

Harms of Prostate-Specific Antigen (PSA) Screening in Prostate Cancer

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CONTEXT

This rapid review examines the harms of prostate-specific antigen screening in prostate cancer to facilitate decisions regarding the benefits versus the harms of screening for prostate cancer.

RESEARCH QUESTION

What are the harms of prostate-specific antigen screening in prostate cancer?

CONCLUSION

There are major harms (unnecessary risks) associated with screening for prostate cancer, including the risks of biopsy and overdiagnosis. There are also minor harms associated with screening for prostate cancer, including the risks of prostate-specific antigen testing. Screening offers no mortality advantage that can be balanced against the harms.

RAPID REVIEW METHODOLOGY

Rapid reviews are completed in 2-4-week time frames. Clinical questions are developed by Health Quality Ontario, in consultation with experts, end users, and/or applicants in the topic area. A systematic literature search is then conducted to identify relevant systematic reviews, health technology assessments, and meta-analyses. The methods prioritize systematic reviews, which, if found, are rated by AMSTAR to determine the methodological quality of the review. If the systematic review has evaluated the included primary studies using the GRADE Working Group criteria (<http://www.gradeworkinggroup.org/index.htm>), the results are reported and the rapid review process is complete. If the systematic review has not evaluated the primary studies using GRADE, the primary studies in the systematic review are retrieved and the GRADE criteria are applied to 2 outcomes. If no systematic review is found, then RCTs or observational studies are included, and their risk of bias is assessed. All rapid reviews are developed and finalized in consultation with experts.

CONTEXT

Objective of Rapid Review

To examine the harms associated with prostate-specific antigen (PSA) screening in prostate cancer. A detailed review of the clinical effectiveness of PSA screening in prostate cancer has been recently completed.¹

Clinical Need and Target Population

PSA screening for prostate cancer is defined as a screening program for prostate cancer in asymptomatic men that incorporates one or more PSA measurements, with or without additional modalities such as digital rectal examination. (1) As part of the informed decision making process, an examination of the benefits and harms of PSA screening should be considered. Currently, controversy still exists around the benefits versus the harms of screening for prostate cancer as the two main randomized controlled trials produced conflicting results. (2)

¹ Pron G. Prostate-specific antigen (PSA)-based population screening for prostate cancer: an evidence-based analysis. *Ont Health Technol Assess Ser* [Internet]. 2015 May;15(10):1–64. Available from: <http://www.hqontario.ca/evidence/publications-and-ohtac-recommendations/ontario-health-technology-assessment-series/prostate-cancer-screening-eba>.

QUESTION, METHODS, AND FINDINGS

Research Question

What are the harms of PSA screening for prostate cancer?

Methods

See Appendix 1 for a detailed description of the search strategy, including terms and results.

Inclusion Criteria

- English-language full-text publications
- published between January 1, 2009, and May 2, 2014
- systematic reviews (SRs), meta-analyses, and health technology assessments
- study design and methods must be clearly described
- relevant outcomes

Exclusion Criteria

- studies not reporting on harms associated with screening or diagnosis

Outcomes of Interest

- harms of PSA testing; e.g., false-positives, anxiety, or psychological distress
- harms of prostate biopsy; e.g., infection, bleeding, and mortality
- overdiagnosis

Findings

The database search yielded 76 citations published between January 1, 2009, and May 2, 2014, (with duplicates removed). Articles were excluded based on information in the title and abstract. The full texts of potentially relevant articles were obtained for further assessment. From the 76 citations identified, editorials, studies based on treatment, technical papers, cost-effectiveness, and non-English papers were excluded. There were 20 potentially eligible papers that underwent full-text review. At this stage, papers on guidelines and papers that were not relevant to the question of interest were excluded.

Eight systematic reviews met the inclusion criteria. The reference lists of the included studies and health technology assessment websites were hand-searched to identify other relevant studies, and no additional citations were identified. After scoring the systematic reviews using the Assessment of Multiple Systematic Reviews (AMSTAR), only 3 systematic reviews were included. (3-5) Scores for the 3 included (AMSTAR score ≥ 7) (3-5) and the 5 excluded (AMSTAR score < 5) (2;6-9) systematic reviews are shown in Appendix 2.

For each included study, the study design was identified and is summarized below in Table 1, a modified version of a hierarchy of study design by Goodman, 1996. (10)

Table 1: Body of Evidence Examined According to Study Design

Study Design	Number of Eligible Studies
RCTs	
Systematic review of RCTs	3
Large RCT	-
Small RCT	-
Observational Studies	
Systematic review of non-RCTs with contemporaneous controls	-
Non-RCT with non-contemporaneous controls	-
Systematic review of non-RCTs with historical controls	-
Non-RCT with historical controls	-
Database, registry, or cross-sectional study	-
Case series	-
Retrospective review, modelling	-
Studies presented at an international conference	-
Expert opinion	-
Total	3

Abbreviations: RCT, randomized controlled trial.

Literature Review Summary

The details of the 3 systematic reviews included have been summarized in Appendix 2. The results by study and outcome (e.g., harms of PSA testing, harms of biopsy, overdiagnosis) are shown below in Tables 2 and 3. Since the evidence for the harms of PSA screening for prostate cancer were taken either from the screening group only or simulation study (e.g., overdiagnosis), the GRADE criteria were not used.

Table 2: Qualitative Summary by Study: Harms of PSA Testing

Study	Summary
Ilic et al, 2013 (3)	<ul style="list-style-type: none"> PSA-complications of 26/10,000 screenings; eg, dizziness, bruising, hematoma, and fainting
Cochrane Review	<ul style="list-style-type: none"> After at least 1 round of screening, FP = 17.8%^a Physical harms from DRE of 0.3/10,000 screenings; eg, bleeding and pain Short-term anxiety (no magnitude of effect)
Chou et al, 2011 (4)	<ul style="list-style-type: none"> PSA-complications of 26/10,000 screenings; eg, bruising and fainting After 3 rounds of screening, FP = 12%^b
AHRQ for USPSTF	<ul style="list-style-type: none"> After an elevated PSA test, 76% of prostate biopsies showed no cancer 5.5% likelihood of undergoing biopsy due to a FP test result Physical harms from DRE of 0.3/10,000 screenings; eg, bleeding and pain FP is associated with adverse psychological harms (no magnitude of effect)
Djulbegovic et al, 2010 (5)	<ul style="list-style-type: none"> Fainting due to PSA testing of 3/10,000 screenings After an elevated PSA test, 75.9% and 82.5% of prostate biopsies showed no cancer Physical harms from DRE of 0.3/10,000 screenings; eg, bleeding and pain Authors conclude there is no information on quality of life^c

Abbreviations: AHRQ, Agency for Healthcare Research and Quality; DRE, digital rectal examination; FP, false positives; PSA, prostate-specific antigen; USPSTF, U.S. Preventative Services Task Force.

^aDifferent thresholds used but a cutpoint of 3 ng/ml was typical.

^bCutpoint of 4 mcg/L.

^cAuthors did not review information on psychological harms.

Table 3: Qualitative Summary by Study: Harms of Prostate Biopsy

Study	Summary
Ilic et al, 2013 (3)	<ul style="list-style-type: none"> Biopsy complications of 68/10,000 evaluations; eg, infection, bleeding, clot formation, urinary difficulties
Cochrane Review	<ul style="list-style-type: none"> Pain-related complications after biopsy (no magnitude of effect) < 30 days: mild or no pain (85%), dizziness (3%), hematuria (7%) ≥ 35 days: pain (44%), fever (20%), hematuria (66%), hematochezia (37%), and hemoejaculate (90%) ≥ 2 weeks post-biopsy: pain (15%), fever (3%), hematuria (20%), hematochezia (5%), and hemoejaculate (60%) No deaths due to biopsy
Chou et al, 2011 (4)	<ul style="list-style-type: none"> Biopsy complications of 68/10,000 evaluations; eg, infection, bleeding, and urinary difficulties
AHRQ for USPSTF	<ul style="list-style-type: none"> After biopsy, harms include the development of a fever (3.5%), urine retention (0.4%), and hospitalization due to prostatitis or urosepsis (0.5%)
Djulbegovic et al, 2010 (5)	<ul style="list-style-type: none"> Biopsy complications of 68/10,000 evaluations; eg, infection, bleeding, clot formation, urinary difficulties No deaths due to biopsy

Abbreviations: AHRQ, Agency for Healthcare Research and Quality; USPSTF, U.S. Preventative Services Task Force.

Overdiagnosis was mentioned in only 1 of the 3 systematic reviews. (4) It describes any diagnosis of prostate cancer that would not have expressed clinical symptoms during the lifetime of the patient. (12) Draisma et al (13) similarly defined overdiagnosis as the detection of low risk cancers, indolent cancers, or “irrelevant cancers” that would have not been diagnosed in a man’s lifetime in the absence of screening. For example, the 20-year mortality rate for low grade cancers is 6/1,000 person-years compared to high grade cancers, which is 121/1,000 person-years. (14) Overdiagnosis can result in invasive treatments (e.g., prostatectomy), and potential complications such as, e.g., infection, (15) incontinence, or impotence. (16)

Overdiagnosis has been estimated based on modeling studies, (13) and consequently reported in current systematic reviews. (4) For annual screening of men aged 55 to 67 years, overdiagnosis is estimated at 50% (range = 46% to 57%). (13)

Additional Information

Extended follow-up of the ERSPC trial (median 11 years vs 9 years in the original publication) (12) has not yet shed additional light on the balance between the benefits and harms of PSA screening; the authors state that data on quality of life outcomes are still underway. (17) Extended follow-up of the PLCO trial (13 years vs 7-10 years in the original publication) (11) has not included additional data on the harms of PSA screening in prostate cancer since their original report. (18)

CONCLUSIONS

Based on the evidence, the following conclusions can be made:

There are major harms (unnecessary risks) associated with PSA screening, including:

- harms associated with prostate biopsy
- overdiagnosis

There are minor harms associated with PSA screening including:

- harms associated with PSA testing

PSA-based screening for prostate cancer results in harms related to the screening process, biopsy procedures, and, most significantly, the treatment of overdiagnosed cases. PSA-based screening of prostate cancer results in overdiagnosis and overtreatment without providing a mortality advantage, thereby exposing men to invasive treatments and potential complications. Consequently, PSA-based screening in prostate cancer results in more harm than benefit.

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APPENDICES

Appendix 1: Research Methods

Literature Search Strategy

A literature search was performed on May 2, 2014, using Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid Embase, EBSCO Cumulative Index to Nursing & Allied Health Literature (CINAHL), and EBM Reviews, for studies published from January 1, 2009, to May 2, 2014. Abstracts were reviewed by a single reviewer and, for those studies meeting the eligibility criteria, full-text articles were obtained. Reference lists were also examined for any additional relevant studies not identified through the search.

Search date: May 2, 2014

Databases searched: Ovid MEDLINE, Ovid MEDLINE In-Process, All EBM Databases (see below)

Limits: 2009-current; English

Filters: systematic reviews, meta-analyses and health technology assessments

Database: EBM Reviews - Cochrane Database of Systematic Reviews <2005 to March 2014>, EBM Reviews - ACP Journal Club <1991 to April 2014>, EBM Reviews - Database of Abstracts of Reviews of Effects <1st Quarter 2014>, EBM Reviews - Cochrane Central Register of Controlled Trials <April 2014>, EBM Reviews - Cochrane Methodology Register <3rd Quarter 2012>, EBM Reviews - Health Technology Assessment <1st Quarter 2014>, EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2014>, Ovid MEDLINE(R) <1946 to April Week 4 2014>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <May 01, 2014>

Search Strategy:

#	Searches	Results
1	exp Prostatic Neoplasms/	94842
2	(prostat* adj2 (cancer* or neoplas* or tumo?r*)).ti,ab.	83949
3	or/1-2	112869
4	exp Mass Screening/	104247
5	exp "Early Detection of Cancer"/	7810
6	screen*.ti,ab.	480637
7	or/4-6	518641
8	exp Prostate-Specific Antigen/	19878
9	(prostate specific antigen* or PSA or kallikrein or semenogelase or gamma seminoprotein or seminin).ti,ab.	39778
10	or/8-9	43901
11	3 and 7 and 10	4990
12	Meta Analysis.pt.	47822
13	Meta-Analysis/ or exp Technology Assessment, Biomedical/	56864
14	(meta analy* or metaanaly* or pooled analysis or (systematic* adj2 review*) or published studies or published literature or medline or embase or data synthesis or data extraction or cochrane).ti,ab.	202030
15	((health technolog* or biomedical technolog*) adj2 assess*).ti,ab.	2784
16	or/12-15	218516
17	11 and 16	162
18	limit 17 to english language [Limit not valid in CDSR,ACP Journal Club,DARE,CLCMR; records were retained]	149
19	limit 18 to yr="2009 -Current" [Limit not valid in DARE; records were retained]	78
20	remove duplicates from 19	76

Appendix 2: Evidence Quality Assessment

Evaluation of Evidence

The AMSTAR measurement tool was used to assess the methodological quality of systematic reviews. (19)

The quality of the body of evidence for each outcome was examined according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group criteria. (20) The overall quality was determined to be high, moderate, low, or very low using a step-wise, structural methodology.

Study design was the first consideration; the starting assumption was that randomized controlled trials (RCTs) are high quality, whereas observational studies are low quality. Five additional factors—risk of bias, inconsistency, indirectness, imprecision, and publication bias—were then taken into account. Limitations in these areas resulted in downgrading the quality of evidence. Finally, 3 main factors that may raise the quality of evidence were considered: the large magnitude of effect, the dose response gradient, and any residual confounding factors. (20) For more detailed information, please refer to the latest series of GRADE articles. (20)

As stated by the GRADE Working Group, the final quality score can be interpreted using the following definitions:

High	High confidence in the effect estimate—the true effect lies close to the estimate of the effect
Moderate	Moderate confidence in the effect estimate—the true effect is likely to be close to the estimate of the effect, but may be substantially different
Low	Low confidence in the effect estimate—the true effect may be substantially different from the estimate of the effect
Very Low	Very low confidence in the effect estimate—the true effect is likely to be substantially different from the estimate of the effect

Table A1: AMSTAR Scores of Included^a and Excluded^b Systematic Reviews

Author, Year	AMSTAR Score ^c	(1) Provided Study Design	(2) Duplicate Study Selection	(3) Broad Literature Search	(4) Considered Status of Publication	(5) Listed Excluded Studies	(6) Provided Characteristics of Studies	(7) Assessed Scientific Quality	(8) Considered Quality in Report	(9) Methods to Combine Appropriate	(10) Assessed Publication Bias	(11) Stated Conflict of Interest
Hayes et al, 2014 (6)	4	1	0	1	0	0	1	1	0	-	0	0
Ilic et al, 2013 (3)	9	1	1	1	1	1	1	1	0	-	1	1
Prescrire Int., 2012 (8)	2	1	0	1	0	0	0	0	0	-	0	0
Allan et al, 2011 (2)	1	1	0	0	0	0	0	0	0	-	0	0
Chou et al, 2011 (4)	7	1	1	1	0	0	1	1	1	-	0	1
Djulbegovic et al, (2010 (5)	8	1	1	1	1	1	1	1	0	-	0	1
Gomella et al, 2011 (9)	1	1	0	0	0	0	0	0	0	-	0	0
Basch et al, 2012 (7)	3	1	0	0	0	0	1	0	0	-	0	1

Abbreviations: AMSTAR, Assessment of Multiple Systematic Reviews.

^aIncluded systematic reviews (AMSTAR of score ≥ 7). (3-5)

^bExcluded systematic reviews (AMSTAR of score < 5). (2;6-9)

^cMaximum possible score is 11. Details of AMSTAR score are described in Shea et al. (19)

Appendix 3: Summary Tables

Table A2: Detailed Summary of Included Systematic Reviews (N = 3)

Author, Year	Research Question	Definition of Screening	Methods	Qualitative Summary of Harms Outcomes
Ilic et al, 2013 (3) Cochrane Review	Primary objective: to determine the efficacy of prostate cancer screening in reducing prostate cancer-specific and all-cause mortality; Secondary objective: to determine the impact of prostate cancer screening on quality of life and any adverse effects (as well document the cost of screening for prostate cancer).	Any type of screening procedure, individually or in combination: DRE, PSA (total, velocity, density, % free, and complex), TRUS.	Systematic review and meta-analysis. Qualitative summary of harms outcomes (no meta-analysis). Searched +2 databases up to 2012. Included were RCTs and quasi-RCTs on screening for prostate cancer.	ERSPC Trial: 26,492 PSA tests/22,699 biopsies; there were no deaths due to biopsy (14 deaths unrelated to biopsy); 7,938 (9.6%) of 82,816 men in the screened group were diagnosed with prostate cancer; false-positive rate of 17.8% (>3 ng/ml and screened at least once); rate of overdiagnosis up to 50%; PLCO Trial: false-positive rate of 10.4%; PSA-complication rate of 26.2 per 10,000, including dizziness, bruising, hematoma, fainting; medical complications from diagnostic procedures of 68 per 10,000 evaluations including infection, bleeding, clot formation, urinary difficulties; CAP study: main immediate short-term adverse event (<30 day) is mild or no pain (85%); main moderate adverse events (up to 35 days post-biopsy) is hemoejaculate (90%); main long-term adverse events (2 or more weeks post-biopsy) is hemoejaculate (60%).
Chou et al, 2011 (4) AHRQ for USPSTF	Primary objectives of the review were related to screening and treatment. (1) Does PSA-based screening decrease prostate cancer-specific or all-cause mortality? The harms of PSA-based screening for prostate cancer were secondary review objectives?	Incorporated 1 or more PSA measurements, with or without additional methods, such as DRE.	Report of previous systematic review and meta-analysis. Qualitative summary of harms outcomes (no meta-analysis). Searched +2 databases up to 2011. Included were RCTs on screening for prostate cancer. (Also reviewed was a comparison of treatments following screen-detected prostate cancer.)	Finnish-ERSPC Trial: false-positive rate of 12% (at least one false-positive result after 3 rounds, 4 mcg/L cutpoint); ERSPC Trial: 76% biopsed-negative PSA-positive; PLCO Trial: false-positive rate (cumulative risk) of 13% (at least one false-positive result after 4 rounds, 4.0 mcg/l cutpoint); 5.5% risk of undergoing at least 1 biopsy due to a false-positive result. Physical harms include bleeding or pain from DRE (0.3/10,000 screened), bruising or fainting due to venipuncture (26/10,000 screened), and biopsy complications such as infection, bleeding, urinary difficulties (68/10,000 evaluations). Netherlands-ERSPC Trial: after biopsy, fever (3.5%), urine retention (0.4%), hospitalization for signs of prostatitis, urosepsis (0.5%). No information from RCTs on psychological harms (anxiety or QoL).

Table A2: (cont'd) Detailed Summary of Included Systematic Reviews (N = 3)

Author, Year	Research Question	Definition of Screening	Methods	Qualitative Summary of Harms Outcomes
Djulbegovic et al, 2010 (5)	In men without a history of prostate cancer, screening by testing for prostate specific antigen with or without digital rectal examination when compared with no screening affects overall and disease-specific mortality. Harms are not a primary objective.	Screening by testing for prostate specific antigen with or without digital rectal examination.	Systematic review and meta-analysis. Qualitative summary of harms outcomes (no meta-analysis). Searched +2 databases up to 2010. Included were RCTs on screening for prostate cancer.	Three centres-ERSPC Trial: reported no excess of mortality due to biopsy; 75.9% PSA-positive/biopsy-negative; PLCO Trial: DRE of bleeding or pain (0.3/10,000 screenings); PSA-screenings including faintings (3/10,000 screenings); medical complications (infections, bleeding, clot formation, urinary difficulties; 68/10,000 diagnostic evaluations); Norrkoping Study: 82.5% PSA-positive/biopsy-negative.

Abbreviations: AHRQ, Agency for Healthcare Research and Quality; DRE, digital rectal examination; ERSPC, European Randomized Study of Screening for Prostate Cancer; PLCO, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; PSA, prostate-specific antigen; QoL, quality of life; RCT, randomized controlled trial; TRUS, transrectal ultrasonography; USPSTF, U.S. Preventative Services Task Force.

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Conflict of Interest Statement

All authors at Health Quality Ontario are impartial. There are no competing interests or conflicts of interest to declare.

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