PROSTATE CANCER SCREENING RECOMMENDATIONS 2014

OVERVIEW

We will review the following:

1. Overview of Prostate Cancer in Canada
2. CTFPHC Scientific Methods
3. Prostate Cancer Screening with the PSA Recommendations
4. Key Findings
5. Considerations for the Implementation of Recommendations
6. Conclusions
7. Additional Resources

CTFPHC BACKGROUND

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CTFPHC Prostate Cancer Screening Working Group:

The Prostate Cancer Screening working group included members from Task Force, the Public Health Agency of Canada (PHAC) and the Evidence Review Synthesis Centre (ERSC) at McMaster University.

Task Force Members:

- Neil Bell (Chair)
- James Dickinson
- Michel Joffres
- Harminder Singh
- Elizabeth Shaw
- Marcello Tonelli

Public Health Agency of Canada:

- Sarah Connor Gorber
- Amanda Shane
- Lesley Dunfield

Evidence Review Synthesis Centre:

- Donna Fitzpatrick-Lewis
- Ali Usman

PROSTATE CANCER: OVERVIEW

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Background

Prostate cancer is the most commonly diagnosed non-skin cancer among Canadian men with 1 in 7 men being detected as having prostate cancer (at current levels of screening). Long term survival with prostate cancer is now >90% in Canada.

The prostate specific antigen (PSA) test was introduced as a screening tool for prostate cancer in Canada in 1986, but its use for screening did not become widespread until about 1996.

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Global Rates of Prostate Cancer Mortality

There is approximately a 25 fold variation in prostate cancer mortality worldwide. This variation and the early reduction in prostate cancer morality are probably due to improvements in treatment with surgery, radiation and hormone therapy rather than screening. For example, the United Kingdom has seen low rates of prostate cancer screening but has continued to experience a reduction in mortality rates for prostate cancer.

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Objective of the 2014 Guideline

The primary objectives of the CTFPHC's 2014 guideline on prostate cancer screening are:

1. To update the 1994 CTFPHC guideline on screening for prostate cancer
2. To review the latest evidence on the benefits and harms of screening for prostate cancer with the PSA
3. To provide recommendations on screening for prostate cancer using the PSA with or without digital rectal examination (DRE) for men in the general population

SCIENTIFIC METHODS

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Methods of the CTFPHC

The CTFPHC is an independent panel of clinicians and methodologists with expertise in prevention, primary care, literature synthesis and critical appraisal. The mandate of the CTFPHC is to apply the latest evidence in preventive health care research to primary care practice and policy across Canada.

The prostate cancer screening working group is composed of 6 Task Force members (listed above) who work with PHAC science officers to establish the guideline research questions and analytical framework.

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The ERSC, in consultation with field experts, then undertakes a systematic review of the literature based this analytical framework, and prepares a systematic review of the evidence with GRADE tables. The ERSC participates in working group and Task Force meetings.

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CTFPHC Review Process

The CTFPHC review process is composed of an (i) internal review process and an (ii) external review process. The internal review process involves the guideline working group, the full Task Force, PHAC science officers and ERSC staff.

The external review process involves review of the guidelines by key stakeholders from generalist and disease specific organizations, federal, provincial and territorial stakeholders. The Canadian Medical Association Journal (CMAJ), where most of the CTFPHC guidelines are published, undertakes its own independent peer review journal process.

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Disease Specific Stakeholders:

- Canadian Urological Association (4 reviewers)
- Prostate Cancer Canada (2 reviewers)
- Canadian Cancer Society (1 reviewer)

Generalist Organizations:

- College of Family Physicians of Canada (1 reviewer)

Federal and P/T Stakeholders:

- Public Health Agency of Canada (2 reviewers)
- Health Canada (1 reviewer)
- Canadian Institutes of Health Research (1 reviewer)
- Council of Chief Medical Officers of Health (1 reviewer)

Anonymous reviewers from CMAJ (5 reviewers)

Prostate Cancer Screening: Analytical Framework

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Prostate Cancer Screening: Key Research Questions

The Task Force prostate cancer screening working group establishes the key guideline research questions. The key research questions for the prostate cancer screening guideline were:

1.1 What is the direct evidence that screening for prostate cancer with prostate-specific antigen (PSA), as a single-threshold test or as a function of multiple tests over time, decreases morbidity and/or prostate cancer-specific and all-cause mortality?
1.2 Is there evidence to support differential screening based on individual risk factors for prostate cancer such as age, black race/ethnicity, family history of prostate cancer or previously assessed increased SPA values – either absolute values or increased PSA measures over time?
7.0 What are the harms of PSA-based screening for prostate cancer?
3.0 What are the benefits of treatment of early-stage or screen-detected prostate cancer?
4.0 Is there evidence that tailoring the method of following up abnormal screening results to patient characteristics lead to clinically important differences in the harms and benefits of screening with PSA?
5.0 What are the harms of treatment of early-stage or screen-detected prostate cancer?

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Prostate Cancer Screening: Key Contextual Questions

The Task Force prostate cancer screening working group establishes the key contextual questions to provide additional information on patient values and preferences and how the guidelines should be implemented within clinical practice. The key contextual questions for the prostate cancer screening guideline were:

Stage one: Assist in making a decision about the direction of the recommendation:

1. What are the patient values and preferences for PSA screening for prostate cancer?

Stage two: Is evidence is sufficient to recommend screening:

1. What process and outcome performance measures or indicators have been identified in the literature to measure and monitor the impact of PSA screening for prostate cancer?
2. What is the optimal screening interval for PSA screening for prostate cancer and should this interval vary based on risk level (e.g., age, prior PSA levels, or other measures such as Gleason score)?
3. What are the most effective (accurate and reliable) risk assessment tools to identify: a) risk of prostate cancer and b) risk of poor outcomes after PSA testing and biopsy?
4. What is the cost-effectiveness of PSA screening for asymptomatic adults for prostate cancer? Costs to the system and to patients will be included if found.

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Prostate Cancer Screening: Eligible Study Types

The primary population of interest for the systematic review was Canadian men in the general population, including men with lower urinary tract symptoms (nocturia, urgency, frequency and poor stream) or with benign prostatic hyperplasia (BPH).

Evidence on the effectiveness of screening on preselected outcomes was obtained from systematic reviews and randomized control trials (RCTs). Evidence on the harms of screening with the PSA test were obtained from both RCT and observational studies. Evidence supporting the contextual questions of the guideline was obtained from studies of varying designs.

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GRADE Methodology

The CTFPHC utilizes the GRADE system for providing clinical practice guideline recommendations based on a systematic review of the available evidence. The **GRADE** acronym stands for: **G**rading of **R**ecommendations, **A**ssessment, **D**evelopment and **E**valuation.

The GRADE system is composed of two main components:

1. The quality of the evidence
2. The strength of recommendation

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GRADE: How is the quality of the evidence graded?

The quality of the evidence is graded as high, moderate, low or very low based on how likely further research is to change our confidence in the estimate of effect. In terms of the quality of evidence, RCT studies often start as high quality evidence and observational studies start as low quality evidence. However, both can be downgraded or upgraded based on various study characteristics.

- High: confidence that the true effect lies close to the estimate of effect
- Moderate: confidence that the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
- Low: confidence that the true effect is close to the estimate of the effect. The true effect may be substantially different from the estimate of the effect
- Very low: any estimate of effect is very uncertain

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GRADE: How is the strength of the recommendations graded?

The strength of the recommendation (strong/weak) is based on the quality of supporting evidence, the degree of uncertainty about the balance between desirable and undesirable effects, the degree of uncertainty or variability in values and preferences, and the degree of uncertainty about whether an intervention represents a wide use of resources.

Strong recommendations are those for which the Task Force is confident that the desirable effects of an intervention outweigh its undesirable effects (strong recommendation for an intervention) or that the undesirable effects outweigh the desirable effects of an intervention (strong recommendation against an intervention).

Weak recommendations are those for which the desirable effects probably outweigh the undesirable effects (weak recommendation for an intervention) or that undesirable effects probably outweigh the desirable effects (weak recommendation against an intervention) but that appreciable uncertainty exists.

GRADE: Interpretation of recommendations

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Insert Table.

It is important to consider the strength of the recommendations when interpreting the Task Force guidelines for implementation in clinical practice, for policy, or for patients in decision making,

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PROSTATE CANCER SCREENING WITH PSA: RECOMMENDATIONS

The following is an overview of the CTFPHC Recommendations on Prostate Cancer Screening using the Prostate Specific Antigen (PSA) test with or without the Digital Rectal Examination (DRE).

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CTFPHC Recommendation: PSA screening for men < 55 years

- For men aged less than 55 years of age, we recommend not screening for prostate cancer with the prostate-specific antigen test (strong recommendation; low quality evidence).

The CTFPHC based this recommendation on the low incidence of prostate cancer and prostate cancer mortality, and the lack of evidence for benefit of screening in this age group, as well as the evidence of harms. The strong recommendation implies that the CTFPHC is confident that the harms of screening and subsequent testing/treating outweigh the benefits.

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CTFPHC Recommendation: PSA screening for men 55-69 years

- For men aged 55-69 years, we recommend not screening for prostate cancer with the prostate-specific antigen test (weak recommendation; moderate quality evidence).

The CTFPHC placed a relatively low value on a small and uncertain potential reduction in the risk of prostate cancer mortality and a relatively higher value on the risk of harms associated with diagnosis and treatment due to false positive results and overdiagnosis. The weak recommendation against screening implies that the harms of screening and subsequent testing/treatment probably outweigh the benefits, but uncertainty exists.

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CTFPHC Recommendation: PSA screening for men > 70 years

- For men aged 70 years and older, we recommend not screening for prostate cancer with the prostate-specific antigen test (strong recommendation; low quality evidence).

The CTFPHC based this recommendation on the lower life expectancy and the lack of evidence for benefits of screening in this age group, as well as the evidence of harms. The strong recommendation implies that the CTFPHC is confident that the harms of screening and subsequent testing/treating outweigh the benefits.

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CTFPHC Recommendations: Summary of recommendations for PSA screening

These recommendations apply to all men who have not been previously diagnosed with prostate cancer, including men with lower urinary tract symptoms (nocturia, urgency, frequency and poor stream) or with benign prostatic hyperplasia (BPH). These recommendations do not apply to the use of the PSA test for surveillance after diagnosis or treatment for prostate cancer.

KEY FINDINGS

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Benefits of Screening with the PSA: Findings

The evidence review identified 6 RCTs of varying quality which investigated the benefits of screening with the PSA test. Of these 6 RCT trials, only 3 had a low risk of bias (RoB) and one of these 3 trials was a report from Gøteborg ,which we chose to regard as a site within the larger multi-centre trial (European Randomized Study of Screening for Prostate Cancer (ERSPC)). This avoids double counting.

Thus, in formulating the recommendations, the prostate cancer working group considered all sites of the ERSPC trial together and based the final recommendations on the results of the 2 low RoB trials (ERSPC and PLCO).

Among the results, the ERSPC trial found a small absolute reduction in prostate-specific mortality with PSA screening, though this was found primarily at two of the sites and not the other five, while the PLCO trial found no effect. Neither of the trials found a reduction in all-cause mortality.

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Harms of Screening with the PSA: Findings

The evidence review did not identify any RCT studies on the harms associated with screening for prostate cancer with the PSA test. Therefore, a number of observational studies (including modeling data) were used to assess the degree of harms related to screening men for prostate cancer using the PSA test. The main harms of screening identified were (i) harms of biopsy, (ii) harms of overdiagnosis, and (iii) false positives.

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Harms of Biopsy

The major harms associated with biopsy were haematuria (average of 30.86% of men who had a biopsy), infection (average of 0.94% of men who had a biopsy), hospitalization (average of 2.07% of men who had a biopsy) and death (average of 0.17% of men who had a biopsy).

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Harms of Overdiagnosis

Overdiagnosis is defined as cancer that is correctly detected but would not have caused symptoms or death during the patient's lifetime. The proportion of overdiagnosis was approximately 40-56% of cases diagnosed. However, this figure is difficult to reliably determine since it is contingent on accurate and high quality post-mortem data.

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Harms of False Positives

Among the potential harms of screening with the PSA test is the harm of false positives, which are cases in which men without prostate cancer screen above the PSA threshold. When this was set at 3ng/ml, the proportion of false positives was 17.8% (at least one false positive). For the higher threshold (>4ng/mL) in the US trial, the proportion of false positives was 11.3%.

However, it should be noted that not all men who screened above threshold had a biopsy and some men had multiple biopsies. Additionally, some men who screen positive (above threshold) on the first round of screening but not diagnosed then, could be diagnosed with prostate cancer on a subsequent round.

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Benefits of Treatment for Prostate Cancer: Findings

The primary treatments of prostate cancer reviewed by the prostate working group included (i) radical prostatectomy (ii) radiation therapy (iii) androgen deprivation therapy (ADT) and (iv) combination therapy.

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Some treatments were found to reduce the risk of prostate cancer-specific mortality, although the quality of evidence was variable.

- Prostatectomy was the only treatment with high quality of evidence
- Hormone therapy alone was found to produce an increased risk of prostate cancer-specific mortality

There was very limited and low quality of evidence to support a reduction in the risk of all-cause mortality for the following treatments:

- Prostatectomy
- Radiation Therapy
- Combination Therapy (Radiation + Hormone Therapy)

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Harms of Treatment for Prostate Cancer: Findings

As noted above, the most common treatments for prostate cancer include radical prostatectomy, radiation therapy and ADT. A number of harms were found for these treatments and included:

- Urinary incontinence
- Erectile dysfunction
- Bowel dysfunction

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The risk of each of these harms of treatment varied depending on the study type (RCT, Cohort, and Observational).

- The relative risk of urinary incontinence in the RCT trials was 3.22 (2.27 to 4.56) 179 more per 1000 (from 102 more to 286 more)
- The relative risk of erectile dysfunction in the RCT trials was 1.39 (0.77 to 2.53) 221 more per 1000 (from 130 fewer to 867 more)
- The relative risk of bowel dysfunction in the RCT trials was 0.42 (0.04 to 4.14) 54 fewer per 1000 (from 27 fewer to 5 more)

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Prostatectomy and Post-Surgical Harms

A number of observational studies found post-surgical harms <30 days for prostatectomy among men 50-75 years. Post-surgical harms included both minor harms (e.g., blood transfusion, urine retention, and infection) and major harms (e.g., blood clots, re-hospitalization, and death).

The absolutely risk of any harms within 30-days was 11.4-21.4% and the absolute risk of 30-day mortality was and 0.36-0.48%.

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Patient Preferences and Values

In the review of the key contextual questions, the Task Force prostate cancer working group found some limited evidence on patient preferences and values with respect to PSA screening. Some of the key findings included:

- Men with perceived self-vulnerability to the disease and physician recommendation are associated with patient request for screening
- High quality evidence is lacking about the best way to facilitate informed decision making about screening
- Practitioners should distinguish between benefits and harms of screening, subsequent investigation and treatment
- Discussions should include overview of diagnostic and therapeutic options in the event PSA test results are abnormal

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Evidence on Resource Implications

The CTFPHC did not consider the costs of screening or treatment of prostate cancer when formulating these recommendations.

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Balancing Benefits and Harms of Screening

There is conflicting evidence of a small and very uncertain potential reduction in prostate cancer mortality in men 55-69 years of age.

- Number needed to treat is 1000 (1 death avoided per 1000 screened)
- If you screen, 5 of 1000 men die of prostate cancer
- If you don't screen, 6 of 1000 men die of prostate cancer
- For one death avoided from prostate cancer 27-28 additional men will be diagnosed with prostate cancer

There is no convincing evidence of a reduction in prostate cancer mortality with PSA screening for any other age group and there is consistent evidence that screening and active treatment lead to harm.

Therefore, the potential small benefit from screening is outweighed by the potential significant harms and the CTFPHC recommends not screening for prostate cancer with the PSA test.

CONSIDERATIONS FOR THE IMPLEMENTATION OF RECOMMENDATIONS

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Considerations for the Implementation of Weak Recommendations

The implication of the weak recommendation for men aged 55-69 years is that clinicians who believe a patient places a high value on the small potential benefit of screening and may not be concerned about harms, may wish to discuss the benefits/harms of screening with men in this age group.

A weak recommendation implies that most people would want the recommended course of action, that is, not to screen, but some may prefer to do so.

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Considerations for the Implementation of Strong Recommendations

The implication of the strong recommendation for men < 55 years of age and > 70 years of age is that clinicians should not routinely discuss screening with men in these ages groups, unless the topic is raised by the patient.

A strong recommendation implies that most men will be best served by the recommended course of action.

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Considerations for High Risk Populations

High risk populations for prostate cancer include men of black ethnicity or men with a family history of prostate cancer. The PLCO study (U.S. Study) included men of black ethnicity, however the results were not broken down by risk level or risk factor.

Instead, the studies provided results for the male population as a whole and included no special considerations. Therefore, there is currently no trial data to suggest that men at high risk should be screened differently from men in the general population.

Clinicians may wish to discuss the benefits and harms of screening men at high risk, with explicit consideration of their values and preferences.

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Comparison of Guidelines

The 2014 CTFPHC recommendations on prostate cancer screening with the PSA are consistent with the recommendations issued on prostate cancer by other industrialized countries including:

- The United States Preventive Services Task Force (USPSTF) 2012 Recommendations
- The Cancer Council Australia 2010 Recommendations
- The National Health Service UK 2013 Recommendations

However, there are other guidelines available which provide conflicting recommendations on PSA screening for prostate cancer.

CONCLUSIONS

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- Among men aged 55-69 years, the harms of screening probably outweigh the benefits, but uncertainty exists
- Therefore, the CTFPHC made a weak recommendation to not screen for prostate cancer with the PSA test in this age group
- The implication of the weak recommendation is that clinicians should discuss the benefits and harms of screening so they can make an informed decision in line with their values and preferences
- Among men younger than 55 years and older than 70 years, there is a lack of evidence for benefit of screening and clear evidence of harms. There is certainty that the harms of screening outweigh the benefits
- Therefore, the CTFPHC made a strong recommendation to not screen for prostate cancer with the PSA test in these age groups
- The implication for the strong recommendation is that clinicians should not routinely discuss screening with men unless the topic is raised.

ADDITIONAL RESOURCES

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Evidence Review and Knowledge Translation Tools

For more information on the details of this guideline or to access the KT tools please refer to the evidence review in the resources section of the website http://canadiantaskforce.ca.