

Early Detection and Treatment of Prostate Cancer

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Prostate cancer is a common disease among men in the United States. Although its high prevalence and potential mortality risk would seem to warrant routine screening programs for early detection and treatment, the utility of such programs is currently under debate, as is illustrated by this case study. This lack of consensus has led to the development of a variety of approaches to informing patients regarding their options.

Cancer-screening recommendations of national medical organizations in the United States differ widely. The American Cancer Society recommends that men 40 years and older be informed by their physicians about the risk for prostate cancer,¹ and that men 50 years and older be offered a digital rectal examination (DRE) as well as the prostate-specific antigen (PSA) test at their annual physical examination.² The American Urological Association endorses the American Cancer Society's recommendations.²

In contrast, most other medical organizations do not advocate routine screening for patients at risk for prostate cancer, citing the significant side effects of surgery for prostate cancer (eg, incontinence, impotence) and the lack of current rigorous evidence that early detection and treatment substantively affect the overall death rate. The US Preventive Services Task Force, the American College of Surgeons, the American Society of Internal Medicine, the National Cancer Institute, the American Association of Family Practitioners, and the American College of Preventive Medicine all indicate that routine screening for prostate cancer is not recommended.^{3,4} Various national organizations in other countries also recommend against routine screening; literature from Sweden indicates that physicians there generally do not screen for prostate cancer and treatment is usually watchful waiting.⁵

Although a strong and legitimate set of groups currently recommend against routine prostate cancer testing, an increasing number of men in the United States

are receiving such testing.⁶ Because of this increased preference for testing, it is ever more important to provide accurate and adequate counseling as to the strengths and weaknesses of the PSA test and the DRE.

Primary care physicians can play a crucial role in the counseling of patients regarding testing for prostate cancer. It has been reported that neither urologists nor radiation oncologists provide a broad view to the patient of the strengths and weaknesses of testing and treatment; instead, they focus upon discussing with the patient the kinds of treatment each can provide.⁷ This approach, however, is problematic because it does not reflect the current acceptance of surgery, radiation therapy, and watchful waiting as each representing acceptable therapy.⁸⁻¹⁰ Further, this approach may inhibit the performance of randomized clinical trials necessary to determine the appropriate clinical approach for prostate cancer at its various stages and differentiation.¹¹

Providing such information to patients is a challenge. Studies on using decision aids to inform patients regarding the risks, benefits, and uncertainties of prostate cancer testing and treatment have provided mixed results. Some studies showed an increase in testing after patients have been exposed to decision aids; some showed differential effects depending upon the site of administration of the decision aids; some

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showed a decreased desire of patients to undergo screening after reading a decision aid; and some showed no effect.^{12–15} Clearly, it is important to find effective methods that communicate information regarding prostate cancer testing and treatment that assists patients in making informed choices appropriate to their current life status.

Prostate cancer is a common disease in the United States with serious consequences. The effects of treatment, however, are not well known, nor are the appropriate circumstances for testing as they relate to prognosis. As clinical trials continue to clarify parameters for screening, testing, and treatment of prostate cancer, the appropriate direction that the physician should take in a given case will become clearer. Even when these issues are addressed, however, a continued focus upon communication of the risks and benefits of all aspects of testing and treatment to the patient will continue to be part of any approach.

INTRODUCTION

Prostate cancer is the most common nondermatologic malignancy and the second leading cause of cancer mortality in men. It was estimated that in the year 2000, 180,400 new cases of prostate cancer would be diagnosed and 31,900 men would die of the disease.¹⁶ Risk factors for prostate cancer include age, family history of prostate cancer, African American race, and possibly dietary fat intake.¹⁷ The total annual Medicare expenditure for prostate cancer exceeds \$1.4 billion.¹⁸

Because prostate cancer is such a prevalent and potentially serious disease and because screening tests and treatment options are available, early prostate cancer detection and treatment would seem a common sense strategy for reducing disease-specific morbidity and mortality. However, conclusive evidence of benefit from this strategy is lacking. This article will clarify what is known about the risks and benefits of prostate cancer screening, describe what information needs to be communicated to patients, and discuss methods for facilitating patient participation in this important health care decision.

CASE STUDY

Initial Presentation

A 67-year-old white man presents to his primary care physician, requesting information about prostate cancer testing.

History

The patient states that he has had “prostate problems” for several years. The patient describes his symp-

toms as nocturia 2 to 3 times per night, increased urinary frequency, and decreased force of his urinary stream. He is worried because he has heard that prostate cancer can cause the urinary symptoms he is having. He denies urinary incontinence or hematuria. The patient has reduced his caffeine and alcohol intake and has begun taking an over-the-counter preparation of saw palmetto extract, with modest improvement in symptoms.

The patient has a history of hypertension and diabetes. There is no family history of prostate cancer. His medications, in addition to saw palmetto, include lisinopril, glyburide, and vitamin E.

Physical Examination

The patient’s physical examination is unremarkable except for the presence of a firm, large prostate without nodules. Results of a urinalysis are within normal limits.

QUESTION

- Should this patient be screened for prostate cancer?

DISCUSSION

The goal of screening for prostate cancer is to detect clinically important cancers early so that treatment can be provided and deaths and disability from prostate cancer prevented. Population-based screening seeks to achieve this goal at a reasonable cost while minimizing the harms of screening. However, there is disagreement as to whether early detection efforts in prostate cancer do more good than harm. The harms of screening are known; however, the benefits of screening are uncertain because the randomized trials needed to vigorously test the effect of early treatment on death from prostate cancer have not been completed. In the absence of results from randomized trials, which will not be available for at least several years, most organizations are recommending against the routine use of screening tests and instead suggest that physicians provide their patients with information about the potential risks and benefits of screening and assist patients in weighing the risks and benefits based on their own values and preferences.^{8,19,20} That is, the decision whether to screen should be shared between physician and patient. This shared decision-making process requires that the physician be familiar with the risk factors and natural history of prostate cancer, the accuracy of prostate cancer screening tests, the available treatment options, and the risks and benefits of screening and treatment.

For patients with lower urinary tract symptoms, there is some debate as to whether the PSA test

Table 1. Risk Factors for Prostate Cancer

Factor	Effect on Prostate Cancer Risk
Age	Increase
African American race	Increase
Family history of prostate cancer	Increase
Agent Orange	May increase
Dietary fat	May increase
Calcium	May increase
Soy	May decrease
Tomato products	May decrease
Selenium	May decrease
Vitamin E	May decrease
Vasectomy	No effect
Benign prostate conditions	No effect
Tobacco	No effect
Herbal supplements	No known risk reduction
Zinc	No known risk reduction

should be considered a screening test or a diagnostic test. Lower urinary tract symptoms are common in elderly men and have many causes, including prostate cancer. The most common cause of such symptoms, however, is benign prostatic hyperplasia (BPH). About one third of men older than 50 years have lower urinary tract symptoms consistent with BPH. Evidence strongly suggests that men with lower urinary tract symptoms are at no greater risk for prostate cancer than asymptomatic men.^{8,21,22} Because mildly elevated PSA values are common in men with BPH and because the efficacy of early detection of prostate cancer is uncertain, PSA testing in men with lower urinary tract symptoms is considered an optional screening test rather than a diagnostic evaluation.⁸

Further Questioning by Patient

The patient is reassured that his symptoms are not likely due to prostate cancer and do not increase his risk for having prostate cancer, but he still wonders whether he should be screened. He has heard “what a big killer prostate cancer is” and wants to protect himself from a prostate cancer death.

QUESTION

- What are risk factors for prostate cancer?

DISCUSSION

Risk Factors

Risk factors for the development of prostate cancer include age, African American race, family history of prostate cancer, and possibly dietary fat intake (**Table 1**).¹⁷ More than 75% of all men diagnosed with prostate cancer are older than 65 years.²³ The prevalence of incidental prostate cancer detected at autopsy is 30% for men over age 50 years and ranges from 12% for men in their 40s to greater than 60% for men in their 80s. Incidence rates for non-organ-confined prostate cancer increase dramatically with age, from 82/100,000 for men from 50 to 54 years of age to 1326/100,000 for men from 70 to 74 years of age.²⁴

Men with a father or brother with prostate cancer are twice as likely to develop prostate cancer as men without affected relatives. Incidence of clinical prostate cancer is low in Asian men and higher in Scandinavian men. It is unclear if this is due to genetic or environmental factors. The age-adjusted incidence and mortality of prostate cancer is higher for African American men (234 and 56 per 100,000, respectively) than for white men (135 and 24 per 100,000).²⁴ The rates for African American men are also higher than for black men living in Africa or Asia.

Many men, including the patient in this case study, use herbal products or dietary supplements to treat or prevent prostate problems. One such supplement, saw palmetto, is well tolerated and provides modest improvement in urinary symptoms associated with BPH.²⁵ However, no herbal products have been demonstrated to reduce the risk of developing prostate cancer. While definitive evidence is lacking, men may be able to lower their risk of developing and dying from prostate cancer by eating diets low in saturated fats (especially red meat) and calcium and high in tomatoes and tomato sauce (lycopenes), soy (isoflavones), vitamin E, and selenium.²⁶ Ongoing randomized controlled trials are determining whether vitamin E, selenium, or finasteride (Proscar, a 5-alpha reductase inhibitor commonly used to treat symptoms of BPH) reduce prostate cancer incidence and mortality. The protective effect of vitamin E and selenium may be due to their antioxidant activity. Because prostate cancer is androgen dependent, drugs like finasteride, which inhibit the conversion of testosterone to dihydrotestosterone, may also decrease the incidence and progression of prostate cancer.

Agent Orange, a defoliant utilized in the Vietnam War, has been associated with increased risk of prostate cancer. Other putative risk factors such as occupation,

sexual behavior, infectious agents, vasectomy, cigarette smoking, and benign prostate conditions have not been demonstrated to alter the risk of prostate cancer.¹⁷

QUESTION

- What is the natural history of prostate cancer?

DISCUSSION

Findings from cohort and autopsy studies suggest that the course of prostate cancer is frequently indolent. It commonly occurs in older men with comorbid conditions who may die of other causes before their prostate cancer becomes clinically significant. Therefore, the natural history of prostate cancer may be different than that of other malignancies in that most men with prostate cancer do not die of their disease.

For a 50-year-old man with a life expectancy of 25 years, the lifetime risks of microscopic, clinically evident, and fatal prostate cancer are approximately 42%, 10%, and 3%, respectively.^{16,27} The lifetime risk of being diagnosed with prostate cancer is 15.9%²⁸; this rate is higher than the rate for clinically evident cancer because it includes asymptomatic disease detected during screening. The disease-specific 15-year mortality rate in men with clinically localized prostate cancer treated with observation and delayed palliative hormone therapy (watchful waiting) ranges from 10% to 40% and varies with the histologic characteristics of the tumor and the comorbidities and age of the patient.^{9,29–31} Morbidity from disease progression includes hematuria, bladder obstruction, and, in men with metastatic disease, pain, weakness, and paralysis.

QUESTION

- How accurate are screening tests for prostate cancer?

DISCUSSION

Digital Rectal Examination

The DRE has historically been part of the periodic routine health examination but has not been clearly demonstrated to prevent advanced or fatal prostate cancer. To test for prostate cancer, the physician places a gloved finger inside the rectum and palpates the posterior aspect of the prostate gland. Among men 50 years and older, approximately 2% to 3% who receive 1 DRE are found to have prostatic induration, marked asymmetry, or nodularity. Such findings increase the odds of finding a clinically significant (> 0.5 mL) localized tumor by up to 2-fold but increase the odds of having extracapsular disease by 3- to 9-fold (Table 2). Thirty percent to 70% of DRE-detected tumors are still confined to the prostate gland—the

Table 2. Estimated Likelihood Ratios for Prostate Cancer for Results of DRE and PSA

Test Result	Likelihood Ratio	
	Organ-Confined Tumor	Extracapsular Tumor
DRE		
Suspicious	01.5–2.0	2.7–8.6
Nonsuspicious	0.83–0.96	0.53–0.72
PSA		
< 4.0 ng/mL	00.7–0.98	0.09–0.5
4.1–10 ng/mL	01.4–3.0	3.2–5.1
> 10 ng/mL	00.4–3.0	23.7–49.6

DRE = digital rectal examination; PSA = prostate-specific antigen. Adapted with permission from Coley CM, Barry MJ, Fleming C, Mulley AG. Early detection of prostate cancer. Part I: Prior probability and effectiveness of tests. American College of Physicians. Ann Intern Med 1997;126:394–406.

type of cancers early detection programs seek to identify. The proportion of clinically localized cancers detected by DRE may actually decrease with subsequent DRE. Studies of inter-rater reliability for DRE show poor reproducibility.³²

Data from community-based studies suggest that the positive predictive value of DRE for prostate cancer is 15% to 30%.^{8,32} Because of the poor sensitivity of DRE, a normal test does not appreciably lower the odds of having clinically significant prostate cancer.

Prostate-Specific Antigen

Another way to test for prostate cancer is to measure the level of PSA in serum. A cutoff of 4 ng/mL is most commonly used to define an abnormal result. PSA measurement appears to be more sensitive but less specific than DRE for detection of prostate cancer.³² It can detect cancers before they are palpable and may be particularly useful for diagnosing aggressive cancer.

The positive predictive value of PSA measurement varies from 17% to 28%, depending on degree of elevation of PSA level. For PSA levels between 4 and 10 ng/mL, the positive predictive value is 21%; this value increases to between 42% and 64% for PSA levels greater than 10 ng/mL. The positive predictive value appears to be independent of age, suggesting that increased disease prevalence is balanced by decreased test specificity in older men.³³ Use of PSA measurement results in a cancer detection rate of 3%, with approximately 60% of tumors found to be confined to the prostate at surgery.³²

An elevation in PSA level greater than 4 ng/mL triples the odds that a man 50 years or older has clinically significant but still localized prostate cancer (Table 2). It also increases the odds of extracapsular tumors by 3- to 5-fold. PSA levels above 10 ng/mL markedly increase the odds that a man has an extracapsular tumor.

PSA testing fails to detect a substantial number of men with prostate cancer. Approximately 20% to 30% of men with prostate cancer have PSA levels below 4.0 ng/mL. Therefore, while a PSA level less than 4.0 ng/mL provides excellent reassurance that a man does not have extracapsular disease, it cannot rule out organ-confined prostate cancer (Table 2). Detection rates and predictive values decline significantly in subsequent years of testing.

PSA measurement is not specific for prostate cancer. It can be elevated in men with noncancerous conditions including BPH, acute prostatitis, urinary retention, and genitourinary instrumentation such as cystoscopy or prostate biopsy. Up to 50% of men with BPH will have elevated PSA levels, but most will be falsely positive for prostate cancer. For example, approximately 400 men out of 1000 with moderate symptoms of BPH will have an abnormal PSA or rectal examination; of these 400, only 30 will have cancer.⁸ But, all 400 will have undergone diagnostic procedures (eg, prostate ultrasound and biopsy), with their attendant costs and potential risks. Modifications to PSA testing, such as measurement of “free and complexed” PSA, PSA density and velocity, and use of age-specific reference ranges, may improve specificity and reduce the number of unnecessary biopsies by up to 20%.³⁴ However, these modifications decrease sensitivity, may require additional blood tests or ultrasound examinations, and have not been demonstrated to improve survival.

Combined Testing Strategy

Because DRE and PSA appear to detect different cancers, most physicians who screen for prostate cancer use both DRE and PSA measurement and recommend biopsy if results of either test are abnormal.³² Combined screening with DRE and PSA increases cancer detection rates to 4% and may increase the proportion of cancers that are still localized upon pathologic examination. Using this combined screening strategy, if either test result is abnormal, the positive predictive value is 15% to 21%. Approximately 1 out of 4 asymptomatic men will have an abnormal PSA measurement or rectal examination, and the proportion of tested men who consequently undergo a prostate biopsy ranges from 15% to 40%, depending on age.^{32,35} PSA and DRE testing may increase cancer-related testing, treatment, and morbidity.^{32,35,36}

QUESTIONS

- What are the benefits, risks, and costs of prostate cancer screening?
- Does screening for prostate cancer improve survival?

DISCUSSION

PSA measurement is a relatively simple and low-cost blood test that could conceivably save a man's life and avert cancer-related morbidity. However, routine DRE or PSA has not been proven to reduce the risk of dying of prostate cancer. Unlike with breast and colon cancer, where several large trials have proven that early detection and treatment lower disease-specific mortality, there have been no randomized trials showing that the detection of prostate cancer by PSA screening or DRE decreases disease-associated morbidity or mortality. Additionally, in contrast to findings from epidemiologic studies indicating that cervical cancer screening is temporally and geographically associated with a large reduction (50%) in disease-specific mortality, epidemiologic and administrative database studies of prostate cancer provide conflicting results and do not clearly demonstrate that prostate cancer screening and treatment decreases mortality.^{28,37–42} Results from randomized controlled screening and treatment trials, which will be available within 5 to 10 years,^{43–46} are needed before we can know if testing and treatment improve survival.

Decision models have been developed to examine the possible outcomes of 1-time DRE and PSA measurement.³⁵ The maximum average health benefit averaged across all patients is no more than a few additional weeks of life expectancy. However, in men receiving a diagnosis of prostate cancer, successful treatment with surgery or radiation may add up to 3 years of life for men in their 50s and 0.4 years for men in their 70s.³⁵ Based on the model, prostate cancer screening is only marginally beneficial for men 70 years and older, even using very favorable assumptions.

Potential risks of screening include the psychological distress and morbidity associated with further testing and treatment. The risks of biopsy are relatively minor but include bleeding and infection in as many as 40 men in 100. However, the psychological consequences of a suspicious screening test result (eg, anxiety, depression) appear to be appreciable.⁴⁷ Additionally, because the false-negative rate of biopsy in the setting of an elevated PSA has been demonstrated to be as high as 10% to 15%, many men may remain anxious about the implications of their PSA measurement even after 1 or more sets of negative biopsies.⁴⁷ Risks of screening also

include the morbidity and small but definite risk of mortality associated with aggressive treatment (*see* “Treatment Options,” below).

Costs of Screening

The cost of a 1-time PSA test is about \$45. However, this does not take into account the costs associated with the cascade of testing, staging, and treatment prompted by an abnormal PSA level. If these costs are included, the cost per person screened is \$400, and the cost for the first year of a 1-year national screening program is more than \$12 billion.³⁵ The costs for subsequent years would be lower because the number of prevalent cancers detected and treated would drop.

If assumptions regarding cancer-specific mortality rates, diagnostic and treatment costs, complications, and effectiveness that favor screening are used in models, the estimated costs of screening per year of life saved are comparable to cost-effectiveness ratios for many proven and accepted screening programs: \$19,000 for prostate cancer screening, \$21,000 for breast cancer screening in women older than 50 years, and \$30,000 for colon cancer screening. However, if these assumptions are replaced with values more consistent with available evidence, the costs of prostate cancer screening rise dramatically (more than \$400,000 per year of life saved).³⁵

QUESTION

- What are treatment options for men with early-stage prostate cancer and what are the risks and benefits of treatment?

DISCUSSION

Available Treatment Options

Prostate cancer treatment goals are to prevent premature death and disability by reducing the risk of prostate cancer morbidity and mortality while minimizing adverse treatment effects. The appropriate therapy for men with clinically localized prostate cancer is not known.^{8,9,32,48} Acceptable treatment options include surgery (radical prostatectomy); radiation therapy (external-beam or interstitial radiation [brachytherapy]); cryosurgery; early hormonal treatment; and surveillance (conservative management, careful monitoring, and utilization of androgen suppression if and when there is evidence of disease progression) (Table 3).

The only available information on survival and complication rates associated with prostate cancer treatment options comes from cohort studies. Treatment selection bias strongly influences the outcomes in such studies (eg, men treated with radical prostatectomy are generally younger, healthier, and have less advanced prostate

cancer than men treated with radiation or surveillance). Until randomized trials comparing survival and complication outcomes for various treatments are completed, we cannot be sure to what extent differences in outcomes and complications across treatments are due to selection bias or to the treatments themselves. For this reason, data derived from a select group of men who received a treatment should not be used to predict outcomes for individual patients.

Radical prostatectomy. Radical prostatectomy involves surgical removal of the prostate gland, seminal vesicles, and surrounding lymph nodes. It offers the potential to completely remove a prostate cancer that can progress and cause disability and death. The 10-year disease-specific survival following radical prostatectomy is about 85% and ranges from 94% for men with well-differentiated prostate cancer to 67% for men with poorly differentiated disease.^{9,49} The 5-year cumulative incidence of men with pathologically organ-confined cancer requiring additional treatment after prostatectomy has been estimated at 24%. Less than 60% of men who undergo radical prostatectomy have pathologically confirmed organ-confined disease. These men are unlikely to have had their cancer completely eliminated and may have received ineffective therapy. For men undergoing radical prostatectomy with pathologically regional cancer, the 10-year disease-specific and metastasis-free survival rates are about 50% and 30%, respectively.⁸ In men with positive lymph nodes at the time of surgery, survival is improved by early utilization of androgen suppression therapy.

Fatal complications occur in approximately 0.5% to 1% of all men treated with surgery but may exceed 2% in men 75 years and older. Approximately 8% of men older than 65 years suffer major cardiopulmonary complications within 30 days of operation.⁸ Additional complications include sexual dysfunction in 60% to 90% of men, urinary incontinence requiring pads or clamps to control wetness (30% to 36%), total urinary incontinence (2% to 4%),^{50,51} urethral stricture (18%), fecal incontinence (5%), and bowel injury requiring surgical repair (1%).⁸

External-beam radiation therapy. External-beam radiation therapy has the potential to kill prostate cancer cells without a surgical procedure through a series of radiation treatments lasting up to 6 weeks. Ten-year disease-specific survival for men treated with radiation therapy has been reported as 76% and ranges from 90% for well-differentiated to 53% for poorly differentiated prostate cancer.^{8,52} Three years after radiation treatment, 24% of men older than 65 years reported follow-up treatment with androgen deprivation for cancer

Table 3. Treatment Options for Clinically Localized Prostate Cancer

Treatment Option*	Potential Benefits	Potential Risks
Surgery	May eliminate cancer; generally well tolerated	Hospitalization for major surgery; operative-related death, incontinence, impotence, bleeding, pulmonary embolism, urethral stricture, bladder neck contracture
External-beam radiation	May eliminate cancer; generally well tolerated	Does not remove prostate gland and may not eradicate cancer; 6–8 weeks of outpatient therapy; death, incontinence, proctitis, cystitis, impotence, urethral stricture, bladder neck contracture, major bleeding
Brachytherapy	May eliminate cancer; generally well tolerated; single outpatient session	May not be effective for larger prostate glands or more aggressive tumors; urinary retention, incontinence, impotence, cystitis/urethritis, proctitis; long-term outcomes from representative national sample not reported
Cryoablation	May eliminate cancer; generally well tolerated; single outpatient session	Does not remove prostate gland and may not eradicate cancer; impotence; incontinence, scrotal edema, sloughed urethral tissue; prostatic abscess; urethrorectal fistula; no long-term outcomes from national sample
Hormonal therapy	Usually lowers PSA levels; slows cancer progression	Gynecomastia, impotence, diarrhea, osteoporosis, lost libido, hot flashes
Surveillance	No immediate side effects or complications; low initial cost; most men do not need therapy and survive the cancer at least 10 years	Cancer could advance, become incurable and cause death; patient's quality of life could be painfully restricted before he dies; additional treatments may be necessary, not effective, and have side effects

PSA = prostate-specific antigen.

*Treatments are listed as options because the available evidence is inadequate to determine whether any given therapy provides superior length or quality of life for men with clinically localized prostate cancer.

recurrence. Complication rates are generally lower in patients treated with radiation than with surgery but include treatment-related mortality (< 0.5%), impotence (30% to 60%), urinary incontinence requiring wearing absorptive pads to control wetness (7%), and chronic bowel dysfunction (10% to 20%).^{8,51,52}

Brachytherapy. Brachytherapy is a form of radiation (interstitial therapy) in which iodine-125 or palladium-103 radioisotope needles are permanently placed into the prostate. Ten-year disease-specific survival rates for men treated with brachytherapy have been reported as high as 98%.⁵² However, most men treated with brachytherapy have small-volume and low-grade tumors (PSA < 10 ng/mL and Gleason histologic scores < 6), which have an excellent long-term prognosis with surveillance. Brachytherapy failure, as defined by PSA levels, is higher in men with high-grade malignancies compared with men treated with radical prostatectomy. If brachytherapy is used in men with high-grade malignancies, additional treatment with external-beam radiation is generally utilized and is associated with higher complication rates. Complications of brachytherapy

include urinary retention (6% to 7%), incontinence requiring pads (12% to 18%), cystitis/urethritis (4% to 7%), proctitis (6% to 16%), and impotence (44% to 79%).^{51,52}

Percutaneous cryosurgical ablation. Percutaneous cryosurgical ablation involves the use of multiple small-diameter cryoprobes that can freeze a number of target areas of the prostate. Transrectal ultrasound monitors probe placement and ice propagation over time. Urethral warming is used to minimize cryo-induced urethral sloughing. Short-term, uncontrolled data from selected centers indicate that 5-year biochemical-free survival for patients treated with cryosurgical ablation exceeded 70% and that the 5-year biopsy-proved disease-free rate was 79%.⁵³ Complication rates for a series of cryoablation studies have been reported: impotence (65%); scrotal edema (10%); sloughed urethral tissue (3%); incontinence, urethrorectal fistula, and prostatic abscess (1%).⁵³

Androgen suppression. Androgen suppression has usually relied on surgery (orchiectomy) to eliminate serum testosterone or estrogens such as diethylstilbestrol

(DES) to provide similar effects. New alternatives include luteinizing hormone-releasing hormone (LHRH) agonists and nonsteroidal antiandrogens. Androgen suppression has been shown to delay clinical progression and/or palliate symptoms of metastatic disease in over 80% of men with advanced prostate cancer.¹⁸ However, it has not been clearly demonstrated to improve survival. Clinicians often monitor PSA levels and offer androgen suppression at the time of cancer diagnosis or when PSA levels rise.^{18,54} Consequently, more men are being considered for androgen suppression and treatment is being initiated earlier in the natural history of the disease.

Because men treated in randomized controlled trials conducted in the 1960s included men who were older and had more advanced cancers than men diagnosed today, the effect of early androgen suppression on length and quality of life is not known. Early use of androgen suppression in asymptomatic men may relieve anxiety by lowering PSA levels and providing patients with the sense that some intervention is being performed.

Potential harms from androgen suppression include weakness, osteoporosis, hot flashes (40%), gynecomastia (9%), impotence (70%), nausea, vomiting or diarrhea (2% to 8%), and loss of libido (5% to 30%). While DES and orchiectomy are relatively inexpensive, the cost of LHRH agonists and/or antiandrogens exceeds several thousand dollars per patient per year. These newer agents are not safer or more effective.¹⁸ The adverse effects and costs are particularly important when considering treatment in men with long life expectancy or treatment durations, such as younger men with lower-grade cancers. Additionally, androgen suppression does not cure prostate cancer. Over time, prostate cancer loses its dependence on androgens, and patients develop hormone refractory disease. The risk of disability and death due to prostate cancer in these men is high.

Watchful waiting. Surveillance (expectant management, conservative management) involves monitoring men and providing palliative therapy if and when there is evidence of disease progression. Prostate cancer-specific survival in men treated with surveillance is approximately 80% after 15 years of follow-up but varies by histologic grade.^{9,29–31} The overall likelihood that men with prostate cancer detected by DRE will remain free of symptomatic progression requiring palliative treatment is 70% at 5 years and 40% at 10 years.

Men with well-differentiated prostate cancer (biopsy specimens with Gleason score of 2 to 4 disease) face a minimal (< 5%) risk of symptoms or death from prostate cancer within 15 years of diagnosis. Conversely, men

whose biopsy shows poorly differentiated prostate cancer (Gleason score 7 to 10 disease, approximately 30% of men diagnosed with prostate cancer) face a high risk of death (42% to 87%) from prostate cancer within 15 years when treated conservatively, and the 5-year disease specific mortality ranges from 20% to 40%. Men with Gleason score 5 or 6 tumors face a modest (15% to 20%) risk of death from prostate cancer that increases slowly over at least 15 years of follow-up. Because the lead time associated with PSA testing is at least 5 years, outcomes after 20 years of follow-up for men with PSA-detected cancers are likely to be similar to the 15-year results reported in men with palpable tumors.²⁹

The advantage of surveillance is that it avoids the early morbidity, mortality, and costs associated with surgery, radiation, cryotherapy, and early androgen deprivation therapy while still providing palliative therapy if symptoms develop.^{9,29–31,49} However, conservative management does not remove a cancer that is potentially curable. If untreated, localized prostate cancer may progress and cause disability or death. Morbidity from local or regional disease progression includes hematuria, bladder obstruction, and lower extremity edema. Metastatic prostate cancer can result in pain, weakness, paralysis, and death. Palliative treatment with delayed androgen suppression can slow disease progression but does not cure prostate cancer. Palliative treatments are associated with adverse effects and costs. Whether early intervention with surgery or radiation decreases the need for subsequent palliative treatment is not known.

Making Decisions About Treatment

Because differences in survival across prostate cancer treatments reported from cohort studies may be explained by differential selection bias, results from these studies do not provide clear-cut evidence for the superiority of any one treatment. Only randomized controlled trials can provide this evidence. However, only a few randomized controlled studies comparing these prostate cancer treatment options have been completed. Two studies directly compared surgery with surveillance or radiation.^{55,56} Both were conducted prior to PSA testing and were too small to definitively conclude that surgery and radiation are ineffective. One trial comparing radiation with surgery indicated that disease recurrence was higher in men treated with radiation.⁵⁶ Another trial comparing radical prostatectomy with surveillance found no difference in survival after a median follow-up of 23 years.⁵⁵ Until results of ongoing randomized controlled trials of screening and treatment are available, decisions about screening and treatment should be tailored to patients' values and

Table 4. Elements of Informed Consent for Prostate Cancer Screening

1. Prostate cancer is an important health problem
2. The benefits of 1-time or repeated screening and aggressive treatment of prostate cancer have not yet been proven
3. Digital rectal examination and prostate-specific antigen measurement can both have false-positive and false-negative results
4. The probability that further invasive evaluation will be required as a result of testing is relatively high
5. Aggressive therapy is necessary to realize any benefit from the discovery of a tumor
6. A small but finite risk for early death and a significant risk for chronic illness, particularly with regard to sexual and urinary function, are associated with these treatments
7. Early detection may save lives
8. Early detection and treatment may avert future cancer-related illness

Adapted with permission from Screening for prostate cancer. American College of Physicians. *Ann Intern Med* 1997;126:480–4.

comorbid conditions. Men most likely to benefit from early intervention have a relatively long life expectancy, high-grade prostate cancer still confined to the prostate gland, low risk of complications from the intervention, and a preference for early intervention after being informed about the potential risks and benefits of the different options.

QUESTION

- What should patients be told about prostate cancer screening and what can physicians do to help patients make an informed decision?

DISCUSSION

Previous studies suggest that informing men about the risks and benefits of prostate cancer screening alters their screening and treatment preferences.^{12,14,57,58} In general, men who are well-informed about the known risks and uncertain benefits of prostate cancer screening are more likely to decline screening and less likely to prefer active treatment if cancer is found than uninformed men.

Specific content lists for informed consent about prostate cancer testing and treatment have been proposed,^{8,59} but the most effective and efficient approach to communicate this information to patients is not known. In addition, full disclosure of all available infor-

mation is not practical and may overwhelm patients. The American College of Physicians (ACP) recommends that patients at least be provided the information in **Table 4** before a screening decision is made.⁸ More exhaustive prostate cancer screening informed consent lists have been proposed by researchers⁵⁹ but have not received official endorsement from professional organizations.

Until a broader consensus is reached regarding the essential content of prostate cancer informed consent, the ACP counseling checklist is a useful summary of the information physicians should communicate to patients. However, effectively communicating to patients even this focused information can be a time-consuming and complex task. Patient education tools are available that may facilitate the process. These tools can be integrated into primary care practice in a variety of ways. Reactive approaches might include reading Wolf and colleagues' standardized script¹⁴ to all patients who raise questions about prostate cancer screening during their appointment or asking patients to review written materials while you step out of the room. Proactive approaches might include mailing patients either informational pamphlets or invitations to view information videos prior to prevention or wellness visits or asking patients visiting the clinic during a designated "prostate cancer screening education month" to review written or video materials while they are waiting to be seen. Since research examining the relative effectiveness and feasibility of these approaches is lacking, the decision of which approach to use should be based on the literacy level of the target population, the availability of resources and support needed to implement each strategy, and the organizational characteristics of the practice (eg, whether patients have scheduled wellness visits, expected length of visits, availability of nonphysician staff for patient education).

Since most of these patient education tools do not cover all of the ACP-recommended information, they should be supplemented with a face-to-face discussion of the issues. As part of this discussion, physicians should ask patients to state their screening preferences and should solicit information about the reasons behind their preferences to ensure that the causal assumptions underlying their preferences are based on fact rather than misconception.

FURTHER DISCUSSION OF THE CASE STUDY Provision of Patient Information and Shared Decision Making

The physician explains that prostate cancer is an important health problem but that the benefits of

screening have not yet been proven. He states that the 2 commonly used screening tests may detect cancer and save lives, but that the tests may fail to detect disease in patients who have cancer, and more commonly, many men without cancer will have an abnormal PSA test. He describes available testing and treatment options in the event of an abnormal PSA result as well as the risks associated with treatment. He states that because of the potential risks and uncertain benefits of screening, practice guidelines recommend that physicians provide patients with information about the risks and benefits of screening and individualize the decision based on the patient's values and preferences. He says that he would like to give the patient some written materials to review and would like to go over any questions or concerns the patient has after reading them.

QUESTION

- **Are there men in whom PSA testing is more likely to be beneficial?**

DISCUSSION

African American men and men with a family history of prostate cancer are at increased risk for developing prostate cancer and may be more likely to benefit from testing. Rather than routinely testing men, counseling about the potential risks and benefits of prostate cancer screening is recommended beginning at age 40 years for African American men or those with a family history of prostate cancer, and for all other men beginning at age 50 years.²² Screening high-risk groups improves the positive predictive value of a screening test because it is used in a population with an enriched probability of a disease. Given the relatively high prevalence of prostate cancer in all groups, however, prior probability is not a concern nor markedly changed by risk group. For both average- and high-risk groups, the question is whether screening and treatment favorably affect outcome. We don't know the answer to this; targeted screening (routine screening of high-risk groups) is not supported convincingly by the evidence.

Younger men may benefit more from screening. Younger men have a much lower prevalence of prostate cancer than older men; however, because they are generally in good health and have a long life expectancy, they have a greater number of years to be exposed to the risk of disease progression and may therefore benefit more from early treatment if they have prostate cancer. In contrast, a man 70 years of age has a 20-fold increased risk of having nonlocalized prostate cancer compared to a man 50 years of age.¹⁷ However, because of shorter life expectancy, the older

man has fewer years for symptomatic disease progression. Therefore, he is less likely to receive the potential benefits from detection and treatment that occur 10 to 20 years in the future, but he is still exposed to their immediate risks.

Although PSA testing is common in men 70 and 80 years old or with coexisting medical conditions, testing is not recommended in men with a life expectancy of less than 10 to 15 years because of the relatively indolent course of prostate cancer and the morbidity associated with early detection and treatment. Routine testing and treatment in these men is more likely to produce net harm.⁸ Prostate cancer screening is also not recommended for men who do not want to know if they have prostate cancer and perhaps for men who would prefer no early treatment if prostate cancer were found.

While routine DREs do not significantly alter PSA values, levels can be elevated for several weeks in men with acute prostatitis or urinary retention and following prostate surgery, biopsy, or instrumentation. Therefore, PSA testing should not be performed in these situations.

CONCLUSION

Increasingly, clinicians are being encouraged to involve patients in clinical decision making. Shared decision making based on patient preferences is particularly important when the optimal management strategy is unknown. This is the case with prostate cancer.

Routine screening for prostate cancer remains controversial. The lack of evidence about the effect of early detection and treatment on mortality leaves clinicians with the responsibility of educating patients and clarifying issues for them so that they might make the decision about screening that is right for them. While most physicians would accept the value of informed consent and shared decision making for prostate cancer screening and treatment, lack of both time and clinical resources are likely to be major obstacles in implementation. Incorporating educational materials and decision support aids into office practice may help to efficiently and effectively involve patients in these important decisions. These steps will in turn improve patient satisfaction and help ensure the delivery of high-quality, evidence-based health care. **HP**

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