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Prostate Cancer: Should We Be Screening?

Do you want to know? A simple blood test and digital rectal exam can help determine if a patient may have prostate cancer. Screening may well prevent death and morbidity from prostate cancer, but it will also detect many cancers that are not likely to threaten patients at all. That is the conundrum in which many men and their physicians find themselves with prostate cancer screening.

Prostate-specific antigen (PSA) is a protein that is produced by the prostate. Small amounts of this protein can leak into the blood and be detected by a simple blood test.

In the decades before the Food and Drug Administration (FDA) approved PSA testing, prostate cancer was the most common source of cancer death in men, and even more men suffered from the complications of metastatic prostate cancer.

Given this, the development of the PSA screening test was revolutionary, and the 1990s saw countless men diagnosed with and treated for prostate cancer. PSA screening caused many men to be diagnosed with prostate cancer at an earlier stage than ever before, which led to improved survival.

But, doctors soon began to notice that although cure rates were improved, some men suffered serious long-term difficulties with urinary control and sexual function. Many doctors

began to question the value of diagnosing and treating a cancer that was causing no symptoms.

This led to the development of two large cancer-screening trials—the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial and the European Randomized Study of Screening for Prostate Cancer (ERSPC)—the early results of which are available (see “Why the Controversy?” on page 2). Despite randomizing more than 250,000 men and spending millions of research dollars, significant questions remain. It continues to be unclear whether the PSA blood test saves lives or whether it exposes men to unnecessary physical and emotional anguish.

Currently, multiple medical associations and government task forces have issued recommendations regarding prostate cancer screening. These range from suggesting absolutely no screening to offering annual screening starting at age 40.

In this special edition of Clinical Update, we explain some of the debate and controversy surrounding prostate cancer screening and provide recommendations for patients and physicians who are perplexed by the controversy.

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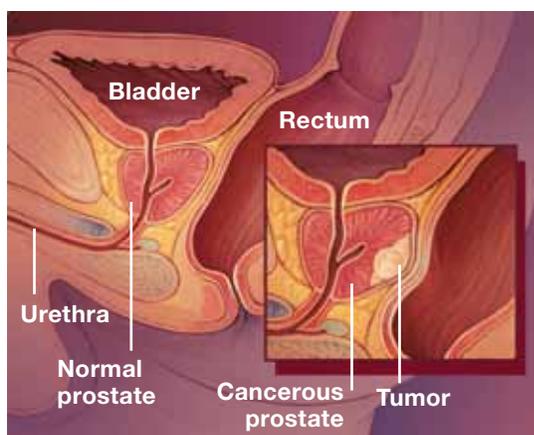


Figure. Prostate cancer occurs in the prostate gland, which is located just below a male's bladder and surrounds the top portion of the urethra, the tube that drains urine from the bladder. This illustration shows a normal prostate gland and a prostate with a tumor.

Why the Controversy?

Two Large Studies, No Clear Conclusions

In 2009, early results from two major studies regarding prostate cancer screening were released in the *New England Journal of Medicine*. In these studies, a total of more than 250,000 men were randomized to screening and followed for prostate cancer death.

These studies have formed the basis for most prostate cancer screening recommendations, yet they are commonly misunderstood. To better assess the implications of these studies, it's important to review study design, strengths and weaknesses in order to place them in context within the larger debate on prostate cancer screening.

Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial

PLCO, a study based in the United States, randomized 76,693 men ages 55 to 74 to either annual screening with PSA and digital rectal examination or "usual care." In this study, approximately 17% more cancers were detected in the screening arm than in the control arm, but there was no difference in cancer-specific death.

Although technically "randomized," a criticism of the study is that it doesn't appear to have been particularly well-controlled. Nearly two-thirds of men randomized in the study underwent PSA screening prior to entry into the study, a factor that undoubtedly eliminated high-risk cancers before the study even began. This limitation has led many to suggest that the

trial was destined to fail from the start.

Further, only 85% of men in the screening group were compliant with screening, while 52% of men randomized to the control arm underwent screening as a part of "usual care." And finally, only 31% of men with an abnormal digital rectal examination and a PSA of more than 4 ng/mL underwent prostate biopsy. These data call into question the reliability of the study's findings—the screening and control groups essentially blended together, reducing the study's ability to detect a difference between the two groups.

European Randomized Study of Screening for Prostate Cancer (ERSPC)

The ERSPC trial was a randomized screening study based in Europe. In this study, 182,000 men were randomized to be either controls (no screening) or receive screening with digital rectal exam and PSA every four years. In this study, 39% more cancers were detected in men in the screening group than the control group. Further, there was a 20-31% reduction in prostate cancer death in the screening arm compared with the control arm.

ERSPC suffers from fewer of the limitations of PLCO. Specifically, very few men were screened prior to entry into the study and "contamination" of the control group was significantly lower at 15%. Compliance with biopsy recommendation was also much higher at 85%. However, ERSPC has been criticized for lack of informed consent in many of the countries, and many more screened men opted for active surveillance in ERSPC than in PLCO (18% vs. 11%).

Finally, although there was a significant benefit to screening, in order to save one life after eight years, nearly 1,400 men needed to be screened and 48 men treated. It should be noted, though, that with longer follow-up and further prostate cancer-related deaths, the number of men needed to be screened and treated to prevent one death will very likely decrease.

Practical considerations

While ERSPC and PLCO both had similar endpoints and objectives, the manner in which the studies were performed and their interpretation were widely divergent. Nonetheless, there are important, complementary data that emerged from both trials.

Table. Comparing PLCO with ERSPC

	PLCO	ERSPC
Origin	United States	Europe
Patients	76,693	182,000
Age range	55-74 years	55-69 years
Randomization	Annual PSA and DRE vs. "usual care"	PSA and DRE every 4 years vs. no screening
% screened before entering study	Nearly 70%	Unknown, but likely very small
Contamination (controls screened)	52%	15%
Median follow-up	7 years	9 years
Increased chance of diagnosing prostate cancer with screening	17%	39%
Outcome	No significant difference in prostate cancer death	20% reduction in prostate cancer death (increasing with time)

First, prostate cancer investigators now have a much better understanding of PSA dynamics on a population scale. This includes the complicated issues surrounding “contamination” and the difficulties in performing large studies where researchers are trying to obtain something as simple as a serum PSA. Also, both studies have demonstrated that men with a very low PSA (0-1.0 ng/mL) are at low risk for developing a clinically significant prostate cancer within the next several years.

The diversity of methodology and data from these trials allows for significant flexibility in their interpretation, which makes it difficult to use them to substantiate across-the-board recommendations. Rather, the decision of whether to screen or not screen—using PSA testing and/or other means—is a decision best made between physicians and their individual patients.

Active Surveillance

Does the Tumor Need Treatment?

A growing number of men are being diagnosed with low-risk prostate cancer. For these men, the best initial treatment may be no treatment at all. Active surveillance is a treatment approach that recognizes the tumor as a long-term and likely slow-growing disease.

“An active surveillance approach may help select patients avoid potential complications from aggressive treatments that might negatively affect their current quality of life,” explains Michael J. Wehle, MD, a urologic surgeon at Mayo Clinic’s campus in Florida. “At the same time, it keeps the door open for treatment at a later date if necessary. Each patient needs to be evaluated carefully to see if he’s a candidate for the active surveillance approach.”

Active surveillance does not mean simply forgetting about prostate cancer. Rather, it involves closely following the tumor with regularly scheduled PSA tests and prostate biopsies. Given that the majority of men with low-risk prostate cancer will not have their cancer spread outside the prostate for many years, this approach enables doctors to follow the cancer to see if it shows any fast-growing characteristics.

If the tumor should start to grow faster than expected, curative treatment—usually radiation or surgery—should be offered. On the other hand, if the tumor appears to be indolent, any potential side effects associated with treatment can be avoided. Using this approach, many men have successfully avoided cancer progression and

“In making this decision, both physicians and their patients should be informed of the benefits and risks of screening or not screening. Other clinical factors, such as age, comorbidities, 10-year life expectancy and patient preferences, should also be taken into account. By being fully informed, patients and physicians are better armed to combat prostate cancer,” says Erik P. Castle, MD, a urologic surgeon at Mayo Clinic’s campus in Arizona.

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treatment side effects for more than a decade.

Best candidates

Active surveillance is not for everyone, but it’s an option that should be discussed with and considered for all patients with low-risk disease. Decision-making criteria include both PSA levels and biopsy results. The best candidates are patients with

- Low PSA levels
- Nonaggressive prostate cancer (as determined by biopsy)
- Small amounts of cancer (as determined by biopsy)

At Mayo Clinic, patients who choose active surveillance are being followed long-term in a prospective database to see which tumors needed treatment and how successful that treatment has been. In addition, blood, urine and tissue samples are collected from these patients, which will be used to study new biomarkers that may help identify the tumors that are truly indolent.

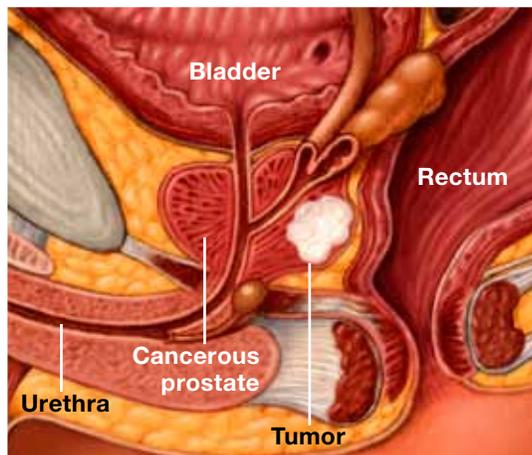


Figure. This illustration shows a prostate gland with a tumor.

The Radical Prostatectomy Registry at Mayo Clinic

Translating Today's Surgery into Tomorrow's Discoveries

Since 1985, Mayo Clinic has been collecting and storing clinical, pathological and follow-up data on men who have undergone radical prostatectomies at its campus in Rochester, Minn.

Because Mayo Clinic is such a high-volume urologic surgery center—on average over the past five years, urologic surgeons at its three campuses have performed an annual total of more than 1,600 prostatectomies—it's possible to estimate morbidity and mortality associated with prostatectomy, monitor long-term outcomes, and investigate the best predictors of outcome.

Today, Mayo Clinic's radical prostatectomy registry includes more than 20,000 patients, making it one of the largest registries of its kind in the world. More than 18,000 of these patients were seen from 1987 and onward—the period during which PSA screening has been standard practice at Mayo. The other several thousand patients were seen at Mayo between 1966 and 1986; their data were retrospectively added to the registry when it was established. Abstractors prospectively maintain the registry by following up annually with patients after surgery (Table, on page 5).

In addition to these data, tissue samples are also collected at the time of surgery, enabling researchers to study potential biomarkers and associate them with clinical outcomes. Contributing to this research are not only Mayo urologic surgeons, but also Mayo investigators with expertise in molecular biology, bioinformatics, pathology and epidemiology. A diverse team of biostatisticians, postdoctoral fellows and many others also support this research and its translation into clinical applications.

Insights from the registry

- **Since the introduction of PSA screening, Mayo has seen fewer cases of lymph node-positive prostate cancer.** Prostate cancer screening practices, which include the use of the PSA test when appropriate, enable detection of early-stage, treatable prostate cancer. Without judicious use of the PSA test, it's possible that clinically localized prostate cancer would not have been detected until it had metastasized; such cases are rarely considered curable (Figure, on page 6).

Discovery of PSA

The discovery and characterization of prostate-specific antigen (PSA), a protein produced primarily by the prostate gland, came about during the course of research related to cancer, forensic science and infertility.

1970

Dr. Richard Ablin and colleagues find an uncharacterized antigen that appears to be specific to the prostate.

1971

Dr. Mitsuwo Hara and colleagues discover gamma-seminoprotein, another prostate-specific protein, in seminal plasma.

1973

Drs. Tien Shun Li and Carl Beling isolate antigens known as E1 and E2.

1978

Dr. George Sensabaugh identifies a protein called p30.

1979

A team including Drs. Tsann Ming Chu and Ming Wang is the first to purify a prostate tissue-specific antigen. It's later shown to be the same as gamma-seminoprotein and p30.

Evolution of PSA Screening

Although it took several years after its introduction for researchers to demonstrate its utility as a screening tool, the PSA test has been available for 25 years.

1938

Drs. Alexander Gutman and Ethel Gutman find that levels of prostatic acid phosphatase are elevated in people with metastatic prostate cancer.

1950s-1980s

Prostatic acid phosphatase testing is used for prostate cancer detection, staging and treatment-response monitoring. The test has low sensitivity, particularly for early-stage prostate cancer.

Table. Registry Variables and Data

Data collected and recorded at time of surgery	Data collected and recorded after surgery
• Demographics	• Use of adjuvant therapy (within 90 days of surgery)
• Preoperative PSA value	• Use of salvage therapy (beyond 90 days of surgery)
• Clinical stage	• Complications, including potency and continence, at 30 days and 1 year after surgery
• Biopsy grade	• Potency and continence at 30 days and 1 year after surgery
• Pathological stage and grade	• Presence of elevated PSA value (biochemical recurrence) after surgery
• Presurgery therapy	• Occurrence of local or systemic clinical progression
• Margin positivity	• Mortality/cause of death
• Dimensions/volume of largest tumor	
• Capsular perforation	
• Seminal vesicle involvement	
• Number of nodes involved	
• DNA ploidy	

• **After radical prostatectomy, prostate cancer recurs in only a small percentage of men.** The vast majority of men tracked in the registry remain cancer-free. An analysis of 12,000 cases of radical prostatectomy from 1987 through 2004 shows systemic recurrence

rates of 5.6% after 10 years and 8.2% after 15 years, with prostate cancer death rates of 2.9% after 10 years and 5.3% after 15 years. These outcomes are markedly better than the cure rates seen before PSA screening, supporting the sensible use of the PSA test.

Continued on page 6

1980

Dr. Lawrence Papsidero and colleagues discover that PSA can be detected in the serum of men with prostate cancer, leading to the first PSA screening test.

1987

Dr. Thomas Stamey and colleagues publish findings showing that serum PSA level is a marker for prostate cancer.

Information in this timeline was gathered from various sources, including articles published in the British Journal of Urology International and Reviews in Urology.

1986

Serum PSA testing is introduced and FDA approves it for monitoring prostate cancer recurrence after treatment, leading to reduced reliance on the prostatic acid phosphatase test.

1991

Dr. William Catalona and colleagues show that PSA testing in addition to DRE is superior for prostate cancer detection than DRE alone.

1993

Prostate cancer deaths peak in U.S.

1994

FDA approves the PSA test as a method for prostate cancer screening.

2011

U.S. Preventive Services Task Force recommends that healthy men no longer undergo PSA testing.

The Radical Prostatectomy Registry at Mayo Clinic

Translating Today's Surgery into Tomorrow's Discoveries

Continued from page 5

- **Long-term side effects after surgery are rare.** Multiple studies have demonstrated that high-volume centers have improved outcomes after radical prostatectomy. Mayo data from 1987 through 2004 show that few patients have severe urinary incontinence after surgery; less than 0.2% have gone on to have additional surgery for problematic leakage within one year. Furthermore, when preservation of nerve bundles is possible, most men are capable of erectile function after surgery with or without assistance.

Looking ahead

Using patient tissue samples linked to data from the radical prostatectomy registry, Mayo clinicians and researchers are investigating new diagnostic and prognostic molecular markers for prostate cancer. Such research is likely to lead to

- **More reliable diagnostic tools.** The best screening and diagnostic tools available today—a combination of the PSA test, digital rectal examinations and core needle biopsies—miss some clinically significant cancers. “Further biomarker research will hopefully enable the development of a highly sensitive, highly specific, potentially noninvasive diagnostic test that can more reliably and effectively detect significant prostate cancer,” says R. Jeffrey Karnes, MD, a urologic surgeon at Mayo Clinic’s campus in Rochester.
- **A better ability to personalize therapy.** Separating cases of indolent cancer and aggressive cancer remains a clinical challenge. At Mayo Clinic, research based on data from the radical prostatectomy registry has already led to the identification of several promising biomarkers that are likely to prove useful in identifying patients with life-threatening prostate cancer. More aggressive treatment may be indicated for patients with high-risk cancers, while active surveillance may be sufficient for those with insignificant cancers.

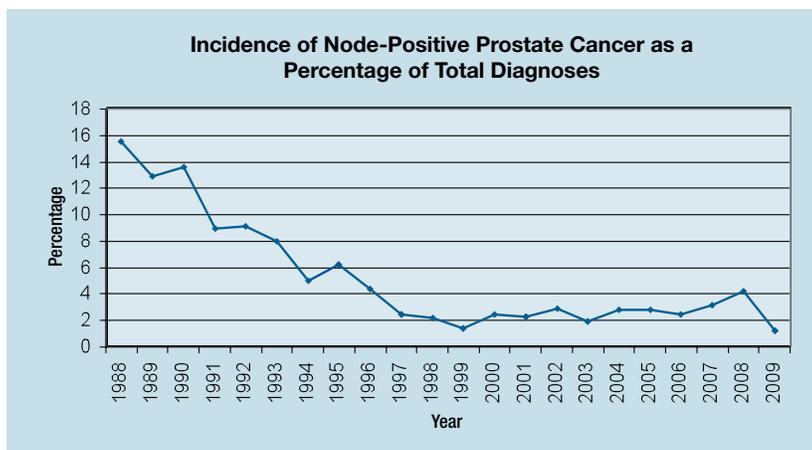


Figure. From 1988 to 2009, there has been a decline in the number of men who had node-positive prostate cancer at their time of surgery at Mayo Clinic.

Source: Mayo Clinic radical prostatectomy registry

After a Diagnosis

What Next?

Prostate cancer is usually a slow-growing disease. Unlike some other cancers, prostate cancer rarely requires immediate treatment. This means the physician and the patient have time to thoroughly evaluate the many available treatment options, which include surgery, radiation therapy, hormone therapy and other interventions. Depending on the patient’s overall health and disease stage, no treatment may be advisable (see “Active Surveillance” on page 3).

A consultation with a urologist who practices within a large academic medical system is a good next step. As prostate cancer surgery and other therapies are continually evolving, this provides the patient with access to the widest array of evidence-based treatment options and highly trained surgeons. These centers also have the most experience with monitoring after surgery and, should it be needed, follow-up treatment.

Mayo Clinic Department of Urology Perspective on Prostate Cancer Screening

Balancing Risks and Benefits

Screening for prostate cancer is a complex and ultimately personal decision—it positions the hopeful prevention of prostate cancer death and morbidity against the possibility of treating an insignificant tumor. That said, most experts agree that prostate cancer is a serious disease and that screening is rather straightforward and detects high-risk prostate cancer.

The debate about prostate cancer screening centers around the fact that it inevitably results in diagnosing some patients with indolent tumors that may never have become clinically significant. The ideal cancer-screening test would be one that is inexpensive and easy to perform, detects clinically significant cancers with high sensitivity and fails to detect slow-growing, indolent tumors. Unfortunately, such a test isn't available today. This means that practitioners must rely on the best available options: PSA screening, digital rectal examinations and prostate biopsies.

It is important to recognize that the benefit of screening is critically tied to downstream factors such as treatment success and morbidity. The identification of a slow-growing prostate cancer should not be viewed as a failure of prostate cancer screening. Rather, it should represent an opportunity to discuss appropriate treatment options and select the right management approach for each patient.

Active surveillance has emerged as a preferred treatment option for many patients who are diagnosed with low-risk prostate cancer. For men who need treatment, advances are continuing to reduce the morbidity associated with surgery and other interventions.

Prostate cancer surveillance, including the sensible use of the PSA test, reduces the morbidity and mortality associated with this disease. What remains to be determined is how often and at what time such screening needs to be performed to maximize its effectiveness and minimize adverse effects.

Individualized screening approach

The Department of Urology at Mayo Clinic recommends an individualized, multifactorial approach to determining whether or not to screen a particular patient for prostate cancer.

Points to Remember

- The purpose of prostate cancer screening with the PSA test is to detect prostate cancer when it is localized and therefore most treatable.
- Prostate cancer screening is controversial because no trials have conclusively demonstrated that the benefits of screening outweigh its risks.
- The majority of prostate cancers detected with screening are low-risk and not immediately life-threatening.
- While prostate cancer screening identifies most prostate cancers, it does not discriminate between high-risk, life-threatening tumors and low-risk, indolent tumors.
- The death rate from prostate cancer has consistently declined approximately 4% per year since prostate cancer screening became commonplace.

This approach, which should begin at age 40, incorporates an individual patient's risk of developing prostate cancer, a comprehensive physical examination, consideration of existing medical comorbidities, and a discussion regarding the benefits and potential risks of screening.

When determining whether to screen:

- Discuss with the patient the pros and cons of screening
- Conduct a physical exam, staying alert for comorbidities that can affect PSA score
- Take a comprehensive family medical history, noting previous biopsy history of the patient and his family members
- Consider the patient's age, recognizing the age-related increase in cancer risk
- Consider the patient's ethnic background, noting that African-American men have the highest risk of prostate cancer

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