# *PSA and the family physician*

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*The need for men to undergo screening for prostate cancer is controversial. Urologists are concerned about finding many men with minimal disease who may not require therapy or may be over-treated, while conversely missing men with clinically significant prostate cancer that could be treated and cured if found at an early enough stage. Most men today present to the physician with some symptoms attributable to the prostate, and then have a prostate-specific antigen (PSA) test to screen for prostate cancer. PSA is still the most effective test to suggest that there may be underlying prostate cancer. In addition to measuring total PSA, other measures such as PSA density, age-related PSA, or PSA velocity can provide further justification that a patient should undergo a prostate biopsy to detect possible cancer. The American Urological Association has developed new guidelines for screening for prostate cancer in men who are not at risk. The key is to use one of the PSA tools to help diagnose prostate cancer at an early stage and then offer aggressive curative therapy, if appropriate, while still providing the best quality of life and least chance of failure, in the right patient at the right time.*

**Key Words:** prostate cancer, biopsy, prostate-specific antigen, guideline

## Background

Prostate-specific antigen (PSA) is specific for the prostate, but it is not specific for prostate cancer. Prostate cancer is still the number one diagnosed cancer in men in North America and it is the second-most common cancer that causes death in men in North America. Physicians are diagnosing prostate cancer at an earlier stage, and patients with this cancer are surviving longer, and mortality from prostate cancer has decreased. These improved outcomes are believed to be due to increased awareness of risk factors for prostate cancer (such as family history) and increased use of PSA screening to detect potential prostate cancer.

According to Dorland's dictionary, "screening" is "examination or testing of a group of individuals to separate those who are well from those who have an undiagnosed disease or defect or who are at high risk."

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## Discussion

### Screening conundrum

Physicians are trained to look for disease in patients who come to them because the patients have concerns about their future health or have physical symptoms. Should physicians be screening for prostate cancer in patients who do not come with concerns or symptoms related to potential prostate cancer?

Dr. Willett Whitmore, an icon in twentieth century urology, described the conundrum about screening for prostate cancer as follows: When the prostate cancer is curable, is screening necessary? When screening is necessary, is the prostate cancer curable? This, unfortunately, is where we stand today. Prostate cancer is a major cause of cancer mortality in North America, but the potential for overdiagnosis and overtreatment is substantial. If the need for prostate cancer screening remains controversial among urologists, what approach for prostate cancer screening should urologists recommend to primary care practitioners?

Many patients and physicians ask: "What is the prostate and why do we need it?"

The prostate is an internal gland in males, which is about the size and shape of a chestnut or walnut and which produces 30% of seminal fluid. The prostate is firm and both glandular and fibromuscular, and normally, it weighs about 20 g. It surrounds the urethra at the base of the bladder, anterior to the rectum. The urethra passes through the prostate like a straw through an orange. The prostatic urethra and bladder neck act as an "internal sphincter," to ensure continence. In a radical prostatectomy to treat prostate cancer, the entire prostate including the capsule and the seminal vesicles are removed. Obstructive and symptomatic benign prostatic hyperplasia (BPH) may be treated by using some type of energy to enucleate the "meat" of the prostate, but leave the capsule intact.

Prostate cancer and BPH are two significant diseases of the prostate. Prostate cancer is very common, if physicians look for it. Numerous autopsy studies have confirmed that there is a significant, age-related risk of detecting microscopic evidence of prostate cancer: 37% of men who are age 40 have microscopic evidence of prostate cancer.[1] What are the chances that this microscopic cancer will become clinically significant? This is the question that needs to be answered.

A number of recent studies of nomograms to predict prostate cancer[2] have provided an indication of the usefulness of PSA screening tests to help detect cancer, the advisability of treating the cancer, and the ability to treat the cancer completely -- depending on the Gleason grade.

### Total PSA and other tests

PSA, a glycoprotein produced in the prostate ducts, acts to liquefy the ejaculate. The concentration of PSA is one million times higher in semen than in the blood, since only a very small amount of PSA leaks into the bloodstream. The concentration of PSA in serum decreases with ejaculation and with hormonal treatment (finasteride, dutasteride) and it increases with significant BPH, urinary tract/prostatic infection, prostate biopsy, or prostatic instrumentation/surgery.

PSA has been a mainstay in the diagnosis of prostate cancer for the past 20 years. We now know that more sensitive, "sophisticated" PSA tests are required to identify all prostate cancers. In a review of results from the Prostate Cancer Prevention Trial, Thompson demonstrated that using a static threshold PSA value was not sufficient to detect all cancers, because even men with very low serum PSA levels could have high grade prostate cancer.[3]

This finding encouraged the development of more sensitive and specific PSA-based tests that physicians could use in cases where they needed more justification to recommend a prostate biopsy.

It is now known that increased PSA is a function of age. The previous belief that only a PSA above 4 ng/mL was abnormal is incorrect. In 1997, Richardson published age-specific reference ranges for PSA.[4]

Even this approach is not all encompassing. Urologists now recommend that a biopsy is required if a total PSA is above 4.0 ng/mL or PSA density is above 1.5 ng/mL for a 30 cc prostate or PSA velocity is increasing by 0.75 ng/mL or greater than a 20% increase in 1 year or age-related PSA is greater than 3.5 ng/mL for a man in his 50s or if the ratio of free-to-total PSA is less than 0.20.

If total PSA or PSA density or age-related PSA or PSA velocity do not provide sufficient evidence that a patient should undergo a prostate biopsy to look for possible cancer, then the newest test that can be performed is the expensive, but very sensitive prostate cancer gene 3 (PCA3) molecular urine assay. The PCA3 score is defined as the ratio of PCA3 mRNA to PSA mRNA times 103. This test is particularly useful to help decide when to repeat a prostate biopsy in men who have already had a biopsy that was negative for cancer. Nakanishi and colleagues[5] reported that prostate biopsies on men who had a PCA3 of less than 25 showed that only 13% of the cancers detected in these men would be clinically insignificant, low grade (Gleason 6 or less), low volume (< .5 cc) prostate cancers. When performing prostate biopsies on men who had a PCA3 of less than 20, more than 95% of the cancers detected would be Gleason score 7 or greater.

Since the standard (total) PSA test and the digital rectal examination (DRE) are the most widely available tests, they were the basis for prostate cancer screening/detection in two very large prostate cancer screening studies -- the European Randomized Study of Screening for Prostate Cancer (ERSPC)[6] and the Prostate, Lung, Colorectal and Ovarian Cancer (PLCO) trial in America.[7]

The American study has been criticized because it was "contaminated" with too many patients who had already had at least one serum PSA test prior to enrolling in the study. This created a selection bias because men who had been found to have a high PSA were not included. Both studies, however, demonstrated that huge numbers of men had to be "screened" in order to prevent one death from prostate cancer.

### *Active surveillance*

Today, urologists are concerned about finding many men with minimal disease who may not require therapy, but have endured the potential risks of a prostate biopsy. For a number of years, many urologists have advocated "active surveillance" for patients with low risk prostate cancer. Most studies show that a man with a PSA of less than 10 ng/mL who has a biopsy that shows three or fewer positive cores (where not more than 50% of any one core has cancer) has only about a 35% chance of having his cancer progress to the point where intervention is either recommended by the physician or demanded by the patient.[8]

With active surveillance, a patient has a PSA test and a DRE every 3 months and has a repeat biopsy usually 1 year after the initial biopsy and then every 2 years.[8] Often, the physician uses a PSA value as a trigger for a "for cause" biopsy. Ideally, the biopsy will only identify high risk patients with Gleason score of 6, or Gleason scores of 7 or higher, which should be treated.

Men who are at high risk of having prostate cancer detected include those who are older, have a family history of prostate cancer, have high testosterone levels, are of African ancestry, have a high-fat diet or are obese or inactive, or have an abnormal DRE.

## New screening guidelines

There are now new guidelines for the "not at risk" male. The American Urological Association's Prostate-Specific Antigen Best-Practice statement (revised 2009) contains an algorithm that suggests that a baseline PSA determination should be done when a patient is 40 years old.[9] If the result is normal for the patient's age (eg < 0.7 ng/mL at age 40), then the test can be repeated every 5 years. If at age 50, the patient's PSA is still below 2.0 ng/mL, then repeating the PSA test every 2 years would prevent the physician from missing a clinically significant cancer.

Similarly, the American Cancer Society suggests annual screening starting at age 50.[10] All groups seem to agree that PSA is still a valid tool in helping to diagnose clinically significant prostate cancer early, when it is still curable. For a discussion of the management of localized prostate cancer, see the How I Do It article on HIFU published recently in *The Canadian Journal of Urology*.[11]

Hormonal deprivation (reducing the production or uptake of testosterone either centrally or peripherally) as a management strategy for non-operable or other stage of prostate cancer has been utilized since the 40s. There are numerous medications available for this approach.[12]

## Medical therapies for prostate cancer

There have been a few newly approved medical therapies for the management of prostate cancer. The luteinizing hormone-releasing hormone (LHRH) antagonist degarelix (Firmagon) was recently approved in Canada. This drug acts at the hypothalamic-pituitary axis, but in contrast to LHRH analogs, because it is a competitive inhibitor at androgen receptors, it causes an almost immediate and complete reduction of testosterone production in the body, with no "flare" (rise) in the production of testosterone for the first month, which can be seen with the LHRH analogs. "At risk" individuals treated with LHRH analogs are pretreated with 1 month of an antiandrogen such as bicalutamide (Casodex) to prevent uptake of the added "flared" testosterone that could stimulate the exploding of potential bony metastases in the spine. Firmagon may also prevent "micro flares" of testosterone rise at the end of the 3 month cycle, which may occur with other agents. Lastly, the drug is believed to prevent the rise of follicle-stimulating hormone (FSH), so it may protect a patient from developing hypogonadal-induced osteoporosis.

Triptorelin (Trelstar) is the newest LHRH analog, which promises better, more reliable suppression of testosterone over the whole course of the depot injection. It is given intramuscularly, with a smaller needle than that used for other preparations.

Denosumab is a new receptor activator of nuclear factor kappa B (RANK) ligand inhibitor, which may help prevent bone mineral loss and skeletal-related events that have been associated with long term hormonal manipulation in prostate cancer patients.

Some other prechemotherapeutic drugs are coming to market for the management of castrate-resistant prostate cancer. There is also an immunologic approach to the metastatic cancer. Sipuleucel-T, an autologous cellular immunotherapy that stimulates a patient's immune system to target and attack prostate cancer, has been shown to increase survival by 4.1 months, with an average cost of approximately $100,000.[13]

Many ongoing studies are aimed at increasing survival in men with prostate cancer who have escaped hormonal control (become castrate-resistant). These are usually men diagnosed with a locally advanced cancer or men who did not accept or could not tolerate a "primary cure" option or men who underwent a primary cure but had a recurrence of prostate cancer that could not be treated with salvage therapy.

## Conclusion

The key message for physicians is to utilize one or more of the PSA tools to help diagnose prostate cancer at an early stage when they can offer the patient aggressive "curative" therapy while still providing the best long term quality of life and the least chance of failure -- in the right patient at the right time. □

## Disclosure

Dr. Jack Barkin is an active urologist and Chief of Staff at the Humber River Regional Hospital in Toronto. He sits on the medical advisory board for Abbott, AstraZeneca, Bayer, Boehringer-Ingelheim, Eli Lilly, GlaxoSmithKline, Merck Frosst, Paladin, Pfizer, sanofi-aventis and Solvay. He has done the clinical research on Androgel, Avodart, Casodex, Cialis, Detrol, Flomax, Hytrin, Levitra, Xatral, Proscar and Viagra. He has spoken all over the world for all of the companies outlined.

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