

Current status of PSA screening

Early detection of prostate cancer

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ABSTRACT

OBJECTIVE To update current evidence for prostate-specific antigen (PSA) screening for prostate cancer and to give readers some practical information to discuss with patients.

QUALITY OF EVIDENCE A MEDLINE search revealed only three randomized studies, two of which are incomplete. Several controlled non-randomized studies were found.

MAIN MESSAGE Two ongoing studies have not yet reported survival data, but have added to evidence for screening intervals. One Canadian randomized study has been criticized for its design and conclusions. Non-randomized studies suggest that screening effectively identifies serious cancers and leads to earlier diagnosis. Mortality from prostate cancer has been falling in most western countries since 1992. This cannot be explained by PSA screening, which would probably not produce survival benefit until at least 10 years after its unofficial introduction in about 1990.

CONCLUSION Indirect evidence suggests that all men older than 45 with at least a 10-year life expectancy should be informed of the potential benefits and drawbacks of PSA screening so they can make an informed decision on whether to have the test.

RÉSUMÉ

OBJECTIF Faire le point sur les données récentes concernant le dosage de l'antigène prostatique spécifique (APS) pour dépister le cancer de la prostate et suggérer au lecteur des stratégies pour en discuter avec les patients.

QUALITÉ DES PREUVES Une recherche dans MEDLINE a identifié plusieurs études contrôlées non randomisées, mais seulement trois études randomisées, dont deux incomplètes.

PRINCIPAL MESSAGE Deux études en cours n'ont pas encore rapporté de données sur la survie; elles ont toutefois fourni des données additionnelles sur la fréquence des dépistages. Le protocole et les conclusions d'une étude canadienne randomisée ont été critiqués. Les essais non randomisés suggèrent que le dépistage détecte efficacement les cancers plus sévères et permet un diagnostic plus précoce. La plupart des pays occidentaux ont connu une baisse de mortalité par cancer de la prostate depuis 1992. Le dépistage par l'APS ayant débuté autour de 1990 de façon non officielle, l'amélioration de la survie ne peut lui être attribuée; en effet, ses effets bénéfiques devraient prendre au moins 10 ans à apparaître.

CONCLUSIONS Certaines preuves indirectes suggèrent que tout homme de 45 ans et plus dont l'espérance de vie est d'au moins 10 ans devrait être informé des avantages et inconvénients possibles du dépistage par l'APS, de façon à pouvoir prendre une décision éclairée à ce sujet.

This article has been peer reviewed.

Cet article a fait l'objet d'une évaluation externe.

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Incidence of prostate cancer exceeds that of any other cancer; about 18 000 cases are expected this year in Canada.¹ The disease accounts for more than 4000 deaths annually, being second only to lung cancer in terms of cancer mortality, and is also an important cause of morbidity. Prostate-specific antigen (PSA), a tumour marker introduced in the late 1980s, is one of the best oncology markers available. It has been used extensively to screen normal healthy men for the disease.

About 13% of Canadian men aged 50 to 59 and 24% of those aged 60 or older have had PSA tests²; screening has been the most common reason for requests for PSA testing among those with no established diagnosis of cancer.³ Screening is controversial, however, because it has not been shown to reduce mortality (unlike mammography for breast cancer, for example) and because the effectiveness of interventions for prostate cancer has been questioned. Family physicians are usually the first ones approached with requests for PSA testing. As use of PSA testing is controversial, they need to be aware of issues that argue for and against testing. This article reviews current evidence for routine use of PSA screening and suggests an approach to use in discussing testing with patients.

Wilson and Jugner⁴ defined criteria for effective screening tests in 1968. Accurate tests are a prerequisite, as are efficacy and acceptability of treatment, cost-effectiveness, and resource availability. Emerging evidence supports the efficacy of curative therapeutic options, such as surgery or radiation therapy, for prostate cancer.⁵ Many more men will die with prostate cancer, however, than from it. A 50-year-old man with a life expectancy of 25 years has a 42% lifetime risk of developing microscopic prostate cancer, a 9.5% chance of having clinical cancer, and a 2.9% chance of dying of it. Treatments are associated with substantial morbidity and reduced quality of life. Initial enthusiasm for widespread testing 10 years ago was replaced

with caution in the later 1990s, but as new evidence emerges, rates of PSA screening appear to be increasing once again.

Literature search

MEDLINE was searched using the terms “prostate neoplasms,” “prostate-specific antigen,” and “diagnosis or mass screening.” From a total of 3619 references, 139 articles reported on controlled (37) or randomized (102) trials. Uncontrolled trials were excluded because they are particularly open to bias in patient selection. Cross-matching of randomized trials revealed that there were, in fact, only three trials, and only one of them has reported results. The other articles either referenced these trials or discussed prostate screening in a different context. From the many controlled trials, I was necessarily selective; interested readers are referred to some of the larger reviews cited.

Natural history of prostate cancer

Prostate cancer represents a spectrum of malignancy. In its earliest forms, it appears to arise from prostate intraepithelial neoplasia and is of low grade. Autopsy series show that a high proportion of healthy men have such early tumours. A 40- to 50-year-old man has about a 34% chance of having early occult prostate cancer,⁶ yet only one in eight men will be diagnosed with cancer during his lifetime. The chance of a man younger than 50 being diagnosed clinically is <0.3%.¹

A placebo-controlled study of finasteride chemoprevention in men older than 55 (with normal results of PSA and digital rectal examination) confirmed a high incidence of occult prostate cancer. Routine sextant biopsies were carried out for 4692 men in the placebo arm; 24% were positive for prostate cancer.⁷ Incidence rapidly increases with age. Most clinically apparent cases are seen in men in their 60s and 70s. More aggressive cancers are associated with higher PSA levels, Gleason grade, and clinical stage. Distant spread to bones and nodes is the common pattern of dissemination that ultimately leads to death. Hormone therapy with

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androgen ablation is typically effective for only 2 to 3 years after metastases are diagnosed.

The challenge for prostate screening programs is, therefore, to pick up clinically significant cancers at an age and stage when intervention will be successful, and to avoid overdiagnosis of occult low-grade cancers, particularly in elderly people, who will likely die of something else or old age long before the tumour progresses.

Unsanctioned PSA screening started in Canada in about 1990 and was accompanied by a rapid increase in incidence of prostate cancer. This evened out a few years later when diagnosed patients were taken out of the “population pool” and incidence fell (**Figure 1**). At the same time, but not necessarily causally, there was a dramatic reduction in incidence of metastatic cancer and advanced tumours. In 2000, more than 80% of patients referred to the British Columbia Cancer Agency had “curable” organ-confined prostate cancer, compared with less than 50% in 1988.⁸

Mortality from prostate cancer has been falling since it peaked in about 1990. In British Columbia, the death rate has fallen 15% among all men and 19% among those younger than 65. While it is tempting to ascribe these results to PSA screening, which was introduced at about the same time, it is unlikely that PSA testing caused the mortality reduction. Although PSA testing can detect cancer

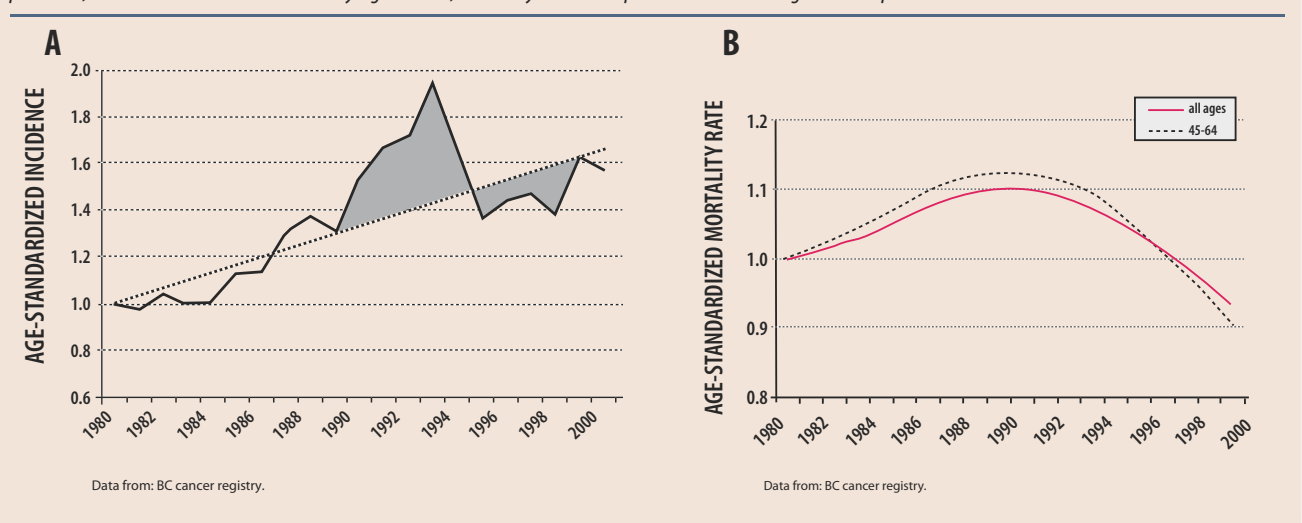
about 5½ years earlier than it can be detected clinically,⁹ and even if subsequent localized treatment (such as radical prostatectomy or radiotherapy) had failed, it is unlikely that metastatic disease would develop for another 4 to 6 years. Hormone therapy would be expected on average to work for 2 to 3 years, giving a minimum likely time from PSA-based diagnosis to death of 10 to 15 years.¹⁰

Accuracy of the test

There is little doubt that PSA can detect prostate cancer. A study of 22 071 healthy men aged 40 to 82 years who had serum stored at baseline showed that 366 developed prostate cancer during the next 10 years.⁹ When PSA was measured in the stored samples, 46% of the cancers were detected. For diagnosis within 5 years of sample date, sensitivity rose to 65% and specificity was an impressive 91%. Overall, 87% of aggressive prostate cancers were detected within the first 4 years, compared with only 53% of nonaggressive cancers. Use of age-adjusted rates is important, because benign prostatic hypertrophy, which is increasingly common as men age, also causes PSA levels to rise: 2.5 ng/mL is abnormally high for a 49-year-old; 6 ng/mL is normal for an 80-year-old.

The free PSA ratio, a refinement of the PSA test, can help distinguish benign from malignant

Figure 1. Age-standardized rates in British Columbia: A) Incidence of prostate cancer normalized to 1980 (similar rates are reported by other provinces). Broken line indicates the underlying trend. B) Mortality rates from prostate cancer during the same period.



sources of PSA. Because PSA binds more avidly to α_1 -antichymotrypsin when it is from a malignant source, a low PSA ratio suggests malignancy. This is most useful when PSA falls into the “gray” zone, 4 to 10 ng/mL. Normal age-adjusted reference ranges should be part of laboratory reports. If they are not reported, they should be obtained from the laboratory. A possible drawback of being tested is the low positive predictive value of the test (25% to 35%, meaning that 65% to 75% of men testing positive turn out not to have cancer after further investigations) and the anxiety this generates.

Ongoing randomized trials

To date, there are no mature randomized studies, but two large studies are ongoing. The American Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial¹¹ completed recruiting 154 000 men and women in July 2001. Mortality results are expected in 2015. In Europe, more than 150 000 men have been randomized in the European Randomised Study of Screening for Prostate Cancer (ERSPC).¹⁰ While mortality results will not be available for another 5 to 10 years, early reports of other end points have been published. The most promising is that incidence of metastatic cancer in the screening arm is only one tenth of that in the control arm¹² (0.6% versus 6.7%) and that screen-diagnosed cancers are at an early stage. Both these findings should translate into a survival advantage with sufficient follow up.¹³

In Canada, a so-called randomized trial was published in 1999.¹⁴ In this population-based study, men were identified from electoral rolls and “randomized” to PSA testing in the experimental arm, but not informed they were in a study in the control arm. The design of the study, the method of analysis, and the fact that only 23% of those approached participated led to serious criticism of the results.¹⁵ In particular, men in the control arm were exposed to risk of prostate cancer for 3 years longer than those in the screening arm. An intention-to-treat analysis actually suggested an increased, rather than reduced, death rate from prostate cancer.¹⁶

Many reviews of PSA screening have been published, but no complete Cochrane systematic review is available. A systematic review published in the United Kingdom carries a balanced summary of the literature to 1996.¹⁷ It recommends PSA screening be discouraged.

Observational studies

A “natural experiment” from the United States describes different PSA screening rates, incidence of cancer, and use of curative treatments in Seattle and Connecticut from 1987 to 1990, and follows outcomes during the next decade.¹⁸ The cancer detection rate in the Seattle area was five times that in Connecticut; the cumulative incidence of diagnosed prostate cancer was 93% greater; and use of radical prostatectomy and radiation was 5.9- and 2.3-fold higher. The mortality rate over 11 years of follow up, however, was similar in the two regions; with Seattle having slightly higher mortality. Although not a randomized comparison, this study argues strongly that increased diagnosis of prostate cancer by PSA testing and subsequent treatment do not affect mortality over the following decade. It does not exclude subsequent benefit, however. The results also suggest that many of the cancers detected and treated were clinically insignificant.

Epidemiologic studies of worldwide mortality in the PSA era show that mortality rates are now lower in several countries.¹⁹ In some countries, the decline began before PSA testing (eg, in Italy in 1988), and in others, it began despite lack of interest in PSA screening (eg, the United Kingdom). Potential explanations include increased (and earlier) use of androgen ablation for metastatic cancers, attribution bias related to death certification, increased use of curative treatment, and a change from high- to lower-fat diets.

In Canada, two similarly designed studies have compared incidence of prostate cancer and mortality in patients in Quebec²⁰ and British Columbia.²¹ Neither study shows a decline in mortality attributable to PSA within 10 years of commencement of community screening. A study of the Tyrol region in Austria, where PSA testing was made freely available

in 1993, showed reductions in mortality throughout Austria, but greater reductions in the Tyrol and adjacent regions.^{22,23} Whether this reduction resulted from the screening program is uncertain.

National and international recommendations

There is no clear consensus on PSA screening. Some groups, such as the American Urological Association, are in favour; most others, such as the Canadian Cancer Society, are not. There is general consensus that men should be made aware of PSA as a screening test and should make an informed decision about whether to have it. The United States Preventive Services Task Force²⁴ concluded that evidence is insufficient to recommend for or against routine screening for prostate cancer using the PSA test or digital rectal examination. In the United Kingdom, perhaps due to a concerted media campaign, the National Health Service has adopted an “on-demand” PSA screening program.²⁵

What patients want

Whatever the controversy among medical professionals, patients want PSA screening.²⁶ This is unsurprising, given that physicians usually suggest that patients present early to examine for lumps, undergo mammography, and so on. Patients think PSA screening offers the benefits of early diagnosis, of taking responsibility for their own health, of avoiding regret if cancer is subsequently diagnosed, of peace of mind, and of the right to information and access to the test.²⁶ Although a physician's views from a public health perspective should agree with his or her views toward an individual patient, the wishes and views of that patient should not be ignored.

Suggested approach to screening

Widespread enthusiasm for PSA screening has been replaced with a more cautious, individualized approach. If a man wants to minimize risk of prostate cancer and maximize his chance of living as long

as possible, PSA screening might be appropriate. If a man wants to maximize his quality of life, minimize his risk of complications (such as impotence and incontinence), and undergo only medical tests that we know to be beneficial, however, PSA screening is unlikely to be of value to him.²⁷


Patients should be informed that PSA testing can lead to earlier diagnosis and that it has both benefits and drawbacks. Useful minimum information and handouts have been published.²⁸ Resources for this and many other cancer topics for physicians and patients can be found on the US National Cancer Institute website (<http://cancer.gov/>). Background documents on prostate screening in the UK for patients and physicians can be found on the National Health Services website (<http://www.cancerscreening.nhs.uk/prostate/index.html>). A Canadian patient information sheet can be downloaded from the BC Cancer Agency website (www.bccancer.bc.ca/HPI/CancerManagementGuidelines/Genitourinary/Prostate/PSAScreening/Recommendations.htm).

The natural course of prostate cancer is long, so patients should be screened only if they have a 10-year life expectancy and are at appreciable risk of cancer. Most authorities that recommend screening include only men between 50 and 70 years, but there could be a good case for extending this to 75 years, as life expectancy at 75 is now 10 years. Optimum screening intervals could depend on PSA velocity and absolute level. Suggested intervals are at age 40 and then 45 to establish a baseline, and then not again until 50. After that, men should be tested every 2 years unless there has been a substantial change in results or levels are raised.²⁹ If PSA is <1 ng/mL, however, it need be checked only every 5 years; if 1 to 2 ng/mL, every 2 years. Such an approach has been predicted to reduce the number of PSA tests by 55% and save \$500 to \$1000 million annually in the United States.³⁰

Current Canadian recommendations vary by province. Saskatchewan, Nova Scotia, and Quebec have funded PSA programs, but most provinces do not. Whether patients pay for tests or not, the approach should be the same: physicians inform patients of the test, discuss advantages and

disadvantages, and take appropriate action (usually referral to a urologist) when abnormal results are detected. Remember that normal ranges are age-specific and that day-to-day variation of up to 25% is common. Unless abnormal results normalize on repeat testing, additional investigation is warranted.

Conclusion

Incidence of prostate cancer increased dramatically when unofficial PSA screening was introduced about 1990. Mortality began declining at the same time, but the decline is not thought to be a consequence of PSA screening. Early results from completed, but unreported, trials of PSA screening indicate that screened patients' cancers are detected at an earlier stage than unscreened patients' cancers. Whether this will translate into a survival advantage is uncertain, and we must await results of ongoing studies, which will not be available for another 5 to 10 years. In the meantime, there is consensus that men should be informed of the availability of the test and of its advantages and disadvantages and should make their own decisions about whether to be tested. 

Competing interests

None declared

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EDITOR'S KEY POINTS

- The challenge for prostate-specific antigen (PSA) screening is to detect clinically significant cancers at an age and stage when cure is likely and to avoid overdiagnosing low-grade tumours.
- Mortality from prostate cancer has been falling for about 10 years; the fall began before widespread PSA testing. No good evidence yet indicates that PSA screening lowers mortality.
- For diagnosis within 5 years, PSA testing has a sensitivity of approximately 65% and specificity of 90%, but its positive predictive value is only about 25% to 35%, meaning 65% to 75% of men tested do not have cancer.
- A suggested approach to PSA screening is to offer it on an individual basis to men aged 50 to 75 with a life expectancy of at least 10 years and to make them aware of the limitations of testing (especially false-positive rates) and of treatments available.

POINTS DE REPÈRE DU RÉDACTEUR

- L'objectif principal du dépistage par l'antigène prostatique spécifique (APS) est d'identifier des cancers cliniquement importants à un âge et à un stade où la guérison est possible, tout en évitant de surdiagnostiquer les tumeurs moins sévères.
- Une baisse de mortalité par cancer de la prostate est observée depuis environ 10 ans; ce phénomène a commencé avant la généralisation du dépistage par l'APS. Il n'existe pas encore de preuves solides que le dépistage réduit la mortalité.
- Pour ce qui est du diagnostic sur cinq ans, le dépistage par l'APS a une sensibilité d'environ 65% et une spécificité de 90%, mais sa valeur prédictive positive n'est que de 25 à 35%, ce qui signifie que 65 à 75% des sujets testés n'ont pas de cancer.
- On suggère d'offrir le dépistage par l'APS de façon individuelle à tout homme de 50 à 75 ans ayant une espérance de vie d'au moins 10 ans, tout en l'informant des limites de ce test (notamment le taux de faux positifs) et des traitements disponibles.

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