Screening for Prostate Cancer with Prostate Specific Antigen

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Section I: Purpose and Background

Prostate cancer is the most commonly diagnosed non-skin cancer in men and the third leading cause of cancer death for men in Canada[1]_.The lifetime risk for diagnosis has been estimated at 16.5%[2], while the lifetime risk for dying from prostate cancer is estimated at 2.7%[3]. The prevalence of prostate cancer in men 51 years and older at autopsy, dying from other causes, ranges from 5% to 81%, depending on age and region of the world[4]. Most cases of prostate cancer have a good prognosis even without treatment. The five-year estimated survival ratio is 96%, and is the highest of all cancers in men[5].

Beginning in the 1990s, screening with the prostate specific antigen (PSA) test has become widespread in clinical practice in the United States and Canada[1,6]. In the United States, it is estimated that the majority of American men aged 50 years and older receive regular PSA tests[7]. A similar trend is observed in Canada, where nearly half of Canadian men aged 50 years and older reported having at least 1 PSA test in their lifetime[8].

However, increased screening can lead to an apparent increase in burden of illness (higher incidence and earlier age at diagnosis) without concomitant improvement in clinically relevant outcomes, such as cancer specific mortality. It has been estimated that the introduction of PSA screening in the United States resulted in more than 1 million additional men being diagnosed and treated for prostate cancer from 1986 to 2005[9]. This growth is most evident in younger men and most of this excess incidence represents overdiagnosis[10,11] or the detection of cancers that never progress to cause symptoms or death[12].

This protocol describes the process by which the Canadian Task Force on Preventive Health Care (CTFPHC) will update its literature review on PSA testing in order to provide updated guidance on screening for prostate cancer.

Section II. Previous CTFPHC Recommendations and Recommendations from Other Guideline Developers

The last CTFPHC guidelines on prostate cancer screening were published in 1994[13]. At that time, the CTFPHC concluded that there was insufficient evidence to include PSA screening in the periodic health examination of men over 50 years of age. Since that time, at least two large randomized trials[14,15] have been published that have formed the basis of updated screening guidelines in Canada and the United States.

CTFPHC Issues on Guideline Development on Screening for Prostate Cancer

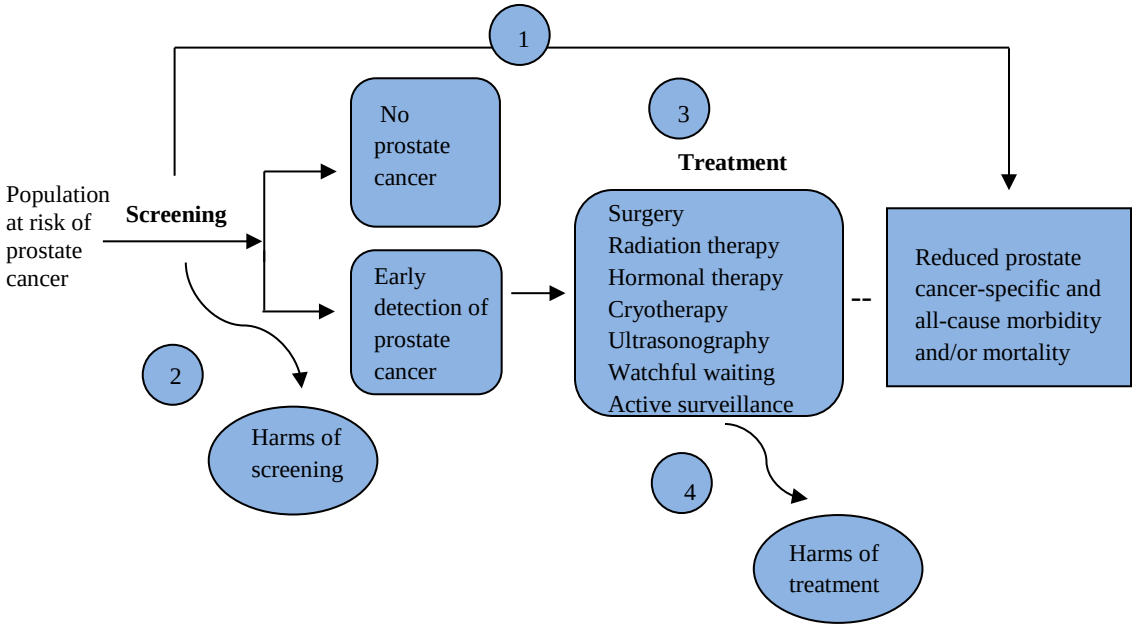
The U.S. Preventive Services Task Force (USPSTF) published a guideline on screening for prostate cancer in May 2012[16] based on literature reviewed to July 2011. In this guideline, the USPSTF recommended against PSA screening for prostate cancer (Grade D recommendation[i]). The Canadian Urological Association[17] also recently published guidelines for prostate cancer screening and recommend screening all men, whose life expectancy is at least 10 years, every one to two years with PSA beginning at age 50. They also recommend that "high risk" men start screening from age 40 years. Towards Optimized Practice (TOP)[18] suggest discussing PSA testing with men over the age of 50 years. Since 2010, several other national organizations have also published prostate cancer screening guidelines and provide differing recommendations[19-25](Appendix 1). All of the above guidelines were developed using essentially the same literature. These guidelines provide conflicting advice to family physicians and other primary care practitioners on the most appropriate approach to screening men for prostate cancer. The lack of current CTFPHC guidance and the conflicting nature of existing guidelines were the basis of selecting this topic for an update. [25]

Section III. Review Approach

This review will be an update of the 2011 USPSTF systematic reviews[26,27] that were used to inform their 2012 recommendation statements. The USPSTF conducted two evidence reviews to support its recommendations, one on screening for prostate cancer[26] and one on treatment of localized prostate cancer[27]. The USPSTF reviews were assessed with AMSTAR[28] by the Office of the CTFPHC and underwent a more detailed methodological assessment to ensure that their process met the methodological standards of the CTFPHC (see Appendix 2: Summary of AMSTAR Assessments of USPSTF reviews and Appendix 3: Content Assessment of the USPSTF reviews for details).

[i] Grade D recommendation – The USPSTF recommends against screening. There is moderate or high certainty that the service has no benefit or that the harms outweigh the benefits.

Analytic framework and key questions.



Key Questions

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?

1b. Is there evidence to support differential screening based on individual risk factors for prostate cancer such as age, African descent, family history of prostate cancer or previously assessed increased PSA values – either absolute values or increased PSA measures over time?

2. What are the harms of PSA-based screening for prostate cancer?
3. What are the benefits of treatment of early-stage or screen-detected prostate cancer?
4. Is there evidence that tailoring the method of following up abnormal screening results to patient characteristics (example: active surveillance vs treatment A vs B) lead to clinically important differences in the harms and benefits of screening with PSA?
5. What are the harms of treatment of early-stage or screen-detected prostate cancer?

Contextual Questions

Contextual questions will be addressed in two stages, depending on whether evidence of PSA test screening performance of screening is identified.

<u>Stage one:</u>

Questions that are necessary to 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:
If evidence of effectiveness is sufficient for the Task Force to recommend screening, the following additional questions will be added:

2. 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?
3. 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)?
4. 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?
5. What is the cost-effectiveness of PSA screening asymptomatic adults for prostate cancer? Costs to the system and to patients will be included if found.

Subgroup Analysis

High risk groups were selected through a review of the literature and guidelines published by generalist and specialist organizations and through input received during our peer review process; high risk groups identified through this process were:
Canadians aged 65 years and older, those with a family history of prostate cancer, those of African descent and those with previously abnormal PSA. The guideline will consider specific recommendations for some or all of these groups if this approach is supported by available data, including subgroup analyses. If additional high risk groups are identified in the studies, these will also be examined.

Literature Search

The USPSTF review on screening searched PubMed for randomized controlled trials, systematic reviews, and meta-analyses indexed between January 1, 2007 and July 1, 2011 (English-language). For the treatment review the search included the Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews (through the second quarter of 2011), and Ovid MEDLINE (2002 to July 2011) for relevant studies and systematic reviews. The same search terms and databases will be used, and all searches will be updated to November 2012.

Inclusion and Exclusion Criteria

The following inclusion/exclusion criteria (Table 1) were used in the USPSTF review and will be used in this update, with the following exception: data from any study design can be used to answer contextual questions (i.e., studies used to address these questions are not restricted to randomized trials).

Table 1. Inclusion and exclusion criteria and definitions used by the USPSTF in the screening and treatment reviews[26]

	Screening	Treatment
Population	Asymptomatic males at risk of prostate cancer (includes men with chronic, mild lower urinary tract symptoms).	Men treated for screen-detected prostate cancer. Because most studies do not describe whether the prostate cancer was screen detected, studies of localized (T1 or T2) prostate cancer were also included (as most screen-detected cancer is localized).
Intervention	One or more PSA measurements, with or without additional methods such as digital rectal examination	Radical prostatectomy, radiation therapy, hormonal therapy, cryotherapy, and high-intensity focused ultrasonography in men with localized prostate cancer.
Comparator	No screening/usual care in asymptomatic general primary care population. Men who have had previous PSA screens are not excluded	Watchful waiting or active surveillance in men with localized prostate cancer both of which are active plans to postpone intervention, with the former involving providing palliative treatment to patients showing symptoms of disease progression and the latter involving a decision to proceed with treatment based on the rate of rise of PSA level and biopsy results)
Outcome	Must report on all-cause or prostate cancer-specific mortality or harms associated with screening.	All-cause mortality, prostate cancer-specific mortality, or harms associated with prostatectomy, radiation therapy, hormonal therapy, cryotherapy, and high-intensity focused ultrasonography.
Study types	Randomized controlled trials, systematic reviews and meta-analysis.	Randomized controlled trials and cohort studies. For harms, uncontrolled observational studies if they reported on perioperative harms. If no randomized trials, cohort studies, or large (n>1,000) uncontrolled studies are available, smaller uncontrolled studies will be used.

Harms	Include but not limited to: false positives, false negatives, physical harms (e.g., bruising, bleeding, complications), psychological harms	Overall and cause-specific mortality, reduced quality of life or function, increased urinary incontinence, bowel dysfunction, erectile dysfunction, surgical complications, psychological or endocrinological effects.

Section IV. Planned Schedule and Timeline

Timelines

- Draft Protocol: November 2012
- Final Protocol: January 2013
- Draft Evidence Review: March 2013
- Final Evidence Review: May 2013
- Draft Recommendation Statement: March 2013
- Published Recommendation Statement: September 2013

Literature will be updated 6 weeks prior to publication to ensure that the recommendations include all relevant data. In addition authors of key studies will be contacted to determine if they are planning to release data on their trials in the immediate future.

Section V: References Cited

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Appendix 1: Summary of recommendation on prostate cancer screening using prostate-specific antigen testing, from Canada and other national/international organizations.

Organization (year) **Guideline Title**	**Age of screening initiation**	**Screening interval**	**Age of screening discontinuation**
United States Preventive Services Task Force (2012)[16] Screening for Prostate Cancer: U.S. Preventive Services Task Force Recommendation Statement	Do not use prostate-specific antigen (PSA)-based screening for prostate cancer.		
Canadian Urological Association (2011)[17] Prostate cancer screening: Canadian guidelines 2011	Average risk: 50 years with at least 10 year life expectancy Increased risk: 40 years	Not specified	70 years
Towards Optimized Practice (2010) Screening and early diagnosis of prostate cancer	Discuss PSA testing with most asymptomatic men over the age of 50 years		
European Association of Urology (2012)[21] EAU Guidelines on Prostate Cancer: Part 1: Screening, Diagnosis and Treatment of Clinically Localised Disease	40 years	Based on baseline PSA. Screening interval of 8 years may be sufficient in men with initial PSA <=1ng/mL	75 years
American Cancer Society (2012)[19] American Cancer Society	Average risk: Discussion should start at age 50 years.	PSA <2.5 ng/mL: 2 years PSA >= 2.5 ng/mL: annual	Men without a 10 year life expectancy should not be offered screening.

Organization (year) Guideline Title	Age of screening initiation	Screening interval	Age of screening discontinuation
recommendations for prostate early detection	Increased risk: Discussion should start at age 40 or 45 years, depending on extent of the risk.		
National Cancer Institute of the National Institutes of Health (2012)[23] Prostate Cancer Screening (PDQ®)	The evidence is insufficient to determine whether screening for prostate cancer with PSA or DRE reduces mortality from prostate cancer.		
National Health Service (2010)[22] Prostate cancer risk management programme: information for primary care; PSA testing in asymptomatic men	Any man over the age of 50 who asks for a PSA test after careful consideration of the implications should be given one.		
American Society of Clinical Oncology (2012)[20] Screening for prostate cancer with prostate-specific antigen (PSA) testing: American Society of Clinical Oncology Provisional Clinical Opinion	In men with life expectancy >10 years, it is recommended that physicians discuss with their patients whether PSA testing for prostate cancer screening is appropriate for them.		
Prostate Cancer Canada (2010)[24] Early Detection Guidelines	Establish baseline PSA at 40 years. Repeat every 5 years until age 50 years. Routine screening: 50 years	Annual or semi-annual.	Not specified
Cancer Council Australia, Australian Health Ministers' Advisory Council (2010)[25] Prostate cancer screening in Australia:	Current evidence is that the harms of population screening with the PSA test outweigh the benefits. Consequently, either alone or combined with DRE, the PSA test does not form the basis of a population-based screening program		

Organization (year) Guideline Title	Age of screening initiation	Screening interval	Age of screening discontinuation
joint key messages (Position Statement)			

Appendix 2: Summary of AMSTAR Assessments of USPSTF reviews

Two members of the Office of the CTFPHC completed the AMSTAR assessment on the USPSTF screening review[26]. The results indicate high agreement between the reviewers.

	Question	Responses from Reviewer 1	Responses from Reviewer 2
1	Was an 'a priori' design provided?	X Yes ☐No ☐Can't answer ☐Not applicable	X Yes ☐No ☐Can't answer ☐Not applicable
2	Was there duplicate study selection and data extraction?	X Yes ☐No ☐Can't answer ☐Not applicable	X Yes ☐No ☐Can't answer ☐Not applicable
3	Was a comprehensive literature search performed?	X Yes ☐No ☐Can't answer ☐Not applicable	X Yes ☐No ☐Can't answer ☐Not applicable
4	Was the status of publication (i.e. grey literature) used as an inclusion criterion?	☐Yes ☐No X Can't answer ☐Not applicable	☐Yes ☐No X Can't answer ☐Not applicable
5	Was a list of studies (included and excluded) provided?	X Yes ☐No ☐Can't answer ☐Not applicable	X Yes ☐No ☐Can't answer ☐Not applicable
6	Were the characteristics of the included studies provided?	X Yes ☐No ☐Can't answer ☐Not applicable	X Yes ☐No ☐Can't answer ☐Not applicable
7	Was the scientific quality of the included studies assessed and documented?	X Yes ☐No ☐Can't answer ☐Not applicable	X Yes ☐No ☐Can't answer ☐Not applicable
8	Was the scientific quality of the included studies used appropriately in formulating conclusions?	XYes ☐No ☐Can't answer ☐Not applicable	X Yes ☐No ☐Can't answer ☐Not applicable

9	Were the methods used to combine the findings of studies appropriate?	☐Yes ☐No ☐Can't answer X Not applicable	☐Yes ☐No ☐Can't answer X Not applicable
10	Was the likelihood of publication bias assessed?	☐Yes X No ☐Can't answer ☐Not applicable	☐Yes X No ☐Can't answer ☐Not applicable
11	Was the conflict of interest stated?	X Yes ☐No ☐Can't answer ☐Not applicable	☐Yes X No ☐Can't answer ☐Not applicable

Appendix 3: Content Assessment of the USPSTF reviews

The content of the USPSTF prostate cancer screening recommendation statement[16] was compared against the research protocol included in the evidence synthesis[26] in order to assess whether the included evidence was consistent with the inclusion/exclusion criteria defined *a priori*. Based on this assessment, the CTFPHC felt that the USPSTF adequately complied with their criteria, which led to the decision to update the USPSTF's review.

Component	As described in protocol	As reflected in recommendation statement	Assessment
Study types	• RCTs • Systematic reviews • Meta-analyses	• 6 RCTs (3 fair; 3 poor) • 0 systematic reviews • 2 meta-analyses	Recommendations were only based on evidence from study types referenced in the protocol.
Search strategy	Database: Pubmed 1. Prostatic Neoplasms[Mesh] 2. Screening OR prostate-specific antigen [Mesh] 3. Early diagnosis[Mesh] 4. PSA velocity[All Fields] 5. Prostate specific antigen velocity[Title/Abstract] 6. PSA doubling time [Title/Abstract] 7. Prostate specific antigen doubling [Title/Abstract] 8. 2 OR 3 OR 4 OR 5 OR 6 OR 7 9. 1 AND 8 10. Limit 9 to English[lang] AND Randomized Controlled Trial [ptyp] AND Publication Date		

	from 2007/01/01 to 2011/07/01 English language only. The search strategy for the Cochrane Library was not provided.		
Data sources	• PubMed • Cochrane Library • Reference lists • Expert suggestions	Search up to July 1, 2011.	
Population	Population at risk of prostate cancer	Men aged 50-74 years. One RCT[29] included n=46,486 men aged 40-84 years.	Age of participants varied for each study.
Intervention	PSA-based screening	PSA-based screening	Neither screening interval nor PSA cut-off point was identified *a priori* as inclusion/exclusion criteria. Cut-off points ranged from 2.5-10ng/mL and the screening intervals ranged from 1 to 4 years (n=1 study only screened participants once).
Comparator	No screening/usual care in asymptomatic general primary care population	No screening/usual care.	There were varying reports of contamination between intervention and control groups.
Outcome	Prostate cancer mortality or all-cause mortality	Prostate cancer mortality or all-cause mortality	Based on information available, it appears that the inclusion/exclusion criteria were adhered-to.
Harms	Information about the harms of screening present in the included study types.	2 RCTs reported harms, including: • False-positive results • Harms of screening • Harms of diagnosis procedures	
Inclusion/ Exclusion	• Not about prostate cancer • Narrative review, commentary or	List of excluded studies was not reviewed.	Based on information available, it appears that the inclusion/exclusion

	editorial • Did not address screening • Ineligible study design • No prostate cancer mortality outcomes	criteria were adhered-to.