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The Man, the Gland, the Dilemmas

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You've been getting annual blood tests to check for prostate cancer. But two big studies in the New England Journal of Medicine just found that screening for PSA -- prostate specific antigen -- doesn't save many lives. Should you keep checking it?

Your biopsy was negative for prostate cancer but your PSA keeps rising. Should you stop worrying -- or have another biopsy?

You've been diagnosed with early-stage prostate cancer. It's probably harmless, but it could turn lethal. Should you just watch it or treat it aggressively and run the risk of impotence or incontinence?

Prostate cancer poses some of the most vexing questions in medicine, and one out of every six men in the U.S. will confront them at some point in their lives. Today's Health Journal is the first of a two-part series that aims to provide some guidance. This article looks at new diagnostic techniques that may help to resolve some of these quandaries. Next week we'll examine the perplexing array of treatment options and weigh the pros and cons of each.

Should You Be Screened?

For all the uproar they created, the recent NEJM studies settled little in the long-running debate over whether prostate-cancer screening is worthwhile.

PSA testing revolutionized detection of the disease in the late 1980s. Before that, doctors relied on a digital-rectal exam, or DRE, and by the time tumors could be felt, some were fairly large. Now, about 90% of prostate cancers are found at an early and highly curable stage.

But PSA screening can flag tumors almost too early, leading to considerable unnecessary surgery or radiation. Most prostate cancers are so small and slow-growing that they don't need treatment. Of the 185,000 U.S. men diagnosed with the disease each year, an estimated 85% would likely die of something else long before their cancer caused problems.

On the other hand, some prostate cancers are aggressive, each year killing some 28,000 men in the U.S. -- and 288,000 worldwide -- who weren't treated in time. It's the second most deadly cancer in men, after lung cancer.

As of now, it's difficult to tell which patients have which kind of tumors in the early stages.

Experts say many more men could safely opt for "watchful waiting" -- monitoring their cancers to see if they grow. But thousands of men each year opt to have their prostates removed surgically or treated with radiation to be on the safe side, and many live with urinary or erectile problems in the bargain.

"Right now we are treating people for anxiety, not cancer," says Faina Shtern, CEO of the AdMeTech Foundation, a nonprofit group that is lobbying Congress to increase federal funding for research into prostate imaging. "We do not know if they will benefit from treatment, but we know they will have complications," Dr. Shtern says.

Weighing all those factors, a U.S. government panel last year recommended that doctors stop screening men age 75 and over for prostate cancer, since the risk of treating it likely outweighed the benefits.

The recent NEJM studies seemed to extend that reasoning to younger men as well. One study of 77,000 North American men showed that regular PSA screening didn't save a significant number of lives over 10 years. A study of 182,000 European men showed a 20% reduction in deaths among those screened regularly. But in that study, 48 men had to be treated for every life saved.

Still, many cancer organizations issued statements defending PSA testing -- in the absence of something better -- and urging men to discuss it with their doctors.

Most doctors believe that men with a family history of prostate cancer should have annual PSA testing, along with African-American men, for whom the death rate from prostate cancer is twice as high as for whites. For others, "you probably don't have to get it tested every year," says Al Barqawi, a urologist at the University of Colorado Health Sciences Center. "If there's a change, then do it more often."

"Blind" Biopsies

A PSA level is cause for concern if it's higher than usual for the man's age or rising rapidly. If so, the next step is usually a biopsy. That's typically done in a urologist's office with an ultrasound probe and a spring-loaded needle gun inserted into the rectum, taking six to 12 samples at random.

The ultrasound can't see well into the prostate, so urologists are effectively sampling blindly. More than 1.2 million American men have such transrectal ultrasound, or TRUS, biopsies each year due to a suspicious PSA level. Less than 15% come back positive for cancer. But TRUS biopsies miss about 20% of cancers, so a negative biopsy isn't completely reassuring.

That's the situation Richard Edelman, president and chief executive of the Edelman public-relations firm, faced in 2007. His PSA had doubled over two years to four nanograms/milliliter, considered elevated for his age of 54. He also had three close relatives with prostate cancer. A standard TRUS biopsy was negative, but a few months later, his PSA had jumped to 7.5 ng/ml.

His doctor suspected a urinary-tract infection, one of several benign conditions that can increase the PSA level, and prescribed an antibiotic. But Mr. Edelman's PSA remained elevated, as did his anxiety.

To get more information, Mr. Edelman enrolled in a clinical trial at the National Cancer Institute, where doctors are hoping to improve tumor detection by scanning prostates with magnetic-resonance imaging. The MRI scans are then used to target biopsies at suspicious-looking areas. Mr. Edelman had a second biopsy, guided by MRI, which found cancer in two of 21 samples. "The value of the MRI was huge," he says.

Imaging of the prostate has lagged far behind imaging for breast cancer in women -- largely because the prostate is deep inside the pelvis and harder to access. "It's medieval and barbaric what we do to men without better imaging," says AdMeTech's Dr. Shtern, who helped advance the use of MRIs for breast cancer at the NCI in the 1990s. She notes that NCI today spends twice as much on research into breast cancer than prostate cancer research, even though prostate cancer is twice as prevalent. Mr. Edelman's firm is helping her group's efforts; as are some equipment manufacturers.

Researchers at NCI and several major medical centers are currently using several kinds of advanced MRIs to scan the prostate for abnormalities that could signal cancer. MRIs with contrast agents can highlight areas of new blood-vessel growth. Other techniques include MR spectroscopy, which looks for telltale chemical changes, and diffusion-weighted MRIs, which measure changes in water flow around cells. Clinical trials are underway to assess whether biopsies guided by such images are better than standard TRUS biopsies at finding cancers.

"None of these tests will absolutely differentiate benign from malignant. They're pointers to areas that should be further biopsied or followed," says Peter Choyke, the NCI's chief of molecular imaging.

MRIs often identify abnormalities that aren't cancerous. They also add $1,000 or more to the cost of a biopsy, which itself runs about $2,000. But Dr. Shtern argues that scanning before performing a biopsy could save money in the long run if it helps to reduce the $2 billion spent annually on standard biopsies that don't find cancer.

"It sounds good, but the burden of proof is on us to show that this makes a difference in detecting cancers," says Peter Pinto, director of the fellowship program at NCI's urologic oncology branch.

Has it Spread?

Once a biopsy confirms cancer, many major medical centers now use MRIs to help determine whether it has spread beyond the prostate and invaded the nearby nerves and blood vessels involved in sexual function and urination. That information can be crucial if a patient is considering surgery, radiation or watchful waiting.

More often, doctors are playing probabilities to determine whether early-stage cancers have spread beyond the prostate. Some use mathematical formulas based on a combination of PSA

levels, a DRE and what's known as a Gleason score, a measure of a cancer's aggressiveness based on the pattern of abnormal cells seen on the biopsy.

And doctors often disagree about what that information signifies. In Mr. Edelman's case, one counseled watchful waiting since his Gleason score was a moderate six. Another doctor suspected Mr. Edelman's cancer had already spread, based on his PSA, and urged radiation and hormone therapy. At Memorial Sloan-Kettering Cancer Center in New York, Mr. Edelman had a second MRI that revealed that his cancer was still confined to the prostate, but was on both sides of the gland and had grown since the first MRI scan.

He opted for a radical prostatectomy last fall -- and he thinks he caught the cancer just in time. "I'm told I have more than a 95% chance of being around for a long time," he says. His last PSA was down to zero.

Doctors who use MRIs caution they aren't always definitive and can't see very small cancers, but even that can be useful. "If I don't see anything on an MRI, it helps reassure me you probably don't have a large, life-threatening cancer." says Peter Scardino, chief of urology at Memorial Sloan-Kettering.

"We are all like the blind men feeling the elephant," Dr. Scardino adds. "I don't rely just on the DRE, the PSA, the biopsy results or the MRI. But if we put all that information together, we can get a pretty good idea of what's going on."

Playing 'Battleship'

Rather than rely on imaging, a small but growing group of urologists prefer to bombard the prostate with more extensive biopsies. A "3D-mapping biopsy" takes 50 or more samples, five millimeters apart, throughout the gland. The needles are inserted through a grid that allows doctors to pinpoint the size, shape and location of any cancers. Practitioners liken it to playing the game Battleship with the prostate. Unlike a standard biopsy done through the rectum, a mapping biopsy is performed through the skin behind the scrotum with the patient under anesthesia.

The cost of a 3D-mapping biopsy is $5,000 to $6,000, due to the extensive pathology needed. They're far too costly and cumbersome for routine screening. But the technique can provide valuable information for making treatment decisions, and is increasingly covered by insurance and Medicare.

In the last three years, Dr. Barqawi at the University of Colorado has performed two hundred 3D-mapping biopsies on patients after they had had TRUS biopsies. Of them, 96 learned that their cancers were more extensive than the first biopsy showed. But 33 patients were reassured that their cancers were small and could just be watched.

Dr. Barqawi says 60 of the patients getting mapping biopsies learned that their tumors were so localized that they opted for new treatments known as targeted focal therapies. With these, doctors are able to destroy just the tumor with cryosurgery or specialized ultrasound and leave the rest of the prostate alone.

"Knowledge is power and that's especially true when managing patients diagnosed with early-stage disease to avoid un-needed surgeries," Dr. Barqawi says.

Molecular Markers

Scientists are also making headway in finding new molecular markers that may be able to signify not just the presence of cancer, but what its lethal potential is.

Researchers at the University of Michigan have identified a molecular waste product of tumors, called sarcosine, that is elevated in the urine of men with advanced prostate cancers. Researchers at Memorial Sloan-Kettering and elsewhere are studying circulating tumor cells -- bits of cancer cells that break off and enter the blood stream -- that may be able to indicate whether cancer has the potential to metastasize.

Some patients have more than one kind of prostate cancer, and scientists are developing PET scans and radioactive dyes that may one day be able to make different kinds of tumors light up like colored Christmas lights -- yellow for benign, red for really lethal.

"We've got potentially game-changing biomarkers that could get us out of the dilemma we are in with PSA," says oncologist Jonathan Simons, president of the Prostate Cancer Foundation, which funds some of that research. With the recent NEJM studies, he says, "We've been reminded again of how much work we need to do."

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