

Summary¹

Prostate cancer is a common and serious malignancy among Medicare-age men. In 1995, 244,000 new cases and 40,400 deaths are anticipated from this disease; men age 65 and older bear most of the burden of illness.

In recent years, the prostate cancer diagnosis rate has increased dramatically, with a slower increase in age-specific mortality. At least in part, the increasing incidence undoubtedly reflects more aggressive efforts at early detection of prostate cancer, particularly through the use of a new blood test, prostate-specific antigen (PSA).

This background paper examines the implications of a potential Medicare benefit to cover prostate cancer screening using a combination of the PSA and digital rectal examination (DRE), a time-honored test performed in the physician's office.

KEY FINDINGS

The Office of Technology Assessment (OTA) concludes that research has not yet been completed to de-

termine whether systematic, early screening for prostate cancer extends lives. The evidence of benefit for other preventive services already covered by Medicare (e.g., breast and cervical cancer screening, influenza and pneumococcal vaccines) is substantially more developed and stronger than for prostate cancer screening. **Because scientific knowledge is limited, but the consequences of prostate cancer and its treatment are serious, an informed and reasonable patient could equally well decide to have screening or forgo it.** Hence, each patient, in consultation with his physician, must use his own values to weigh the potential benefits of screening against the risks of incontinence, impotence, and other adverse outcomes that may result from treating cancers uncovered by screening.

Given the state of current knowledge about prostate cancer, it may be reasonable for Medicare to consider reimbursement of the screening test. Reimbursement could be seen as ensuring that out-of-pocket screening expenses (however small) not

¹The literature review and quantitative analyses discussed in this background paper are drawn from a paper prepared under contract for OTA (27). OTA's analysis also benefited from another contract paper that reviewed the epidemiology of prostate cancer in the United States (277), and a third contract paper that provided the estimates of resources used and costs associated with prostate cancer screening and treatment for Medicare-age men in the United States (121). However, the conclusions and, in some cases, the analysis are solely those of OTA and do not represent those of the authors of these contract papers.

Chapter 1 is a summary of the detailed literature reviews and quantitative analyses that follow in the subsequent chapters. References to support statements in this chapter are noted in the relevant sections of the chapters. The structure of this chapter closely parallels the organization of the remainder of the document.

impede well-informed discussion and decisionmaking between physician and patient. Such a Medicare screening benefit could be unrestricted as are similar benefits for cervical and breast cancer screening. However, an unrestricted, permanent benefit might imply that science actually has established the benefit of early detection. An alternative would be to offer screening on a temporary basis subject to reconsideration as evidence from clinical trials about the effectiveness of screening and treatment becomes available. Such a benefit could also be coupled with efforts by the federal government to involve as many patients as possible in effectiveness research and to ensure patients and physicians are well informed about potential benefits and risks of treating cancers discovered by screening.

The technical analysis in this background paper shows that in terms of the expected cost per life-year saved, prostate cancer screening could indeed be as cost-effective as other disease screening services already covered by Medicare. However, this conclusion is extremely sensitive to assumptions about: 1) the effectiveness of treating prostate cancer, and 2) the rate at which untreated cancers spread to other parts of the body and ultimately cause death. Relatively small changes in these assumptions make the same prostate cancer screening benefit appear very expensive without any health benefit, and the true values for these assumptions are unknown to medical scientists due to the lack of appropriate research noted above. As also indicated above, treatment of detected cancers would result in complications including death, substantial rates of impotence and incontinence, and heart disease.

Why Might Screening Not Be Beneficial?

Intuitively, one would expect that early detection efforts should find more prostate cancers before they have spread outside of the prostate gland, which should in turn lead to more prostate cancer cures with aggressive treat-

ment. Indeed, evidence shows that patients with cancers discovered by screening tend to do well. Furthermore, most men who have a positive PSA test followed by surgery that reveals the cancer has not yet spread beyond the prostate gland strongly believe that early detection and treatment have saved their lives. One of the factors that may act to strengthen this belief is the fairly large number of men who become impotent or incontinent as a result of surgery. The belief that surgery was necessary to avoid a fatal illness could be an important means of accepting these troublesome symptoms.

However, it is not clear that these outcomes are the result of screening and subsequent treatment. Good outcomes may reflect the fact that screening advances the point of diagnosis, without changing the destined course of the cancer (lead-time bias); or that screening may preferentially find slower-growing cancers already destined to do well (length bias). Because of these biases, early diagnosis would *appear* to improve survival, even if treatment were worthless (or harmful).

These problems are compounded by the fact that in most cases, prostate cancer is a slow-growing disease. Most men whose localized prostate cancers are discovered by screening might never suffer any effects of their disease, ultimately dying from some other cause. Hence, even if treatment is ultimately proven to be beneficial for men with very aggressive localized prostate cancers, it would still be unnecessary for most. The dilemma for policymakers arises from the fact that current diagnostic measures are not sufficient to determine *a priori* and precisely which cancers are likely to cause harm. Were there no risks or costs associated with treatment, it might more clearly make sense to treat all cancers found. However, in light of these treatment risks and the current uncertainty about treatment benefit, the decision about screening and any subsequent treatment must currently rest with the patient in consultation with his physician. As our un-

derstanding of this disease and of our ability to intervene in it grows, science will be able to provide more definitive guidance to both clinical and policy decisions.

PROSTATE CANCER IN OLDER MEN

Screening Recommendations

While the American Cancer Society (ACS) and the American Urological Association recommend adding PSA to annual digital rectal examination for early detection of prostate cancer, the U.S. Preventive Services Task Force and Canadian Task Force on the Periodic Health Examination, citing lack of evidence of benefit from controlled studies, do not.² All of these groups agree that research has yet to document that on a population-wide basis, PSA testing reduces the risk of dying from prostate cancer. The differences in recommendations reflect different philosophies about whether clinical medicine and public policy should encourage the use of potentially beneficial, but unproven, cancer prevention strategies before controlled studies definitively establish that they do more good than harm.

Prostate Cancer Biology and Risk Factors

The prostate is a golf-ball-sized gland that helps produce semen, the fluid ejaculated with sperm. It is found below the bladder and surrounds the urethra through which urine passes as it is voided. Most early prostate cancers seem to be slow-growing, with doubling

times of two years or more. The future course of prostate cancer is predicted by tumor grade (the extent to which cancerous cells are different from normal cells) and stage (extent of cancer spread); patient age does not seem to influence the rate at which tumors spread and become life-threatening. Determining the stage of prostate cancer without surgery is unreliable.³ Once prostate cancer spreads to bones or other organs, hormonal treatments can only achieve temporary remissions often measured in months.⁴

Those most at risk for prostate cancer are African American men and men with a family history of prostate cancer. Recently, prior vasectomy and a high-fat diet have been proposed as possible additional risk factors. In addition, the probability of harboring an asymptomatic prostate cancer increases as men age: about 22 percent of men in their 60s and 39 percent of men in their 70s. For those cancers greater than 0.5 mL in volume (which are more likely to cause future problems), the age-specific probabilities of having prostate cancer are about 9 and 15 percent, respectively.

TECHNOLOGIES TO DETECT PROSTATE CANCER

DRE and PSA are both feasible tests for early detection of prostate cancer. Transrectal ultrasound (TRUS) and transrectal needle biopsy (TRNB) are followup tests used to further investigate suspicious results on DRE or

²The National Cancer Institute (NCI) previously recommended that men over age 50 receive a digital rectal examination, but not a prostate-specific antigen test. Recently, however, NCI has decided not to make any recommendations concerning cancer screening, deferring instead to the evidence-based policy guideline development processes used by the U.S. Preventive Services Task Force and the U.S. Agency for Health Care Policy and Research (AHCPR). AHCPR has not issued any guidelines concerning prostate cancer screening. NCI does summarize evidence on prostate screening effectiveness in its Physicians Data Query (PDO) database, noting the existence of only one, negative case-control study of DRE and the lack of evidence from well-controlled research concerning the use of PSA for early detection (199). The College of American Pathologists recommends that PSA not be used for screening among the general asymptomatic male population, reserving its use in cases where prostate cancer is suspected (200). The American Association of Family Physicians and American Society of Preventive Oncologists currently have no guidelines or recommendations concerning prostate cancer screening (31, 43). The College of American Physicians is currently developing such guidelines (26).

³Many cancers felt to be confined to the prostate preoperatively will be found to have already spread through the prostate capsule once surgery is performed.

⁴However, a significant minority (about 15 percent) of men with advanced prostate cancer have long-term survival measured in years (199).

PSA. The true false-negative rates⁵ of DRE and PSA are unknown, because studies have generally not determined what proportion of men with nonsuspicious DRE and PSA results in fact harbor cancer.

Digital Rectal Examinations

Among older men, digital rectal examinations are less likely to detect small and probably insignificant cancers than PSA, but it is more likely to detect cancers that have already spread beyond the prostate. Available data indicate that a suspicious DRE raises the likelihood that a patient has intracapsular (and possibly curable) prostate cancer 1 1/2- to 2-fold above the average risk faced by men of the same age. In a recent large study, DRE was suspicious in 15 percent of male volunteers over age 50, and 21 percent of men with a suspicious DRE had prostate cancer at biopsy. However, these high percentages were dependent upon a low threshold for considering the DRE abnormal, and upon the performance of multiple biopsies on volunteers with a suspicious DRE. In fact, about half the cancers found by TRNB in this study were found elsewhere in the prostate than the palpably suspicious area.⁶

Prostate-Specific Antigen

The prostate-specific antigen is a protein produced by prostate tissue and measurable in blood. It can be elevated in men both with and without prostate cancer, and the level at which a PSA measurement should be considered suspicious is controversial. On the two most commonly used assays, levels above 4 nanograms per millili-

ter (ng/mL) of blood are often considered abnormal.⁷ Available data suggest that a PSA elevation from 4.1 to 10.0 nanograms per milliliter (ng/mL) of blood raises the likelihood that a man harbors an intracapsular prostate cancer one and one-half to threefold above the average risk for men his age. Methods to improve the ability of PSA to discriminate between men with and without cancer are under active investigation; at present, there is no consensus on an optimal method. PSA does a particularly poor job at separating men with benign prostatic hyperplasia (BPH), a common nonfatal disease of aging, from men with intracapsular, possibly curable prostate cancer.

Combined DRE and PSA Screening

What is gained by doing both DRE and PSA rather than just DRE? Research indicates that by adding PSA testing to DRE in a one-time screening program, and by adopting an aggressive strategy of systematic prostatic biopsies for suspicious results on either test, prostate cancers can be found in about 4.2 percent of men age 65 (as opposed to about 2.4 percent with DRE alone), at a cost of performing multiple biopsies in 19 percent. At age 75, cancer would be found in about 7.2 percent of men (as opposed to 3.5 percent with DRE alone), with 27 percent of men requiring biopsy. Some of the cancers that are found in screening programs are discovered because of the high percentage of men who undergo multiple systematic biopsies, rather than because of the discriminating capacity of the tests themselves.

⁵The false-negative rate is the probability that someone with a negative screening test actually has prostate cancer. See box 3-1 for fuller description of concepts used to describe the accuracy of screening technologies.

⁶Given the inaccuracies of DRE (and PSA) along with these results, screening may behave something like a lottery in determining who receives the more accurate detection technology, TRNB.

⁷Alternatively, some experts recommend age-specific reference ranges, which take into account the rise in PSA levels seen with aging. For example, one study suggests a PSA should be considered abnormal if it is above 4.5 ng/mL for men in their 60s or 6.5 ng/mL for men in their 70s.

Followup Testing

TRUS is not accurate enough to serve as a primary screening test. TRNB is the test usually used to confirm whether cancer is present, and TRUS is often used to help direct where tissue samples are taken during biopsy. Many experts now recommend that patients with a suspicious DRE or PSA undergo multiple (four to six) prostatic biopsies (usually done in a single session). TRNB is uncomfortable and has a low but finite risk of bleeding and infection.

THE EFFECTIVENESS OF TREATMENT

For the early detection of prostate cancer to improve outcomes, treatment for cancers found at screening needs to be effective. In other words, knowledge of the presence of cancer will not save any lives unless treating those cancers makes a difference. There is considerable controversy regarding optimal treatment for cancer that does not appear to have spread beyond the prostate gland. Urologists generally argue that radical prostatectomy, a procedure to remove the entire prostate gland, results in the best outcomes for these men. As a result, rates of this procedure have risen dramatically in recent years, in response to the precipitous increase in diagnosis of early prostate cancer. However, expectant management (also called “watchful waiting”), in which the clinician treats symptoms and complications without attempting a cure, and radiation therapy are two other commonly used treatment strategies. Prostate cancer management tends to be more conservative in Western European countries than in the United States. No trial that shows which of the various treatment strategies saves the most lives (if any) has yet been completed.

Controversy about treatment effectiveness exists because of a lack of well-controlled studies comparing the main strategies for managing localized prostate cancer. To date, the only completed studies are based on observational studies. To the extent that any of these studies show that patients receiving a particular treatment option do better than those receiving another treatment, one cannot definitively conclude that the observed result was due only to treatment and not due to other differences between the patient groups.

Determining Cancer Stage

Before men begin treatment for a prostate cancer discovered by DRE or PSA, they would often undergo some staging tests to help determine the best treatment strategy. Patients with cancers that have already spread outside the capsule of the prostate gland, and particularly cancers that have spread to lymph nodes in the pelvic area or to bones are much less likely to be helped by aggressive treatments with curative intent. Computerized tomography (CT) or magnetic resonance imaging (MRI) scans and surgical examination of pelvic lymph glands, commonly employed to determine if the cancer has spread, are not particularly accurate for this purpose. As a result, even if a CT or MRI scan suggests spread, clinicians often proceed to treatment out of fear of withholding a potential cure. Despite some substantial misclassification rates, recent mathematical models designed to predict cancer spread suggest clinicians could use some staging tests more sparingly.⁸

Expectant Management

Expectant management is a strategy of reserving treatment for symptoms or complications related to

⁸For example, some patients with prostate cancers discovered by screening have a low enough risk of metastasis that they do not need bone scans or surgical removal of their pelvic lymph glands before proceeding with curative treatment.

prostate cancer, without necessarily attempting a cure. It is commonly used in Western Europe, and until recently, for many men with cancers found incidentally during surgery for BPH. Men treated expectantly risk developing symptoms due to local progression of their cancer (such as bladder outflow obstruction) or from spread of the prostate cancer to other parts of the body (which may lead to death).⁹ The prognosis for men with clinically localized prostate cancer depends on the aggressiveness of the cancer, particularly its grade. A recent synthesis of data from several studies of expectant management suggests a 10-year cancer-specific death rate of 13 percent for men with well and moderately differentiated prostate cancer (the most common types found by early detection with DRE and PSA) compared with a 66 percent death rate for men with poorly differentiated cancers.¹⁰

Radiation Therapy

Radiation therapy for prostate cancer, most commonly delivered as external beam x-irradiation, attempts to deliver a maximal dose of radiation to the tumor while minimizing the side effects from exposure to other, nearby radiation-sensitive tissues. Patients usually receive five weekday treatments over six or seven weeks (i.e. 30 to 35 treatments total). Although much recent literature has focused on surgical treatment of prostate cancer (radical prostatectomy), as late as 1990 radiotherapy was the most common treatment administered for every stage of prostate cancer in the United States.¹¹

The comparative effectiveness of radiotherapy versus radical prostatectomy or expectant management has

not been well studied. The medical literature suggests worse outcomes for patients with localized prostate cancer treated with radiotherapy compared with these other two strategies, but results are confounded by radiotherapy series including more older patients whose tumors have less favorable prognostic characteristics. While urologists have raised concerns about the high proportion of patients treated with radiotherapy having subsequently positive biopsies for cancer or rising PSA levels post-treatment, selected series suggest very good outcomes in terms of rate of future metastatic disease and cancer death. Although radiation therapy is more likely to result in bowel injury than is radical prostatectomy, other side effects are less common than those associated with prostatectomy.

Radical Prostatectomy

Radical prostatectomy entails removing the entire prostate with its fascial coverings and the seminal vesicles. More aggressive early detection efforts for prostate cancer in recent years have been accompanied by precipitous rises in population-based rates of radical prostatectomy. Recent modifications in surgical technique, resulting in an “anatomic” radical prostatectomy, have reduced the risk of surgical complications in some centers. While some men with prostate cancer treated surgically have done extremely well, the benefit of radical prostatectomy is unclear; only one controlled study has compared its outcomes against other treatment strategies. This single randomized trial, which showed no difference in mortality between radical prostatectomy and

⁹Obstructions of the bladder or urinary tract may require surgery, and distant spread of the cancer is usually treated with hormonal therapy (“androgen deprivation”).

¹⁰The data did not stratify men by age, but the estimates do adjust for other potential causes of death that do vary by age. The mean age in the sample was 70. Age was not predictive of *cancer-specific* survival in this study.

¹¹Recent data suggest that this trend reversed in 1991 with radical prostatectomy become the more common treatment strategy.

expectant management, was too small to detect a clinically important benefit from surgery, if it really existed.

The risks of radical prostatectomy include operative death, perioperative medical complications, incontinence, impotence, and urethral stricture formation. In a recent survey of a random sample of all Medicare patients who underwent this procedure in the United States between 1988 and 1990, 31 percent of men were wearing pads to help deal with wetness, 60 percent reported no full or partial erections since the surgery, and 20 percent indicated they had been treated for a stricture. The attributable¹² 30-day postsurgical death rate was 0.6 percent.

Followup Treatment

Men whose initial cancer has spread to other parts of the body, or men who are found to have cancer that has spread postoperatively can be treated with hormonal (androgen deprivation¹³) therapy. After initial treatment by radical prostatectomy, clinicians also often consider adjuvant radiation or androgen deprivation therapy for men considered at higher risk of harboring residual cancer. Cancers that have spread to other parts of the body tend to be responsive initially to hormonal treatment, but then become unresponsive (“refractory”). There are no data from well-controlled studies that indicate that any adjuvant therapies improve survival.

BENEFITS, RISKS, AND COSTS OF SCREENING

In the absence of controlled studies documenting that early detection of prostate cancer does more good

than harm, this analysis used a quantitative decision model to estimate risks, benefits, and costs of an early detection program under different sets of assumptions. It examined the implications of an **illustrative, one-time screening program** for three cohorts of 100,000 men, ages 65, 70, and 75, respectively.

Realistically, a Medicare benefit would most likely cover periodic screening, for example, a DRE and PSA every year as the ACS currently recommends, or every two or three years as Medicare currently does for breast and cervical cancer screening respectively. Understanding the true effects of an actual Medicare benefit would also require accounting for the fact that some men would have already received screening before their 65th birthday. However, as this analysis demonstrates, current understanding does not allow a definitive assessment of the cost-effectiveness of even a one-time benefit with its relatively simplified set of assumptions, much less a more complex, but realistic periodic benefit. The uncertainty concerning treatment effectiveness and the true rate at which smaller cancers eventually spread and cause death overwhelm other assumptions in the model.

Modeling an Illustrative Screening Benefit

The model employs a quantitative tool known as a Markov process¹⁴ to calculate what happens to men in each of the three age groups examined once they are screened for prostate cancer. It initially incorporates many assumptions favorable to early detection and treatment, including: 1) relatively high metastatic rates (that predict a higher-than-actually-observed lifetime proba-

¹²The “attributable” death rate is the total death rate minus deaths that would have been expected to occur during the 30 days even if patients had not received surgery.

¹³Clinicians can accomplish androgen deprivation through drugs or by orchiectomy (surgical removal of the testes).

¹⁴Chapter 5 provides more detail about the model and Markov processes.

bility of prostate cancer death in the cohorts),¹⁵ and 2) a 100-percent cure rate by surgery for cancers that have not spread beyond the prostate (resulting in overall cure rates of 97, 70, and 56 percent for all well-, moderately, and poorly differentiated cancers respectively). The analysis estimates the impacts of a one-time screening program under these assumptions, and then examines how relaxing the favorable assumptions about treatment efficacy changes the results.

Health Effects of Screening

Using the baseline assumptions, the model predicts a very favorable mix of potentially curable cancers would be discovered by early detection efforts with DRE and PSA. A large number of prostate biopsies would be performed as a result of this program; a much higher proportion of patients would require further invasive evaluation as a result of their initial testing than for other commonly used cancer screening strategies, such as guaiac testing for colorectal cancer or mammography for breast cancer. The proportion of men screened who undergo biopsy would range from 19 percent at age 65 to 27 percent at age 75. Treating cases of clinically localized prostate cancer with radical prostatectomy would render about 300 out of every 100,000 men *screened* incontinent, about 1,400 to 1,600 out of every 100,000 men *screened* impotent, and an additional 400 to 500 out every 100,000 both incontinent and impotent. About another 20 out of every 100,000 screenees would die from biopsy or treatment complications.

However, at the same time, early detection might save as many as 4,353 life-years in the 65-year-old cohort of 100,000 men, 2,774 life-years in the 70-year-old

cohort, and 1,415 life-years in the 75-year-old cohort.¹⁶ The benefits diminish considerably as the assumption of relatively high rates of metastasis and treatment effectiveness are relaxed.

Cost-Effectiveness

The analysis also estimates the cost-effectiveness of this illustrative, one-time DRE/PSA screening benefit. Adopting a Medicare perspective to estimate costs associated with screening and subsequent treatment, the model incorporates charges for physician services using the 1992 Medicare fee schedule and appropriate diagnosis related group (DRG) reimbursements for hospital services. The analysis discounts both future costs and health benefits at 5 percent annually.

The costs per year of life saved with the favorable assumptions (compared to doing no screening at all) was competitive with other commonly-used early detection maneuvers ranging from \$14,200 per year of life saved at age 65 to \$51,290 per year of life saved at age 75. However, these results are extremely sensitive to the assumptions made about the effectiveness of treatment and the rate at which intracapsular cancers spread and cause death. Reducing the estimates of future risk of metastases modestly to levels found elsewhere in the published literature and assuming treatment cures only half of all intracapsular cancers greater than 0.5 mL in volume substantially raises the estimated costs per year of life saved; under these assumptions, these estimates would range from \$94,458 at age 65 to \$506,909 at age 75.

As indicated earlier, current scientific evidence is insufficient to know the true risk of metastasis or whether treatment actually enhances survival, and hence,

¹⁵This includes making the assumption that metastatic rates for intracapsular (and possibly curable) cancers were as high as metastatic rates for cancers that have spread outside the prostate.

¹⁶These results do not discount future health benefits or adjust for quality of life.

whether or not prostate screening (even under the simplified assumptions needed to analyze a one-time program) is similar to other early detection programs for Medicare in its cost per life-year saved, or substantially more expensive. Regardless of whether screening and subsequent treatment extend life and regardless of the cost of any such health benefit, it is certain that population-based screening would subject men to the risks of impotence, incontinence, and other health problems caused by screening and treatment.

RESEARCH TO RESOLVE UNCERTAINTIES

Very little data from controlled studies are available to determine whether the benefits of early detection and treatment of prostate cancer outweigh the risks. One case-control study suggested that digital rectal exams do not reduce the risk of developing late-stage prostate cancer. And one trial of inadequate size showed no difference in the survival of men treated with expectant management versus radical prostatectomy. However, researchers are now initiating a number of well-designed

randomized trials of adequate size to address this issue. Trials comparing expectant management versus aggressive treatment with radical prostatectomy or radiation therapy for men with known clinically localized prostate cancer are underway or about to start in Scandinavia, the United Kingdom, and the United States. Trials comparing intensive screening with DRE and PSA versus no screening or “usual care” are being initiated in both Europe and the United States. Unfortunately, from the perspective of policymakers, the relatively indolent nature of many prostate cancers means that 10 to 15 years may be required to see enough prostate cancer deaths among men in these studies to obtain adequate comparisons of the strategies being tested.

This analysis of the estimated risks, benefits, and costs of early detection of prostate cancer highlights the uncertainty surrounding this topic. Any decision in the shortterm about whether Medicare should cover (and, hence, encourage) prostate cancer screening must weigh the resources required and the known complications that will result from screening and treatment against an uncertain health benefit.