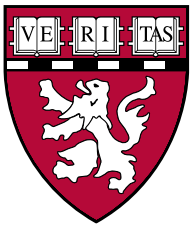

HARVARD MEDICAL SCHOOL

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Annual Report
on
Prostate Diseases

Covering advances in the diagnosis and treatment of prostate cancer, BPH, erectile dysfunction, prostatitis, and related issues

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A message from Editor in Chief Marc B. Garnick, M.D.

No easy answers to prostate questions

Few men think about their prostate, a walnut-sized gland that's part of the reproductive system, until they develop some type of problem. Then they can't stop thinking about it. That's because changes in this small gland can have a significant impact on a man's life. Men with an enlarged prostate, for example, may find daily activities and nighttime sleep interrupted by frequent trips to the bathroom.

Prostate disorders usually develop after age 50, but some men experience them at a younger age. The three most common conditions are prostatitis, benign prostatic hyperplasia (BPH), and prostate cancer. Even though they share some of the same symptoms, they are quite different. Treatments vary, too. Men with the same condition might opt for treatments as divergent as radical surgery and doing nothing at all.

Even getting screened for prostate cancer, which seems like it would be a no-brainer, requires thoughtful consideration. One large study recently showed that screening with the prostate-specific antigen (PSA) test and digital rectal exams offers no survival benefit. Yet most men usually feel compelled to undergo treatment if cancer is diagnosed, risking complications like impotence that can undermine quality of life.

Whether you are thinking about screening or treatment for prostate disease, review your options carefully. This report, which provides an objective assessment of the risks and benefits of various procedures, can help. More than a primer on prostate conditions, this unique publication includes roundtable discussions with experts at the forefront of prostate cancer research; assessments of different therapies from Harvard Medical School doctors; interviews with patients about their treatment decisions; and the latest thinking on complementary therapies. A companion Web site, www.harvardprostateknowledge.org, offers additional features and research updates throughout the year.

The goal of this publication is not to relate easy answers, because, as you've probably gathered, there really aren't any at the moment. Rather, our mission is to provide you with the information you need to understand the current controversies, avoid common pitfalls, and work with your doctor to make informed choices about your prostate health. After you've had a chance to read this unique report, please send us your thoughts. We'd love to hear from you.

Marc B. Garnick, M.D.
Editor in Chief, 2010 *Annual Report on Prostate Diseases*

Prostate cancer screening

Studies question benefit of PSA screening

Does PSA screening save lives by enabling doctors to treat aggressive prostate cancers early? Or does it harm men who would never die from the disease by subjecting them to the side effects of treatment? Two studies—one conducted in the United States and the other in Europe—were supposed to settle the debate.

The American study. The Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial began in 1993, enrolling 76,693 men ages 55 to 74 with no history of prostate, lung, or colorectal cancer. Investigators randomly assigned half of the men to be offered annual PSA testing for six years, along with an annual digital rectal examination (DRE) for four years. A PSA level above 4 ng/ml was reported as abnormal and usually led to a prostate biopsy. Men in the control group continued to receive their usual medical care, which may have involved some prostate cancer screening or none at all.

After seven years, the researchers found a relative increase of 22% in the rate of prostate cancer diagnosis among the men offered regular PSA screening compared with those who received their usual medical care. However, even though PSA screening increased the diagnosis of prostate cancer, it did not improve the prostate cancer survival rate, and the two groups showed no real differences in the numbers of deaths from other causes. For about two-thirds of the men, complete follow-up data were available for 10 years, and the results after 10 years were similar to the findings after seven years.

The European study. Investigators with the European Randomized Study of Screening for Prostate Cancer (ERSPC), which began in the early 1990s, enrolled 162,243 men ages 55 to 69 in seven countries. The investigators then randomly assigned about 73,000 of the men to be offered PSA screening once every four years, on average; those with a PSA level of 3 or 4 ng/ml or higher, depending on the country, were referred for a prostate biopsy. The rest of the men—the control group—had their usual medical care, which might include screening.

After about nine years of observation, 214 men in the PSA screening group and 326 men in the control group had died of prostate cancer. The relative risk of dying from prostate cancer was 20% lower in the screening group and 27% lower among those actually screened. What does that mean to the typical American man? In the United States, the lifetime risk of dying from prostate cancer is 3%. A 27% relative risk reduction would mean that, with screening, the risk of dying from prostate cancer would drop from 3% to 2.19%.

In Europe, that modest benefit came at a steep price. The researchers calculated that 48 men who are not at risk of dying from prostate cancer would have to be treated in order for screening to prevent one death from the disease over nine years. In other words, 48 men would risk the side effects of treatment to save one life.

One conclusion that can be drawn from the studies: men should think carefully about PSA screening and discuss the risks and potential benefits with their doctors before having the test. For more detailed discussions of PSA screening, see pages 19, 53, and 59.

Sources: Andriole GL, Crawford ED, Grubb RL III, et al. Mortality Results from a Randomized Prostate-Cancer Screening Trial. *New England Journal of Medicine* 2009;360:1310–19. PMID: 19297565.

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Monitoring prostate health

A look at the prostate and some tests you might need

How can a gland that weighs only about an ounce cause so much trouble? To answer this question, one must look at its position in the body. The prostate is located in front of the rectum and just below the bladder. It wraps around the upper part of the urethra, the tube that carries urine from the bladder out of the body (see Figure 1). Its position near urinary and sexual organs means that certain prostate problems (and treatment of those problems) can affect urination and sexual function.

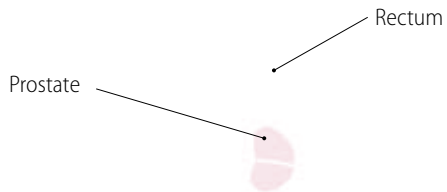
The prostate consists mostly of connective and glandular tissues, and it produces a thick, milky-white fluid that forms part of the semen, the liquid ejaculated during sexual activity. To function properly, the prostate requires adequate amounts of certain hormones. These include testosterone, produced by the testicles, as well as others from the pituitary and adrenal glands.

Doctors can use several approaches to evaluate the prostate. The most common are as follows.

Digital rectal exam

During a digital rectal exam (DRE), the doctor inserts a lubricated, gloved finger into the rectum (see Figure 2). Because the prostate sits in front of the rectum, the doctor can feel part of it through the rectal wall. A normal pros-

Figure 2. Digital rectal exam (DRE)



To perform a DRE, the doctor inserts a lubricated, gloved finger into the rectum and presses against the rectal wall to determine the size of the prostate and feel for irregularities. Early-stage cancer may be felt as a small lump on the surface of the prostate.

tate is small—about an inch and a half from side to side—and feels smooth and rubbery. Swelling, lumps, firm knots, or abnormally textured areas may indicate prostate cancer or another condition.

There are two schools of thought about the best position for the DRE. Some physicians prefer that the patient stand and bend at the waist, with his arms extended on the examination table. Others opt to have the patient lie on one side with one or both knees drawn up toward the chest. There are no data showing one position superior to the other.

Some men find the DRE uncomfortable and embarrassing, so they postpone or avoid going to a physician altogether. But the exam can provide your doctor with important information about your health, and it shouldn't be painful. (If it is, say so!) The exam usually doesn't last very long, but it should be done slowly enough that the doctor can assess the size of the prostate, feel its lobes, and detect any bumps, hardness, or changes in consistency from one side to the other. Although every rectal exam should be thorough, some patients report that specialists seem to be more meticulous than their general practitioners in performing a DRE.

The DRE is a useful screening test, but it isn't foolproof. Its accuracy depends on the skill of the physician doing the test. Moreover, early cancerous tumors are often too small to detect during a DRE, and some are located in areas a doctor's finger can't reach. For these reasons, clinicians who use DRE alone to screen for prostate cancer sometimes miss the smallest and most treatable tumors. That's why many physicians also perform a PSA test. On the other hand, small tumors that can't be felt by the physician may be less likely to cause future problems.

Prostate-specific antigen (PSA) test

This blood test measures the level of a protein called prostate-specific antigen (PSA), which is made by cells in the prostate. Doctors use the test to detect prostate cancer, but it does not provide a definite diagnosis. That's because an above-normal PSA level—more than 4 nanograms per milliliter (ng/ml) of blood—doesn't always indicate the presence of cancer. Likewise, levels of 4 ng/ml or less don't always mean the prostate is cancer-free. For this reason, some experts adjust for a man's age or consider a normal level to be 2.5 ng/ml. That's also why doctors aren't likely to use the PSA test as a simple, one-time indicator but, instead, to observe how a man's PSA level changes over time and with age.

The PSA test can provide clues to other conditions besides cancer. Indeed, most men who have mildly elevated PSA levels don't have cancer. Elevated PSA levels can accompany the noncancerous conditions known as benign prostatic hyperplasia (see "Prostate enlargement," page 25) and prostatitis (see "Inflammation of the prostate," page 41). Complicating things further, an elevated PSA may simply mean that a man's prostate naturally

releases more of the protein into the blood. Moreover, some studies suggest that ejaculation can elevate PSA levels for up to 48 hours. In addition to using the PSA test to identify problems, doctors also use it for follow-up after prostate cancer treatment and to predict which patients with BPH are likely to develop troublesome symptoms.

Some things can cause the PSA level to remain low or drop, even when cancer is present. For example, obese men tend to have lower PSA levels than men at a healthy weight. Some medicines (including those used to treat baldness and urinary symptoms) and herbal remedies may also lower PSA, potentially masking cancer. That's why it's important to tell your doctor about all of the medications and supplements you take.

Since its introduction in the late 1980s, the PSA test has become increasingly popular because it can help detect prostate cancers that are too small to feel during a DRE. Indeed, the test has been credited with finding many more cancers in early stages than had been found in the past. (The American Cancer Society estimates that 192,280 men were diagnosed with prostate cancer in 2009, making it the most commonly diagnosed cancer in men other than skin cancer.) The early diagnosis of aggressive prostate tumors means that they can be treated before they become life-threatening. In fact, not long after the PSA test became a routine part of a medical exam in most men over age 50, the death rate from the disease in the United States began to drop. Some experts point to widespread PSA testing as the reason. Others, however, attribute the decline to different factors, such as better-targeted treatments and changes in the American diet.

The downside to testing is that an elevated PSA cannot differentiate aggressive tumors from slow-growing, harmless ones that might never cause symptoms during a man's life. Nor can it differentiate cancer from BPH or prostatitis. As a result, it can cause needless worry—and may lead to costly and invasive procedures, such as biopsies, to determine if cancer is present. Conversely, PSA screening doesn't detect all cancers, so a normal PSA level may offer a false sense of security. Many men with cancer confined to the prostate have normal PSA values. Even advocates of PSA testing doubt its value in men with less than a 10-year life expectancy (ages 75 or older, for men in average health) because these men are more likely to die of something else first.

Two eagerly awaited studies—one conducted in the United States and the other in Europe, the results of which were published in *The New England Journal of Medicine* in March 2009—were supposed to settle the debate over the value of the PSA test (see "Studies question benefit of PSA screening," page 7). But they came to differing conclusions about whether screening saves lives. Both agreed, however, that subsequent treatment of detected prostate cancers often comes at a high cost—erectile dysfunction and uri-

nary incontinence. (For an in-depth discussion about the controversy surrounding screening, see "PSA screening: What makes sense?" on page 53.)

Rather than subject everyone with an elevated PSA level to a biopsy, especially patients with a level between 4 and 10 mg/ml, some doctors will do additional PSA tests. (Only about 25% of men with a PSA in this range have prostate cancer.) These tests include the following:

PSA velocity. Increasingly, doctors use a measure called PSA velocity or series. This is the rate at which a man's PSA level increases over time. PSA scores tend to rise more rapidly in men with cancer than in those with BPH. A 2004 study in *The New England Journal of Medicine* showed that men with prostate cancer who have rapid increases in PSA were more likely to die from the cancer than those with slower-rising levels (see "PSA velocity," at right).

Free PSA. Doctors sometimes look for the level of "free" PSA. PSA circulates in the blood in two forms, either bound to other proteins or unbound (free). Several studies suggest that men with elevated PSA levels who have a very low percentage of free PSA are more likely to have prostate cancer than a benign prostate condition. The free PSA level doesn't give a definitive answer, but it may be useful when considering whether a biopsy is the appropriate next step. Many doctors recommend biopsies in men with a free PSA level of 10% or less, and advise men to consider a biopsy if the free PSA level is between 10% and 25%.

PSA density. This number is calculated by dividing the PSA level by the size of the prostate in grams, as measured by ultrasound. (Prostate size can't accurately be determined by DRE because only one side of the gland can be felt.) The higher the PSA density, the greater the likelihood of cancer. In general, doctors consider a PSA density under 0.07 indicative of a benign condition; a PSA density greater than 0.15 is suspicious for cancer. If your PSA density falls between those two numbers, its meaning is uncertain.

PSA velocity

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