

Screening for prostate cancer: the current evidence and guidelines controversy

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Introduction: Prostate cancer presents a global public health dilemma. While screening with prostate specific antigen (PSA) has led to more men diagnosed with prostate cancer than in previous years, the potential for negative effects from over-diagnosis and treatment cannot be ignored.

Materials and methods: We reviewed Medline for recent articles that discuss clinical trials, evidence based recommendations and guidelines from major medical organizations in the United States and worldwide concerning prostate cancer screening.

Results: Results from the European Randomized Screening for Prostate Cancer (ERSPC), the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial, and Göteborg Swedish trials regarding prostate screening are controversial with the ERSPC and Göteborg showing a reduction in prostate cancer mortality and the PLCO trial showing no benefit. Recommendations from the American Urological Association (AUA), Japanese Urological Association (JUA), and National Comprehensive Cancer Network (NCCN) have recommended that all men obtain a baseline PSA beginning at age 40. The American Cancer Society (ACS) stratifies screening recommendations based on age and risk, but states that screening should take place only after an informed discussion between provider and patient. The United States Preventative Health Service

Task Force (USPSTF) states that evidence is insufficient to assess the risks and benefits of prostate cancer screening in men younger than 75 years. Other major international health organizations offer a similar reserved approach or recommend against screening for prostate cancer. Most groups indicate that screening to determine who should undergo prostate biopsy typically includes both a serum PSA and digital rectal examination, with the latest ACS publications noting that the rectal exam is optional. A common theme from all groups is that an informed discussion with the patients is strongly recommended and that screening does increase the number of men diagnosed with non-metastatic, early disease

Conclusions: Prostate cancer screening guidelines vary widely between countries and between different medical organizations within individual countries including the United States. Further, the evidence for and against prostate cancer screening remains highly controversial. Longitudinal follow up of completed screening trials is ongoing and may yield additional findings as the time course of prostate cancer outcomes can be protracted. The literature controversy suggests that no standard of care exists for prostate cancer screening today. Until there is agreement in guidelines between major professional organizations who have weighed in on this topic, patients and physicians should be encouraged to consider engaging in shared and informed decision process concerning screening for prostate cancer.

Key Words: cancer screening guidelines, prostate cancer screening, PSA screening

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Introduction

Prostate cancer currently represents a significant burden to men's health. In 2011, an estimated 240,890 new cases of prostate cancer will be diagnosed in the United States which accounts for 25% of newly

diagnosed cancers.¹ Approximately 32,050 men died in 2010 due to prostate cancer with 33,320 expected to die in 2011, trailing only lung cancer as a cause of cancer death in men.² Presently, an estimated 1 in 6 men in the United States will be diagnosed with this disease in their lifetime.² Global statistics for prostate cancer generally mirror those found in the United States. In 2008, approximately 900,000 men were diagnosed with prostate cancer worldwide, with the highest rates primarily in developed countries of Europe, North and South America, and Oceanic nations.³

In spite of its high incidence and prevalence, the progression of prostate cancer in most men is relatively slow. Most tumors remain organ confined allowing for potentially life-saving treatments to be instituted in such cases.⁴ In fact, the number of cancer-related deaths has decreased by approximately 35% over a 10 year span from 1997 to 2007.^{5,6} Although improved cancer therapies, earlier use of hormonal therapy, and lifestyle changes can all partially explain this phenomenon, the temporal association with the advent of large scale population screening with the prostate specific antigen (PSA) blood test is evident and has probably had substantial impact on temporal changes in incidence and mortality rates.⁷⁻¹⁰ However, the death rate has remained relatively constant over the last several years, suggesting a need for improvements in our strategies to detect prostate cancer at an earlier and potentially more curable state.

PSA, a glycoprotein secreted by prostate epithelial cells, was first introduced in the 1980s as a serum marker for monitoring disease status after definitive treatment in men with prostate cancer.¹¹ Prior to this development, the digital rectal examination (DRE) was the primary tool employed by physicians for detection of prostate cancer. In conjunction with DRE, PSA has since become a widely used clinical tool to help identify men with prostate cancer.^{12,13} However, PSA does not diagnose prostate cancer with 100% certainty, as its serum value can be elevated in both benign and malignant conditions of the prostate and not all men with prostate cancer will have high PSA levels. Despite this fact, the use of PSA has evolved to become the main serum marker utilized in prostate cancer screening protocols.¹⁴ An elevated PSA level or an abnormal rectal exam are the most common indications for a prostate biopsy. In this article, we review the current prostate cancer screening literature published by various national and international societies, and report on the present Level 1 evidence examining the effects of prostate cancer screening.

Prostate cancer screening

The primary goal of prostate cancer screening is the early detection of men with clinically significant cancers resulting in a reduction of overall morbidity and mortality associated with this disease. Screening may allow for diagnosis of more localized cancers, resulting in improved cancer specific mortality with appropriate treatment. However, earlier detection can also result in over-diagnosis of clinically indolent cancers, resulting in over-treatment and untoward treatment-related side effects, which impact quality of life as well as produce unnecessary costs and burdens to our healthcare system. The potential for introducing lead or length-time bias cloud the picture. These conundrums lead to the current confusion and disagreement among urologic and public health societies regarding which patients should be offered screening for prostate cancer.

United States screening guidelines

The current prostate cancer screening recommendations from several United States national health organizations are not uniform. The American Cancer Society (ACS), National Comprehensive Cancer Network (NCCN), United States Preventive Services Task Force (USPSTF), and American Urological Association (AUA) all have differing opinions regarding this complex problem, Table 1.¹⁵⁻²⁰

The ACS stratifies screening recommendations based on age and risk, and recommend that screening should take place only after an informed discussion has taken place between the healthcare provider and patient regarding the benefits and harms associated with testing. More specifically, the discussion regarding screening should begin in men age 50 with life expectancy over 10 years, in men age 45 who are at high risk (e.g. African-American men or those with a first degree relative diagnosed at age < 65 years), or men age 40 with the highest risk (e.g. several first degree relatives diagnosed with prostate cancer).^{15,16} After discussion, men who wish to be screened should be offered a PSA with or without a DRE.

The NCCN provides a set of sequential recommendations, or trigger points, regarding prostate cancer screening.¹⁷ Similar to the ACS guidelines, a thorough discussion between physician and patient regarding the risks and benefits of screening is recommended. Guidelines also recommend that a complete history and physical with questions regarding general health, medical comorbidities, family history, race, social history, and any prior history of prostate cancer testing or treatment should be conducted prior

TABLE 1. United States prostate cancer major organization screening recommendations as of May 2011¹⁵⁻²⁰

Organization	Recommendation
U.S. Preventative Services Task Force (USPSTF)	<ol style="list-style-type: none"> 1. Current evidence insufficient to recommend screening 2. No screening in any man > 75 years of age 3. Informed discussion held with patient if he wishes to be screened
American Cancer Society (ACS) American College of Physicians (similar to the ACS)	<ol style="list-style-type: none"> 1. Not in favor of routine screening 2. After informed discussion held for those who wish to be screened: <ul style="list-style-type: none"> • Screen all men with PSA, with or without DRE, at 50 years of age with > 10 years life expectancy • Screen men at 45 years of age with high risk^a • Screen men at 40 years of age with highest risk^b • No screening in any man > 75 years of age
National Comprehensive Cancer Network (NCCN)	<ol style="list-style-type: none"> 1. Baseline DRE and PSA at 40 years of age^c 2. Repeat screening at 45 years of age if PSA < 1.0 ng/mL 3. Annual screening at 50 years of age 4. Informed discussion with all patients
American Urological Association	<ol style="list-style-type: none"> 1. Baseline DRE and PSA at 40 years of age 2. Screening stopped at age 75, but may be continued if the patient has a life expectancy of 10 years or more 3. Informed discussion with all patients

^adefined as those who are African-American or have a 1st degree relative diagnosed with prostate cancer at < 65 years of age

^bdefined as those who have several 1st degree relatives diagnosed with prostate cancer at < 65 years of age

^ccategory 2B recommendation as defined by the NCCN: based on lower level evidence and there is non-uniform NCCN consensus (but no major disagreement)

to any screening. It is expected that this process will eventually lead to a decision regarding screening that is patient specific. The NCCN stresses that their practice guidelines are not an attempt to provide support for national screening protocols but to merely provide a framework for patients and physicians who choose to undergo screening for prostate cancer.

The USPSTF states that the current evidence is insufficient to assess the risks and benefits of prostate cancer screening in men younger than 75 years.^{18,19} Inadequate data are available to determine if treatment of prostate cancer detected by screening improves health-related outcomes compared with treatment after clinical detection alone. The USPSTF recommends against screening any man older than 75 years of age stating that the harms outweigh the benefits in this scenario.¹⁹ Furthermore, the USPSTF takes the position that a PSA test should not be ordered by the physician until a full discussion regarding the potential risks and benefits are discussed with the patient. It is important to note, that these guidelines were published prior to recently published large randomized trials regarding prostate cancer screening.

The AUA presented a PSA best practice statement in an update in 2009.²⁰ Similar to previous guidelines,

a statement regarding individualized care and a discussion of the risks and benefits between patient and physician is recommended. Analogous to the ACS, the AUA stresses early detection in men starting at 50 years of age and younger in those at higher risk. Men who wish to be screened must have both a PSA and a DRE. Additionally, the AUA promotes obtaining a baseline PSA value in all men at 40 years of age.²⁰ Although the AUA acknowledges that the prevalence of prostate cancer in this age group was low and that there is risk of over-diagnosis and treatment, they presented several arguments for their decision. First, age adjusted mortality for prostate cancer in men ages 55 to 64 is approximately 18 per 100,000 males and if time from diagnosis to death is on average 15 to 20 years then younger men who will die from the disease may have benefited from earlier diagnosis.^{21,22} Second, cancer detected in men less than 50 years of age often represents lower stage disease and offers a higher success rate for curative therapies.²³⁻²⁵ Finally, PSA in a 40 year old is more specific as there are fewer opportunities to misinterpret its result due to confounders (e.g. BPH) that can potentially raise its value.²⁶ The AUA discourages screening in those men with less than

TABLE 2. International prostate cancer screening recommendations as of May 2011²⁷⁻³⁰

Organization	Recommendation
European Association of Urology U.K. National Health Services New Zealand National Health Committee	1. Against national screening due to risk of over-treatment 2. Men should be evaluated on case by case basis and discuss all risks and benefits with their physician
Japanese Urological Association	1. Baseline PSA, with or without DRE, at 40 years of age 2. Annual PSA at 50 years of age 3. No upper age limit cut-off for PSA testing

10 year life expectancy. Similar to the statements made by the NCCN the AUA maintains that their recommendations should be used as a resource for both physicians and patients and do not represent a fixed set of guidelines for prostate cancer screening.

International screening guidelines

Variation in international prostate cancer screening guidelines reflects the situation found in the United States. The European Association of Urology (EAU), United Kingdom National Health Services (UK NHS), New Zealand National Health Committee (NHC), and Japanese Urological Association (JUA) differ in opinion regarding the role of PSA and DRE for national screening of prostate cancer, Table 2.²⁷⁻³⁰

The EAU position statement published in May of 2009 states that the current available evidence argues against recommending national screening for prostate cancer because of significant risk of over-treatment.²⁷ This position is based on concern that screening would lead to over-diagnosis of prostate cancer and subsequent treatment related comorbidities that outweigh the benefits obtained from early detection. Lack of support for screening is also influenced by the low specificity among current screening algorithms and the inability of screening tests to selectively diagnose those with high risk or aggressive disease. In lieu of national screening, it is recommended that men who wish to consider screening should be evaluated on a case by case basis.

The UK NHS and the New Zealand NHC present a similar guideline statement as the EAU – there is currently insufficient evidence at this time to recommend national screening protocols for prostate cancer.^{28,29} United Kingdom and New Zealand guidelines also state that after a discussion is held regarding all risks and benefits of prostate cancer testing and treatment, individualized screening programs are suggested for physicians and patients in these countries.

In contrast to the stance taken by the above organizations, the JUA makes a firm recommendation in favor of prostate cancer screening in guidelines published in 2010.^{30,31} The JUA recommends that men should obtain a PSA, with or without a DRE, starting at 50 years of age and those with a positive family history should have one at 40 years of age. The JUA also states that every man should have a baseline PSA checked at 40 years of age regardless of risk.³⁰

Current evidence

The guidelines provided by the above health organizations have been largely formulated around the evidence from several large randomized trials with regards to the impact of prostate cancer screening using PSA and DRE. Among the first was a Canadian trial which was first reported in 1999 in the journal *The Prostate*.¹⁰ The Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial and the European Randomized Screening for Prostate Cancer (ERSPC) were both large multi-institutional trials that published their initial reports simultaneously in March of 2009 in *The New England Journal of Medicine*.^{7,8} The results from these two large studies have been the most quoted by health organizations when making arguments for or against national prostate cancer screening programs. Less discussed, but equally important, is a study from Göteborg Sweden published in 2010 that has added further evidence to the growing debate.⁹

Quebec prostate cancer trial

One of the first randomized controlled trials in favor of prostate cancer screening originated from Quebec Canada in the late 90s.¹⁰ A total of 46,193 men aged 45 to 80 years were randomized to no screening or screening with PSA and DRE at their first initial visit and PSA only thereafter. A PSA level of 3 ng/mL was used as a trigger for further work up (e.g. transrectal ultrasound guided biopsy). The patient groups were

randomized to a 2:1 ratio in favor of screening to compensate for possible low numbers due to a lack of awareness of prostate cancer in their target population. Cancer specific mortality was the primary endpoint. The study reported 137 deaths among 38,056 non-screened men and only 5 deaths among 8,137 screened individuals. The follow up period for this study was 7 years. An odds ratio of 3.25 (p value < 0.01) in support of prostate cancer screening was given. Unfortunately, the results of this article have been criticized due to several methodological problems.³² Those men not screened for prostate cancer had on average a 3 year lead time to develop the disease over those that were screened. Additionally, the analysis of the data as an observational study instead of a randomized control trial, introduced several biases that ultimately over-estimated the effects of screening. Cross over from patients who were not invited for screening but were then screened further muddled the data. As such, this study has largely fallen out of favor as a reference for those that support prostate cancer screening.

Prostate, lung, colorectal, and ovarian (PLCO) cancer screening trial

The PLCO trial was a United States based multi-institutional randomized controlled trial of 76,693 men, Table 3.⁸ This elegantly designed trial reported

information on prostate cancer incidence, cancer specific mortality, all-cause mortality, and cancer staging and is one of few with high compliance rates and total patient accrual. Patient characteristics between the screened and non-screened men were virtually identical. Men in the screening group received an annual PSA for 6 years and a DRE for 4 years. A total of 7 years of follow up was provided (from the years 1993 to 2001). The reported incidence of prostate cancer per 10,000 person-years in the screening group was 116 compared to 95 in the control group (rate ratio 1.11 95% CI [1.16 to 1.39]). The cancer specific mortality per 10,000 person-years was 2.0 in the screened group and 1.7 in the unscreened population (rate ratio 1.13; 95% CI [0.75 to 1.70]). The percentage of those diagnosed with low stage I or II cancers were also similar regardless of the group. Based on these results, neither prostate cancer incidence nor mortality demonstrated difference due to screening.

Although the PLCO has several methodological strengths, several key points warrant further discussion. First, although the trial appears to be equally randomized between study groups, approximately 44% of patients in the control group had at least one PSA test prior to entry and by the 6th year 52% of the control population had been screened. This suggests that the controls may contain men who are not only less likely to have prostate

TABLE 3. Recent randomized control trials regarding prostate cancer screening⁷⁻⁹

Trial	Methods and materials	Summary of results	Study strengths or weaknesses
ERSPC	<ul style="list-style-type: none"> • 182,000 men aged 50-74 years • 7 European countries • PSA every 4 years vs. no PSA • 82% in screened group with \geq one PSA 	<ul style="list-style-type: none"> • 8.8 years of follow up • Relative risk reduction of 20% • 41% reduction in incidence of metastatic disease • Adjusted rate ratio for death from prostate cancer 0.8 • NNS = 1410 and NNT = 48 	<ul style="list-style-type: none"> • Different PSA cut-offs to trigger biopsy • Short follow up time: if data extrapolated out to just 12 years then NNT = 503 and NNT = 18
PLCO	<ul style="list-style-type: none"> • 76,693 men • 10 U.S. institutions • Annual PSA for 6 years and DRE every 4 years vs. usual care • 86% compliance in screened group 	<ul style="list-style-type: none"> • 7 years of follow up • Incidence of prostate cancer 116 per 10,000 person years in screened group vs. 95 in controls • No difference in risk of death between groups 	<ul style="list-style-type: none"> • Not true randomization: 52% of control group had a PSA and 44% of men prior to randomization had PSA • PSA cut-off of 4 ng/mL used to trigger further workup • Short follow up time
Göteborg	<ul style="list-style-type: none"> • 20,000 Swedish men • PSA every 2 years vs. no screening • 76% first time compliance rate 	<ul style="list-style-type: none"> • 14 years median follow up • 58% increased diagnosis of prostate cancer and 44% fewer prostate cancer deaths in screened arm • NNS = 293 and NNT = 12 	<ul style="list-style-type: none"> • Younger patient population • Shorter interval of screening • Lower rate of contamination • Long duration of follow up than ERSPC (14 yrs vs 9 yrs) • Subset of ERSPC study

cancer but also less likely to have higher-stage or life-threatening disease. Studies have closely examined the rate of contamination in the control arm of the PLCO trial demonstrating rates of routine PSA screening of 33% at year 0 to 46% at study year 5 while rates of any PSA testing at year 5 was as high as 55%.³³ Comparing this study scenario to one with no contamination and perfect compliance, the methodological parameters of the PLCO trial will tend to show relative risk outcomes which demonstrate no difference between arms and thus the ability to show significant mortality benefit between arms is made more difficult. Additionally, as a portion of patients initially enrolled already had an established baseline PSA, some cancers detectable on initial screening may have been already removed from the randomized population. Second, a PSA level of 4 ng/mL was used to trigger further work up. Generally, lower cut-off values may lead to detection of more cancers especially those that have lower stage and are associated with better cancer specific survival data. Third, the follow up time of 7 years, although long for contemporary prostate cancer screening literature, is not sufficient, given the long natural history of prostate cancer. Ten to 15 year follow up results will yield additional information about prostate cancer specific mortality rates.

A re-analysis of PLCO with consideration of existing comorbidities revealed a significant decrease in the risk of prostate cancer specific mortality (22 versus 38 deaths; adjusted hazard ratio [AHR] 0.56; 95% CI [0.33 to 0.95]; p value = 0.03) in men with no or minimal comorbidity randomly assigned to intervention versus usual care. The additional number needed to treat (NNT) to prevent one prostate cancer death at 10 years was five. This reanalysis suggests that the selective use of PSA screening for men in good health appears to reduce the risk of prostate cancer mortality with minimal over treatment.³⁴

European randomized study of prostate cancer

The ERSPC was a European based multi-institutional randomized control trial initiated in the 1990s which accrued 182,000 men between the ages of 50 to 74, Table 3.⁷ Median follow up time was 9 years in duration. The screening group received a PSA test every 4 years and demonstrated a cumulative prostate cancer incidence of 8.2% versus 4.8% in the control group. The rate ratio for cancer specific mortality in the screened population was 0.80 (95% CI [0.65 to 0.98]) with an absolute risk difference of 0.71 prostate cancer deaths per 1000 men. A 20% corresponding relative risk reduction in mortality was determined with the number needed to screen (NNS) at 1410 men and NNT at 48 men to prevent one prostate cancer related death demonstrating a moderate advantage for screening. However, a 41% reduction of

metastatic cancers were detected in the screening group in addition to the identification of a higher percentage of patients with low risk disease – Gleason scores 6 and 7 of 72.2% and 27.8% respectively in the screened group versus 54.8% and 45.2% in the controls.

Additional analysis of the ERSPC data may further improve the mortality reduction and screening benefit found in the study. First, reports have estimated that after adjustment for non-compliance in the screening population and contamination in the control arm the mortality benefit found in the ERSPC population can be as high as 30% – increasing the initial benefit by half.³⁵ Second, similar to the PLCO trial, the relatively short median follow up time of 9 years likely underestimates the survival benefit in those who were screened for prostate cancer. In fact, the NNS and NNT decrease to 503 and 18 respectively when data is extrapolated out to a modest 12 years of follow up.³⁶ Third, data was gathered cumulatively from several European nations and the PSA cut-off value that triggered further work up was non-uniform among study centers. While most institutions used a value of 3 ng/mL as a point for biopsy referral, others used higher values and incorporated factors such as DRE and PSA kinetics to determine if further work up was necessary.

Like all screening trials, the results of the ERSPC study should be examined with certain caveats. Risk of over-diagnosis was estimated by some to approach 50% while the benefits of screening were restricted to the core age group of 55 to 69 years at the time of randomization. While demonstrating a mortality benefit associated with screening, the ERSPC also revealed a high likelihood of over-diagnosis and over-treatment. Some have argued that unequal treatment decisions in both arms of the study may have impacted mortality results. Close analysis shows that control arm patients with high risk prostate cancer were more likely to receive radiotherapy (OR 1.43, p = 0.047), expectant management (OR 2.92, p = 0.007), or hormonal therapy (OR 1.11, p = 0.02) instead of radical prostatectomy. However, the trial arm had only a minor role in the treatment choice when compared to other variables demonstrating that differences in treatment between arms is unlikely to play a major role in interpreting mortality results in the ERSPC trial.³⁷

Göteborg Sweden trial

The results of a randomized control trial from Göteborg Sweden that appeared in *Lancet Oncology* in August of 2010 have been far less publicized than its two predecessors; the ERSPC and PLCO, Table 3.⁹ A total of 20,000 men aged 50-64 years were randomized in a 1:1 ratio to screening with PSA every 2 years versus no screening. The primary endpoint was cancer specific

mortality analyzed using an intent-to-screen modality with a follow up time of 14 years. There was a 76% first time compliance rate among those offered screening resulting in a total of 1138 men diagnosed with prostate cancer with a cumulative incidence of 12.7%. In the matched controls 718 men were diagnosed with prostate cancer at an incidence of 8.2% with a calculated hazard ratio of 1.64 (95% CI [1.50-1.80]). Those patients screened with PSA were also diagnosed more frequently with both lower stage disease and lower incidence of metastases. The rate ratio for death was 0.56 for those screened versus non-screened. Additionally, compared to the results reported by the ERSPC study the NNS and NNT were a modest 293 and 12 respectively in the Swedish trial.

The Göteborg study demonstrated better outcomes with screening compared to both the larger ERSPC and PLCO trials. Interestingly, data from the cohort of patients in this study were part of the results reported in the larger ERSPC trial. Components of the Göteborg trial design including: younger patient population (median 56 years of age compared to > 60 years in ERSPC/PLCO), shorter interval of screening (every 2 years compared to 4 years of the ERSPC), lower rate of PSA testing prior to entry (approximately 3% compared to 44% in the PLCO), lower rate of contamination in the control group, and longer duration of follow up from randomization (median 14 years) all contribute to the findings showing benefit to prostate cancer screening. The 44% relative risk reduction in death demonstrated from this study may be the strongest evidence that screening for prostate cancer with PSA can be effective in lowering cancer specific mortality.

Discussion

Despite the publication of the results of several long-awaited randomized trials, the controversy surrounding prostate cancer screening continues. Various groups have different guidelines regarding screening with the majority favoring individualized programs after discussion between physician and patient. This non-uniform view between health organizations is problematic as it provides a mixed message to the general patient population and healthcare provider alike.

The interpretation of the current Level 1 evidence based on PSA testing is also varied. Concerns over statistical analysis issues, contamination of control groups, insufficient follow up time, differing levels of PSA triggering work up, and inappropriate screening intervals have led to the wide range of findings in these randomized control trials. Nonetheless, screening program data from the ERSPC and Göteborg compare favorably to those of breast and colon cancer, where

routine screening is widely recommended. In 2009, meta-analysis of breast cancer data showed NNS with mammography of 377 for women aged 60 to 69 years and 1339 for women aged 50 to 59 years after 11 to 20 years of follow up.^{38,39} For colorectal cancer screening with fecal occult blood test the NNS after 10 years of follow up was 1173 while the number for flexible sigmoidoscopy was 489 at a median follow up of 11 years.^{40,41} In this regard, testing with PSA is at minimum comparable to mammograms and fecal occult blood tests or sigmoidoscopy.

The use of serum PSA as a primary diagnostic tool in the current screening trials may not possess high enough specificity and sensitivity for prostate cancer diagnosis but it appears to be arguably one of the best screening markers available.⁴² In a man at age 50 with a PSA < 1.5 ng/mL his risk of developing prostate cancer in the next 7-8 years is < 5%. With a PSA level of 2.5 ng/mL the risk increases to greater than 20% and at a PSA of 4.0 ng/mL the risk approaches 40%. There is a trend towards a PSA determination at a younger age in an attempt to identify those men who harbor aggressive disease and are destined to suffer consequences if left undiagnosed until later in life. Organizations such as the AUA recommend annual screening with a DRE and serum PSA test starting at age 40 for all men with a life expectancy of more than 10 years.

Consideration to using the on line prostate cancer risk assessment tools when involved in joint decision making may be useful.^{43,44} This nomogram (<http://deb.uthscsa.edu/URORiskCalc/Pages/uroriskcalc.jsp>) is based on the Prostate Cancer Prevention Trial (PCPT) and may help in the decision to undergo prostate biopsy.⁴³

Screening efforts in the future will need to focus more on determining who harbors aggressive life threatening cancer and who has indolent cancer. Novel markers such as urinary PCA3 or single-nucleotide polymorphisms (SNPs) may help identify those with higher risk cancers when compared to PSA alone.⁴⁵⁻⁴⁷ Advanced imaging modalities such as contrast enhanced ultrasound for targeted biopsies of the prostate and improved MRI techniques may also aid in differentiating indolent from aggressive disease detected by PSA.⁴⁸⁻⁵⁰ In the interim, selective use of PSA testing in healthy men appears to reduce the risk of prostate cancer specific mortality. The risk of over-treatment can be lessened by either selective or an active surveillance approach with the potential for deferred treatment in certain men.⁵¹ For completeness in this discussion, the Tyrol Prostate Cancer Demonstration Project was a population comparison between a screened and unscreened region of Austria.⁵² In the Tyrol region where treatment and screening were widespread, there was a reduction in

prostate cancer mortality rates significantly greater than the reduction in the rest of Austria. While a “positive” study in support of screening it cannot be considered as a Level 1 evidence randomized trial.

The data from the recently randomized control trials needs to be followed up in future published articles as the potential benefits of prostate cancer screening may take an extended period of time to be recognized as significant. A large UK based trial known as ProtecT (Prostate testing for cancer and Treatment) will provide additional data on screening in the coming years.⁵³ Recommendations and guidelines will evolve as new data is presented.

Conclusion

The benefits of screening are clear and in general supported by the major professional organizations in the United States: earlier diagnosis of cancer, discovery of more localized disease, and reduction in initial diagnosis of metastases. The improvement in prostate cancer specific mortality is supported by several studies, but not supported by others. These benefits must be weighed against the current limitations: potential downsides of over-diagnosis and over-treatment of clinically insignificant cancers.

This controversy in the literature suggests that no “standard of care” exists for prostate cancer screening at the present time. Healthcare providers and patients should continue to have conversations regarding the heterogeneous nature of PSA testing. To further reduce morbidity and mortality from prostate cancer, newer approaches for screening, early detection, and prevention are needed.⁵⁴ If a decision is made to screen and the patient is ultimately diagnosed with prostate cancer, patients should seek expert advice from those who are able to provide objective information on all treatment options. Those options for localized disease should include a discussion of active surveillance if appropriate, before deciding on any definitive treatment. □

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Editor's Note

At the time of publication of the October issue of the *Canadian Journal of Urology (CJU)*, the US Preventative Services Task Force was preparing to publish an article in *Annals of Internal Medicine* recommending that healthy men no longer receive PSA testing to screen for prostate cancer (Cancer Letter, Vol 37, No 37 Oct. 7, 2011). Their conclusions were based in large part on the screening trials reviewed in this article and will cite PSA screening as having a “D” level of evidence rating. The “D” rating means that “there is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.” There is no doubt that this recommendation to abandon PSA based screening will continue to fuel the evidence and guidelines controversy discussed in this paper.

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