.asp?PageID=2749&ParentID=4 (2 January, 2002)
Canadian Task Force on Preventive Health (formerly, Canadian Task Force on the Periodic Health Examination) [93]	Update on hold pending release of new evidence - the CTF still endorses its 1994 recommendations on prostate cancer screening: "In the absence of acceptable evidence for early detection efforts, one turns to a search for sound evidence of the effectiveness of therapy for the condition once it is identified. Unfortunately, there is no adequate evidence from comparative studies to evaluate the main therapeutic options for prostate cancer, particularly for early stage lesions. A randomized controlled trial to evaluate screening is underway and a randomized trial to evaluate therapy is in the planning stages in the U.S. European trials evaluating various aspects of therapy are also underway but no results are as yet available. "Based on the absence of evidence for effectiveness of therapy and the substantial risk of adverse effects associated with such therapy; and the poor predictive value of screening tests, there is at present insufficient evidence to support wide-spread initiatives for the early detection of prostate cancer. The Task Force does not recommend the routine use of PSA as part of a periodic health examination. While PSA can detect earlier cancer, it is associated with a substantial false positive rate. This, combined with poor evidence to support the effectiveness of subsequent therapy and clear evidence of substantial risk associated with such therapy, means that the widespread implementation of PSA would expose more men to uncertain benefit, but to definite risks. For these reasons the Task Force recommends that PSA be excluded from the periodic health examination (D Recommendation).	Http://www.ctfphc.org/ (28 December 2001) Reviews in Progress (August 2001)

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Organization	Recommendation	Source / Date
	The Task Force debated recommending the exclusion of DRE from the periodic health examination because of its limited performance as an early detection test. However, DRE has been routine practice for many physicians for the early detection of prostate abnormalities and the available evidence was not considered sufficiently powerful to advise physicians who currently include DRE as part of a periodic health examination in men aged 50 to 70 to discontinue the practice. At the same time, the evidence is insufficient to advocate the inclusion of DRE for those physicians who do not currently include it as part of the periodic health examination for men aged 50 to 70. Hence, the decision to retain a C Recommendation for DRE – there is insufficient evidence to include DRE or exclude it from the periodic health exam. Based on the available evidence for TRUS, the Task Force recommends against the routine use of this procedure as part of a periodic health examination (D Recommendation). “	
Canadian Urological Association [94]	"The digital rectal examination (DRE) and prostate specific antigen (PSA) measurements increase the early detection of clinically significant prostate cancer. Men should be made aware of the potential benefits and risks of early detection so that they can make an informed decision as to whether to have this test performed."	http://www.cua.org/ (28 December, 2001) “These guidelines or position papers reflect the current viewpoint of the Canadian Urological Association. – Approved June 1996
HSURC [95]	The guidelines state that physicians should not use the prostate specific antigen (PSA) test to screen men without signs or symptoms of prostate cancer. A working group of Saskatchewan experts concluded the PSA test is not an effective screening tool because of problems with test reliability, the nature of prostate cancer, risks associated with procedures used to follow up elevated PSA levels, and the absence of evidence from RCTs. (Guideline recertified Feb 2001)	Guideline recertified – February 2001. http://www.hsurc.sk.ca/research_studies/research.php3?rid=11&rstatus=3 (2 January, 2002)
USA		
American College of Preventive Medicine [96]	Recommends against routine population screening with DRE and PSA. Men age 50 or older with a life expectancy of greater than 10 years should be given information about the potential benefits and harms of screening and limits of current evidence and should be allowed to make their own choice about screening, in consultation with their physician, based on personal preferences. Methods and tools for helping patients review this information are available; however, the ACPM recommends further research be conducted in optimizing the process of patient education and informed consent.	http://www.acpm.org/prostate.htm (30 December, 2001)
American College of Physicians – American Society of Internal Medicine [97]	“In the absence of evidence that early detection of prostate cancer and aggressive treatment of localized cancer does more good than harm, such screening should be optional pending results of controlled trials. Cutoff age is a controversial point even among advocates of screening; for older men, localized cancers become less likely to cause death given "competing hazards." Many urologists recommend screening only men with a minimum of a 10-year life expectancy (about age 74 given average health). Recommendations by the American Cancer Society (ACS) create medicolegal concerns among primary care physicians. One approach is to explain the pros and cons of prostate cancer screening and try to help the patient make an individualized decision and then document the decision. This is the current approach recommended by the ACP-ASIM.	http://www.acponline.org/vas2000/sessions/cancer.htm (2 January, 2002) 2000 Annual Session ACP-ASIM Oncology: Screening for Breast, Colorectal, and Prostate Cancer

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Organization	Recommendation	Source / Date
	The informational value of serum PSA is poor in patients with symptomatic BPH, but because of the medicolegal aspects, discussing the availability of testing with these patients and documenting is reasonable.	
American Cancer Society [98]	The prostate-specific antigen (PSA) test and the digital rectal examination (DRE) should be offered annually beginning at age 50 to men who have a life expectancy of at least 10 years. Men at high risk should begin testing at age 45. Information should be provided to patients about benefits and limitations of testing. Specifically, prior to testing men should have an opportunity to learn about the benefits and limitations of testing for early prostate cancer detection and treatment.	www.cancer.org (American Cancer Society, Prostate Cancer Screening Guideline, Jan Feb 2001 Issue of CA – A Cancer Journal for Clinicians
American Academy of Family Physicians [99]	Decisions about screening should be individualized and reached after a discussion with the patient of the potential benefits and established harms of screening, diagnosis, and treatment. Screening for prostate cancer is controversial and neither the U.S. Preventive Services Task Force nor the American Academy of Family Physicians has recommended screening because of the known risks and uncertain benefits	http://www.aafp.org/afp/20000815/practice.html (31 December, 2001)
American Medical Association [100]	The launching of mass screening programs for the early detection of prostate cancer is premature at this time. All men who would be candidates for and interested in active treatment for prostate cancer should be provided with information regarding their risk of prostate cancer and the potential benefits and harms of prostate cancer screening, sufficient to support well-informed decision-making. Prostate cancer screening, if elected by the informed patient, should include both prostate-specific antigen (PSA) testing and digital rectal examination (DRE). Men most likely to benefit from tests for early detection of prostate cancer should have a life expectancy of at least 10 years and include: Men 40 years of age or older of African-American descent; men 40 years of age or older with an affected first-degree relative; and men 50 years of age or older.	Recommendations by the Council on Scientific Affairs, were adopted as AMA policy at the 2000 AMA Annual Meeting Last updated: Jun 08, 2001 http://www.ama-assn.org/ama/pub/article/2036-2928.html (31 December, 2001)
American Urological Association [101]	PSA testing should be offered to men 50 years of age or older who have an estimated life expectancy of at least 10 years and to men over 40 with established risk factors (e.g., family history is positive or the patient is African-American). It should be performed in conjunction with the digital rectal exam (DRE), since the combination of the two tests is more sensitive for diagnosis than either one alone. The PSA 'Best Practice Policy' report developed by a multi-disciplinary panel of physicians and released by the AUA in February 2000 also recommends that "decisions regarding early detection of prostate cancer should be individualized and benefits and consequences should be discussed with the patient before PSA testing occurs.	http://www.auanet.org/media_press/press_releases/prostate.cfm (31 December, 2001)
National Cancer Institute [102]	No recommendation. *For whom might a PSA screening test be recommended? How often is testing done?* "The benefits of screening for prostate cancer are still being studied. The National Cancer Institute (NCI) is currently conducting the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial, or PLCO trial, to determine if certain screening tests reduce the number of deaths from these cancers. The DRE and PSA are being studied to determine whether	http://search.nci.nih.gov/search97cgi/s97_cgi CANCER FACTS National Cancer Institute ° National Institutes of Health fact sheet was reviewed on 1/11/01

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Organization	Recommendation	Source / Date
	yearly screening to detect prostate cancer will decrease one's chance of dying from prostate cancer. Doctors' recommendations for screening vary. Some encourage yearly screening for men over age 50; others recommend against routine screening; still others counsel men about the risks and benefits on an individual basis and encourage patients to make personal decisions about screening."	
U.S. Preventive Services Task Force [103]	Routine screening for prostate cancer with digital rectal examinations, serum tumor markers (e.g. prostate-specific antigen), or transrectal ultrasound is not recommended.	http://www.aafp.org/fpr/971000fr/12.html (2 January 2002)
UK		
British Association of Urologists [104]	SUMMARY OF RECOMMENDATIONS Population screening should only be performed in the UK within the context of a controlled trial PSA testing in asymptomatic men is not recommended for routine clinical use, and after request should only be offered following full counseling about the implications. Counseling prior to PSA estimation should include the following information i. the test may detect a cancer and a stage where curative treatment can be offered ii. that the test may detect early prostate cancer in around 5% of men aged 50 to 65 years old iii. that the test will fail to detect some early tumours iv. PSA testing and subsequent treatment of early prostate cancer may incur risk and may not improve life expectancy in all men Patients with significant lower urinary tract symptoms should not be denied access to a PSA test Patients in which the initial assessment suggests a possible diagnosis of prostate cancer should have rapid access to appropriately trained surgeons for further investigation.	http://www.nelh.nhs.uk/guidelinesdb/html/Prostate-ft.htm (2 January, 2002) GUIDELINES ON THE MANAGEMENT OF PROSTATE CANCER - BRITISH ASSOCIATION OF UROLOGICAL SURGEONS, Produced by representatives of The Royal College of Radiologists, the British Association of Urological Surgeons, the Medical Research Council Prostate Cancer Advisory Group, the British Prostate Group, and by experts in nursing, general practice and pathology. THE ROYAL COLLEGE OF RADIOLOGISTS' CLINICAL ONCOLOGY INFORMATION NETWORK 1999 Royal College of Radiologists
National Health Service – UK [105]	On the 4th of July, 2001, the following policy was officially introduced by Public Health Minister. If a patient requests a PSA test: He should first be provided with information about the advantages and disadvantages of PSA testing He should be offered the opportunity to discuss his interpretation of the information, using the more detailed information contained in: one of the leaflets that are available; Frequently Asked Questions about Prostatic Cancer and the PSA Test; the National electronic Library for Prostate Cancer (part of the National electronic Library for Cancers)	4th July 2001 – launch of informed choice project for prostate cancer http://www.nelc.org.uk/docs/psa/psa_frame.htm (31 December 2001)

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Organization	Recommendation	Source / Date
	If the patient wishes to have the PSA test, it should only be arranged with a laboratory participating in the National External Quality Assurance Scheme (NEQAS) scheme; The patient whose test result indicates the need for further investigation should be referred to a urologist; he should be given more information about treatment options, including the opportunities to enter randomised controlled trials. The NHS will not be inviting men for Prostatic Specific Antigen (PSA) testing and does not expect GPs to raise the subject of PSA testing with asymptomatic male patients.	
Other		
Advisory Committee on Cancer Prevention – European Union [106]	Screening not recommended as a healthcare policy	European Journal of Cancer 2000;36:1473-1478
Urological Society of Australia [107]	Individual men aged 50 to 70 years with at least a 10 year life expectancy should be able to be screened by annual DRE and PSA testing, after appropriate counseling regarding the potential risks and benefits of investigations and the controversies of treatment. It should be left to the individual doctor to decide whether to advocate testing in a man not requesting it. Population screening of asymptomatic men is not recommended.	Reviewed March 1999 http://www.urosoc.org.au/info/psa.html (2 January, 2002)

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Appendix 6 Health Technology Assessments and Systematic Reviews

Citation	Country/ Year	Population-based PSA screening?	Commentary
Faisst K. Int J Tech Assess Health Care, 2001 [48]	Switzerland 2001	No	No systematic population-based screening Many family physicians and urologists use DRE and PSA. In a published leaflet, men >50 and <70 are targeted for screening every 2 years with DRE and PSA. PSA test covered by insurer when ordered by family physician or urologist.
Wild C. Int J Tech Assess Health Care, 2001 [41]	Austria 2001	No	Only used in opportunistic manner: practice pattern is men 50-74 with life expectancy of minimum 10 years. Not broadly available. DRE routinely used in preventive examinations. If symptoms found, patient referred to urologist who is able to order PSA testing under health benefits. Cancer Aid leaflet recommends DRE and PSA >45 years of age-PSA is not promoted.
Vermeulen V. Int J Tech Assess Health Care, 2001[42]	Belgium 2001	No	No population-based testing. Physicians decide when to use PSA tests which are only reimbursed if men are >50 and have symptoms/complaints
Perleth M. Int J Tech Assess Health Care, 2001 [43]	Germany 2001	No	German screening program for men >45 (established 1971) includes DRE and medical history, not PSA. However, PSA widely used. German Scientific Working Group believes that PSA testing is still experimental and shouldn't be used as a screening tool until scientifically proven in long-term RCTs.
Mousiama T. Int J Tech Assess Health Care, 2001 [44]	Greece 2001	No	No population-based screening programs. No explicit screening guidelines because of mounting evidence of inadequacy of PSA. No restrictions on PSA as left to discretion of treating physicians or patient Tests are reimbursed since 1999.
Favaretti C. Int J Tech Assess Health Care, 2001 [45]	Italy 2001	No	No standardized population-based screening. Many PSA tests are prescribed by physicians. No recommendation because of lack of scientific evidence of the effectiveness of screening. Will not be done until long-term RCT done demonstrating screening has a major impact on morbidity and mortality.
Banta HD. Int J Tech Assess Health Care, 2001 [46]	Netherlands 2001	No	Opportunistic screening only; DRE is part of routine physical exam. PSA used only as diagnostic tool and is only reimbursed when used in this fashion; is not reimbursed if used for screening. Screening cannot be justified on the available evidence and is not recommended.
Jonsson E. Int J Tech Assess Health Care, 2001 [47]	Sweden 2001	No	Routine screening neither recommended nor practiced; only opportunistic screening exists. No recommendations for PSA because of lack of evidence of benefit and considerable risk.
Muir Gray JA. Int J Tech Assess Health Care, 2001 [50]	UK 2001	No	No population-based PSA screening. National Screening Committee concluded that PSA should not be introduced based on evidence and on the balance of benefit and harm.

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