Prostate-specific antigen tests and prostate cancer screening: an update for primary care physicians

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Prostate cancer is a highly prevalent malignancy. Using serum prostatic-specific antigen (PSA) levels to screen for prostate cancer has led to a greater detection of this cancer, at earlier stages. However, screening for prostate cancer by determining PSA levels remains controversial. Concerns include the risk of overdiagnosis and conversely, the failure to detect all prostate cancers. This article, aimed at primary care practitioners, reviews the characteristics of an ideal screening test, in relation to the characteristics of the PSA test. It then discusses the implications of recent findings from two large, randomized, prospective screening trials: the American Prostate, Lung, Colorectal and Ovarian Cancer (PLCO) screening trial and the European Randomized Study of Screening for Prostate Cancer (ERSPC) trial. The latter trial demonstrated a modest survival benefit from PSA screening. Lastly, the article summarizes recommendations from recently updated guidelines about PSA testing from the American Urological Association (AUA), and it discusses when a primary care practitioner might refer a patient to a urologist.

Key Words: prostate adenocarcinoma, prostate-specific antigen, review, early cancer detection

Introduction

Of all the aspects of prostate cancer, none is more relevant to the primary care physician than screening for this cancer. Treatment of prostate cancer is typically directed by specialists, but the primary care physician is generally the gatekeeper and expert in screening patients for prostate cancer and detecting cancer cases.

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For a complete review of the "diagnosis and management of prostate cancer" the primary care physician should refer to the *Urology Update for Primary Care Physicians 2008*, The Canadian Journal of Urology supplement.[1,2] This article discusses two large trials of prostate cancer screening[3,4] and new American Urological Association (AUA) guidelines for prostate cancer screening[5] that have been published since then. The need for widespread prostate cancer screening by measuring prostate-specific antigen (PSA) levels remains controversial.[6]

PSA is a protein produced by the prostate. It is a normal secretary product of the prostate that is present in seminal fluid in mg/mL levels but only present in

serum in ng/mL levels -- a million-fold difference in concentration.[7] Its physiologic role and its function in reproduction is to liquefy semen.[8]

PSA was originally a forensic laboratory test to confirm the presence of semen.[7,8] Subsequently, researchers recognized that patients with a diagnosis of prostate cancer often had relatively high levels of serum PSA, particularly when they had more advanced stages of the disease.[9] PSA testing in patients not known to have prostate cancer began, which revealed a substantial increased ability to detect prostate cancer compared to existing methods.[10] PSA screening essentially began without fully evaluating it as a screening test, and measurement of PSA levels has become widespread.

Characteristics of an ideal screening test

An ideal screening test exists when certain disease, test, and population features are present.[11,12] The disease should have a significant effect on quality or length of life. It should have an asymptomatic period during which detection and treatment can result in better outcomes. It should also have available, acceptable, potentially curative treatments. The test should have sufficient sensitivity (few false negatives) and specificity (few false positives) and be acceptable to patients. The population should have sufficiently high disease prevalence and be compliant with and accepting of subsequent testing and treatment.[11,12]

Disease features

Prostate cancer is the most commonly diagnosed cancer in men in North America, and it is the most commonly diagnosed noncutaneous cancer in men and women combined.[5,13] It has a significant health impact. Prostate cancer ranks as the third most prevalent "cancer killer" in men. In 2009, in Canada, an estimated 4400 men died from prostate cancer, which is comparable to the number of men who died from colon cancer (about 4900) and the number of women who died from breast cancer (about 5400).[13] A man's lifetime risk of being diagnosed with prostate cancer is 1 in 7, and his lifetime risk of dying from prostate cancer is 1 in 27.[13]

Prostate cancer does not typically have any symptoms in its early stages, and it is often incurable once symptoms become apparent. Therefore, the critical point for diagnosing prostate cancer is prior to development of symptoms. The potential benefit of a screening test for prostate cancer seems self evident.

Whereas an estimated 4400 men in Canada died from prostate cancer in 2009, an estimated 25 500 new cases were diagnosed.[13] Thus, there is an almost 6:1 ratio of diagnosis of prostate cancer to death from prostate cancer, supporting the belief that many prostate cancers are indolent and not life threatening. This creates concerns about overtreating these prostate cancers, resulting in unnecessary cost, morbidity, and side effects that diminish quality of life.

In fact, the presence of histological prostate cancer is very high. Autopsy studies of men who had died from other causes did not detect any prostate cancer in men who died at age 10 to 19, but it detected small foci of prostate cancer in 0%-2% of men who died at age 20 to 29, in 27%-29% of men who died at age 30 to 39, in 32%-34% of men in who died at age 40 to 49, in 55% of men who died at age 50 to 59, and in 64% of men who died at age 60 to 69.[14,15] Thus a man's risk of harboring some prostate cancer appears to be approximately equal to his age in years, at least after age 30. Several important points can be extrapolated from this study. The presence of some histological cancer potentially predates a clinical diagnosis by decades. Prostate cancer can be extremely slow to progress. A great many prostate cancers will never be clinically important. Prostate cancer screening, unlike screening for most diseases, is potentially limited by the disease being too common (too many clinically "insignificant" cancers). Ideally screening for prostate cancer would involve identifying "clinically significant" cancers, not necessarily all cancers.

Test features

Table 1 summarizes how parameters of screening tests -- specificity, sensitivity, and negative and positive predictive values--are defined. Most studies report that using a traditional upper-normal cutoff of 4.0 ng/mL, current PSA tests have a sensitivity of 70% to 80% and a specificity of 60% to 70%.[16] The positive predictive value of a PSA > 4.0 ng/mL is about 30%,[17] which means that among men who have a PSA level higher than 4 ng/mL, biopsies would confirm (detect) prostate cancer in only 30% of the men.

Whether it is possible to determine absolute values (presence or absence of prostate cancer) from PSA test results is debatable. In determining the binary possibilities of "cancer" or "no cancer," "true cancer" is generally defined as cancer detected with a transrectal ultrasound (TRUS)-guided biopsy. However, as discussed above, the presence of small amounts of histological prostate cancer at autopsy is very high: some prostate cancer is present in close to 30% of men in their fourth decade,[14,15] an age when clinical diagnosis of this disease is very rare.

TABLE 2. **A 4 x 4 chart comparing cancer presence or absence to screening test results**

	Cancer is present	**Cancer is absent**
Screening test is positive	True positive (TP)	False positive (FP)
Screening test is negative	False negative (FN)	True negative (TN)

Test characteristics are defined as follows:

$$\text{Positive predictive value} = \frac{TP}{TP+FP}$$

$$\text{Negative predictive value} = \frac{TN}{TN+FN}$$

$$\text{Sensitivity} = \frac{TP}{TP+FN}$$

$$\text{Specificity} = \frac{TN}{TN+FP}$$

Like the PSA test, analysis of biopsy samples is subject to concerns about sensitivity and negative predictive value (that is, is cancer being missed?). Historically, six core samples were taken at the time of a TRUS-guided biopsy. Researchers subsequently determined that the six-core technique had 30% more false negatives than the 12-core technique.[18,19] Guidelines now recommend performing an extended biopsy in most cases, and six sample cores are no longer considered sufficient.

If the primary care physician is referring patients directly for biopsies, he or she should ensure that the procedure is done using an up-to-date technique with sampling of ten or more cores, as reviewed by Laspina and Haas.[1] On the other hand, biopsies with sampling of more than 12 cores have been associated with increased risk of adverse events without increased cancer detection.[18] Care should be taken not to interpret a negative biopsy finding as an absolute confirmation of the absence of cancer, as there is a continued risk of a false negative result. Where appropriate, patients should have ongoing monitoring and undergo repeat biopsies, as needed.

Efforts to diagnose prostate cancer have typically focused on patients with elevated PSA levels and a perceived increased risk of cancer. However, the placebo arm of the Prostate Cancer Prevention Trial (PCPT) provides data from men with "normal" PSA and digital rectal exam (DRE) findings. In this trial, 2950 men in the placebo arm who had a PSA of 4.0 ng/mL or lower and a normal DRE underwent an end-of-study biopsy. Prostate cancer was diagnosed in 15.2% of the men.[20] Since 90% of men over age 50 have a PSA of 4 ng/mL or lower,[21] this suggests that most men over age 50 with prostate cancer detected by means of a needle biopsy have "normal" serum PSA levels. This is consistent with autopsy findings discussed earlier, although the detection of cancer in a needle biopsy sample from a living tissue sample suggests the presence of greater disease than the detection of small, histologic foci of cancer in an autopsy sample.

Table 2 illustrates a hypothetical group of 1000 men undergoing biopsy with the assumption of 10% with PSA > 4.0 ng/mL, a positive predictive value of 30% for PSA > 4.0 ng/mL, and 15% cancer rate when the PSA is 4.0 ng/mL or less. The specificity is 92%, but the sensitivity is only 18%.

A subanalysis of PCPT trial results showed that even very low serum PSA levels did not predict the complete absence of cancer. The prevalence of prostate cancer was 6.6% among men with a PSA level up to 0.5 ng/mL, 10.1% among men with a PSA of 0.6-1.0 ng/mL, 17% among men with a PSA of 1.1-2.0 ng/mL, 23.9% among men with a PSA of 2.1-3.0 ng/mL, and 26.9% among men with a PSA of 3.1-4.0 ng/mL.[20] Nevertheless, PSA levels do clearly correlate with the likelihood of cancer. Furthermore, PSA also correlates with higher-grade cancer and tumor volume.[20,22,23]

TABLE 2. **A hypothetical comparison of 1000 men undergoing prostate biopsy**

	Cancer present	**Cancer absent**
PSA > 4.0 ng/mL	30	70
PSA 4.0 ng/mL or less	135	765

Population features

Prostate cancer is common in Canadian men. The risk of prostate cancer increases with age, but the potential benefit from treatment decreases with age, since the potential number of years of life lost to disease decreases and morbidities and mortalities from other diseases increase. Guidelines typically recommend screening men aged 50 to 70 years old, to be able to detect cancer early in younger men and to avoid overdiagnosing and treating older men who would most likely die from other diseases. Men with a family history of prostate cancer and men of African ancestry have a greater chance of being diagnosed with prostate cancer, compared to men without these risk factors.[1]

PSA determination is an attractive screening test, as it requires simply drawing a blood sample, and high patient compliance with testing is expected. Similarly, a DRE is an inexpensive test with a low morbidity. Patients should, however, be aware that screening with PSA and DRE is only an initial step, which may then lead to TRUS-guided biopsy. Patients need to be informed of the consequences of screening and the risks and benefits of treatment, even though this is a complex topic.

Screening should be performed during a "well visit," for example, during an annual physical examination. Table 3 summarizes the characteristics of patients who should not be screened for prostate cancer. In addition, screening should not be performed when the patient has had an acute event such as urinary infection or urinary retention which can lead to falsely elevated PSA levels.[24] Other factors such as ejaculation and DRE have not consistently been shown to effect the PSA levels.[5]

The prevalence and characteristics of prostate cancer in the population being screened will influence the effectiveness of screening. In fact, if screening is effective, it will alter the population by removing cases of prostate cancer. With PSA screening this would leave a progressively higher proportion of patients in the population with PSA elevations from benign conditions, thus reducing the effectiveness of PSA screening.

Since the introduction of PSA testing there has been a trend towards diagnosis of prostate cancer at earlier stages. Beginning in 1991, the incidence of advanced-stage or metastatic prostate cancer decreased at an annual rate of 17.9%, which has been interpreted as being the result of PSA screening.[25] Stamey reported in1989 that cancer volume was the primary determinant of serum PSA levels in men undergoing radical prostatectomy.[26] The same author concluded in 2002 that serum PSA had a "clinically useless" relationship with cancer volume, and that BPH is a strong contender for the cause of PSA elevation.[27]

The screening "no man's land"

Many of the previously mentioned issues -- particularly the potentially high rate of cancer in patients with low PSA levels-- raise serious questions about the utility of PSA determinations in screening for prostate cancer. Lowering the PSA cutoff or simply performing biopsies on all men of a certain age will increase the detection of cancer, but it will also increase the number of patients who will unnecessarily undergo investigations. Furthermore, the increased cancer detection will lead to diagnosis and treatment of more patients with potentially indolent or insignificant disease.

A PSA threshold above which biopsies need to be performed may, however, still be useful in that it defines the lower limit of a "no man's land" or a grey zone of PSA levels where cancer is detectable at reasonable rates, at an early enough stage to be curable, but which spares many men from unnecessary and potentially harmful investigation. It is believed that biologically active prostate cancer will typically result in an increasing PSA level at some point in its natural history. Even in men with cancer and initially low serum PSA levels (e.g. < 4 ng/mL), PSA levels are expected to rise above the cutoff at some point if the disease progresses. The cancer is "picked up" when the PSA goes above the threshold into the "no man's land" (e.g. > 4 ng/mL). If the threshold is too high, then the cancer will be detected at too advanced a stage. With a PSA between 4 and 10 ng/mL, 75% of prostate

TABLE 3. **Characteristics of patients who should not undergo prostate cancer screening with PSA and DRE**

- Patient does not want screening
- Patient would not wish to undergo biopsy or further pursue management and treatment for prostate cancer
- Patient is too old and/or ill to potentially benefit from prostate cancer management
- Patient is too young, or otherwise in too low a risk group for prostate cancer to potentially benefit from screening
- Patient has an acute event that is likely to confound screening results (e.g. infection, urinary retention)

cancers are confined to the prostate, but this drops below 50% when the PSA is higher than 10 ng/mL.[28] A review of 875 men who underwent radical prostatectomy concluded that cure rates appeared constant in men with preoperative PSA levels up to 9 ng/mL, suggesting that earlier diagnosis does not lead to added benefit.[29]

Extensive attempts have been made to argue "for" or "against" screening, but only recently, with the publication of two very large trials, have substantial randomized control data become available.

The PLCO trial[3]

The prostate, lung, colorectal and ovarian cancer (PLCO) screening trial is an American study that was designed to evaluate the value of screening for these four cancers.

In this study, 76 693 men aged 55 to 74 years were randomized to a "screened group" or to a "usual care" (control) group. Patients in the screened group were offered annual PSA testing for 6 years and an annual DRE for 4 years. In the screened group 85% of the patients were compliant with PSA testing and 86% were compliant with DRE. Patients in the usual care group could receive some form of screening, but this was not necessarily regular or annual screening. By the sixth year 52% of the patients in the usual care group had undergone PSA testing at least once.

At 7 years, the incidence of prostate cancer in the screened population was 116 per 10 000 and it was 95 per 10 000 in the control group. The incidence of death was 2.0 per 10 000 in the screened group and 1.7 per 10 000 in the control group, which was not a statistically significant difference.[3]

This study looked at a very large number of patients, and failed to show a benefit from screening for prostate cancer. The study raises several important points.

First, compliance with screening is imperfect, yet as many as 52% of men in the control group in the PLCO study received some type of screening. Approximately 44% of the men in both groups had undergone previous PSA testing, and the population was thus to an extent prescreened prior to the trial. This would have removed some cancers that would have been detected in one of the randomized groups. The cancer incidence was only slightly higher in the screened group (rate ratio 1.22). One would expect the incidence to be much higher in a screened population; in fact a concern of screening is overdiagnosis.

Historically the introduction of PSA testing has resulted in a marked increase in the incidence of prostate cancer. From 1986 in the pre-PSA testing era to 2005 after many years of PSA testing the relative incidence of prostate cancer increased 1.91 times for men aged 60 to 69 years and 3.64 for men aged 50 to 59 years.[30] Since PSA and DRE are the prime methods of developing suspicion of cancer, the comparable rates of diagnosis in the screened group and in the usual care group in the PLCO study suggest that these tests are being carried out sufficiently often in both groups and yield a similar detection of cancer.

The mortality incidence was also low in both groups in the PLCO study. The overall rate of prostate cancer mortality in Canada is 2.3 per 10 000 across the male population of all ages.[11] This suggests the population studied in the PLCO study is at low risk for prostate cancer mortality, or both groups are undergoing effective treatment. Although 10-year analysis was included (which was consistent with analysis of 7-year data), the follow up may be somewhat short. Patients with early localized prostate cancer demonstrate a significant increase in cancer mortality 15 years after diagnosis.[31]

Overall, the PLCO study demonstrated no benefit from the study's screening program compared to usual care, probably because the men in the study had already undergone some form of screening. What this really means is that the "usual care population" was not an unscreened population.

Researchers used a different approach in the European Randomized Study of Screening for Prostate Cancer (ERSPC) trial.

The ERSPC trial[4]

The ERSPC trial identified 182 000 men aged 50 to 74 years who were randomized to a screened group that was offered screening with PSA at an average of once per 4 years or a control group that was not offered screening. In the screened group, 82% of men were screened at least once. The median follow up was 9 years. The cumulative incidence of prostate cancer was 4.8% in the control group and 8.2% in the screened group. The rate of prostate cancer death was 20% lower in the screened group. To prevent one death, 1410 men would need to be screened and 48 would need to be treated.[4]

This study demonstrates an expected increased incidence in prostate cancer in a screened group. It is likely that the control group in this study was less "contaminated" by screening tests such as PSA tests than the control group in the PLCO study. Therefore, this study may be a purer comparison of screening versus no screening. The frequency of PSA testing was relatively low, at an average of once every 4 years. The traditional

annual PSA test is perhaps more frequent than necessary. In the ERSPC trial, the mortality benefit was small, but statistically significant. As screening generally detects cancer early in its natural history and because prostate cancer is often slow to progress, the benefits of screening, if they exist, only become apparent over time. In the ERSPC trial, the mortality curves of screened men versus men who were not offered screening only separated around the 7-year point. It may be that longer-term follow up will show a greater benefit from screening. Nevertheless this study as well as the PLCO trial illustrates a high rate of overdiagnosis.

The American Urological Association (AUA) PSA best practice statement[5]

The AUA updated its statement on PSA tests in 2009. The recommendations include[5]:

- The decision to use PSA should be individualized and patients should be informed of the known risks and benefits.
- Early detection and assessment should be offered to asymptomatic men 40 years or older who wish to be screened and have an estimated life expectancy of more than 10 years. Testing at this age may help to identify men at a curable stage who would otherwise die from prostate cancer between age 55 to 64 years.
- Men younger than 50 years old are more likely to have curable cancer.
- PSA is a more specific test for cancer in younger men because increased PSA from benign prostate enlargement is less common at that age. Compared to annual testing beginning at age 50, infrequent testing of men in their 40s and men age 50 and older might reduce prostate cancer mortality and the cost of screening.
- Establishing a baseline PSA level for use in evaluating PSA velocity (the rate of annual increase in PSA) could help identify men with life-threatening prostate cancer when a cure is still possible.
- Screening intervals should be based on the patient's PSA level. For men with PSA levels of 2 ng/mL or lower, screening every 2 years is unlikely to miss curable cancer.
- No specific upper age limit for PSA testing is advised.
- A physician should assess a patient's individual health status to determine the appropriateness of PSA testing at any age. A distinction should be made between screening and treatment. It may be helpful for an older man to know that he has a diagnosis of prostate cancer, but he may not require treatment. Older men with aggressive prostate cancer, however, should not be denied the opportunity for diagnosis and treatment.
- Screening should include both a PSA test and a DRE.
- TRUS adds no additional diagnostic information, but it is useful to guide biopsies.
- A single threshold PSA value is not recommended. The decision to biopsy should be based primarily on a patient's total PSA level and DRE findings, but it should also take into account multiple factors including values for free PSA, PSA velocity, and PSA density (serum PSA level/prostate volume), as well as the patient's age, ethnicity, family history, prior biopsy history, and comorbidities.

Indications for urology referral

The AUA recommendations are relevant for the primary care physicians, but present challenges as

TABLE 4. **Possible indications for urology referral**

Abnormal DRE: nodule, asymmetry, induration, irregularity
Elevated PSA > 4.0 ng/mL
Elevated age-specific PSA[31]
40-49 yrs > 2.5 ng/mL
50-59 yrs > 3.5 ng/mL
60-69 yrs > 4.5 ng/mL
70-79 yrs > 6.5 ng/mL
Low free/total PSA ratio < 0.10
PSA velocity: increase of 0.75 ng/mL or greater per year (at least 3 PSA levels over 18 months)
Sufficient concern raised by family history, African ancestry, or patient anxiety to warrant referral

there is no distinct, recommended PSA cutoff, and multiple risk factors need to be balanced in decisions about who to screen and biopsy. Depending on the primary care physician's comfort level about making treatment decisions, any of the patient findings listed in Table 4 might warrant a referral of the patient to a urologist.

Conclusions

Prostate cancer screening remains controversial. It is important for the primary care practitioner to note that if a patient presents with BPH symptoms, this patient deserves a PSA test to help rule out prostate cancer as the cause of their symptoms. In this setting the PSA test is not considered to be a 'screening test. As further randomized controlled study data with longer follow up to better demonstrate survival benefits become available, the possible benefit or lack of benefit of PSA testing may become clearer. It is reasonable to offer the PSA test to a motivated, informed patient who believes in the potential long term benefit of early prostate cancer detection.

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