

Screening for Prostate Cancer With Prostate-Specific Antigen Testing: American Society of Clinical Oncology Provisional Clinical Opinion

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A B S T R A C T

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Purpose

An American Society of Clinical Oncology (ASCO) provisional clinical opinion (PCO) offers timely clinical direction to the ASCO membership after publication or presentation of potentially practice-changing data from major studies. This PCO addresses the role of prostate-specific antigen (PSA) testing in the screening of men for prostate cancer.

Clinical Context

Prostate cancer is the second leading cause of cancer deaths among men in the United States. The rationale for screening men for prostate cancer is the potential to reduce the risk of death through early detection.

Recent Data

Evidence from a 2011 Agency for Healthcare Research and Quality systematic review primarily informs this PCO on the benefits and harms of PSA-based screening. An update search was conducted to March 16, 2012, for additional evidence related to the topic.

Results

In one randomized trial, PSA testing in men who would not otherwise have been screened resulted in reduced death rates from prostate cancer, but it is uncertain whether the size of the effect was worth the harms associated with screening and subsequent unnecessary treatment. Although there are limitations to the existing data, there is evidence to suggest that men with longer life expectancy may benefit from PSA testing. Adverse events associated with prostate biopsy are low for the majority of men; however, several population-based studies have shown increasing rates of infectious complications after prostate biopsy, which is a concern.

Provisional Clinical Opinion

On the basis of identified evidence and the expert opinion of the panel (Table 1 provides a description of how recommendations and evidence are rated):

- In men with a life expectancy \leq 10 years,* it is recommended that general screening for prostate cancer with total PSA be discouraged, because harms seem to outweigh potential benefits.**
Type and strength of recommendation. Evidence based: strong.
Strength of evidence. Moderate: based on five randomized clinical trials (RCTs) with intermediate to high risk of bias, moderate follow-up, and limited data on subgroup populations.
- In men with a life expectancy $>$ 10 years,* it is recommended that physicians discuss with their patients whether PSA testing for prostate cancer screening is appropriate for them. PSA testing may save lives but is associated with harms, including complications, from unnecessary biopsy, surgery, or radiation treatment.**
Type and strength of recommendation. Evidence based: strong.
Strength of evidence. For benefit, moderate; for harm, strong: based on five RCTs (and several cohort studies) with intermediate to high risk of bias, moderate follow-up, indirect data, inconsistent results, and limited data on subgroup populations.
- It is recommended that information written in lay language be available to clinicians and their patients to facilitate the discussion of the benefits and harms associated with PSA testing before the routine ordering of a PSA test.**
Type and strength of recommendation. Informal consensus: strong.
Strength of evidence. Indeterminate: evidence was not systematically reviewed to inform this recommendation; however, randomized trials are available on the topic.
 *Calculation of life expectancy is based on a variety of individual factors and circumstances. A number of life expectancy calculators (eg, <http://www.socialsecurity.gov/OACT/population/longevity.html>) are available in the public domain; however, ASCO does not endorse any one calculator over another.

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Table 1. Guide for Rating Recommendations and Strength of Evidence

Recommendation/Rating	Definition
Recommendation	
Evidence based	Sufficient evidence from published studies to inform recommendation to guide clinical practice
Formal consensus	Available evidence deemed insufficient to inform recommendation to guide clinical practice; therefore, expert panel used formal consensus process to reach this recommendation, which is considered best current guidance for practice; panel may choose to provide rating for strength of recommendation (ie, strong, moderate, or weak); results of formal consensus process are summarized in guideline and reported in online data supplement
Informal consensus	Available evidence deemed insufficient to inform recommendation to guide clinical practice; recommendation is considered best current guidance for practice based on informal consensus of expert panel; panel agreed that formal consensus process was not necessary for reasons described in literature review and discussion; panel may choose to provide rating for strength of recommendation (ie, strong, moderate, or weak)
No recommendation	Insufficient evidence, confidence, or agreement to provide recommendation to guide clinical practice at this time; panel deemed available evidence as insufficient and concluded it was unlikely that formal consensus process would achieve level of agreement needed for recommendation
Strength of recommendation	
Strong	High confidence that recommendation reflects best practice based on: strong evidence for true net effect (eg, benefits exceed harms); consistent results, with no or minor exceptions; minor or no concerns about study quality; and/or extent of panelists' agreement; other compelling considerations (discussed in guideline literature review and analyses) may also warrant strong recommendation
Moderate	Moderate confidence that recommendation reflects best practice based on: good evidence for true net effect (eg, benefits exceed harms); consistent results, with minor and/or few exceptions; minor and/or few concerns about study quality; and/or extent of panelists' agreement; other compelling considerations (discussed in guideline literature review and analyses) may also warrant moderate recommendation
Weak	Some confidence that recommendation offers best current guidance for practice based on: limited evidence for true net effect (eg, benefits exceed harms); consistent results, with important exceptions; concerns about study quality; and/or extent of panelists' agreement; other considerations (discussed in guideline literature review and analyses) may also warrant weak recommendation
Strength of evidence	
Strong	High confidence that available evidence reflects true magnitude and direction of net effect (ie, balance of benefits v harms); further research very unlikely to change either magnitude or direction of this net effect
Moderate	Moderate confidence that available evidence reflects true magnitude and direction of net effect; further research unlikely to alter direction of net effect; however, it might alter magnitude of net effect
Weak	Low confidence that available evidence reflects true magnitude and direction of net effect; further research may change either magnitude and/or direction of net effect
Insufficient	Evidence is insufficient to discern true magnitude and direction of net effect; further research may better inform topic; use of consensus opinion of experts is reasonable to inform outcomes related to topic

INTRODUCTION

The American Society of Clinical Oncology (ASCO) has established a rigorous, evidence-based approach—the provisional clinical opinion (PCO)—to offer rapid responses to emerging data in clinical oncology. The PCO is intended to offer timely clinical direction to ASCO members after publication or presentation of potentially practice-changing data from major studies. The Appendix (online only) provides information on how PCOs are developed. A 2011 systematic review developed by the Agency for Healthcare Research and Quality (AHRQ) on behalf of the US Preventive Services Task Force (USPSTF) provided the opportunity to develop a PCO on the ASCO position on the screening of men for prostate cancer using prostate-specific antigen (PSA) testing.

STATEMENT OF THE CLINICAL ISSUE

Prostate cancer is the second leading cause of cancer deaths among men in the United States,^{1,2} with the estimated number of deaths exceeding 28,000 in 2012.³ The rationale for screening asymptomatic men for prostate cancer in the general population is the potential for reducing mortality rates through early detection of the disease. How-

ever, much controversy exists between the potential harms of screening and the potential benefits.

The issue of PSA testing is fraught with challenges: many individuals do not have adequate information to help them decide whether to be screened for prostate cancer, and providers may not have adequate time, information, or training to help them provide appropriate medical advice. Furthermore, there is controversy regarding the indications for biopsy and treatment. Weighing the potential benefits and harms for each of these decisions is complex, involving many tradeoffs, including the significant issues of overdiagnosis, overtreatment, adverse events, and quality of life. This PCO focuses on PSA testing for prostate cancer screening and also touches on the harms and benefits associated with prostate biopsy. The role of digital rectal examination and associated scientific evidence are not considered in the context of this PCO. In addition, the treatment of prostate cancer is outside the scope of this report, although brief mention of treatment considerations, such as the role of active surveillance, is included in the discussion.

Because PSA testing is already in wide use, the realistic scientific challenge is to identify which men will not benefit from screening and its downstream consequences. It is therefore essential to develop risk-stratification and selective strategies as they pertain to screening, biopsy, and treatment. These strategies should be based on the best

available evidence and guide future research addressing one of the most common decisions faced by men and practitioners every day. Moreover, it is essential to be cognizant when interpreting the results of randomized controlled screening trials that treatment patterns may have a substantial impact on results, which may reflect imperfect screening or treatment strategies. Nevertheless, recent epidemiologic trends have shown a steady drop in prostate cancer mortality rates and a lower proportion of men diagnosed with advanced prostate cancer. The results of the randomized trials will help to determine whether prostate cancer screening is a potential explanation for these trends.

Clinical Question

For asymptomatic men in the general population, do the benefits of PSA testing for prostate cancer screening outweigh the potential harms?

Population of Interest

Asymptomatic men from the general population considering PSA-based screening for prostate cancer.

Interventions and Comparisons

As part of prostate cancer screening for asymptomatic men in the general population: PSA testing compared with no PSA testing.

Outcomes

All-cause mortality; prostate cancer–specific mortality; adverse events, including urinary incontinence, bowel dysfunction, erectile dysfunction, psychologic effects, and surgical complications; and quality of life.

Literature Search Strategy

For this PCO, the literature search of the systematic review conducted by the AHRQ^{4,5} was used as the basis of an update search to March 16, 2012. In addition, personal files and a targeted search for studies on the harms associated with prostate biopsy were conducted using PubMed (2010 to 2012).

Literature Search Results

From the AHRQ systematic review,^{4,5} the benefits and harms of PSA-based screening were informed by five randomized controlled trials (RCTs)⁶⁻¹² and one report from a single center¹³ participating in an RCT.⁷ The authors also identified two systematic reviews informing the topic.^{14,15} In a companion clinical practice guideline developed by the USPSTF,¹⁶ five clinical practice guidelines were identified,¹⁷⁻²¹ two of which have been updated.^{22,23} The literature search yielded 13-year follow-up results²⁴ for the PLCO (Prostate, Lung, Colorectal, and Ovarian) RCT⁶ and 11-year follow-up results²⁵ for the ERSPC (European Randomized Study of Screening for Prostate Cancer) RCT.⁷ In addition, two population-based cohort studies^{26,27} and an analysis from the Rotterdam section of the ERSPC trial²⁸ were also identified to describe the adverse events associated with prostate biopsy.

Quality of the Evidentiary Base

The quality of the identified RCTs in the AHRQ systematic review^{4,5} was rated from poor to fair quality by the authors of the AHRQ review using the quality appraisal methods of the USPSTF.²⁹ These ratings were consistent with the quality appraisal provided by the two identified systematic reviews.^{14,15} The reasons for the downgrading of RCT evidence included insufficient follow-up, differences in the proportion of men with

previous PSA testing, noncompliance, contamination, and differences in PSA cutoff levels, screening intervals, and treatment choices.

Concerning the primary outcomes of interest, it should be noted that it is difficult to design randomized screening trials to detect statistically significant differences in overall mortality because of the interference, in the statistical sense, of death from other causes. The sample size requirements needed to adequately power such trials are generally not practicable. Instead, cancer-specific mortality is often used as a quantifiable end point (eg, similar to evaluations of breast, colon, and cervical cancer screening).

LITERATURE REVIEW AND ANALYSIS

For asymptomatic men in the general population, do the benefits of PSA-based screening for prostate cancer outweigh the potential harms?

Benefits

The AHRQ systematic review^{4,5} reported on five randomized trials,⁶⁻¹² including data from a single center,¹³ and two systematic reviews.^{14,15} Compared with controls, men randomly assigned to PSA-based screening experienced a statistically significant increase in prostate cancer incidence; however, there were no significant differences in overall or prostate cancer–specific mortality.^{4,5} Those results were driven primarily by the two largest and highest quality–rated (fair quality) RCTs: the PLCO⁶ and ERSPC⁷ trials. In those trials, because there were not specific guidelines about how screen-positive men were treated, it is not clear whether the lack of benefit resulted from limitations of screening, limitations of risk-stratification strategies for selecting treatment, or both.^{6,7} In addition, there are well-detailed methodologic and logistic limitations associated with these trials.^{4,5,30}

In the PLCO trial, which involved 76,685 men age 55 to 74 years, the intervention arm was offered six annual PSA tests compared with the control arm, which received usual care (which may have also included PSA testing). The PSA threshold to warrant further investigation was > 4 ng/mL. After 7 years of follow-up, no statistically significant differences in overall or prostate cancer–specific mortality were detected. In that trial, approximately half of the patients in the control arm also received PSA screening. After 13 years of follow-up, the authors reported similar results, with no statistically significant differences in overall or prostate cancer–specific mortality detected.²⁴

In contrast, the ERSPC trial, which involved 182,160 men age 50 to 74 years, offered PSA testing approximately once every 4 years and established a PSA threshold of > 3 ng/mL. The lower PSA threshold resulted in more positive results and hence more false positives; however, the ERSPC trial did not experience a contamination effect, as clearly shown in differences in stage distribution between the control and PSA-screened groups at the time of diagnosis. After 9 years of follow-up, in a predefined subgroup analysis of 162,388 men between the ages of 55 and 69 years, a 20% reduction in prostate cancer–specific mortality but not overall mortality was detected with PSA testing.⁷ That result was maintained after 11 years of follow-up.²⁵ In addition to the combined reporting of results of the participating centers of the ERSPC trial, the Göteborg trial,¹³ a component of the ERSPC trial, reported separate data on 20,000 men after 14 years of follow-up. In that trial, statistically significant differences in prostate cancer–specific mortality of up to 56% were detected in favor of the PSA-screened

arm.¹³ The Göteborg trial began as an independent study before the initiation of the ERSPC trial, and it was predetermined that results would be presented separately. The data from the Göteborg trial¹³ are included in the ERSPC analyses.^{7,25}

The remaining three RCTs⁸⁻¹² were rated as being of poor quality.^{4,5} Given the availability of the larger and higher-quality RCTs,^{6,7} they did little to inform the issue of PSA screening.

Overall, using the ERSPC trial data of 162,388 participating men age 55 to 69 years, the relative reduction in the risk of death resulting from prostate cancer was 21% (rate ratio, 0.79; 95% CI, 0.68 to 0.91; $P = .001$), with prostate cancer death rates of approximately four per 1,000 men screened versus five per 1,000 men screened. In other words, in the best-case scenario to date, 1,055 men would be needed to be invited for screening, with two to three PSA tests over 11 years of follow-up (and 37 cancers detected), to prevent one death resulting from prostate cancer.²⁵

Harms

The AHRQ systematic review^{4,5} reported that the false-positive rates associated with PSA screening were 12.9% in the PLCO trial⁶ after four rounds of screening and 12.5% in one center of the ERSPC RCT⁷ after three rounds of screening. In the PLCO trial, harms associated with diagnostic evaluations, including biopsy, were reported to be infection, bleeding, and urinary difficulty (68 events per 10,000 evaluations).⁴⁻⁶ In one center of the ERSPC trial, among 5,802 biopsies performed, reported harms were fever (3.5%), urinary retention (0.4%), hospitalization for signs of prostatitis or urosepsis (0.5%), and hematuria (22.6%) and hematospermia (50.4%) more than 3 days after biopsy.^{4,5}

Nam et al²⁶ were the first to show an increase in complication rates after a transrectal ultrasound-guided biopsy over a 10-year period (1996 to 2005) from a large, population-based study of more than 75,000 men. The hospital admission rate for urologic complications within 30 days of the procedure was 1.9%. Over the study period, the 30-day hospital admission rate increased from 1.0% in 1996 to 4.1% in 2005 (P for trend $< .001$), with the majority of patients (72%) seen for infection-related reasons. In that study, the overall 30-day mortality rate was 0.09%.²⁶ This finding was confirmed by a subsequent study comparing 30-day hospital admission rates from Medicare participants in the Surveillance, Epidemiology, and End Results regions from 1991 to 2007.²⁷ The 30-day hospital admission rate was 6.9% among 17,472 biopsied men, which was approximately 2.5 times higher than that among a random sample of 134,977 population controls. Admission rates increased over the study period, with infectious causes being greater in more recent years.²⁷

Further analysis of the 10,474 patients who underwent a biopsy is available from the Rotterdam section of the ERSPC randomized trial.²⁸ Patients assessed by questionnaire 2 weeks after biopsy reported a 4.2% rate of fever and hospital admissions, with 81% related to infection.²⁸ Year of biopsy was the only positively associated factor associated with increased hospital admission rate.

DISCUSSION

The quality, quantity, and limitations of the identified literature make definitive recommendations around the role of PSA screening for prostate cancer difficult. This is reflected in the recommendations of other major US health organizations that have provided recommendations on the topic.¹⁶⁻²³ Although there is general agreement that

screening is not helpful for men who do not have a reasonable life expectancy beyond 10 years, recommendations have ranged from supporting general population screening^{21,23} to screening selected groups of men who are fully informed of the harms and benefits.^{18,20,22}

In addition, several groups cited inconclusive evidence to make a recommendation for or against PSA screening for men younger than age 75 years.^{16,17,19} Of note is the update of the USPSTF recommendation statement for 2012, which recommends against routine screening.^{30a}

Despite the uncertainty, for those men who choose to undergo PSA screening, more cases of prostate cancer will be identified. A large proportion of those men will ultimately be diagnosed with low-risk disease, which may not have presented itself clinically over their lifetimes. For men with low-risk disease who seek treatment, it is not clear if the risk of dying as a result of prostate cancer, or any other cause, is reduced compared with men who chose active surveillance.^{31,32} In the Swedish study in which men were randomly assigned to surgery or watchful waiting, cancer-specific survival was higher among men who underwent surgery. However, the study patients did come from a PSA-screened population, and the external validity of the results may be low.³¹ On the other hand, the PIVOT (Prostate Cancer Intervention Versus Observation Trial) study involved a North American screened population and showed no difference in overall survival rates between men randomly assigned to either surgery or watchful waiting.³² However, in a subgroup analysis, a survival advantage for surgery was found for patients who had a PSA > 10 ng/mL at diagnosis. It is important to emphasize that to date, these results have not been published and have only been presented in abstract form.³² A critical review of the data and results will be required before any definitive conclusions can be made from this study. In addition, a National Institutes of Health consensus statement concluded that men with low-risk prostate cancer may be better candidates for active surveillance rather than immediate treatment, although the authors acknowledged a lack of standard approaches and of high-quality evidence for recommending when to move from active surveillance to treatment.³³ In contrast, for those who do not choose PSA-based screening, there is the risk of missing more aggressive forms of localized prostate cancer that might be successfully treated if detected early with screening.

Screening with PSA may identify prostate cancers earlier, but better screening approaches are needed, such as risk stratification for screening and assessing individualized risk for prostate cancer. It is well established that a patient's age and level of comorbidity need to be considered when deciding whether to screen for prostate cancer.³⁴⁻³⁶ Assessing risk for prostate cancer has been achieved through development of prostate cancer risk calculators. These factor not only PSA but other risk factors and tumor markers for prostate cancer as well. Rather than using a cutoff value, individual probabilities for any and aggressive prostate cancers are calculated, with the decision for biopsy based on patient and physician views on that risk. Thompson et al³⁷ were the first to develop a prostate cancer risk calculator, followed by others in Canada³⁸ and Europe.³⁹ Although the latter tools have been evaluated and validated by external populations,^{38,39} there is no evidence to support that these tools have affected the success of screening programs to date. Further research will be required to determine how patients perceive their individual risk-threshold probabilities for prostate cancer to better evaluate the impact of prostate cancer risk calculators in the context of a prostate cancer screening program.

Table 2. Clinical Tools and Resources

Type	Resource/Tool
Prostate cancer risk calculator for general population	
Prostate Cancer Prevention Trial prostate cancer risk calculator	http://prostatecancerinfolink.net/risk-prevention/pcpt-prostate-cancer-risk-calculator/
Sunnybrook nomogram-based prostate cancer risk calculator	http://deb.uthscsa.edu/URORiskCalc/Pages/uroriskcalc.jsp
European Randomised Study of Screening for Prostate Cancer risk calculator	http://www.prostaterisk.ca
Screening for prostate cancer	http://www.prostatecancer-riskcalculator.com/en/prostaatwijzer_vooraf.html
American Cancer Society: Testing for prostate cancer—"Should I be tested? Is this the right choice for me?"	http://www.cancer.org/acs/groups/content/@nho/documents/document/acspc-024618.pdf
CDC: Prostate cancer screening: 2006 decision guides (one specific to African American men)	http://www.cdc.gov/cancer/prostate/basic_info/screening.htm
Health dialog: Is a PSA test right for you? 2011 Web booklet and videos	https://www.healthcrossroads.com/example/crossroad.aspx?contentGUID=fc326615-5b29-47f1-87c3-9a3e2d946919
Prosdex: University of Cardiff 2005 online resource	http://www.prosdex.com/index_content.htm
Healthwise: Prostate cancer screening: Should I have a PSA test? 2010 decision aid	http://www.healthwise.net/cochrane/decisionaid/Content/StdDocument.aspx?DOCHWID=aa38144
Mayo Clinic: Prostate cancer screening: Should you get a PSA test? 2011	http://www.mayoclinic.com/health/prostate-cancer/HQ01273
USPSTF: How to talk with your patients when evidence is insufficient. 2008 short video	http://www.uspreventiveservicestaskforce.org/uspstf/uspSprca.htm

Abbreviations: CDC, Centers for Disease Control; PSA, prostate-specific antigen; USPSTF, US Preventive Services Task Force.

The issues surrounding PSA testing are complex and may be difficult to convey during the limited time of a routine office visit.⁴⁰ Although there is little risk associated with obtaining a PSA test, the downstream implications of the test results necessitate shared and informed decision making. Formal written consent may not be necessary, but at a minimum, a discussion of the known risks and potential benefits should take place and be documented in the patient's medical record.⁴⁰ In addition, as part of the informed and shared decision-making process, it is important that discussion include the topic of men who are not appropriate candidates for PSA testing. Frank discussion around life expectancy is important, and for those who would clearly not benefit, it should be communicated that PSA testing as part of prostate cancer screening is not indicated. To aid with the discussion, decision aids, which have been shown in randomized trials to influence decision making around prostate cancer screening,^{41,42} should be available to patients before the decision on whether to pursue PSA testing for prostate cancer screening. Although ASCO does not endorse any one decision aid over another, a sample of information sources is provided in Table 2. In addition, an ASCO decision aid based on this PCO is available at www.asco.org/pco/psa.

The rationale for screening men for prostate cancer is the potential to reduce the risk of death through early detection, and there is some evidence to suggest screening is beneficial for some groups of men. Although not ideally informed, PSA testing is already in wide use, and the realistic scientific challenge is to identify which men will benefit from screening or its downstream consequences and which men will not. There has been tremendous effort to evaluate new biomarkers for prostate cancer to replace the PSA test for prostate cancer screening. The spectrum of biomarkers has ranged from genetic-based markers (eg, single nucleotide polymorphisms) to serologic protein markers, particularly from the Kallikrein family of proteins, of which PSA is a member, to urinary-based markers. To date, none have been able to replace the PSA test for prostate cancer screening.

At this point in time, it is uncertain whether the benefits associated with PSA testing for prostate cancer screening are worth the harms associated with screening and subsequent unnecessary treatment. Better evi-

dence is needed regarding the benefits and risks of screening in high-risk subgroups, including those with family history of the disease and those of African American descent. There is no evidence that populations with a higher overall prevalence of prostate cancer have a different degree of benefit or risk related to PSA-based screening compared with the general population. Areas of future research include the search for other screening tests that improve the predictive accuracy of PSA for clinically meaningful outcomes related to prostate cancer and the need for high-quality evidence comparing radiation with surgery for screen-detected localized prostate cancer. Because the evidence does not clearly inform the issue around PSA-based screening and its downstream effects, the importance of informed and shared decision making becomes paramount.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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