The role of prostate-specific antigen (PSA) testing in screening for prostate cancer

Charlotte Hunter (Meds 2015) and Paul Zamiara (Meds 2016)

Faculty Reviewer: Dr. D. Scott Ernst, MD, FRCPC (Department of Oncology, Division of Medical Oncology)

Prostate specific antigen (PSA) is a serine protease expressed mainly by the prostate gland and detectable in normal, benign hypertrophic, and neoplastic prostate tissue. While the majority of the PSA produced by the prostate gland is released into semen, a small amount (approximately one million-fold lower) normally leaks into the circulation and is detectable by immunoassay. In the hyper- and neoplastic prostate, though, its secretion into prostate ducts is lost and consequently more PSA is released into extracellular fluid and the circulation.¹ Serum PSA levels can therefore be used to track the growth or shrinkage of prostate tumors; indeed, the FDA approved its use to monitor cancer progression (i.e. tumor growth, response to treatment, recurrence) in already diagnosed men in 1986.²

PSA became the first biomarker (indicator of biological state) approved for screening asymptomatic men for cancer in 1994, when the FDA approved its use in conjunction with the digital rectal exam (DRE) to screen for prostate cancer. A PSA level of 4.0 µg/L was traditionally considered the upper limit of normal, and a prostate biopsy was recommended to patients exceeding this level. However, prostate cancer screening based on PSA level has limited specificity (33%, versus 86% sensitivity³), as inflammation (prostatitis) and benign growth (benign prostatic hyperplasia) of the prostate will also elevate PSA levels.²

Therefore, despite the PSA test's utility in monitoring tumor progression and response to treatment, its use as a screening test for prostate cancer in asymptomatic men remains controversial. Because of the considerable public health burden imposed by prostate cancer – it was the most diagnosed cancer in males in 2008 (about 899 000 cases and 258 000 deaths worldwide), with 72% of cases occurring in developed countries⁴ – proper screening tools and guidelines are extremely important.

The Canadian Cancer Society has suggested that the benefits of having a PSA test for screening purposes include the peace of mind granted by a normal result; identification of those in need of further testing (if the result is higher than expected for the patient's age); and the ability to detect prostate cancer before it is symptomatic and/or before it has spread beyond the prostate.⁵ However, they also point out the potential for harm associated with prostate cancer screening, such as the unnecessary anxiety caused by a false positive; the potential for a false negative and the propensity to then ignore worrisome symptoms that may emerge later; and the risks associated with treatment of slow growing prostate cancer that could have been left alone.

The current guidelines for prostate cancer screening in Ontario state that PSA testing should not be used as a population-wide screening tool for early detection of prostate cancer in asymptomatic men.⁶ Instead, physicians should discuss the benefits and potential harms of testing with men who are between the ages of 50 and 75 and have a life expectancy of at least 10 years. This discussion should also include men over

40 with a first degree relative who has had prostate cancer, and men of African ancestry. With this information, men can then decide for themselves whether they would like to undergo testing. A PSA value >4.0 µg/L or an abnormal DRE warrants further investigation.

Dr. George Kim (personal communication, December 4, 2012), a family physician working in Southwestern Ontario, restricts his ordering of PSA tests to symptomatic men. In the event of a worrisome change in prostate-related symptoms (i.e. increased urinary urgency or frequency, or poor urinary stream with urinary tract infection unlikely, especially when the patient is of African descent or has a first degree relative diagnosed with prostate cancer prior to age 65), he prefers to send patients for prostate ultrasound and possible biopsy. However, Dr. Kim finds the PSA test to be a convenient test in the interim if the ultrasound cannot take place within 10 days. In terms of screening, Dr. Kim believes patients would like to undergo a simple test, like the PSA test, that could definitively detect cancer; because of this desire for certainty, patients may have unrealistic expectations regarding the validity of test results. He therefore recommends discussing with patients the advantages and limitations of PSA testing (including its low specificity), and explaining why it cannot replace other surveillance methods (i.e. the DRE).

Taking a more extreme stance than the Ontario guidelines, the U.S. Preventive Services Task Force recently recommended against any PSA-based screening for prostate cancer, regardless of age, based on their conclusion that many men are harmed by this screening test and few benefit from it.⁷ The Task Force's conclusions were largely based upon two ongoing studies: the U.S. Prostate, Lung, Colorectal & Ovarian Cancer (PLCO) Screening Trial and the European Randomized Study of Screening for Prostate Cancer (ERSPC).

The PLCO trial involved 76 693 men between the ages of 55 and 74 who were randomized to annual PSA screening for 6 years, combined with a DRE for 4 years, or care as usual.⁸ A PSA value >4.0 µg/L was used as the cutoff for a positive screen result. The incidence of prostate cancer was significantly higher in the screening group after 7 years of follow-up (RR, 1.22 [95% CI, 1.16-1.29]), but there was no significant difference in prostate cancer mortality (RR, 1.13 [95% CI, 0.75-1.70]). The 10 year follow-up data, while only 67% complete, was also consistent with these findings.

The ERSPC trial randomized 182,000 men between the ages of 50 and 74 to either the screening group, which received a PSA test every 2-7 years (depending on the centre), or the control group, which received care as usual.⁹ Most centres in the trial used a PSA cutoff value of 3 µg/L, with a positive screen result warranting a biopsy. After a median follow-up of 9 years, there was no statistically significant difference in prostate cancer mortality between the men assigned to the screening group and the controls (RR, 0.85 [95% CI, 0.73-1.00]). However, in a

HEALTH PROMOTION

prespecified subgroup of 162 243 men aged 55 to 69 there was a significant absolute risk reduction in prostate cancer mortality for the men assigned to screening (RR, 0.80 [95% CI, 0.65-0.98]).

Beyond the fact that the results of these two trials do not provide us with a consistent answer to the question of whether PSA-based screening reduces prostate cancer mortality, the U.S. Preventive Services Task Force was somewhat critical of the methods used in these trials. Both trials failed to exclude men who had had previous PSA testing, the PLCO trial had substantial contamination of the control group (up to 52% of controls received a PSA test during the trial), and the ERSPC trial used a range of PSA cut-off points (>2.5 to $4 \mu\text{g/L}$) and screening intervals depending on the centre.¹⁰

The Task Force's decision-making was also influenced by harms associated with PSA-based screening. For example, 75.9% of men who underwent a biopsy because of an elevated PSA value in the ERSPC trial had received false-positive results.⁹ Complications of diagnostic evaluations occurred in 68 of 10 000 procedures in the PLCO trial, and included bleeding, infections, and urinary difficulty.⁸

Given the uncertainty surrounding the interim results of these two major trials, it will be important to see whether longer-term follow-up of the study participants conveys a clearer message about whether PSA-based screening reduces mortality. Even with the current evidence, the Task Force's strict recommendation against any PSA testing for screening purposes has been criticized for preventing patients from being involved in decision-making.¹¹ In a New England Journal of Medicine commentary written in response to the Task Force's report, Drs. McNaughton-Collins and Barry (two prostate cancer specialists affiliated with Harvard Medical School and Massachusetts General Hospital) argued for a strategy similar to Ontario's guidelines in which patients are made aware of the benefits and harms associated with PSA-based screening and are able to decide for themselves whether the potentially small benefit is worth it to them.¹¹ However, they also suggested that if physicians continue to order PSA tests for screening purposes they must do a better job of emphasizing the potential harms associated with PSA testing, rather than touting only the benefits of screening. Physicians must also make sure that they are not overtreating patients who might benefit more from a "watchful waiting" approach.

Thus far, measurement of absolute PSA level for the purposes of prostate cancer monitoring and screening have been discussed. There are other measurements to increase screening specificity that are currently being explored. A recent retrospective cohort study evaluated the utility of a measure called the PSA velocity (PSAV) risk count in 18 214 men enrolled in a prostate cancer screening study.¹² PSAV refers to the yearly change in PSA units, and the risk count is a measure of the number of times PSAV exceeds $0.4 \mu\text{g/L}$. A PSAV risk count ≥ 2 (i.e. two consecutive yearly increases in PSA levels exceeding $0.4 \mu\text{g/L}$) showed 96% specificity (compared to the reported 33% specificity for the absolute PSA level³) and was associated with a significantly increased risk of prostate cancer (OR 8.2 [95% CI, 7.0-9.6]). In this study, the odds ratio for prostate cancer determined by PSA level, in contrast, was only 1.25 (95% CI, 1.22-1.28). These results suggest that further investigation of PSAV utility in prostate cancer screening is warranted.¹² The US National Cancer Institute also lists PSA density of the transition zone (PSA level divided by the volume of the prostate's transition zone) and age-specific PSA reference ranges as parameters under investigation for improvement of PSA screening specificity.² While these alternative screening options are being investigated, Ontario's recommendation that patients should be properly informed about PSA testing and encouraged to participate in decision-making seems appropriate.

REFERENCES

1. Stenman U-H, Leinonen J, Zhang W-M, Finne P. Prostate-specific antigen. *Semin. Cancer Biol.* 1999;9:83-93.
2. National Cancer Institute. Prostate-Specific Antigen (PSA) Test. Reviewed July 24, 2012. <http://www.cancer.gov/cancertopics/factsheet/detection/PSA> (Accessed on December 1, 2012).
3. Hoffman RM, Gilliland FD, Adams-Cameron M, Hunt WC, Key CR. Prostate-specific antigen testing accuracy in community practice. *BMC Fam. Pract.* 2002;3:19.
4. Center MM, Jemal A, Lortet-Tieulent J, Ward E, Ferlay J, Brawley O, et al. International variation in prostate cancer incidence and mortality rates. *Eur. Urol.* 2012;61(6):1079-92.
5. Canadian Cancer Society. What you should know about PSA testing. March 4, 2010. http://www.cancer.ca/Canada-wide/Prevention/Getting%20checked/What%20you%20should%20know%20about%20PSA%20testing.aspx?sc_lang=en (Accessed on November 27, 2012).
6. Ministry of Health and Long-Term Care. Ontario Prostate Specific Antigen (PSA) Clinical Guidelines – Summary. June 27, 2012. http://www.health.gov.on.ca/english/providers/pub/cancer/psa/psa_summary/summary.html. (Accessed on November 27, 2012).
7. U.S. Preventive Services Task Force. Screening for prostate cancer. July 2012. <http://www.uspreventiveservicestaskforce.org/prostatecancerscreening.htm>. (Accessed on November 27, 2012).
8. Andriole GL, Crawford ED, Grubb RL 3rd, Buys SS, Chia D, Church TR, et al. Mortality results from a randomized prostate-cancer screening trial. *N Engl J Med.* 2009;360(13):1310-9.
9. Schröder FH, Hugosson J, Roobol MJ, Tammela TL, Ciatto S, Nelen V, et al. Screening and prostate-cancer mortality in a randomized European study. *N Engl J Med.* 2009;360(13):1320-8.
10. Lin K, Croswell JM, Koenig H, Lam C, Maltz A. Prostate-Specific Antigen-Based Screening for Prostate Cancer: An Evidence Update for the U.S. Preventive Services Task Force. Evidence Synthesis No. 90. AHRQ Publication No. 12-05160-EF-1. Rockville, MD: Agency for Healthcare Research and Quality; October 2011.
11. McNaughton-Collins MF, Barry MJ. One man at a time – resolving the PSA controversy. *N Engl J Med.* 2011;365(21):1951-1953.
12. Loeb S, Metter EJ, Kan D, Roehl KA, Catalona WJ. Prostate-specific antigen velocity (PSAV) risk count improves the specificity of screening for clinically significant prostate cancer. *BJU Int.* 2012;109:508-14.