CANADIAN PARTNERSHIP AGAINST CANCER
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Screening Action Group

PSA Toolkit: PSA Screening and Testing for Prostate Cancer

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Objective

This toolkit is intended to provide background information regarding PSA screening and PSA testing (opportunistic screening, case-finding or ad-hoc testing). It is not a guideline, and is based on an assessment of the current available evidence on screening for prostate cancer. The toolkit includes screening practices to be considered as well as those to be avoided.

Summary Conclusion

The expert panel's synthesis of the evidence is that expansion of PSA screening practices beyond the current ad hoc situation is not justified, and indeed may produce net harm.

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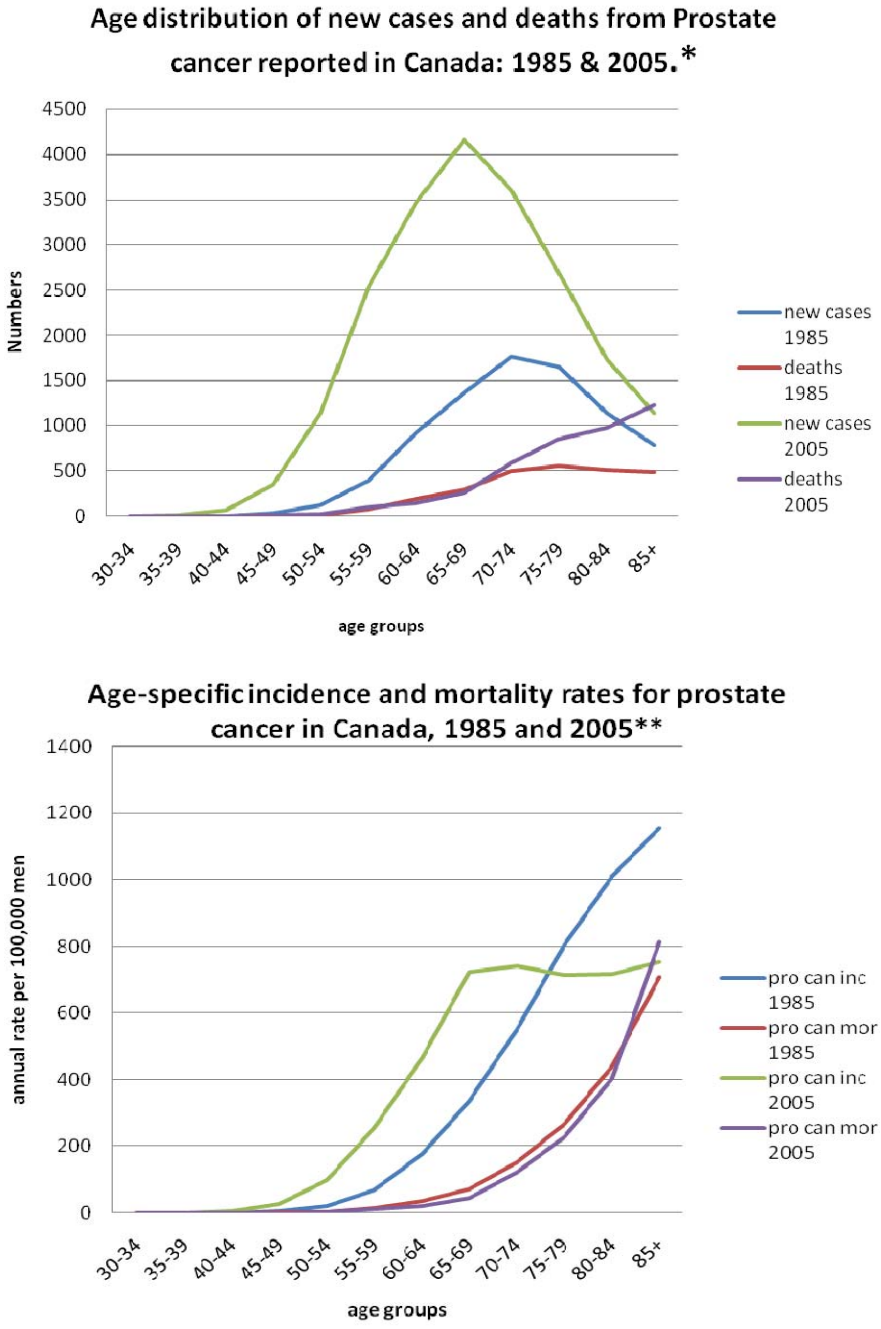
Clinical Context and Introduction

Prostate Cancer

- Commonest cancer in Canada[1]
  - Autopsy detection rate is very high: 40% at age 50 years, 80% by 90 years
  - Approximately 24% of men with a PSA level > 3 ng/ml will have cancer detected by *ultrasound-guided biopsy* (TRUSbx), 20% when the PSA level is 2–3 ng/ml and 17% when level is 1–2 ng/ml[2]
  - Current detection rate is approximately 1 in 8 men
  - Prevalence is slightly higher in men with a family history of prostate cancer
  - May occur at an earlier age in some ethnic groups
  - Age-standardized incidence rates increased for all age groups in the early 1990s but have declined in the elderly (over 70 years) since then, largely as a result of PSA testing[3]
- May grow slowly (*indolent cancer*) and never cause symptoms
- Risk can probably be reduced
  - With a healthy diet, weight control and exercise
  - By 25% with the use of 5-α reductase inhibitors—but at a high cost and some toxicity[2]
- Third commonest cause of cancer death in males[1] but death occurs mainly among older men.
  - Causes 4,300 deaths per year in Canada and is a significant cause of morbidity, but most (80%) men with prostate cancer die of other diseases
  - Even if fast growing, seldom causes death within 10 years if treated
    - The 5-year prostate-specific death rate in men diagnosed with prostate cancer is approximately 7%
  - The mortality rate has been falling since 1994 after an earlier rise. The fall is slightly greater in those under 70 years[3]

PSA screening practices in Canada vary by province. It is estimated that 35–75% of the male population over 50 years has had at least one PSA test. This testing has changed the age structure of the disease, as shown in the figure: the figure shows the comparison of age-specific incidence and mortality rates from 1985 through 2005.

Figure: Cancer Incidence and Mortality by Age Group, 1985–2005



*Data calculated from Canadian cancer statistics 2005, Cancer Surveillance Online, Cancer Mondial, IARC 1985 and WHO 1985.
**Data calculated from Cancer Surveillance Online, annual demographic statistics 2005, Cancer Mondial 1985, WHO 1985 and Canadian cancer statistics 2005.

Graphs prepared by Dr. Rajeswari Aghoram, under a grant from the Alberta Cancer Board.

PSA Test

- *Prostate specific antigen* is a substance that can be measured in the blood.
- Testing is performed by private and provincial labs at a typical billing cost of $30.
- The test can detect cancer 5–12 years before it would have been clinically diagnosed.[4]
- Testing misses some cancers because cancer can be present at low PSA levels.
- Cancer may be absent at high PSA levels.
- The test is more accurate than the *digital rectal examination* (DRE).

Current PSA Testing in Canada

- Depending on the province, 35–75% of men aged 50–75 years have had at least one PSA test.
- PSA testing for asymptomatic men is funded in some provinces, but no formal PSA screening program exists in any province.

Ad-hoc testing (case finding/opportunistic screening) does not always target the right age group, and those with abnormal findings may not be followed with appropriate investigation or intervention, potentially leading to both over- and under-treatment.

Diagnosis and Treatment for Prostate Cancer

- If the patient has symptoms and a suspicious DRE, referral to a urologist is advised.
- If a PSA test has been done and results are reported abnormal, referral to a urologist is advised to consider other causes of a raised PSA level and to arrange TRUSbx.
- Prostate cancer includes a wide spectrum of malignancy that ranges from low-grade indolent disease to high-grade cancers that have a propensity to spread.
- The diagnosis of prostate cancer always requires prostate needle biopsy samples to be examined by a pathologist.
- Risk assessment and consultation with both a urologist and a radiation oncologist follow if the biopsy shows the presence of cancer.
- Men whose biopsies suggest indolent cancer should be managed conservatively with *active surveillance*, which is monitoring the cancer and treating it only if it shows significant growth, while still curable.
- Prostate cancer may be cured by surgery or radiation therapy.
  - Generally, men younger than 65 are more likely to benefit from treatment with curative intention than from *watchful waiting.*[5]
  - Curative treatment costs the health care system about $10,000 in initial costs.
  - Men with reduced life expectancy owing to age or co-morbidity may not benefit from treatment.
- All treatments carry risks of impotence (50%+), incontinence (3% total, approximately 20% partial) and short-term impact on quality of life.[6]

Principles of Screening

WHO Criteria

The principles of screening articulated by the World Health Organization[7] include the following:

- The test should be suitable: accurate, acceptable, safe and relatively inexpensive.
- There should be an agreed policy on whom to treat as patients.
- Facilities for diagnosis and effective treatment should be available.

Organized screening programs should be implemented only if

- There is good evidence of reduced cancer-specific mortality
- A population-level benefit can be achieved with appropriate balance of benefits and harms.

PSA screening may be organized or opportunistic. Organized screening programs are population-based programs that target asymptomatic men in a specific age group, with specific mechanisms to ensure men attend for screening and if found to have abnormal test results attend for diagnosis and treatment. No such programs exist in Canada at present. Opportunistic screening occurs when the test is available, but no specific mechanisms are set up to target the at-risk group. PSA screening in Canada is currently opportunistic. When screening is offered, the following will be noted:

- Where the cancer incidence is low (e.g., in those aged less than 50 years), the pick-up rate will be low and the false-positive rate and costs consequently unacceptably high.
- Fast-growing cancers are less likely than slow-growing cancers to be detected at a curable stage.
- Slow-growing cancers will be over-represented (length bias).
- For prostate cancer especially, detection of cancer is not an appropriate screening endpoint; population-based disease-specific mortality, morbidity and quality of life effects are.
- Survival cannot be used as an endpoint because of biases associated with screening: lead time, length bias, selection bias and *over-diagnosis* bias.

Current PSA testing practices have already led to large numbers of men being "over-diagnosed." Over-diagnosis is the discovery of a cancer that would never otherwise come to light or cause any symptoms or problems for the remainder of the man's life.

- Over-diagnosis occurs in about 40% of cases detected in North American men.[8]
- Active surveillance is a management strategy that attempts to deal with the consequences of over-diagnosis. It is discussed later.

Strategies to Mitigate Harm and Maximize Benefits of PSA Testing

Mitigating the harm of testing and its consequences is important in Canada, and there are programmatic elements that could be put into place to achieve this. Randomized trials have shown substantial over-diagnosis.

Table 1: Strategies to Mitigate Harm

Potential harms	Mitigating strategies	Programmatic elements
Inappropriate use of PSA testing in terms of age, frequency of testing, monitoring or surveillance	Clinical practice guidance on appropriate use of PSA test regarding: • Target populations (start/stop, ages, those at increased risk, testing intervals for "normal" results) • Monitoring, evaluation and surveillance including monitoring appropriateness of other testing approaches and results	• Single reporting source for all PSA tests in a province, with centralized registry; development of performance indicators and evaluation reports • Evidence-based guideline development and updating as new evidence emerges, with clinical practice tools, especially for informing men about their choices
Inappropriate follow-up for asymptomatic, healthy men with elevated PSA test results	Follow-up algorithms for abnormal PSA test results	Evidence-based guideline development and updating as new evidence emerges, with clinical practice tools
Ineffective program	Monitor PSA test use, track outcomes (stage shift, test use and practice patterns, effect on mortality) over time	Monitoring of performance
Inconsistent quality of PSA testing processes and interpretation; inadequate prostate biopsy processing and diagnostic reporting	Standards for lab practice	Development of standards and monitoring of performance; mandatory external proficiency testing (blind specimens); synoptic pathology reporting
Lack of access to appropriate treatment options for men newly diagnosed, leading to additional adverse effects of treatments that may not be the best option	Information for health-care providers and patients on all treatment options available and their potential benefits and risks, supporting use of active surveillance approaches where appropriate	Development of standards for surgical and oncologic care of prostate cancer patients; multidisciplinary consultations
Miscommunication	See section 5: to increase awareness of issues, benefits and harms	Develop mechanisms for obtaining informed consent prior to testing

What Are the Benefits and Risks of PSA Screening?

The publication of the interim results of two randomized trials in March 2009[9,10] has not provided a definitive answer to the questions of potential benefit and risk. Indeed, the medical community has not reached consensus.

The European Randomized Study of Screening for Prostate Cancer (*ERSPC*) showed a 20% reduction in prostate cancer deaths from screening at four-year intervals, whereas the Prostate, Lung, Colorectal and Ovarian (*PLCO*) trial of annual screening showed a non-significant small increase in the prostate cancer death rate. Some believe that the European trial results are proof that there is a benefit in a situation where initially there was little background PSA screening. Others regard the data as premature and possibly spurious owing to bias, perhaps as a result of differences of treatment intensity between groups.

Similarly, some regard the PLCO trial as being a negative trial that proves PSA screening has no role in a situation where background (opportunistic) screening rates are similar to those in Canada. Others, however, interpret the trial in the light of high contamination rates (background screening) and lack of power to detect a small mortality differential, and feel it adds little to the debate. A summary of the main findings of the two trials appears in the Appendix.

The expert panel's synthesis of the current evidence is that expansion of PSA screening beyond the current informal position is not justified, and indeed may produce net harm. However, there is insufficient evidence to discourage present opportunistic PSA screening practices.

Treatment practices in Canada are more similar to those in the United States than to those in Europe in the early to mid-1990s, which is the era in which the mortality benefit was observed in the ERSPC trial. The panel believes, therefore, that the mortality benefit observed in the European trial would not be seen in Canada if PSA screening were to be more widely adopted than it is currently.

Based on the results of the European trial, an estimate of the possible numerical risks and benefits of PSA screening may be derived (Table 2) and may be useful as an illustration of the pros and cons for an individual. These data compare a screened patient with a control patient who has not previously undergone testing. Data from the U.S. trial differ because of high baseline PSA testing rates in the control arm, and no mortality benefit was observed in that trial.

Table 2: Estimate of effects experienced by 10,000 men aged 55–69 years, each screened every 4 years, compared with those not screened (all followed for 9 years)

	Screened	Not screened	Net effect	Net benefit	Net harm
Number invited for screening/not screened	10,000	10,000			
Number of positive PSA results (> 3 ng/ml)[10]	1,620				
Number of biopsies[10]	1,393				
Number of cancers detected[10]	820	480	+340		
Number of potentially aggressive cancers (Gleason score > 7) [10]	228	217		11	
Number of low-grade cancers[10] (≤ Gleason score 6)	592	263			329
Number undergoing radical prostatectomy[11]	220	100	+120		
Number undergoing radiotherapy[11]	227	123	+104		
Complications of therapy[12]					
Urinary problems	30	15			15
Sexual dysfunction	317	158			59
Bowel problems	125	62			63
Number of deaths due to prostate cancer	29	36		7	

Numbers calculated based on results of the ERSPC trial.

Elements of a Good Screening Strategy

The PSA Test

Specimen type and storage requirements for total PSA

Serum is often the recommended specimen type, but EDTA and heparinized plasma have better stability during storage. Whole blood should be centrifuged to separate cells within 5–6 hours of phlebotomy (store at room temperature or refrigerate until separation). Maximum storage times for serum, for less than a 10% decrease of PSA result are 24 hours at room temperature, one week at 4ºC, 2 years at −20ºC and 3 years or more at −80ºC. Up to five freeze-and-thaw cycles of serum have no effect on PSA level.[13,14]

Calibration/standardization

PSA exists in different forms in the blood, the most important being bound PSA and free PSA, representing on average 90% and 10% of total measurable PSA in blood. Use of the World Health Organization "90-10" calibrator has brought PSA test results obtained using different instruments closer together. However, differences of up to 20% can be found among different methods.[15] PSA test results should be from the same laboratory or the same method to minimize these differences.

Pre-analytical factors affecting PSA results

Many factors contribute to differences in PSA results, even within the same patient. Analytical variation is relatively small, typically less than 5%. Total within-subject variation is considerably larger, with estimates ranging from 6% to 58%.[14] Invasive procedures such as needle biopsy or transurethral resection of the prostate lead to very significant elevations of PSA level. Less-invasive interventions, such as prostate massage and cystoscopy, can cause minor elevations. Use of anti-androgen drugs such as finasteride lead to a decrease in PSA level of approximately 50%. Other factors affecting PSA levels in some, but not all, studies include ejaculation, vasectomy and prolonged exercise. There is also a diurnal variation in PSA.[14]

Consecutive PSA test results

Clinicians are often faced with the question of whether today's PSA result is different from the previous one. Answering that question requires data from the method used for analytical variation (CVa) and an estimate of within-subject biological variation (CVb). These data combine to give a total variation (CVt), as follows: $CVt = (CVa^2 + CVb^2)^{0.5}$. With two measurements being compared, the 95% confidence intervals are $1.96 \times 1.41 \times CVt = 2.77 \times CVt$. Using estimates for CVa and CVb of 5% and 15%[16] (www.westgard.com) leads to a 95% confidence interval of +/− 40%. For example, with a first result of

3 ng/ml, the second result must increase to 4.2 ng/ml or decrease to 1.8 µg/L to be clinically different.

Pathology Considerations

Gleason Rating

The definite diagnosis of prostate cancer is made by microscopic examination of prostate biopsies. Based on the microscopic appearance of the carcinoma, the pathologist is able to determine the differentiation grade (i.e., *Gleason score*), the single most important prognosticator of prostate cancer outcome. The Gleason score comprises the commonest pattern seen (on a scale of 1–5), as well as any secondary pattern, and is numerically expressed as $n + n = n/10$. The score may vary in prostate biopsies from 5 to 10, with a score of 5 or 6 representing low-risk prostate cancer and a score of 10 representing highly aggressive cancer.

Standards of Reporting

It is now recommended that pathologists use synoptic reporting for diagnosis of prostate cancer because this has been shown to improve the completeness and quality of pathology reporting.

- Appropriate standards of pathological technique are vital.
- Synoptic reporting should be used.
- Data should be captured in the screening database.
- Processes for quality assurance must be in place.

Standards of Biopsy

The gold standard biopsy technique is *trans-rectal ultrasound-guided peripheral zone biopsy* (TRUSbx). Digitally directed biopsies are inadequate and are an unacceptable alternative. The biopsy can be carried out by, or under the direction of, a urologist or a radiologist. Plans must be in place to deal with infections and other complications. The chance of finding prostate cancer in a prostate biopsy sample increases with the amount of prostate tissue in the biopsy. The chance is also influenced by number and quality of prostate biopsies and the processing of the biopsies by the pathology lab. Although systematic sextant prostate biopsies were standard previously (they were also used in most ERSPC screening centres), the current standard is 8–12 biopsies per session, taken under the guidance of an ultrasound device. The number and size of the submitted samples should be recorded.

Estimate of Error Rates

The risk of a false positive diagnosis of prostate cancer must now be estimated at considerably less than 0.4% of the biopsies reported as positive for prostate cancer, while a false negative diagnosis may be more common—up to about 5% of biopsies.[17]

If Done, Who Should Initiate Screening?

- Informed consent is not straightforward, given that there are both potential benefits and harms from screening and intervention. Consent is addressed elsewhere in this document.
- The primary care physician (PCP) is in a good position to determine the relative importance of a possible prostate cancer diagnosis in the context of the patient's medical history
  - The PCP can advise against screening (e.g., when life expectancy is less than 10 years)
  - The PCP can carry out a DRE, if required, although DRE adds little to the accuracy of prostate screening and was dropped in the ERSPC, and contributed little to PLCO.[4]

The PSA result should be interpreted with screening algorithms, taking into account relevant clinical factors for the patient, such as age, but the PCP can help discuss implications with the patient.

Screening Intervals

- Intervals of 1, 2 and 4 years have been used.[4]
  - Patients with PSA levels < 1 ng/ml may be screened less often (e.g., every 8 years).[18] Those with PSA levels of 2–3 ng/ml may be screened more often.
- There is no single "safe" PSA level; it is, rather, a continuum of risk.
  - The positive predictive value (PPV) for the first screen is related to the PSA level:[19]
    - 10% PSA 1–1.9
    - 14% PSA 2–2.9
    - 22% PSA 3–3.9
  - North American data[20] suggest that the PPV is higher, even at low levels:
    - 17% PSA 1.1–2
    - 24% PSA 2.1–3
    - 27% PSA 3.1–4
- Interval cancers will occur; these carry a worse prognosis, but a shorter screening interval may not necessarily lead to reduced mortality.[21]
- A shorter re-screening interval has been considered in patients with a negative screen. The payback is small, however: 1,441 biopsies would be required to detect one more cancer that would be potentially incurable if the patient had waited until the next re-screen at the longer interval.[21]
- For many other diseases for which screening exists, decreasing screening intervals adds little to improved outcomes, but does increase the number of false positive results almost linearly with the increased number of tests.

The Abnormal PSA Result

- A PSA level > 3 or 4 ng/ml was the trigger for further investigation in the screening trials.
  - Age-adjusted triggers were not used in either trial.

  - Patients taking 5-α reductase inhibitors (e.g., finasteride) have PSA values approximately halved after a year, and this should be factored into the interpretation of results. The degree of reduction varied among individuals.
- Abnormal results need verification before referral because many will prove to be lower on repeat testing.
- Persistent abnormal results should prompt referral to a urologist or a screening clinic.
- PSA kinetics (velocity or doubling time) appear unhelpful in the screening context.[18]

Individual Risk Assessment

- Symptomatic men should be investigated appropriately, but note that usually symptoms of urinary frequency and nocturia are caused by lower urinary tract symptoms (*LUTS*): there are no cancer-specific symptoms until the late stage.
- Screening is not appropriate when estimated life expectancy is less than 10 years because the patient is unlikely to live long enough to benefit from treatment.[4,5]
- Men unfit for curative intervention should not be screened.
- Men unwilling to accept curative treatment if cancer were found should not be screened.
- Those who support PSA testing generally recommend testing for men aged 50–70.
- Some have advocated screening younger men (45–50 years).[22]
  - At age 50, a PSA level > 1 ng/ml carries a 4-fold increased risk of having prostate cancer over a level of < 1 ng/ml. 23
  - Men with lower-than-median PSA levels in their 40s (0.63 ng/ml) have a low risk of developing prostate cancer. [22]
  - Those in their 40s with PSA levels above the median are at greater risk.
- High-risk groups (family history, African ethnicity) and low-risk groups (e.g., Southeast Asian ethnicity) have a relatively small altered risk and probably should not be treated differently.[24]

Database Registration

If an organized screening program is planned, a provincial database would bring the following benefits:

- Mitigation of harm, maximization of accuracy, etc.:
  - uniform reporting
  - call-back
  - cost containment
- Facilitation of research opportunities, including studies on cost-effectiveness.

Cost Implications

- The cost-effectiveness of screening can be estimated only once efficacy of screening is agreed.
- Substantial cost reductions in the management of prostate cancer cases detected by PSA testing can be achieved by adopting a strategy of active surveillance.
- Quality assurance, evaluation and educational strategies to support informed decision-making will add to the costs, but will help improve the cost-effectiveness of screening (Table 2).

Education and Consent

Patient education strategies, including user-friendly packaging of information on both the potential benefits and potential harm of screening for prostate cancer, must be available. Below are suggestions for topics to be covered. Information sources already in use (e.g., in British Columbia[25]) may be reproduced or adapted.

It has been shown that when men are informed in a balanced way about the test and its meaning, the number who go ahead with the test is reduced. However, this education takes time and is not possible in ordinary primary care practice. An information program needs to be established that PCPs can recommend to men to review on their own, then return for the test if they decide to do so.

An education program should address the following topics:

Potential Effect on Mortality Rates

- PSA test positivity rates by age group:
  - From the first round of screening in the United States (approximately one-third previously PSA-tested) (PSA > 4 ng/ml)

Age group	Population with approx. 30% prior screening
50–59	4%
60–64	7%
65–69	11%
70–74	**14%**
All ages	8%

- Information on what follow-up investigations are required after a positive result[26]
  - Recheck the abnormal result, then TRUSbx will be recommended.
  - For men with an initial negative biopsy, the probability of having a repeat biopsy within 3 years of the initial biopsy was 43%.
- Proportion of tests that will detect cancer; false positives, false negatives
  - In the PLCO trial, at the first screen 14 cancers were detected per 1,000 PSA tests and 9 per 1,000 on re-screening; approximately 80% of the PSA tests reported as abnormal were false positives,[27] the proportion of false negatives is not yet known.
  - From the placebo arm of the Prostate Cancer Prevention Trial (PCPT),[20] a PSA level > 4 ng/ml had a sensitivity of 24% for biopsy-detectable

cancers and a specificity of 93%. Many of these cancers would be indolent and not require treatment.

- Information about the cancers detected, addressing the fact that not all cancers are the same and including those that are
  - Curable cancers, with clinical detection (few for prostate) or early detection by screening
  - Not curable even with early detection—that is, aggressive cancers
  - Over-detected cancers—they would not have been clinically diagnosed or caused morbidity or mortality in the patient's lifetime
    - The rate for over-detection could be as high as half of all cancers detected as a result of PSA testing in asymptomatic men (ERSPC).
    - Cancer has been identified at autopsy in 50% of men aged 60 years.
  - Indolent cancers, which are slow-growing and not aggressive in their behaviour, and which may receive unnecessary treatment.
- Potential mortality reduction benefit, presented as both the relative (%) reduction in mortality and also the absolute numbers compared between the screening and control groups.
- The fact that in Canada the lifetime risk of dying from prostate cancer is 3.7%. If a 25% reduction in mortality were to be realized this is about a 0.9 percentage point drop in risk—to 2.8%.

Potential Harms

The potential harms of prostate cancer screening need to be communicated to patients, and include:

- False positive and false negative PSA test outcomes
- Failure of PSA screening to detect many cancers, although generally it detects those most likely to cause death
- The morbidity that can be experienced from diagnostic investigations such as biopsies
- The potential for physical and psychological adverse effects from treatment

Numerical estimates (see page 8) of the chance of testing positive vastly exceed the number of lives saved from subsequent treatment. In the European trial, 1,410 men were invited for screening and 48 underwent treatment, to save one life. In the U.S. trial there was no mortality reduction from increasing PSA screening intensity beyond background levels.

Substantial numbers of men treated by radical prostatectomy will become incontinent (3% totally; up to 20% will use pads) and impotent (on average 70%) and rarely, there will be post-operative deaths.

Men should be informed that the evidence for benefit of PSA testing is incomplete.

They should be told that it is OK not to be tested, because any potential gain in life expectancy needs to be balanced against the substantial risk of side effects from treatment, and other issues may be more important to the individual.

Patients should be informed that the majority of medical organizations that have examined the science have recommended against screening. Urology organizations, and cancer organizations in the United States, tend to stand apart in their advocacy of screening.

Others to be Educated

Physicians and other primary care providers also need user-friendly educational material that covers the test characteristics, potential benefits and potential harms that can result from routine PSA testing in healthy asymptomatic men.

Other key stakeholders involved in setting policy on service provision, insurance coverage, etc. need appropriately packaged information that addresses the same points. Specific information on the appropriate interpretation and use of abnormal results should be provided.

Management of the Screen-Detected Patient

How Were Patients Managed in the Screening Trials?

In the U.S. (PLCO) trial, the results of the screening test were reported to the participant and his physician, and they decided on management. Patients with an abnormal suspicious test result (defined as a PSA level > 4 ng/ml) usually had a repeat test; if results were still elevated, the patient was usually referred to a urologist. Biopsies were not mandated and often were not performed until there was evidence of persistent elevation of the PSA (and/or rising PSA levels). Over a 4-year period more than 80% of patients with abnormal results achieved resolution, most following biopsy, but nearly 20% reverted to a normal PSA level. In this trial, the treatment received by those diagnosed with prostate cancer in the intervention and usual-care arms was very similar by stage.

In the ERSPC trial, biopsy was mandated for those with an abnormal PSA level (in most countries, > 3 ng/ml); more than 80% underwent a biopsy within a year of the abnormal PSA being reported. Those diagnosed in both trial arms were referred to the regular care system in their country.

Patient Assessment

- Most screen-detected cancers will be suited to several treatments.
- Consultation with both a urologist and a radiation oncologist is recommended as specialists tend to favour their own treatments, without good evidence that any one treatment is superior.
- *Risk grouping*[28] categorizes patients into the following risk strata (percentages are those expected to arise from the initial screening round; at subsequent rounds, the numbers of patients with advanced disease will decrease):[27,29]
  - Low risk, approximately 50% (including minimal-risk, over-diagnosed cancer, about 25%)
  - Intermediate risk, approximately 35%
  - High risk, approximately 12%
  - Metastatic, approximately 3%.
- The screening trials excluded men with reported symptoms at the time of enrolment. Although true screening does likewise, it is likely that cancer detection rates through a PSA screening program in Canada would include some symptomatic men, and cancer detection rates may be higher than in the randomized studies.

Risks of Over-treatment

- The majority of screen-detected cancers will be early prostate cancer and the patient will have at least normal life expectancy.
- From a population perspective, benefits from screening may be outweighed by harm to a greater number of patients from over-treatment.

- Immediate treatment may allay anxiety, but will cause significant morbidities and loss of income and will incur government costs.
- Selected patients with low-risk cancer may be best managed by active surveillance rather than immediate curative intervention.

Active Surveillance

- Active surveillance is[30]
  - Selection of patients with probable indolent cancer
  - Periodic monitoring by means of
    - PSA testing every 6 months
    - DRE every 6–12 months
    - Initial repeat biopsy and re-biopsy every 2–3 years
  - Intervention if
    - The PSA doubling rate (PSAdt) is faster (i.e., less) than 3 years
    - There is upgrading or upstaging on repeat biopsy
    - The patient chooses it
- Patients with slowly- or non-progressive cancer may be identified from their PSA test results, grade and volume of cancer present, and other clinico-pathologic findings.
  - Nomograms can be used to select such men for active surveillance.[31]
- Active surveillance is being studied in a head-to-head randomized comparison against immediate intervention (START trial, PR11, NCIC-CTG), but results will not be known for 10–20 years.
- Results of active surveillance from Canada and Europe show that half of suitable patients can delay treatment for 5–8 years.
  - For an active surveillance strategy to be successful, resources need to augment such a program to ensure patient recruitment and retention, such as education (for physicians and patients), database capture, close adherence to recommended schedules of repeat investigation, and psychosocial support.
- A strategy of active surveillance will save significant costs.
- Currently, active surveillance is performed in about 10% of patients.

Curative Treatments

Men should be counselled regarding their treatment options by specialists who perform cancer treatments (urologists and radiation oncologists). These specialists may need the support of other health-care professionals in the assessment and counselling of patients, especially if patient numbers surge significantly. Those with advanced metastatic cancer should initially be managed by urologists with input from medical oncologists and radiation oncologists after failure of first-line *androgen deprivation therapy* (ADT; hormone therapy).

Surgery (radical prostatectomy) may be performed laparoscopically (manual or robotic) or by open prostatectomy. The former has a shorter hospital stay (1 day) than the latter (2–4 days) but offers no additional cancer control

advantage.[32] Surgery is generally performed on men with low- and intermediate-risk cancer, and selected men with high-risk cancer. Men over age 70 are usually not offered surgery because of the lack of proven benefit and increased risk of complications.

About one-third of men who undergo surgery will have *positive margins*. These men may require post-operative radiation therapy, which has been shown to improve their survival.

Brachytherapy is used for low-risk and selected intermediate-risk cancers. It is not available in all provinces or all cancer centres. Cancer control rates with this treatment appear excellent with acceptable side effects.[33] Use of brachytherapy is expected to grow as a result of increased detection of early cancers through screening.

External beam radiation therapy (EBRT) is the commonest treatment for prostate cancer. It is used for all risk groups. For high-risk cancer it is usually combined with ADT for 2–3 years, as this has been shown to improve survival rates over those with EBRT alone.

Each of these treatments is similar in cost, with variation depending on the complexity of radiation, the use of ADT and the type of surgery. The costs range between $7,000 and $11,000 per case. Other treatments, such as cryotherapy (freezing) or high-intensity focused ultrasound (HIFU; heating) lack evidence for efficacy and therefore are not generally accepted curative treatment options[34] and are not publicly funded.

Watchful Waiting and Metastatic Cancer

Watchful waiting is a strategy of palliative intervention when symptoms develop. It does not attempt to cure. It is used for elderly men who are unfit for curative therapy, often with reduced life expectancy. It has been shown to be equivalent to surgery for men with clinically detected cancer, over the age of 65.[5] It should not be confused with active surveillance.

Metastatic cancer is treated with ADT (surgical or medical castration) and palliative radiation therapy, as well as chemotherapy. It cannot be cured, but patients may live for several years.

Knowledge Gaps and Future Developments

As results of the ERSPC and PLCO trials filter through the medical community, many new questions—as well as some answers—will emerge. Provinces should consider establishing expert panels to keep abreast of the changing knowledge base.

Other Tests for Prostate Cancer

PSA is not specific for prostate cancer and as a result, many other benign prostate conditions—age-related hypertrophy (benign prostatic hypertrophy; BPH), infection, inflammation, prostatitis, recent sexual activity, etc., can cause an elevated result. The positive predictive value of an abnormal PSA result (> 3–4 ng/ml) is 25%, which is similar to that of mammography, but still leads to unnecessary biopsies and anxiety.

New diagnostic tests are under development. One of the more promising is PCA3, a gene-based marker that is highly expressed in prostate cancer but apparently absent in benign disease. PCA3 is measured in the urine after prostate massage by DRE. Analysis is much more complex and costly than PSA testing. ROC (receiver-operating curve) analysis shows that the area under the curve with PSA testing (approximately 0.55) can be improved to 0.75 using algorithms incorporating PCA3, TRUSbx volume and PSA.[35]

Other candidate biomarkers include other molecular forms of PSA (pro-PSA, PSA-A2M, etc.) and early prostate cancer antigen (EPCA). Reviews of the field are referenced.[23,36,37]

Alternate Screening Thresholds/Targeting Certain Groups

Individual risk of prostate cancer may be calculated using online nomograms, such as the UT Health Sciences Centre Risk of Biopsy-Detectable Prostate Cancer,[24] which factor in age, race and prior biopsy history.

Active Surveillance

Although active surveillance is seen by many experts as a solution to the burden of over-treatment, there is no current Level 1 evidence that outcomes of active surveillance are equivalent to those of immediate treatment. Accrual to trials and careful ongoing monitoring of patients in active surveillance programs is important so that these data can be generated. The infrastructure to capture these data should be provided.

Glossary

Active surveillance	A strategy of careful monitoring, by means of clinical examination, PSA changes and repeat biopsy. The intent is to delay treatment until the cancer shows signs of definite tumour growth, but before the chances of cure are diminished. Has the advantages of delaying treatment-related toxicity and can save or defer costs. Also see *watchful waiting.*
Androgen deprivation therapy (ADT)	Medication to reduce testosterone levels to near zero. May also be achieved by surgical removal of the testicles (orchiectomy). ADT carries significant toxicity and cost. It has been shown to improve the survival rates of men with locally advanced, high-risk and metastatic cancer. Its use in lower-risk cancers is generally discouraged.
Brachytherapy	The placement of approximately 100 tiny radioactive seeds in the prostate. Done as day surgery under general or spinal anaesthetic. Requires specialist expertise and is not available in all provinces or centres.
Digital rectal examination (DRE)	Examination of the posterior surface of the prostate by rectal examination using a (gloved) finger. Very subjective. Difficult in obese men. The clinical T stage is assigned on the basis of the DRE and is generally unreliable as a prognostic indictor.
ERSPC	European Randomized Screening trial for Prostate Cancer[4]
External beam radiation therapy (EBRT)	Radiation delivered by linear accelerators as a course of treatment over 7–8 weeks. Sophisticated techniques such as image guidance radiotherapy (IGRT) and intensity modulated radiotherapy (IMRT) have improved results over older techniques.
Gleason score	Under the microscope, prostate cancer may assume five distinct patterns of growth—Gleason grades 1–5. Often a prostate cancer may display more than one growth pattern; in these cases the two most predominant growth patterns are combined to produce the Gleason score (e.g., Gleason score 7 consists of a dominant pattern 3 and a second dominant pattern 4). The Gleason score can be determined on biopsies as well as prostatectomy specimens and represents the strongest predictor of the prostate cancer's behaviour.

Indolent cancer	Minimal cancer, generally defined as only one or two cores positive for (maximum) Gleason grade 6/10 cancer of ≤ 3 mm extent. PSA level < 10 (or up to 15 if the prostate volume is large, defined as a PSA density < 0.15 ng/ml/cc).
Lower urinary tract symptoms (LUTS)	Myriad urinary symptoms including nocturia, frequency, slow stream and dribbling. Usually a sign of benign prostate hypertrophy (BPH), which becomes common above the age of 60.
Over-diagnosis	The detection of a cancer not destined to present clinically in a subject's lifetime. This is a statistical rather than a biological definition. It is not equivalent to indolent cancer.
PLCO	Prostate, Lung, Colorectal, and Ovarian screening trial (National Cancer Institute)[38]
Positive margins	Pathological examination of the prostate removed at prostatectomy showing tumour at the cut edge. The implication is that the cancer has not all been removed. Associated with a recurrence rate of approximately 50%, which can be reduced by half with the use of adjuvant radiation therapy, which has been shown to improve overall survival. Positive margins are related to case-selection and surgeon experience. Typical rates are 30%, but range from 10–90%.
Prostate specific antigen (PSA)	A protein produced by the cells of the prostate gland. PSA is present in small quantities in the serum of healthy men and is often elevated in the presence of prostate cancer and in other prostate disorders.
Radical prostatectomy	An attempt at cure by total removal of the prostate. Usually performed via an abdominal excision (open); it can also be carried out laparoscopically (manual or robot-assisted). All techniques require a skilled surgeon; low hospital and surgeon case-loads have been shown to affect outcome adversely.
Risk grouping	Conveniently grouping patients into prognostic groups according to initial PSA level, Gleason score and T stage. Used to help choose appropriate management options and to give prognosis. Low risk: all PSA levels ≤ 10, T stage ≤ 2b, Gleason score < 7 Intermediate: neither low nor high High risk: any PSA level > 20, Gleason score ≥ 8, T stage ≥ 3

Trans-rectal ultrasound-guided biopsy (TRUSbx)	Allows measurement of the size of the prostate and can guide the location of biopsy needles, which should be directed to the peripheral zones of the prostate in a systematic manner sampling the base, apex and mid-zones. TRUS is often ineffective at visualising the actual cancer.
Watchful waiting	A strategy of palliative intervention when symptoms develop. It does not attempt to cure. Usually used for elderly men or those with co-morbidity with a life expectancy < 10 years. Differs from *active surveillance* (qv).

References

1. Canadian Cancer Society. CCS stats 2008. Available at http://www.cancer.ca/Canada-wide/About%20cancer/Cancer%20statistics/Canadian%20Cancer%20Statistics.aspx.
2. Thompson IM, Goodman PJ, Tangen CM, et al. The influence of finasteride on the development of prostate cancer. N Engl J Med. 2003;349(3):215-24.
3. Neutel I, Gao R, Blood P, Gaudette L. The changing age distribution of prostate cancer in Canada. Can J Public Health. 2002;98(1):60-64.
4. Schroder FH. Screening for prostate cancer (PC)—an update on recent findings of the European Randomized Study of Screening for Prostate Cancer (ERSPC). Urol Oncol. 2008;26(5):533-41.
5. Bill-Axelson A, Holmberg L, Filen F, et al. Radical prostatectomy versus watchful waiting in localized prostate cancer: the Scandinavian prostate cancer group-4 randomized trial. J Natl Cancer Inst. 2008;100(16):1144-54.
6. Litwin MS, Gore JL, Kwan L, et al. Quality of life after surgery, external beam irradiation, or brachytherapy for early-stage prostate cancer. Cancer. 2007;109(11):2239-47.
7. Wilson JM, Jungner YG. [Principles and practice of mass screening for disease]. Bol Oficina Sanit Panam. 1968;65(4):281-393.
8. Draisma G, Etzioni R, Tsodikov R, et al. Lead time and overdiagnosis in prostate-specific antigen screening: importance of methods and context. J Natl Cancer Inst. 2009;101(6):374.
9. Andriole GL, Crawford ED, Grubb RL 3rd, et al. Mortality results from a randomized prostate-cancer screening trial. N Engl J Med. 2009;360(13):1310-9.
10. Schroder FH, Hugosson J, Roobol MJ, et al. Screening and prostate-cancer mortality in a randomized European study. N Engl J Med. 2009;360(13):1320-8.
11. Barry MJ. Screening for prostate cancer—the controversy that refuses to die. N Engl J Med. 2009;360(13):1351-4.
12. Potosky AL, Legler J, Albertsen PC, et al. Health outcomes after prostatectomy or radiotherapy for prostate cancer: results from the Prostate Cancer Outcomes Study. J Nat Cancer Inst. 2000;92(19):1582-92.
13. Jung K, von Klinggraff P, Brux B, et al. Preanalytical determinants of total and free prostate-specific antigen and their ratio: blood collection and storage conditions. Clin Chem. 1998;44(3):685-8.
14. Price CP, Allard J, Davies G, et al. Pre- and post-analytical factors that may influence use of serum prostate specific antigen and its isoforms in a screening programme for prostate cancer. Ann Clin Biochem. 2001;38(Pt 3):188-216.
15. Slev PR, La'ulu SL, Roberts WL. Intermethod differences in results for total PSA, free PSA, and percentage of free PSA. Am J Clin Pathol. 2008;129(6):952-8.
16. Fraser C. Biological variation: from principles to practice. AACC Press; 2006.

17. Van der Kwast TH, Lopes C, Martikainen PM, et al. Report of the Pathology Committee: false-positive and false-negative diagnoses of prostate cancer. BJU Int. 2003;92(Suppl 2):62-5.

18. Schroder FH, Carter HB, Wolters T, et al. Early detection of prostate cancer in 2007. Part 1: PSA and PSA kinetics. Eur Urol. 2008;53(3):468-77.

19. Raaijmakers R, Wildhagen MF, Ito K, et al. Prostate-specific antigen change in the European Randomized Study of Screening for Prostate Cancer, section Rotterdam. Urology. 2004;63(2):316-20.

20. Thompson IM, Tangen CM, Klein EA, Lippman SM. Phase III prostate cancer prevention trials: are the costs justified? J Clin Oncol. 2005;23(32):8161-4.

21. Schroder FH, Bangma CH, Roobol MJ. Is it necessary to detect all prostate cancers in men with serum PSA levels <3.0 ng/ml? A comparison of biopsy results of PCPT and outcome-related information from ERSPC. Eur Urol. 2008;53(5):901-8.

22. American Urological Association. Prostate-Specific Antigen Best Practice Statement: 2009 Update. Available at www.auanet.org/content/guidelines-and-quality-care/clinical-guidelines/main-reports/psa09.pdf.

23. Lilja H, Ulmert D, Bjork T, et al. Long-term prediction of prostate cancer up to 25 years before diagnosis of prostate cancer using prostate kallikreins measured at age 44 to 50 years. J Clin Oncol. 2007;25(4):431-6.

24. UT Health Sciences Centre. Risk of biopsy-detectable prostate cancer. Available at http://deb.uthscsa.edu/URORiskCalc/Pages/uroriskcalc.jsp. Accessed July 21, 2009.

25. BC Cancer Agency. PSA Screening information for patients, May 2009. Available at http://www.bccancer.bc.ca/HPI/CancerManagementGuidelines/Genitourinary/Prostate/PSAScreening/default.htm.

26. Pinsky PF, Crawford ED, Kramer BS, et al. Repeat prostate biopsy in the Prostate, Lung, Colorectal and Ovarian cancer screening trial. BJU Int. 2007;99(4):775-9.

27. Grubb RL 3rd, Pinsky PF, Greenlee RT, et al. Prostate cancer screening in the Prostate, Lung, Colorectal and Ovarian cancer screening trial: update on findings from the initial four rounds of screening in a randomized trial. BJU Int. 2008;102(11):1524-30.

28. National Comprehensive Cancer Network. Risk stratification scheme. Available at http://www.nccn.org/professionals/physician_gls/PDF/prostate.pdf. Accessed July 21, 2009.

29. van der Kwast TH, CiattoS, Martikainen PM, et al. Detection rates of high-grade prostate cancer during subsequent screening visits. Results of the European Randomized Screening Study for Prostate Cancer. Int J Cancer. 2006;118(10):2538-42.

30. BC Cancer Agency. Active surveillance guidelines, 2007. Available at http://www.bccancer.bc.ca/HPI/CancerManagementGuidelines/Genitourinary/Prostate/Management/LowRisk.htm.

31. Steyerberg EW, Roobol MJ, Kattan MW, et al. Prediction of indolent prostate cancer: validation and updating of a prognostic nomogram. J Urol. 2007;177(1):107-12.

32. Hu JC, Wang Q, Pashos CL, Lipsitz SR, Keating NL. Utilization and outcomes of minimally invasive radical prostatectomy. J Clin Oncol. 2008;26(14):2278-84.

33. Morris WJ, Keyes M, Palma D, et al. Population-based study of biochemical and survival outcomes after permanent 125I brachytherapy for low- and intermediate-risk prostate cancer. Urology. 2009;73(4):860-7.

34. Pickles T, Goldenberg L, Steinhoff G. Technology review: high-intensity focused ultrasound for prostate cancer. Can J Urol. 2005;12(2):2593-7.

35. Kirby RS, Fitzpatrick JM, Irani J. Prostate cancer diagnosis in the new millennium: strengths and weaknesses of prostate-specific antigen and the discovery and clinical evaluation of prostate cancer gene 3 (PCA3). BJU Int. 2009;103(4):441-5.

36. Shariat SF, Karam JA, Margulis V, Karakiewicz PI. New blood-based biomarkers for the diagnosis, staging and prognosis of prostate cancer. BJU Int. 2008;101(6):675-83.

37. Sardana G, Dowell B, Diamandis EP. Emerging biomarkers for the diagnosis and prognosis of prostate cancer. Clin Chem. 2008;54(12):1951-60.

38. Gohagan JK, Prorok PC, Hayes RB, Kramer BS. The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial of the National Cancer Institute: history, organization, and status. Control Clin Trials. 2000;21(6 Suppl):251S-272S.

39. Schroder FH, Roobol MJ. A comment on prostate cancer screening in the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial: update on findings from the initial four rounds of screening in a randomized trial. BJU Int. 2008.

Appendix

Summary of results of the ERSPC and PLCO randomized trial results

	ERSPC	PLCO
	European Randomized Screening Trial of Prostate Cancer[4,39]	*Prostate, Lung, Colorectal and Ovarian screening trial*[4,28]
Web link for publication	http://content.nejm.org/cgi/content/full/NEJMoa0810084	http://content.nejm.org/cgi/content/full/NEJMoa0810696
Web site	http://www.erspc.org/	http://prevention.cancer.gov/programs-resources/groups/ed/programs/plco
Start date	1993	1993
Accrual	182,000	77,000
Median follow-up	9 years	11.5 years
Randomization method	4 countries: Individual consent 4 countries: Population registry identified men for screening, then men consented	Individual consent
Which countries	8 European countries, some with differing screening criteria. 1 joined late and was excluded from first analysis	United States: 10 centres, same criteria in each
Ages screened	Varies: mostly 55-70 years Some countries started at 50 years Some countries up to 75 years	55-74 years
Screen design	Once every 4 years (Sweden every 2 years)	Annual PSA screen for 6 years Annual DRE for 4 years
PSA level for action	3 ng/ml. Initially 4 ng/ml with DRE/TRUS, Sweden 2.5 ng/ml	4 ng/ml
DRE	Dropped in 1997, as shown to be less sensitive than a PSA of 3 ng/ml	Used throughout. Rarely useful if PSA was normal
Action on abnormal screen	Directed by the trial investigators; 86% proceeded to biopsy	Patient and physician informed and decided on next step, which for many was monitoring for changes in PSA; 68% had biopsy, although delays of over a year occurred in half; in some, PSA declined to < 4 ng/ml and no biopsy was performed
Off-trial background PSA testing rates	Not specified; thought to be unusual in 1990s, more common recently	45% had had PSA test in the 3 years prior to study entry; unknown how many had PSA test prior to that; control group screening rates increased from 40% in 1st year to 52% by 6th year

	ERSPC	PLCO
PSA above threshold on first screen	16.2%	7.9%
Positive predictive value of abnormal PSA result	24.1%	17.9% at first screen (10-12% subsequently)
Positive predictive value of abnormal DRE	n/a	DRE abnormal, PSA < 4 (5.4% of men): PPV ~3% DRE abnormal and PSA > 4 (1.2% of men): PPV ~38%
Cancer diagnosis rate	Screened: 8.3%; control: 4.8%	Screened: 9.0%; control: 7.8%
Stage & Grade distribution (adjusted for null)	Low stage: screened: 6.7%; control: 2.8% High stage: screened: 0.79%; control: 1.0% Low grade (≤ Gleason 7): screened: 7.6%; control: 4.0% High grade (> G7): screened: 0.6%; control: 0.8% Metastatic rate: screened $2.3/10^5$; control: $3.9/10^5$	Low stage: screened: 8.6%; control: 7.3% High stage: screened 0.1%; control: 0.1% Low grade (≤ G7): screened: 5.9%; control: 4.7% High grade (> G7): screened: 0.8%; control: 0.9% Metastatic: screened 0.2%; control: 0.2%
Deaths from prostate cancer	Screened: 0.29% (n = 214); control: 0.36% (n = 326) P = .04	Death rate: screened $2.0/10^5$; control $1.7/10^5$ Deaths: screened 0.13% (n = 50); control 0.11% (n = 44) P = n.s.
Number needed to screen/treat	NNS to prevent 1 death: 1,410 NNT to prevent 1 death: 48	n/a

	ERSPC	PLCO
Comments	– Immature data – Big increase in cases diagnosed with screening but these were of lower stage and grade – Fewer high-grade and metastatic cancers in the screened arm indicates likely greater mortality difference with more follow-up – Little detail on the treatments received, which may differ in intensity between groups – Mortality reduction comes at a high cost in terms of over-diagnosis and over-treatment – No evidence of a mortality reduction above 70 years or below 55 years – Current Canadian baseline PSA screening practice differs from that of the trial control group	– Baseline PSA prior test rate in both arms at least 45%, thus contamination was high in control arm and increased as the trial progressed – Designed to detect a 25% reduction in prostate cancer mortality, but power was less owing to high baseline PSA testing rates and fewer events than expected – Non-significant increase in cancer diagnosis in screened arm and little stage-shift to earlier cancers, thus unlikely that a mortality difference will be observed with more follow-up – "Usual care" for positive tests followed in accordance with standard U.S. practice – No evidence of mortality benefit at any age – Showed mortality rates in control arm similar to those of screening arm of European trial – Current Canadian baseline PSA screening practice similar to that of trial control group

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