Costs and Effectiveness of Prostate Cancer Screening in Elderly Men

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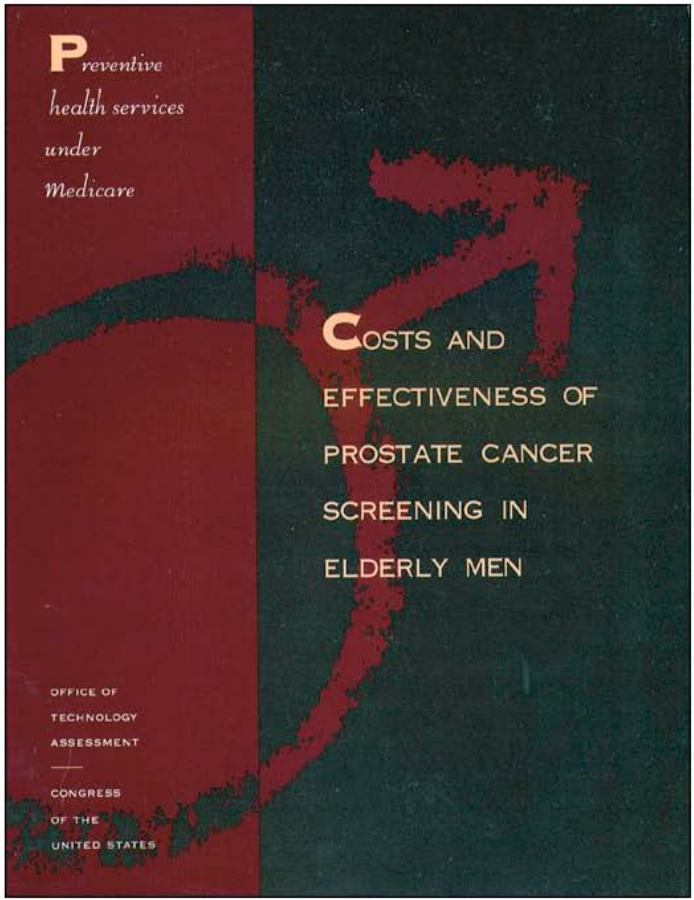

Foreword

Over the last 15 years, interest in strategies to promote health and prevent disease among elderly people has grown substantially. This trend has at least partially resulted from the desire to moderate rising health care costs among this segment of the population. As it has done in the case of this background paper, the House Committee on Ways and Means has periodically asked the Office of Technology Assessment to analyze the costs and effectiveness of providing selected preventive health services to elderly men under the Medicare program. The Senate Committee on Labor and Human Resources had earlier requested that OTA provide information on the value of preventive services to the American people.

Past work by OTA on prevention for elderly people has focused on studies of the costs and effectiveness of pneumococcal and influenza vaccines, and screening for breast, cervical, and colorectal cancer and for glaucoma and elevated cholesterol. This background paper focuses on the procedures of digital rectal examination and the more recently developed, less-invasive prostate-specific antigen blood test—both used to help detect prostate cancer.

The background paper summarizes the evidence on the effectiveness and costs of prostate cancer screening and treatment in elderly men and explores the implications for Medicare of offering this preventive technology as a Medicare benefit. This analysis illustrates the hard policy choices in deciding whether to expend federal resources for screening and treatment as well as risk their attendant complications before scientific research has definitively established the effectiveness of different technologies attempting to cure disease detected in varying stages and circumstances.

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Abbreviations

ACS	American Cancer Society
ACS-NPCDP	American Cancer Society National Prostate Cancer Detection Project
AMA	American Medical Association
AUA	American Urological Association
BPH	benign prostatic hyperplasia
CA	cancer
CDC	Centers for Disease Control and Prevention
CI	confidence interval
CPT-4	*Current Procedural Terminology*, 4th Edition
CT	computerized tomography
DRE	digital rectal examination
DRG	diagnosis-related group
FDA	Food and Drug Administration
HCFA	Health Care Financing Administration
HMO	health maintenance organization
HT	hormonal therapy
LY	life-years
MRI	magnetic resonance imaging
ng/mL	nanograms per milliliter
NPV	negative predictive value
PC	prostate cancer
PCS	Patterns of Care Studies
PDQ	Physicians Data Query
PIVOT	Prostate Cancer Intervention Versus Observation Trial
PL	pelvic lymph node dissection (metastasis)
PLCO	Prostate, Lung, Colorectal, and Ovarian Screening Trial
pPSA	predicted prostate-specific antigen
PPV	positive predictive value
PSA	prostate-specific antigen
PSAD	prostate-specific antigen density
RBRVS	resource-based relative value scale
RCT	randomized controlled trial
RPX	radical prostatectomy
RT	radiation therapy
RTOG	Radiation Therapy Oncology Group

TNM	tumor-node-metastasis
TRNB	transrectal needle biopsy (of the prostate)
TRUS	transurethral ultrasound
TURP	transrectal resection of the prostate
TX	treatment
UCR	usual, customary, and reasonable
VACURG	Veterans Administration Cooperative Urologic Research Group

Contents

CHAPTER

1

Summary[1]

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 determine 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 pneumoccocal 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

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[1]The 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 treatment. 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

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[2]The 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 (PDQ) 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).

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

[4]However, 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 rates[5] 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 milliliter (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.

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[5]The 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.

[6]Given 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.

[7]Alternatively, 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

[8]For 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

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

[10]The 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.

[11]Recent 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 attributable[12] 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 deprivation[13]) 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 process[14] 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-

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[12]The "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.

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

[14]Chapter 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,

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[15]This 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.

[16]These 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.

CHAPTER

2

Prostate Cancer in Older Men

Prostate cancer is a major health problem in the United States. In 1995, 244,000 new cases (up 44,000 from 1994) of prostate cancer and 40,400 deaths (up 2,400 from 1994) due to this disease are expected among all American men (199). However, most cases of prostate cancer and deaths from the disease occur in older men. Of the 32,378 U.S. prostate cancer deaths observed in 1990, 12,423 (38 percent) occurred in men ages 55 to 74 and 19,622 (61 percent) in men ages 75 and above. See table 2-1 for a comparison of the number of prostate cancer deaths with other causes of death for older men (40). The lifelong probability of dying of prostate cancer for men in the United States is 2.5 to 3 percent (308, 314).[1]

Patients who are diagnosed because they report symptoms (such as bone pain or difficulty urinating) generally have cancer spread outside of the prostate gland, and are incurable. Although these patients may initially show some improvement through treatment, these responses often do not last, and followup treatments have been disappointing (131).

Given this burden of illness and the difficulty in treating symptomatic disease, early detection using a simple clinical procedure called *digital rectal examination* (DRE) and a blood test called *prostate-specific antigen* (PSA) measurement would seem to be a commonsense strategy for reducing the morbidity and mortality from prostate cancer in the United States. This background paper examines the validity of this conclusion. This chapter gives an overview of the rationale for screening and provides background on the nature of prostate cancer. Chapter 3 discusses technologies for the screening and diagnosis of prostate cancer, and chapter 4 reviews evidence on the effectiveness of treating the disease. Chapter 5 presents some illustrative analyses of the potential costs and effectiveness of a one-time prostate cancer screening program and considers its implications for a potential Medicare screening benefit.

SCREENING VERSUS DIAGNOSIS

Before proceeding, it is useful to consider what is meant by the term *screening* and how it differs from *diagnosis*. While screening is an attempt to identify a condition in the absence of symptoms, diagnosis is performed in response to a patient's symptoms. This distinction has important public policy implications since the

[1]By comparison, in 1985 the lifelong probability of dying of other cancers were: 3.37 percent for breast cancer (among women), 0.96 percent for uterine cancer (among women), 2.8 percent for colorectal cancer, and 5.42 percent for lung cancer (308, 345).

TABLE 2-1: NUMBERS OF DEATHS BY LEADING CAUSES, U.S. MEN AGES 55 TO 74 AND 75+, 1990

Ages 55 to 74		Ages 75+	
All causes	430,713	All causes	447,303
Heart disease	152,323	Heart disease	173,558
Cancer (other than prostate)	129,364	Cancer (other than prostate)	75,117
Chronic obstructive lung disease	21,964	Cerebrovascular disease	33,594
Cerebrovascular disease	18,602	Chronic obstructive lung disease	25,580
Prostate cancer	12,423	Pneumonia, influenza	24,897
		Prostate cancer	19,622

SOURCE: Office of Technology Assessment, 1995. Data from C.C. Boring, T.S. Squires, Tong, T., et al. "Cancer Statistics, 1994," *CA-A Cancer Journal for Clinicians* (44):7-26, 1994.

federal Medicare program that provides health insurance to almost all Americans over age 65 pays for outpatient diagnosis, but it only pays for limited types of disease screening. Currently, prostate cancer screening is not among the services covered by Medicare. In this background paper, the use of prostate cancer detection technologies in mass screening programs as well as by clinicians in their offices are considered together as "early detection."[2]

RATIONALE FOR EARLY DETECTION AND TREATMENT

Theoretically, surgical removal of the entire prostate (radical prostatectomy) or radiation therapy (curative radiotherapy) should cure prostate cancer that is confined within the prostate capsule. The survival probabilities for patients with early-stage prostate cancer are clearly and dramatically better than for patients with late-stage disease, such as is commonly seen in the absence of screening. Screening tests are currently available that result in the detection of disease that is more often localized to the prostatic capsule than would be the case among men presenting with symptoms. Therefore, it is tempting to conclude that screening for prostate cancer will result in the curative treatment of pre-symptomatic cancers destined to cause future morbidity and mortality, reducing the burden of illness among older men (95, 295). However, this hypothesis has not yet been tested in well-controlled scientific research and, despite its attractiveness, might not be correct.

Why might screening fail to result in reducing prostate cancer mortality and morbidity? These potential problems are both general to screening for any cancer, and relatively specific to prostate cancer. Data from uncontrolled screening studies that report the probability of detected cancers progressing to more serious stages (stage shift data) do not necessarily predict long-term reductions in cancer mortality. This is because of "**lead-time bias**," the phenomenon of a screening test finding cancers earlier in their courses without changing their ultimate outcomes, and because of "**length bias**," in which a test may preferentially find low-risk, slow-growing

[2] Some experts have suggested that, since many men over age 50 have at least some lower urinary tract voiding symptoms, most office-based DREs and PSA tests are done for *diagnosis*, rather than case finding (361). However, despite traditional wisdom to the contrary, recent screening studies have *not* suggested that lower urinary tract symptomatology consistent with benign prostatic hyperplasia (prostatism) confers a higher risk for prostate cancer (72, 235). If symptoms of prostatism are indeed unrelated to the presence or absence of prostate cancer, looking for cancers in these men would be considered part of early detection as well.

cancers (81, 136). As described by Sackett and colleagues (292), on the basis of stage shift data, "...early diagnosis will always appear to improve survival, even when therapy is worthless!"

Prostate cancer screening, in particular, presents some additional conceptual challenges. Prostate cancers are commonly discovered by chance at autopsy and during a surgical procedure called *transrectal resection of the prostate* (TURP) performed for symptoms of a common, noncancerous enlargement of the prostate, benign prostatic hyperplasia (BPH). Many of these cancers would never have caused any symptoms, and would not place the patient at increased future risk of more serious cancer. Advocates of screening believe that the screening tests currently available for prostate cancer cannot generally detect these small, harmless cancers (12, 295); however, aggressive strategies of performing systematic biopsies of the prostate following suspicious screening tests will increase their detection (338).

The true, untreated, natural history of cancers discovered by screening (i.e., whether they would ultimately cause any harm to the patient) is unknown. Because many prostate cancers grow relatively slowly, the true benefit of treating cancers detected by screening remains unknown. The fact that many prostate cancers, even those detected by screening, have already spread through the prostate capsule, further dilute any benefit of screening. Furthermore, according to one theory drawn from observations of breast cancer (and untested for prostate cancer), prostate cancers destined to cause mortality may actually spread outside the prostate early on, even when they appear to be confined to the prostate upon examination of tissue removed in a prostatectomy (17, 240). And finally, aggressive curative treatment of prostate cancer carries risk itself; these risks, which include post-operative heart disease, impotence, incontinence, and a small chance of surgical death, must be weighed against evidence of reductions in mortality to make screening worthwhile.

TABLE 2-2: LIFE EXPECTANCY FOR U.S. MEN BY AGE AND RACE (Years)

	Life expectancy	
Age	White men	African American men
50	26.7	22.5
55	22.5	19.0
60	18.7	15.9
65	15.2	13.2
70	12.1	10.7
75	9.4	8.6
80	7.1	6.7
85	5.2	5.0

SOURCE: U.S. Bureau of the Census, *Statistical Abstract of the United States: 1993,* 113th Ed.,) (Washington, DC: U.S. Government Printing Office, 1993).

SPECIAL ISSUES IN SCREENING MEDICARE-AGE MEN

This report focuses on screening Medicare-age men, 65 and older. Because prostate cancer prevalence and mortality increases substantially with age, Medicare beneficiaries would appear especially likely to benefit from screening (assuming treatment works). However, these men also have a higher risk of dying from medical problems other than prostate cancer, and they have fewer years of life expectancy during which to reap the potential benefits of screening (see table 2-2). Furthermore, some of the risks of aggressive prostate cancer treatment also increase with age, making these men pay a higher "price" for any expected benefit of screening. The difficulty of current screening technology in distinguishing between potentially curable prostate cancer and the noncancerous condition BPH, whose prevalence increases

with age, also reduces the value of screening.[3] Finally, older men are also at higher risk of harboring large cancers and cancers with a poor prognosis that have already spread outside the prostate (233).

CONFLICTING GUIDELINES ON EARLY DETECTION

At present, the American Cancer Society (ACS) and the American Urological Association (AUA) recommend DRE and PSA determinations to evaluate the prostate gland for cancer starting at age 50 (age 40 for men at increased risk), although ACS acknowledges that, "reduction in mortality from screening has not yet been documented" (11, 237). ACS recommends annual exams. In addition, the American Medical Association (AMA) recommends that PSA should be covered every three years for men over age 50 as part of standard insurance benefits package (10).

ACS and AUA do not specify a definite "stopping age" for screening, although ACS recommendation acknowledges that, "generally, men with a life expectancy of at least ten years after detection may benefit from examination." These guidelines, which were adopted after the introduction of PSA into usual urologic practice, are consistent with recent published reviews that suggest physicians reserve early detection and aggressive treatment for men with a life expectancy of more than ten years (50, 204); in the United States, for men with average comorbidity, this threshold would come at about age 73. AMA recommends coverage of PSA testing up through age 70 (10).

The 1993 U.S. Preventive Services Task Force update (352) and the 1991 Canadian Task Force on the Periodic Health Examination (57) found evidence insufficient to recommend for or against DRE, and fair evidence to exclude PSA, from the periodic health examination. The College of American Pathologists recommends that PSA not be used for screening among the general asymptomatic male population, reserving its use for cases where prostate cancer is suspected (200).

The National Cancer Institute (NCI) used to recommend that men over age 50 receive a DRE, but not a PSA 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) (199).[4]

Reasons for Conflicting Recommendations

In the absence of well-controlled studies that establish the risks and benefits of screening for prostate cancer, or even large, controlled trials that document the benefit of aggressive curative treatment for cancer that has not spread beyond the prostate, it is possible to interpret the nonexperimental data that do exist to support any of these guidelines. However, differences in perspectives among policymakers, clinicians, and patients also contribute to the current controversy about prostate cancer screening. For example, Adami and colleagues (2) recently concluded that, given the possibility that early detection of prostate cancer does more harm than

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[3] According to one estimate, BPH is found in 40 percent of men over age 60 (133).

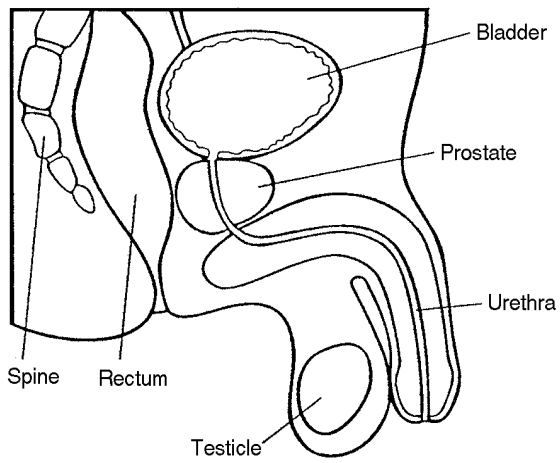
[4] NCI does summarize evidence on prostate screening effectiveness in its Physicians Data Query (PDQ) database, noting the existence of only one, negative case-control study of DRE and the lack of evidence from well-controlled research concerning the use of PSA for early detection (199). AHCPR has not issued any guidelines concerning prostate cancer screening. 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).

good, even a randomized trial of screening for prostate cancer might be unethical.

From a policy perspective, some experts emphasize an ethical imperative to avoid the harms of early detection efforts in general, and mass screening in particular, unless there is definitive proof of a net benefit from clinical trials (34, 80, 167, 302, 322). Others emphasize the need to do everything possible to lower the risk of cancer until the results of those studies are available (12, 13, 68, 131, 217, 258). Sackett (291) has referred to the protagonists represented in these basic ideological disputes as either advocates of the scientific method (”snails”), or advocates of screening (“evangelists”). The former perspective is incorporated into sets of criteria used by many groups for determining the net benefit of preventive maneuvers in general and cancer screening in particular, including the Canadian Task Force on the Periodic Health Examination (56), the U.S. Preventive Services Task Force (351), and the World Health Organization (368). No matter what expert groups recommend for populations, on the level of individual patients and clinicians, differences of opinion and variations in actual practice will exist (219, 238, 247).

The rapid increase in medical care costs in recent years has placed greater scrutiny on the effectiveness of medical interventions. In the past, medical interventions that seemed conceptually sound were often administered until clinical trials proved they did not work (111). More recently, the burden of proof for some interventions has begun to shift to those who want to use the treatment, suggesting that these interventions be withheld until clinical trials establish that they work (112). Although recommendations may also vary depending on whether they consider the health care costs associated with early detection, none of the guidelines described above directly took these costs into account.

FIGURE 2-1: CROSS-SECTIONAL ILLUSTRATION OF NORMAL MALE PELVIC REGION



SOURCE: The American Prostate Society, Inc.

BASIC BIOLOGY OF PROSTATE CANCER

The prostate is a golf-ball-sized gland whose primary function is the manufacture of semen, the fluid ejaculated with sperm. It is found below a man’s bladder and surrounds the urethra through which urine passes on its way from the bladder (see figure 2-1). Prostatic carcinoma (prostate cancer) is a relatively slow-growing malignancy, with the potential for spread related to both volume of the tumor and degree of cell differentiation (the extent to which the cancerous cells are different from the normal cells from which they arose),[5] which themselves are related.

[5] The greater the differentiation, the less likely it is to spread and the better the prognosis for the patient.

In careful studies of autopsy material, McNeal and colleagues have documented that tumors less than approximately 0.5 mL are commonly found among older men, and are rarely associated with penetration of the prostate capsule (called capsular penetration) (233). Above 0.5 mL, penetration of the prostatic capsule begins to be seen, and overt metastases (spread of the cancer) begin to be seen with tumors above 1 mL, and particularly above 3 mL, along with more frequent capsular penetration and invasion of the surrounding tissue. Older patients have larger tumors, and larger tumors are more likely to be less well differentiated. Clinically localized cancers are estimated to have a doubling time of two years or more (299, 325, 328). Based on epidemiologic observations, Stamey and colleagues (328) doubt that cancers less than 0.5 mL in volume are likely to cause future morbidity and mortality given this long doubling time; however, all large prostate cancers were undoubtedly small at some point.

Prostate cancers are described by tumor grade (the extent of cell differentiation) and stage (how advanced the cancer has become). In studies of the natural history of prostate cancer, grade and stage are used to predict malignant behavior. The most common grading system is the Gleason score, which yields a sum of 2 to10 based on the two most common patterns of cell differentiation in the tissue sample. Tumors assigned scores of 2 to 4 are considered "well differentiated"; 5 to 7, "moderately differentiated"; and 8 to 10, "poorly differentiated."

The two predominant staging systems for prostate cancer are the Whitmore (A-D) system and the Tumor-Node-Metastasis (TNM) system (245).[6] Table 2-3 describes the two predominant systems. Although increasing stages of prostate cancer generally indicate a poorer prognosis, different stages can behave similarly (i.e., Stage T1b/A2 and T2/B1 (340).[7] As will be discussed later, clinicians' attempts to stage patients' cancers are unreliable, and many cancers thought to be localized to the prostate are found to be more advanced upon surgery. In addition, the grade of a tumor evaluated from a biopsy (a procedure for removing a small sample of tumor to determine if it is cancerous) may diverge from the grade determined from an examination of the surgically removed prostate (7). These phenomena make it difficult to compare the prognosis of prostate cancer patients staged and treated by different methods.

RISK FACTORS FOR PROSTATE CANCER

The cause of prostate cancer is not known, although evidence points to both genetics and environment as having roles (62, 85, 273, 310):

- **Age** is the most important risk factor, with the incidence[8] of both prostate cancer diagnosis and death increasing sharply with age (table 2-4).[9]
- **Family history** is also a determinant of risk. Men with one immediate relative with prostate cancer have a twofold increased risk, which increases to roughly

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[6] Other variants of these systems have been proposed (41, 42, 146, 336).

[7] In these descriptions of cancer stage, the notations before the slash (T1b and T2) refer to the TNM system, and the notations after the slash (A2 and B1) refer to the Whitmore system.

[8] *Incidence* refers to the number of new cases of a condition found in a population during a period of time. It is distinguished from *prevalence*, which refers to the total number of cases (discovered or undiscovered) of the condition in a population at a given point in time.

[9] Even though prostate cancer risk rises with age, recent research has found small areas of prostate cancer in about 30 percent of men in their 30s and 40s (293).

TABLE 2-3: STAGING SYSTEMS FOR PROSTATE CANCER

Clinical stage		
Whitmore (A-D)	**TNM system[a]**	**Definition**
1. Clinically nonpalpable cancers		
A_1	T_{1a}	Incidental finding of cancer in ≤ 5% resected (removed) tissue from TURP.
A_2	T_{1b}	Incidental cancer finding > 5% resected tissue. Moderately or poorly differentiated grade with < 5% resected tissue from TURP.[b]
B_0	T_{1c}	Cancer detected by needle biopsy (e.g., following elevated PSA).
2. Palpable cancers apparently confined within prostate capsule		
B_1	T_{2a}	Involves one-half of one lobe of the prostate or less.
B_1	T_{2b}	Involves more than one-half of one lobe, but not both lobes.
B_2	T_{2c}	Involves both lobes of gland but apparently confined (B_2, but not T_{2c} cancers can be greater than 1.5 cm but still involve only one lobe).
3. Local extra-capsular penetration		
C_1	T_{3a-3b}	Penetration of the prostate capsule palpable without evidence of invasion of the seminal vesicles outside the prostate.
C_2	T_{3c}	
	T_{4a-4b}	Palpable invasion of seminal vesicles. Invasion of the bladder neck, external sphincter, rectum, or pelvic muscles.
4. Metastatic Disease		
	Nx	Cannot assess; no apparent nodal involvement.
D_1	N_1 N_2 N_3	Metastasis in a single lymph node 2 cm, metastasis single nodes 2-5 cm, or multiple nodes (all ≥5 cm), metastasis in node ≥ 5 cm.
D_2	M_1	Distant metastasis.
	M_{1a}	Lymph nodes outside the region of the prostate.
	M_{1b}	Bone.
	M_{1c}	Other site(s).

[a] In the "TNM" system, "T" refers to characteristics of the tumor, "N" refers to the extent cancerous cells are found in lymph nodes, and "M" refers to the extent of metastasis (spread of the cancer).

[b] Criteria for cancer grade (well-, moderately-, or poorly-differentiated) and percentage of resected volume for defining stage A_2 varies across different studies.

KEY: PSA = prostate-specific antigen blood test.

TURP = Transurethral resection of the prostate, a procedure for treating benign prostatic hypertrophy (BPH), a noncancerous enlargement of the prostate, by surgically removing parts of the gland.

SOURCE: Office of Technology Assessment, 1995. Based on information presented in M.J. Barry, C.M. Coley, C. Fleming, et. al, "The Safety, Effectiveness, and Cost of Early Detection and Treatment of Prostate Cancer Among Older Men: A Report to the Congressional Office of Technology Assessment," OTA contract paper no. K3-0546.0, Massachusetts General Hospital, Boston, MA, June 30, 1994.

fivefold with two affected family members (323, 332). A recently described hereditary clustering of prostate cancer in families may be responsible for about 40 percent of cases in men under age 55 and 10 percent of prostate cancer cases overall (59, 60).

- **African American men**, who have generally been unrepresented in voluntary prostate cancer screening programs (104), have a 1.3 to 1.6 fold higher risk of prostate cancer than do non-African-American men

TABLE 2-4: AGE-SPECIFIC INCIDENCE AND MORTALITY FROM PROSTATE CANCER FOR ALL U.S. MEN

Age	Incidence per 100,000 man-year	Deaths per 100,000 man-years
50-54	33	4
55-59	105	14
60-64	259	36
65-69	525	81
70-74	799	157
75-79	1,024	268
80-84	1,186	437
85+	1,182	662

SOURCE: Office of Technology Assessment, 1995. Based on data from SEER, 1992.

(21). In the 50 to 54 year age group, the risk is twofold higher (73).

- Research has shown a statistical association between **dietary fat**, particularly animal fat from red meat, and prostate cancer (142, 286). Although fat may not directly cause prostate cancer, it may contribute indirectly by affecting certain hormone levels in men (272).
- Several studies have found a weak statistical association between **prior vasectomy** and prostate cancer (140, 141, 288). However, because the association is weak, because contradictory data exist (14), and because there is no convincing biological explanation for this result, causality cannot be considered proven (153, 169).

The lack of data on risk factors that could change (except perhaps reductions in dietary fat intake) makes the potential for preventing prostate cancer before it develops modest at this point. However, considerable interest has arisen in trying to prevent prostate cancer with drugs. A randomized clinical trial of prostate cancer prevention using finasteride, a drug employed in treating some cases of BPH, is just getting underway (343).

THE PREVALENCE OF PROSTATE CANCER

In order to analyze the potential impact of a screening program as is attempted in chapter 5, it is necessary to know the age-specific prevalence of latent prostate cancer in the population. Table 2-5 presents estimates for prostate cancer prevalence derived from a synthesis of autopsy studies (24, 113, 128, 134, 159, 222, 293, 305) together with McNeal's analysis of the volume of cancers found at autopsy (233). It presents estimates of the probabilities of men age 65 and older falling into one of the four following states of health: no cancer, cancers 0.5 mL or less in volume, cancers greater than 0.5 mL still confined to the prostate, and cancers greater than 0.5 mL spread beyond the prostate capsule.

Appendix A describes the methods used to derive table 2-5. These probabilities can only be considered estimates because patients coming to autopsy may not be representative of the general population, and because scarce data exist describing distributions of autopsy cancers by host age, and tumor volume and extent. However, autopsy studies were excluded from this analysis unless patients with cancers suspected before death were specifically excluded.

PROSTATE CANCER MORTALITY

The discussion of treatment effectiveness in chapter 4 reviews epidemiologic data on the natural history of untreated, clinically-significant prostate cancer. The age-standardized mortality rate for prostate cancer increased from about 21 to 25 per 100,000 males in the United States between 1960 and 1988 (39); meanwhile, the incidence of prostate cancer in the United States has increased much more dramatically, at first due in part to wider use of the surgical procedure, transurethral resection of the prostate, for symptoms of BPH (274). Increasing early detection efforts have sustained this trend in re-

TABLE 2-5: PREVALENCE OF PROSTATE CANCER BY TUMOR VOLUME AND AGE SYNTHESIZED FROM EIGHT AUTOPSY STUDIES[a]

Age	Overall prevalence [b]	Cancer < 0.5 mL[c]	Cancer > 0.5 mL, intracapsular[d]	Cancer > 0.5 mL, extracapsular[e]
40-49	12%	7.2%	3.5%	1.3%
50-59	15	9.0	4.4	1.6
60-69	22	13.2	6.4	2.4
70-79	39	23.4	11.4	4.2
80 +	43	25.8	12.6	4.6

[a]Appendix A describes the methods used to derive this table.
[b]Numbers rounded to the nearest whole. Weighted average for men over age 50 is 30% (547/1811).
[c]Estimated weighted mean prevalence of prostate cancers less than O.5 mL in men over age 50 is 18%.
[d]Estimated weighted mean prevalence of intracapsular prostate cancers exceeding 0.5 mL for men over age 50 years is 8.8%.
[e]Estimated weighted mean prevalence of extracapsular prostate cancer exceeding 0.5 mL in men over age 50 years is 3.2%.

SOURCE: Office of Technology Assessment, 1995. Data sources described in appendix A.

cent years (105). These trends are reflected in an increased tendency to diagnose cancer at less advanced stages, and improved stage-specific five-year survival rates (238, 330).

These statistics also emphasize the danger of using "stage shift" data to make conclusions about underlying cancer mortality; a shift toward more localized cancers and better outcomes for individual patients in recent years has actually been accompanied by a small *increase* in the rate of prostate cancer mortality, from a national perspective. However, since aggressive early detection efforts are a relatively new phenomenon, some years may be required before this strategy results in any decrease in population-based rates of prostate cancer mortality.

CHAPTER

3

Technologies To Detect Prostate Cancer

The most commonly used technologies for detecting and diagnosing prostate cancer are digital rectal examination (DRE), prostate-specific antigen (PSA) measurement, transrectal ultrasound (TRUS), and transrectal needle biopsy of the prostate (TRNB). For primary-care based case-finding and mass screening, TRUS and TRNB would be logistically difficult to include as primary screening tests given their relative complexity and invasive nature. Moreover, the marginal value of TRUS above DRE and PSA seems to be small (18, 91, 215), and the risk and discomfort of TRNB would seem to obviate its use as a primary screening test. Therefore, this chapter considers the use of DRE and/or PSA as primary screening tests, and TRUS and TRNB as followup, confirmatory tests.

To analyze the impact of screening, it is necessary to know the "operating characteristics" of each screening technology. In general, the operating characteristics, which refer to the ability of a test to find all cancers that would cause harm and to find only those cancers, are expressed in terms of the sensitivity and specificity of the test. (Box 3-1 describes these concepts.) Unfortunately, the "true" operating characteristics of DRE and PSA cannot be defined since few studies have evaluated them in populations where the true underlying prevalence of clinically-significant prostate cancer is known. The fact that small volume, well-differentiated cancers should be considered as "nondisease" and that it is relatively easy to detect advanced cancer which may offer no therapeutic benefit further complicates the design and analysis of these studies.

What are usually available are studies of the "positive predictive value" of tests, the proportion of positive or suspicious test results that ultimately turn out to be cancer (see box 3-1); in these studies, patients with "negative" test results do not receive followup TRNB (even though they may harbor significant prostate cancers that the screening test did not find). Furthermore, these studies use different combinations of primary screening tests and different strategies of followup evaluation. Finally, the studies do not uniformly provide age-specific predictive values, which are important to an analysis of screening older men.

To overcome these problems, this analysis presents "likelihood ratios" of disease (292) for DRE and for PSA. These likelihood ratios are estimates of how many times more likely a patient with a particular test result is to have a given type of cancer than if the patient did not have the test. The probabilities of cancer with no test are the prevalence estimates found in table 2-5. Appendix C

BOX 3-1: DESCRIBING THE ACCURACY OF SCREENING TESTS

To analyze the impact of a screening program, it is necessary to understand the accuracy of each screening technology, sometimes referred to as the "operating characteristics" of the test. These operating characteristics, which include the ability of a test to find all existing disease and to find only disease, are usually expressed in terms of the test's sensitivity and specificity. **Sensitivity** is the percentage of all screened people with disease who test positive, while **specificity** is the percentage of all healthy screened people who test negative. In other words, sensitivity is the ability of a test to find people with disease, while specificity represents the test's ability to label healthy people correctly. These characteristics relate inversely to the **false-positive** rate (the percentage of people free of disease who test positive) and the false-negative rate (the percentage of people afflicted by the disease whose screening results are negative). For example, a test with sensitivity between 70 and 95 percent would have a false-negative rate of 5 to 30 percent. The figure below displays the calculation of sensitivity and specificity and the relationship of these indicators to false-positive and false-negative rates.

CALCULATION OF SENSITIVITY AND SPECIFITY

Calculation of Sensitivity and Specificity

		Disease	
		Present	Not present
Test result:	Positive	a	b
	Negative	c	d
		a+c	b+d

a+b+c+d = Total number of tests administered

Sensitivity = $\frac{a}{a+c}$ Specificity = $\frac{d}{b+d}$

False-negative rate = 1-sensitivity = $\frac{c}{a+c}$

False-positive rate = 1-specificity = $\frac{b}{b+d}$

SOURCE: Office of Technology Assessment, 1990.

Calculating sensitivity and specificity requires that one know the true underlying prevalence of disease in the screened population, regardless of screening test results. In other words, it would require performing definitive followup tests on all screenees, even those whose screening test is negative. This is usually not done in studies of prostate cancer screening because of the invasiveness, costs, and risks of such followup procedures (usually transrectal needle biopsies). Hence, most studies report a less useful measure of a screening technology's accuracy, **the positive predictive value (PPV).** The PPV is the percentage of people with positive test results who ultimately turn out to have cancer. Conversely, the **negative predictive value (NPV)**, is the percentage of people with negative test results who ultimately turn out to be free of disease. Calculation of PPV does not require knowing the true underlying prevalence of disease among all people screened. The PPV for a specific condition is directly related to the prevalence of the condition being screened for and, all else being equal, is inversely related to the false-positive rate. A low PPV usually indicates a high false-positive rate, although it is sometimes possible to have both a low PPV and a low false-positive rate. This occurs if the disease is rare. With rare conditions, because the prevalence of a previously undetected disease would decrease as the frequency of testing increases, prolonged studies implementing periodic rescreening normally yield declining PPVs as the studies progress.

The PPV is a limited measure of screening accuracy. In most circumstances a low PPV indicates that for every cancer detected a substantial number of individuals undergo the risks and costs associated with followup testing. However, policymakers or clinicians may decide that reductions in mortality and morbidity associated with screening in a population are large enough to justify the risks and costs associated with screening and followup among healthy individuals. The uncertainty concerning whether this is true for prostate cancer screening is a major issue in the analysis presented in this background paper.

SOURCE: Office of Technology Assessment, 1995.

discusses the methods used in making these estimates. The estimates themselves are presented in the sections on DRE and PSA respectively below.[1]

A potential problem with these estimates is that the positive predictive value in different studies depends heavily on the aggressiveness of the followup strategy employed for a suspicious test. Studies tend to find more cancer by performing multiple systematic biopsies (and even repeated sets of multiple systematic biopsies) in response to a suspicious primary test (70). Using this methodology, a test that has poor sensitivity and specificity but is "positive" in a large proportion of the population will appear to perform well if one examines only the predictive value of the strategy. For example, a strategy of performing multiple sets of biopsies on all men with brown eyes would probably have a rather high "yield" in terms of the number of prostate cancers detected, despite eye color having no information value as a test for prostate cancer. Eye color, in essence, becomes a lottery for receiving the more accurate diagnostic test, TRNB. A recent study of DRE and PSA suggests that this phenomenon occurs with prostate cancer screening (72, 123). Although the predictive value of a suspicious DRE in this study was about 22 percent (72), the percentage of palpably suspicious quadrants of the prostate that yielded cancer was only about 11 percent, implying that roughly half the cancers found as a result of selecting patients for biopsy based on a suspicious DRE were actually found elsewhere in the prostate as a result of the systematic biopsy.

DIGITAL RECTAL EXAMINATION

The digital rectal examination, in which the clinician attempts to feel abnormalities in the size or shape of the prostate gland through the rectum, is a time-honored test for the early detection of prostate cancer despite very weak agreement among published guidelines about its value (100). The DRE is limited in sensitivity because of an inability to detect tumors deep within the prostate gland. Because larger tumors are easier to feel, DRE is unlikely to detect insignificant cancers (although this risk will increase if a suspicious DRE triggers a set of systematic biopsies in addition to a biopsy of the suspicious area). The detection of larger cancers also means that a relatively high percentage of DRE-detected tumors (half or more) will have already spread beyond the confines of the prostatic capsule (139, 279, 271). Many investigators have been concerned about variation among physicians in their ability to detect cancers by DRE (271), especially the possibility that DREs performed by primary care physicians may not be as discriminating as urologists' exams. However, little empirical evidence exists to address this concern (354).

Appendix C lists studies of primary DRE screening for prostate cancer, with brief descriptions of study methods and results. Comparisons are difficult given different patient populations, different thresholds for calling a DRE "suspicious," and different strategies of followup testing. One study by Chodak and colleagues (79) provides the most detailed presentation, and allows es-

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[1] This method is methodologically inferior to knowing the underlying disease state of all individuals in each study, but probably superior to the alternative methods used in the screening literature, such as screening a population with multiple modalities (often DRE, PSA, and TRUS) and assuming all clinically significant cancers have been detected, or testing only patients with documented clinical disease status (e.g., men scheduled for radical prostatectomy for known cancer). The former method overestimates sensitivity and specificity since some clinically significant cancers would likely be undetected by all modalities; the latter method overestimates sensitivity if cancers in the tested population are more advanced than those that would be identified by screening, or if the screening test were actually used in the process of identifying them in the first place.

TABLE 3-1: ESTIMATED LIKELIHOOD RATIOS FOR RESULTS OF DIGITAL RECTAL EXAMINATION CHANGING THE ODDS OF SIGNIFICANT[a] PROSTATE CANCER (>0.5mL) OF DIFFERENT PATHOLOGIC EXTENTS[b]

	Likelihood Ratio	
DRE result	**Intracapsular cancer**	**Extracapsular cancer**
"Suspicious"		
Chodak (1989)[c]	1.5	8.6
Richie (1993)[d]	2.0	2.7
"Nonsuspicious"		
Chodak (1989)	0.96	0.53
Richie (1993)	0.83	0.72

[a] Probability of prostate cancer <0.5mL = 11% based on J.E. Oesterling, V.J. Suman, H. Zincke et al., "PSA-Detected (Clinical Stage T1c or BO) Prostate Cancer: Pathologically Significant Tumors," *Urologic Clinics of North America* 17:719-737, 1990.

[b] See appendix C for methods deriving these estimates.

[c] G.W. Chodak, P. Keller, and H.W. Schoenberg, "Assessment of Screening for Prostate Cancer Using the Digital Rectal Examination," *Journal of Urology* 141:1136-1138, 1989.

[d] J.P. Richie, W.J. Catalona, F.R. Ahmann, et al., "Effect of Patient Age on Early Detection of Prostate Cancer with Serum Prostate-Specific Antigen and Digital Rectal Examination," *Urology* 42:365-374, 1993.

SOURCE: Office of Technology Assessment, 1995. Based on information from M.J. Barry, C.M. Coley, C. Fleming et. al, "The Safety, Effectiveness, and Cost of Early Detection and Treatment of Prostate Cancer Among Older Men: A Report to the Congressional Office of Technology Assessment" OTA contract paper no. K3-0546.0 Massachusetts General Hospital, Boston, MA June 30, 1994.

timation of the likelihood of cancers with and without capsular penetration (table 3-1) for each DRE test result.[2] Appendix B discusses the methods used to produce these estimates. No clinical trials of the use of DRE alone for the early detection of prostate cancer are available. However, neither a case-control study (129) nor a decision model (241) has suggested an important survival benefit for men screened with DRE.

PROSTATE-SPECIFIC ANTIGEN

Prostate-specific antigen is a glycoprotein produced in the prostate gland with a probable role in the transport of semen. Because cancerous prostate tissue, gram for gram, produces greater quantities of PSA than does normal or benignly enlarged tissue, and because prostate cancer may increase the likelihood that PSA "leaks" into the general circulatory system, serum (blood) PSA levels appear to have some discriminating capacity for prostate cancer (99, 257). Preliminary evidence suggests prostate cancers need to be greater than 1 mL in volume before they cause an increase in serum PSA (49).

Three PSA assays have been commonly used clinically and described in the literature (172). Hybritech's Tandem PSA assays detect PSA with monoclonal antibody

[2] In a more recent study, with a policy of systematic biopsy for abnormal DRE results, 15 percent of 6,630 male volunteers over age 50 had an abnormal DRE, and 21 percent of the men with an abnormal DRE had cancer at biopsy; the overall detection rate of cancer for DRE in this series was 3.2 percent, reflecting the more aggressive use of biopsies (72). A new followup study has suggested better outcomes for men diagnosed at initial rather than followup screening with DRE (139); this finding may represent the effect of length bias with one-time screening (discussed in chapter 2).

probes; these assays use radioactive antibodies and enzymatic reactions to perform the measurement. The Tandem PSA tests are currently the only assays approved by the U.S. Food and Drug Administration (FDA) for use in conjunction with DRE as an aid in the detection of prostate cancer in men over age 50.[3] Abbott's IMx PSA assay uses a microparticle enzyme immunoassay technique. Yang's Pros-Check PSA assay uses a polyclonal antibody probe to measure PSA (356). The levels of PSA measured by the Hybritech and Abbott assays appear roughly similar (190, 355), while the polyclonal assay runs values about 1.6-fold higher (148, 339). However, investigators have recently raised concerns about the calibration of the Hybritech and Abbott assays (48, 149, 226, 266), which together dominate the PSA assay market. Clinicians need to know which test their laboratory uses, and to consider a switch in assays in the "differential diagnosis" of a changing PSA in a given patient.

One potential difficulty with this screening test is that factors other than prostate cancer can temporarily elevate PSA levels for several weeks: acute inflammation of the prostate (prostatitis), acute urinary retention, a diagnostic medical procedure called rigid cystoscopy, TRUS, TRNB, or prostate surgery (193, 262). A recent study has also found temporary elevations in PSA following ejaculation (250). However, several studies have now documented that there is no clinically important elevation in PSA values following routine DRE (95, 371), an important finding since physicians often perform DRE and PSA at the same visit.

TABLE 3-2: PROPOSED AGE-SPECIFIC NORMAL REFERENCE RANGES FOR PROSTATE-SPECIFIC ANTIGEN MEASUREMENTS

	Normal reference range (ng/mL)	
Age	**Oesterling, 1993c [a]**	**Dalkin, 1993[b]**
40-49	0 - 2.5	-
50-59	0 - 3.5	0 - 3.5
60-69	0 - 4.5	0 - 5.4
70-79	0 - 6.5	0 - 6.3

[a] J.E. Oesterling, S.J. Jacobsen, C.G. Chute, et al., "Serum Prostate-Specific Antigen in a Community-Based Population of Healthy Men: Establishment of Age-Specific Reference Ranges," *Journal of the American Medical Association.* 270:860-864, 1993.

[b] B.L. Dalkin, F.R. Ahmann, and J.B. Kopp, "Prostate Specific Antigen Levels in Men Older Than 50 Years Without Clinical Evidence of Prostatic Carcinoma," *Journal of Urology* 150:1837-1839, 1993.

SOURCE: Office of Technology Assessment, 1995. Based on information from M.J. Barry, C.M. Coley, C. Fleming et. al, "The Safety, Effectiveness, and Cost of Early Detection and Treatment of Prostate Cancer Among Older Men: A Report to the Congressional Office of Technology Assessment", OTA contract paper no. K3-0546.0, Massachusetts General Hospital, Boston, MA June 30, 1994.

Most studies consider an Abbott or Hybritech PSA level up to 4.0 nanograms per milliliter of serum (ng/mL) (equivalent to a Yang PSA level up to 7 ng/mL) as nonsuspicious (148, 339).[4] However, "normal" PSA values increase as a man ages, reflecting the increasing size of the prostate with age (88). Two recent articles have proposed age-specific reference ranges for normal PSA values (table 3-2). One study used the 95th percentile of serum PSA among men without evidence of prostate cancer as the upper boundary of the reference range

[3] The FDA approved the Tandem PSA assays for detection on August 25, 1994. The Tandem tests, the Abbott IMx, the Toschmedix, AIA pack, and the Ciba-Corning ACS assays are all approved for monitoring men with previous prostate problems (228).

[4] Some investigators prefer a lower threshold on the Abbott or Hybritech assays of 3.0 ng/mL to improve test sensitivity (201). For a given underlying prevalence of true cancer, lowering the threshold increases the proportion of all true cancers found by screening, but at the cost of having to do more biopsies (which, as described later in this paper carries cost and risk in itself) and an increased number of false-positive screening results. In other words, in setting the threshold for conducting a biopsy, there is a tradeoff between false-negative and false-positive test results.

(260, 261), while the other used a slightly different, but methodologically similar approach[5] to define the upper limit (101).[6] Another recent study compared the performances of several PSA test kits as part of an international PSA standardization conference (329).

Appendix D lists published studies that use PSA as the primary screening tool to detect prostate cancer (DRE used only to followup a suspicious PSA).[7] Although these studies generally have a somewhat higher proportion of subjects with a cancer detected than do the studies of primary DRE, these proportions are likely underestimates of the maximal attainable yield since patients were often not biopsied unless a followup DRE or TRUS was also suspicious. Using data from the Catalona and Brawer studies, likelihood ratios for Hybritech PSA results of different categories were calculated as described in appendix B and are provided in table 3-3 (44, 66, 70).[8]

Variations in the use of PSA for screening have been proposed to improve the operating characteristics of this test for prostate cancer (96, 182). These variations, each of which has its own drawbacks, include: 1) *PSA density* (PSAD), a method of correcting the raw PSA value by the volume of the prostate, as measured by TRUS (32, 33, 284); 2) a *predicted PSA* (pPSA) based on gland volume against which measured PSA is compared to make decisions about proceeding to biopsy (206); and 3) *PSA velocity,* the rate of change of PSA over time (63, 64).[9] Research currently underway may lead to a test for more specific types of PSA (36, 37, 106, 211, 212, 213) or other types of biological substances (171, 298) that more precisely identify men with prostate cancer.

One-Time Versus Repeated PSA Screening

Much less is known about the results of repeated screening with PSA than about one-time screening. This gap in our knowledge is significant since a Medicare prostate cancer screening benefit would most likely cover periodic screenings, not one screening per lifetime. The few studies that are available suggest a decrease in the proportion of screenees with cancer over repeated screenings (46, 47), while the proportion of patients with cancer confined to the prostate capsule appears to increase: 71 percent as opposed to 63 percent in one series (13, 70), and 87 percent versus 56 percent in another series (46). Appendix E summarizes these studies.

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[5] Dalkin and colleagues (101) selected two standard deviations above the mean of the distribution of log-transformed age-specific PSA values to define the upper limit of the reference range.

[6] If the references ranges in table 3-2 are interpreted as age-dependent thresholds for conducting followup tests, they implicitly assume that the costs of a false-positive relative to a false-negative test increase with age. This assumption makes conceptual sense, as older men have a greater risk of treatment complications, and fewer years of life expectancy over which to reap the benefits of screening (on the other hand, younger men also have more years of life to live with any complications engendered by treatment). However, some clinicians are unwilling to trade sensitivity for specificity, regardless of age (255).

[7] In addition, a single, recent case-control study published just prior to publication of this report suggests that PSA may actually preferentially identify aggressive cancers early with relatively high sensitivity and specificity (130).

[8] In a recent study, a group of 72 men underwent systematic sextant biopsies despite a PSA less than 4 ng/mL and a normal digital rectal exam; these men had lung masses on chest radiography and were being evaluated to rule out metastatic prostate cancer as a cause. Prostate cancer was discovered in 3 out of 72 men (4 percent), compared to 9 out of 77 men (12 percent) with a normal digital rectal examination but an elevated PSA (160). This data yields a **likelihood ratio of 0.51** for a normal PSA and 1.51 for an elevated PSA (assuming these cases were consecutive), not inconsistent with the **likelihood ratios** presented in table 3-3.

[9] Because of normal fluctuations in PSA values within a given patient, a PSA velocity based on only two measurements probably has little value in clinical decisionmaking (280). Most recently, the concept of adjusting serum PSA by transition zone volume, rather than whole prostate volume, has been introduced (181).

TABLE 3-3: ESTIMATED LIKELIHOOD RATIOS FOR DIFFERENT RESULTS OF PROSTATE-SPECIFIC ANTIGEN TESTING CHANGING THE ODDS OF SIGNIFICANT (>0.5 mL)[a] PROSTATE CANCER[b]

	Likelihood ratio	
PSA result[c]	**Intracapsular cancer**	**Extracapsular cancer**
Pooled Catalona, 1991[d] and Brawer, 1992[e]		
<4.0 ng/mL	0.98	0.09
4.1-10 ng/mL	1.4	5.1
>10 ng/mL	0.4	49.6
Richie, 1993[f]		
<4.0 ng/mL	0.7	0.4
≥4.1 ng/mL	3.0	4.6
Catalona, 1993c[g]		
<4.0 ng/mL	0.8	0.5
4.1-10 ng/mL	2.8	3.2
>10 ng/mL	3.0[h]	23.7

[a] As described in appendix C, probability of a detected cancer <0.5 mL is assumed to be 11% based on J.E. Oesterling, V.J. Suman, H. Zincke, et al., "PSA-Detected (Clinical Stage T1c or BO) Prostate Cancer: Pathologically Significant Tumors," *Urologic Clinics of North America* 17:719-737, 1990.

[b] See appendix C for methods of deriving these estimates.

[c] Results based on Hybritech assay.

[d] W.J. Catalona, D.S. Smith, T.L.. Ratliff, et al., "Measurement of Prostate-Specific Antigen in Serum as a Screening Test for Prostate Cancer," *New England Journal of Medicine* 324:1156-1161, 1991.

[e] M.K. Brawer, M.P Chetner,, J. Beatie, et al., "Screening for Prostatic Carcinoma with Prostate Specific Antigen," *Journal of Urology* 147:841-845, 1992.

[f] J.P Richie, W.J. Catalona, F.R. Ahmann, et al., "Effect of Patient Age on Early Detection of Prostate Cancer with Serum Prostate-Specific Antigen and Digital Rectal Examination," *Urology* 42:365-374, 1993.

[g] W.J. Catalona, D.S. Smith, T.L. Ratliff, et al., "Detection of Organ-Confined Prostate Cancer Is Increased Through Prostate-Specific Antigen-Based Screening," *Journal of the American Medical Association* 270:948-954, 1993.

[h] The discrepancy between this value and the corresponding derivation (0.4) from the pooled earlier studies is explained by the observed difference in probability of pathological localization for cancers (>0.5 mL) detected by PSA >10 ng/mL (32% vs. 5%).

SOURCE: Office of Technology Assessment, 1995. Based on information from M.J. Barry, C.M. Coley, C. Fleming, et. al, "The Safety, Effectiveness, and Cost of Early Detection and Treatment of Prostate Cancer Among Older Men: A Report to the Congressional Office of Technology Assessment," OTA contract paper no. K3-0546.0, Massachusetts General Hospital, Boston, MA June 30, 1994.

PSA Screening Among Men with Symptoms of BPH

As noted earlier, benign prostatic hyperplasia (BPH) can raise PSA levels complicating PSA measurement. Given the widespread prevalence of urinary symptoms indicative of BPH among older men, PSA screening for prostate cancer among this large group may yield little useful information. Men with symptoms of BPH do not appear to be at much greater risk of harboring cancer (except as conferred by their age) (235) and in one large study, when controlling for age, men with symptoms of prostatism actually had a *lower* chance of being found to have cancer through DRE and PSA screening (72). In addition, because BPH and prostate cancer share symptoms and the likelihood of elevated PSA levels, the specificity of PSA deteriorates to 50 to 79 percent among men with clinical evidence of BPH (173, 309). Furthermore, there appears to be a great degree of overlap

among men with *localized* (intracapsular) prostate cancer and BPH, further limiting the value of PSA testing among men with these symptoms (309).[10]

COMBINATION OF DRE AND PSA

Although combination screening with both DRE and PSA may currently, be the most popular strategy of aggressive office-based early detection of prostate cancer among U.S. urologists, studies of the predictive value of this strategy are only just becoming available for low-risk populations. DRE and PSA each detect some cancers not identified by the other modality; therefore, the yield of a screening program (the percentage of screenees who ultimately have a cancer confirmed) can be increased (to roughly 4 percent) by combining both tests. In addition, the studies of combination testing reported recently have generally performed a set of systematic biopsies if either test is suspicious, as well as biopsies of suspicious lesions noted on followup TRUS; this more aggressive use of TRNB also contributes to the higher yield seen in these studies.

However, these more aggressive strategies result in performing biopsies on up to a third of all screenees; the additional cancers detected must be weighed against the cost and risk of biopsy. Furthermore, these studies were conducted among volunteers, and some data suggest that volunteers may have a higher "prior probability" of prostate cancer than unselected men in the community (261).[11]

The newest studies where DRE and PSA are performed in the same men make it clear that PSA is a better single test than DRE in terms of detecting cancers and of detecting cancers still confined within the prostatic capsule (28, 72, 119, 263, 279).

FOLLOWUP TESTING

Increasingly, followup strategies for a suspicious DRE or PSA include both TRUS and TRNB. Most investigators use TRUS to guide biopsies of areas determined to be suspicious by DRE or TRUS. Many clinicians now perform multiple systematic (four to six) biopsies of the prostate (in a single procedure) in addition to biopsies of suspicious areas, since a patient with a normal TRUS may actually harbor cancer 12 to 33 percent of the time (depending on the PSA level) (157). Others base decisions about whether to perform systematic biopsies on raw PSA values or PSAD values (29, 99, 306). Although some investigators advocate simply following men with mild PSA elevations (i.e., in the 4.1 to 10.0 ng/mL range) if the DRE and TRUS are negative, when aggressively evaluated, this group yields the highest percentage of intracapsular cancers, the real targets of screening.

There is also variability in how clinicians follow men who have a negative set of biopsies after a suspicious PSA test. Some urologists recommend repeating the systematic biopsies at least once (particularly for a PSA greater than 10 ng/mL); others perform followup PSA

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[10] As mentioned in chapter 2, the FDA has approved the drug finasteride for treatment of BPH. It reduces PSA levels through its intended physiological effects. However, it is not clear, given the need to expect lower PSA levels when screening men on finasteride for prostate cancer, that this drug reduces the (already fairly low) information value of PSA among men with BPH (145, 154, 155, 289). Because of a trend toward less invasive management of BPH, the issue of adequate pretreatment screening of men with a diagnosis of BPH for coexistent prostate cancer is becoming a hotly debated issue (179).

[11] When Oesterling (261) applied the same screening strategy to randomly selected men in the community, only 1 percent were found to have prostate cancer compared with 4 percent in the volunteer studies.

tests more frequently than annually and rebiopsy for either persistent elevations or a rising PSA value. Often then, a suspicious screening test, even if followed by a negative biopsy, will lead to heightened surveillance for prostate cancer and further tests and biopsies in the future. On the other hand, this more intensive surveillance in turn increases the yield of screening to some degree.

Transrectal Ultrasound

Because of the anatomy of the prostate gland itself, TRUS has much better sensitivity for cancers found in certain parts of the prostate than for others (334). Appendix F lists studies that use TRUS as a primary means for early prostate cancer detection. In one of these studies, a demonstration project of the American Cancer Society, about 14 percent of men had a suspicious TRUS, and 15 percent of these men had cancer, a lower predictive value than studies of DRE or PSA alone (Mettlin, 1991). In the absence of a suspicious DRE or elevated PSA, the predictive value in this series dropped to 5.4 percent (19, 215). In a study based in a urologic practice where the prevalence of cancer was especially high (detection rate of 14.6 percent), and where about half of the men were biopsied based on results of combined screening (DRE, PSA, and TRUS), Cooner and associates found that if men had a PSA less than 4 ng/mL and a nonsuspicious rectal exam, the yield of ultrasonographic screening was about 2 percent. Put in another way, the overall yield of the testing strategy only increased from 13.5 to 14.6 percent through the performance of TRUS in addition to DRE and PSA (91).

Several studies provide more direct evidence about the true sensitivity and specificity of TRUS than is available for DRE and PSA. Two studies were able to estimate the operating characteristics of preoperative TRUS performed on men already scheduled for radical prostatectomy for cancer or BPH. The study on men scheduled for prostatectomy for cancer showed a TRUS sensitivity of 52 percent and a specificity of 68 percent (61), and the study of men with BPH showed a sensitivity of 30 percent (315). These relatively low sensitivity estimates for TRUS are a major reason for the increasing tendency to perform systematic biopsies for suspicious DRE or PSA results, even if TRUS does not indicate anything suspicious. Furthermore, these and other studies (337) suggest that TRUS tends to underestimate the size of cancers that are detected, making it a problematic technology for identifying men with small cancers who may not need aggressive treatment. Finally, evidence also suggests that BPH may also erode the ability of TRUS to detect cancer (74).

TRUS itself does not appear to pose any risk for patients, although it does pose costs to patients or their health insurers. In 1992, Medicare reimbursements were $89 for a diagnostic TRUS by itself and $189 for a TRUS-guided biopsy.

Transrectal Needle Biopsy

Modern transrectal needle biopsies (TRNBs) are usually done with ultrasound guidance using a needle mounted in a spring-loaded biopsy "gun." Biopsies can be directed toward areas deemed suspicious by DRE or TRUS, or performed systematically to sample the entire prostate; often six biopsies are taken in a sextant pattern from different parts of the prostate gland (326). TRNB is uncomfortable and can be complicated by infection or bleeding (89). Complications of biopsy include urinary tract infections in 0.5 to 5 percent of patients and urosepsis in an estimated 0.5 percent (no deaths), despite routine antibiotic prophylaxis (16, 91, 109, 160). Some patients also experience bleeding (less than 1 percent) with very few (one out of 835 biopsies in one study) requiring transfusion (91, 109).

TRNB is often considered the "gold standard" test for the diagnosis of prostate cancer; however, it is increasingly clear that the gold standard is "tarnished" to some degree. In terms of the sensitivity of TRNB, investigators from Washington University have found that when men are found to have a persistent mild elevation in PSA (4 to 9.9 ng/mL), repeated biopsies find a large number of cancers presumably missed by previous biopsies. In one preliminary report, 25 percent of these men with one previously negative biopsy had cancer, as well as 14 percent with two previously negative biopsies and 10 percent with three previously negative biopsies (187). Although many of these patients had original biopsies that were directed by abnormal DRE or TRUS results instead of multiple, systematic biopsies, simulation modeling has also suggested systematic biopsies may be relatively insensitive (103).

In terms of specificity, TRNB can detect "incidental" cancers of less than 0.5 mL in volume, which (as discussed in chapter 2) may likely pose no threat to the patient's health, making them conceptually equivalent to "false positives." This risk increases as more biopsies are performed, and particularly with repeated systematic biopsies. Terris and colleagues recently estimated that the probability of finding an incidental cancer on a set of six biopsies was approximately 4 percent (338).

SCREENING THE MEDICARE POPULATION

Age has a complex effect on the results of screening for prostate cancer. The prior probability of cancer increases with age, but the percentage of organ-confined cancers decreases. Furthermore, the specificity of PSA, and probably DRE as well, deteriorates as more men in the population have greater amounts of BPH. Richie and colleagues (279) present the net effect of these factors using data from their large, six-center study of screening:

- The deteriorating specificity of the tests with age resulted in a steeply increasing number of patients with suspicious results on either DRE or PSA that would generate a recommendation for biopsy: 15 percent at ages 50 to 59, 28 percent at ages 60 to 69, and 40 percent at ages 70 to 79.
- The rising prevalence of cancer maintained the predictive value relatively constant, so that cancer was detected in 2, 4, and 7 percent of these age groups, respectively.
- Among men whose cancers were pathologically staged, the percentages that were organ confined (definition not specified) by age groups were 74, 76, and 60 percent.
- In this study, for men ages 60 to 69, adding PSA increased the percentage of men with a suspicious screening evaluation from 16 percent (with DRE alone) to 28 percent; interestingly, the percentage of patients with pathologically localized cancer did not decrease with the addition of PSA in this age group. For men ages 70 to 79, adding PSA to DRE increased the percentage of suspicious evaluations from 20 41 percent, with an increase in the resulting percentage of organ- confined cancers detected from 45 to 60 percent.[12]

All of these data suggest that as screening programs, especially those employing PSA as one screening technology, are directed toward older populations, the number of patients requiring more costly, invasive, and

[12] The proportion of men with organ-confined cancers in this study is much higher than in previous studies, presumably because of the performance of systematic biopsies in all patients, rather than only screenees with an abnormal DRE or TRUS. The high proportion of screenees with an abnormal DRE in this study also suggests a very low threshold for considering this exam suspicious.

riskier followup also increases, with a larger number of the cancers ultimately found being confined within the prostate and quite possibly not destined to cause health problems. For policymakers, the decision about whether to support screening depends on the number of followup tests and incidental cancers they are willing to endure in order to find more cancers that may threaten patients' health or lives. This balance may depend on medicine's ability to cure more aggressive prostate cancers, the question addressed in chapter 4.

CHAPTER

4

Treating Prostate Cancer

There is controversy about the optimal treatment for clinically localized prostate cancer (i.e., cancer that appears not to have spread beyond the prostate based on information available without performing surgery).[1] In the United States, the preference is for aggressive treatment, with urologists generally preferring radical prostatectomy (203, 318). However, recent research has revealed considerable variability in stage-specific treatments actually administered (219, 238, 247). In other developed countries, urologists have tended to be more conservative regarding both early detection (78, 302, 303) and treatment (5, 175, 364).

Although observational studies exist to determine the outcomes of men who receive different treatments and to measure their risks of adverse outcomes, few well-designed trials exist to determine whether observed outcomes are actually the result of the treatment or due to some other uncontrolled and unmeasured factor. As shown in chapter 5, this uncertainty about treatment effectiveness is the greatest impediment to evaluating the cost-effectiveness of a potential Medicare prostate screening benefit.

STRATEGIES TO DETERMINE CANCER STAGE

One problem with current strategies for early detection of prostate cancer is that screening will detect some cancers that are not destined to cause morbidity or mortality and do not need treatment, as well as some cancers that have already spread through the prostate capsule and are less likely to be cured or slowed by treatment. Unfortunately, many patients may need to undergo a surgical staging procedure such as pelvic lymphadenectomy, or even radical prostatectomy itself, to establish the true stage of their cancer. Better, less invasive staging tests might allow physicians to withhold treatment from patients unlikely to benefit, sparing both the risks and costs of these procedures.

In terms of determining preoperatively whether cancers are likely to be insignificant (which this background paper defines as well-differentiated and less than 0.5 mL in volume), clinicians have developed some algorithms using data from systematic biopsies, and if necessary, rebiopsies (338). Unfortunately, however, other investigators have documented that these algorithms

[1] As discussed in the preceding chapters, unless otherwise indicated, cancers that are confined within the prostate, less than 0.5 mL in volume, and well differentiated are assumed not to pose any threat to a patient's health and would not require treatment unless they grow or change in grade.

predict incorrectly in a quarter to a third of cases (98, 191, 192).

As far as predicting preoperatively which tumors have spread to other parts of the body, detection of metastasis to bone by using radiographic bone scans is relatively straightforward, and algorithms do exist to help identify low-risk subsets of men in whom bone scans are unlikely to be helpful (84, 357). However, the use of other diagnostic technologies (e.g., computerized tomography (CT), magnetic resonance imaging (MRI), transrectal ultrasound (TRUS)) have not yet replaced operative pathological examinations to determine if the cancer has spread to the pelvic lymph nodes (76, 164, 281) or to determine if the cancer is extracapsular (97, 137, 285). Models that use the results of multiple tests to assess the probability of organ confinement and lymph node involvement also result in substantial misclassification rates for most patient groups (1, 191, 192, 267, 283, 369).

While better staging techniques, such as molecular staging strategies currently under active investigation (185), may allow better prediction of which tumors are likely to be dangerous enough to threaten a patient's longevity but still potentially curable, selective treatment of only those tumors most likely to benefit may still be practically difficult. As shown later in this chapter, evidence establishing the effectiveness of treatment is currently weak. Once a clinician finds cancer, in the absence of data that there is not at least some net benefit from treating even apparently inconsequential or unconfined cancers, patients and physicians may have difficulty in forgoing therapy, even when the expected net benefits are clearly less than for other types of cancers.

Many patients with negative bone scans undergo a dissection of the pelvic lymph nodes to determine if the cancer has spread in the region of the prostate prior to a radical prostatectomy, one type of treatment with curative intent.[2] Most clinicians would not proceed with a radical prostatectomy in light of the discovery of involved pelvic nodes, although a minority feel that aggressive surgical treatment of node positive disease improves outcomes (254, 375). Recently, some urologists have begun to question the need for a pelvic lymph node examination prior to radical prostatectomy among men with better differentiated tumors, or in men with lower prostate-specific antigen (PSA) values (38, 102, 126, 138).

Another new strategy sometimes employed before radical prostatectomy is the use of hormonal drugs to decrease the likelihood that the cancer is found to extend beyond the outside of the prostate capsule or beyond the surface of the surgically removed specimen (known as *surgical margin positivity*). Controversy exists about whether this treatment (known as *androgen ablation therapy*) actually causes a shrinking of the tumor (*regression*) as opposed to only decreasing PSA levels (223, 259, 321). Although a recently presented clinical trial suggests that preoperative androgen ablation therapy actually does cause some regression (202), there is no evidence such treatment improves patient outcomes with prolonged followup.

THE EFFECTIVENESS OF TREATMENT

This chapter examines three strategies for treating prostate cancer: 1) expectant management (or "watchful

[2]This examination can be done as a traditional, open surgical procedure or less invasively using a laproscope that requires only a small incision (188, 290, 304). It can be done as a separate procedure, or as the first stage of a combined pelvic lymph node examination and radical prostatectomy.

waiting"), 2) radiation therapy, and 3) radical prostatectomy.

Expectant Management

Expectant management, a commonly used strategy for clinically localized cancer worldwide (367), can take two basic forms: 1) only monitoring the patient for symptoms related to cancer progression and treating these symptoms as necessary or 2) monitoring for disease progression and attempting cure with radiation treatment or prostatectomy in that circumstance. Even in the United States, where the approach to prostate cancer is much more aggressive, a 1990 study by the American College of Surgeons Commission on Cancer found that almost two-thirds of Stage A cancers were not actively treated (238).

Many men with prostate cancer treated expectantly will have evidence of local progression by digital rectal examination (DRE) over time (342). Local progression of prostate cancer can cause symptoms from bladder outlet obstruction or invasion of surrounding tissues. Bladder outlet obstruction can be treated mechanically (by transrectal resection of the prostate (TURP)[3] or, less commonly, stenting).

Treatment involving deprivation of the male hormone testosterone (an androgen) is often used as part of an expectant management therapy when the disease becomes symptomatic (168) or, more recently, for evidence of cancer progression in asymptomatic men.[4] Clinicians can accomplish androgen deprivation therapy by orchiectomy (surgical removal of the testes) or by medical means with other hormones or drugs (301). The latter option is more common despite considerably higher costs and the risk of patient noncompliance, at least partially because of patient preference (53, 65, 311).[5] Although the initial response to hormonal therapy for advanced prostate cancer is often gratifying, it is also frequently short-lived, with the results of subsequent chemotherapy generally disappointing (94, 108).

What Is the Effect of Expectant Management?

Although the outcomes of expectant management have been studied around the world (3, 4, 114, 135, 175, 176, 249), few investigators in the United States have done so (178, 366).

A number of case series of men with clinically localized prostate cancer in "watchful waiting" strategies have been reported from around the world. As shown in table 4-1, a recent structured literature review and synthesis of 23 nonexperimental studies showed that receiving expectant management for localized prostate cancer had rates of metastasis and death no different from radical prostatectomy and lower than radiation therapy (362). However, these comparisons are inferior to well-controlled, experimental results (333, 362). This literature synthesis has been criticized for the inclusion of series describing predominantly the outcomes of early, inconsequential Stage T1a/A1 cancers, and for including series using early androgen deprivation therapy (132, 360). In addition, patients receiving radiation therapy had more poorly differentiated patients than those receiving other treatment options.

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[3]TURP does not seem to have an unfavorable impact on the prognosis of prostate cancer (372).

[4]The effect of early androgen deprivation on the natural history of clinically localized prostate cancer is not well defined; some nonexperimental studies demonstrated little effect (23, 114).

[5]Recently, clinicians have increasingly used combination therapy involving two agents, a GnRH agonist and an androgen blocker (flutamide), with some evidence from clinical trials that this approach increases median survival time to a degree (94, 108).

TABLE 4-1: PATIENT CHARACTERISTICS AND OUTCOMES OF LOCALIZED PROSTATE CANCER TREATMENT

	Watchful waiting		Radiation therapy		Radical prostatectomy	
	Median (CI)	**n**	**Median (CI)**	**n**	**Median (CI)**	**n**
Patient characteristics						
Age	71		66		63	
	(69-73)	27	(64-66)	49	(61-64)	33
Percent of cancers poorly differentiated	7		21		11	
	(6-11)	19	(13-24)	45	(6-25)	22
Outcomes						
Annual mortality rate						
All causes	.060		045		.032	
	(.050-.04)	27	(.040-.052)	45	(.020-.044)	27
Cancer-specific	.009		.023		009	
	(.006-.012)	23	(.010-.030)	22	(.007-.013)	23
Metastatic rate	.017		.050		.023	
	(.011-.043)	15	(.030-.095)	17	(.014-.025)	18

KEY: CI = 95% confidence interval; n = number of studies, which varies since not all studies supply all data of interest.

SOURCE: Office of Technology Assessment, 1995. Data from J.H. Wasson, C.C. Cushman, R.C. Bruskewitz, et al, "A Structured Literature Review of Treatment for Localized Prostate Cancer," *Archives of Family Medicine* 2:487-493, 1993.

A literature synthesis of seven studies (586 patients) of outcomes of men with *palpable*, clinically localized cancers (Stage T2) reported since 1980 yielded rates of metastasis, overall mortality, and prostate cancer-specific mortality higher than those presented in the Wasson review described above (6). However, one would expect these higher rates in an analysis restricted to palpable cancers. Only two studies provided data on cancer-specific survival at 10 years among men treated expectantly with a mean of 84 percent. In this analysis, the results of studies reporting outcomes of radical prostatectomy were better, while studies reporting outcomes for radiation therapy were worse.

One of these expectant management studies enrolled men with localized prostate cancer from a well-defined geographic area in Sweden between 1977 and 1984 and has an unusually long duration of followup (175, 176, 177). It excluded men with moderately or poorly differentiated cancer or a few men receiving curative treatment, leaving a sample of 223 with a mean age of 72. At 12.5 years of average followup, there have been 23 prostate cancer deaths in the cohort (10 percent), and 148 deaths from other causes (66 percent). Ten-year metastasis-free survival (corrected for deaths from other causes) was 83 percent. Tumor grade was the dominant predictor of prognosis.[6]

[6]Although this study has been criticized for enrolling too many older men and too many with insignificant cancers discovered during TURP and for having insufficient followup to detect a late upsurge in hazard of prostate cancer death, neither age nor stage (controlling for grade) was an independent predictor of the prostate cancer death rate in this study. In addition, the study's "T0l" tumors (a unique stage different from T1a or A1) included tumors encompassing up to 25 percent of the volume of the TURP specimen (as opposed to up to 5 percent for T1a or A1 tumors in the United States), and there has been no increase in hazard rate noted with followup to 12.5 years. Moreover, a subset analysis for men who would be considered candidates for radical prostatectomy yielded similar results. Concerns have also been raised about identification of prostate cancer by means of aspiration cytology, as was generally the mode of diagnosis in this study (214, 296); however, this method had similar results to core biopsy in one Scandinavian study (358).

Another recent study with long-term followup showed similar results. It presented data from men diagnosed with clinically localized prostate cancer in Connecticut between 1971 and 1980, and treated with immediate or delayed hormonal therapy when necessary. Again, grade, but not age, predicted cancer-specific survival. For men over 65, cause-specific 15-year survivals were: well differentiated, 82 to 93 percent; moderately differentiated, 67 to 78 percent; and poorly differentiated, 46 to 53 percent (194).

Chodak and colleagues have recently conducted a meta-analysis including 828 men (mean age 70) enrolled in expectant management studies from six centers with 10-year adjusted cancer survival rates: well differentiated, 87 percent; moderately differentiated, 87 percent; and poorly differentiated, 34 percent (82, 83). Grade was once again the dominant independent determinant of the rate of prostate cancer mortality. The predicted metastasis-free survival at 10 years was lower than the survival statistics would indicate: 81, 58, and 26 percent for well, moderately, and poorly differentiated disease, respectively.[7]

The Risks of Expectant Management

The risks of expectant management for clinically localized cancer include any higher rate of the development of metastases and prostate cancer-specific mortality that this strategy imposes over and above the rates seen with active treatment.[8] The magnitude of these added risks, if any, has not been defined. More clearly, men managed expectantly have increased risks of local cancer progression compared with men treated with radical prostatectomy; however, the clinical significance and quality-of-life implications of local cancer progression have not been well studied (343). Johansson reported that 22 percent of the men in his study developed evidence of progression by DRE to Stage T3 over 10 years; however, he recently reported that in only six cases were local problems "substantial" and resistant to treatment (176).[9]

Radiation Therapy

Radiation therapy administered for cure (also known as radiotherapy) usually involves x-rays from an external source delivered in maximal doses to the prostate, lesser doses to the seminal vesicle (located above the prostate), and minimal radiation to the small bowel, rectum, anal canal, and urethra (270). Adjustments are made in the dose and targets based on the specific tumor and host. Much less commonly, radioactive "seeds" are placed in the prostate as primary therapy, or in combination with external beam radiotherapy, to increase the dose delivered to the prostate while better protecting nearby tissues. Patients usually receive external beam radiotherapy in five weekday treatments over six or seven weeks (20). Research is actively underway to identify new methods of radiotherapy, such as three-dimensional conformal therapy, that may avoid underdosing the prostate while more effectively excluding surrounding normal tissues, reducing the associated risks (209).

The relatively little attention given to radiation therapy in the recently published literature on prostate cancer detection and treatment may reflect the fact that urol-

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[7]The reason for the discrepancy between the rate of metastatic disease and prostate cancer mortality, particularly for men with moderately differentiated cancer, is not well understood; to some degree, early detection of a low burden of asymptomatic metastatic disease with periodic bone scans in these series may explain some of the apparent delay between the development of metastases and cancer death implicit in these results (278).

[8]Waiting for signs of clinical progression will result in fewer cancers being pathologically localized at the time clinicians attempt curative treatment.

[9]Thirty patients did undergo TURP for obstructive symptoms, only about half of whom had cancer in the removed tissue (176).

ogists, who most often recommend radical prostatectomy for localized prostate cancer, have conducted these studies (362). However, as recent as 1990, a study by the American College of Surgeons Commission on Cancer found that radiotherapy was used more commonly than radical prostatectomy in the United States for *every stage* of prostate cancer (238).[10] In addition, a recent study suggested that prostate cancer patients in health maintenance organization settings were more likely to receive radiotherapy rather than surgery compared with patients in fee-for-service settings (152).[11]

How Effective Is Radiation Therapy?

The effectiveness of radiotherapy, compared with either expectant management or radical prostatectomy, for reducing mortality and morbidity among men with clinically localized cancer has not been well studied. A single randomized clinical trial of 97 men with Stage A2 or B cancers found a significant improvement in time-to-recurrence with surgery compared with radiation, but no mortality difference (269, 359). However, because many patients "crossed-over" to the other treatment after randomization and the analysis was based on "treatment given" rather than "intention to treat," these conclusions may not be valid.

Although the results of only one imperfect clinical trial are available, some additional evidence is available from two cohort studies[12] of patients with clinically localized cancer treated with radiotherapy for cure -the Patterns of Care Studies (PCS) (161, 197) and the Radiation Therapy Oncology Group (RTOG) study (#7706) (15). At 10 years, overall survival among patients receiving radiation was no different than expected survival for age-matched men without cancer (63 percent in PCS and 64 percent in RTOG). In the 1978 PCS, about 83 percent of the 10 year survivors had no evidence of disease. For men with palpable, clinically localized T2 cancers, overall survival at 10 years was 46 percent (i.e., about 20 percent lower than for cancer-free men of similar age), with about 74 percent of the survivors classified as disease-free (165). Radiation oncologists argue that, out to 10 years, these outcomes are equivalent to radical prostatectomy, particularly given the unknown nodal status of the radiotherapy patients (87, 117, 161, 163, 165, 184, 208). In fact, for a subset of men in RTOG study with negative lymph node dissections, most of whom had T2 cancers, cancer-specific survival was 86 percent after 10 years, with 79 percent metastasis-free survival (162).

In one of the literature reviews mentioned in the section on expectant management, only one study was found to have stratified patient outcomes following radiotherapy by grade and stage of disease (362). In all the available cases of patients treated with radiotherapy, these men had higher median rates of development of distant metastases and cancer- specific mortality than men treated with radical prostatectomy and expectant management, but they also had more men with poorly

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[10]Presumably, some patients who underwent a surgical examination of the pelvic lymph nodes prior to radical prostatectomy subsequently underwent radiotherapy instead because of nodal involvement.

[11]However, registry data indicate that for the U.S. population as a whole, this trend reversed itself in 1991 with radical prostatectomy becoming the more commonly used treatment strategy (166).

[12]Cohort studies are often used to compare the outcomes of two groups of patients similar in important characteristics other than the outcome of interest -in this case, treatment strategy. Because of the inability to control retrospectively for all factors that might be related to treatment choice and outcome, the results of such a study are inferior to a prospectively randomized clinical trial.

differentiated cancers than series of either of the other treatments (table 4-1). These nonexperimental comparisons may also be invalid because of the older age of radiotherapy patients, and the fact that patients with lymph node involvement are included in radiotherapy series but excluded from surgical series.

Many urologists worry that evidence of residual cancer in many men following radiotherapy augurs poorly for the prognosis of men treated this way (51, 75, 183, 210, 294, 297, 327, 359). On the other hand, rates of biopsies after radiotherapy have been lower in some recent small series of Stage T1 and T2 disease (cancers confined to the prostate) given radiation treatment in a particular manner (125), and the prognosis for men with positive biopsies after radiotherapy is debated (275).

Risks of Radiation Therapy

Injury from radiotherapy to the radiosensitive tissues of the bladder and urethra can cause cystitis[13] and incontinence. Injury to the rectum can cause proctitis,[14] and injury to the nerves and blood vessels adjacent to the prostate can cause impotence (205). Table 4-2 provides estimates of these risks based on a structured review of the medical literature published since 1981 (362).[15] This literature does not allow estimation of the hazards of radiotherapy specifically among Medicare-age men. However, preliminary analysis of a survey of complications of external beam radiotherapy among Medicare-aged men suggests that about 5 percent of men use pads to deal with incontinence and that 35 percent had noted no partial or full erections since their treatments (27). These results compare favorably to published data on the complications of radical prostatectomy collected using the same methods and discussed below (127).

Radical Prostatectomy

The third treatment strategy, radical prostatectomy, entails removing the entire prostate with the tissues that cover it and the seminal vesicles that sit above the gland. In recent years, modification of the procedure by Walsh and colleagues and a better understanding of the anatomy of the area (50) has allowed wider excision around the prostate, but with special attention to nearby nerves and blood vessels to reduce blood loss and post-operative incontinence and impotence. However, attempts to preserve these nerves in cases of capsular penetration increases the risk of surgical margin positivity[16] (267, 287).

How Effective Is Radical Prostatectomy?

Observational data indicate that men who undergo radical prostatectomy tend to do well with prognosis dependent on disease stage (331). Those with organ-confined cancer have a low risk of recurrence and normal life expectancies. For men with unconfined disease, one recent study noted localized recurrence in 8 percent of men within five years as opposed to metastases in 30 percent.[17] This suggests that prostatectomy improves cancer control in the area around the prostate, even in situations when the rate of development of metastatic disease elsewhere in the body may be unchanged (50, 248).

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[13]Cystitis is an inflammation of the bladder.

[14]Proctitis is inflammation of the rectum.

[15]As with radical prostatectomy, complications from radiotherapy may depend on the expertise of the radiotherapist and treatment center. While some radiation oncologists at major referral centers may have better outcomes than reflected in table 4-2, as reported recently by Shipley (312), a nationwide prostate cancer early detection program may outstrip the capacity of these centers.

[16]Margin positivity refers to the discovery of cancerous tissue right up to the edge of the surgically removed tissue, raising the possibility that the operation may not have removed all of the cancer.

[17]This is the opposite of the pattern described earlier for men who are treated by expectant management.

TABLE 4-2: PERSISTENT ADVERSE OUTCOMES OF LOCALIZED PROSTATE CANCER TREATMENT (from literature published since 1981)

	Radical prostatectomy	External beam radiation
Mortality		
Weighted mean	1.1%	0.2%
Sample size (number of men)	400.0	496.0
Median probability[a]	2.0%	0.0%
Number of studies	6.0	8.0
Any incontinence		
Weighted mean	26.6%	6.1%
Sample size (number of men)	301.0	443.0
Median probability[a]	16.0%	6.5%
Number of studies	8.0	6.0
Complete incontinence		
Weighted mean	6.8%	1.2%
Sample size (number of men)	719.0	739.0
Median probability[a]	6.0%	1.0%
Number of studies	11.0	11.0
Any bowel injury		
Weighted mean	2.7%	11.4%
Sample size (number of men)	407.0	1,148.0
Median probability[a]	1.5%	13.5%
Number of studies	4.0	12.0
Bowel injury (requiring long-term treatment or colostomy)		
Weighted mean	1.3%	2.3%
Sample size (number of men)	551.0	1,680.0
Median probability[a]	1.0%	1.0%
Number of studies	6.0	17.0
Stricture requiring long-term treatment		
Weighted mean	12.4%	4.5%
Sample size (number of men)	542.0	959.0
Median probability[a]	9.0%	2.5%
Number of studies	9.0	12.0
Impotence		
Weighted mean	84.6%	41.5%
Sample size (number of men)	374.0	415.0
Median probability[a]	62.0%	44.0%
Number of studies	7.0	5.0

[a] Median probability across reported studies.

SOURCE: Office of Technology Assessment, 1995. Data from J.H. Wasson, C.C. Cushman, R.C. Bruskewitz, et al., "A Structured Literature Review of Treatment for Localized Prostate Cancer," *Archives of Family Medicine* 2:487-493, 1993.

However, the *attributable* benefit of radical prostatectomy is less clear.[18] The structured literature synthesis of prostate cancer treatment, already described in the discussion of expectant management, found rates of death and metastasis that were not statistically different for radical prostatectomy and expectant management (table 4-1) (362). The good outcomes for men receiving radical prostatectomy noted in observational studies are in part due to better preoperative staging, and the exclusion of men whose cancer is found preoperatively to have spread to the pelvic lymph nodes. Hence, nonexperimental comparisons of outcomes of expectant management, radiation therapy, and radical prostatectomy are potentially confounded by different mixes of cancer among these studies.

Only one clinical trial has compared expectant management and radical prostatectomy directly. In a Veterans Administration Cooperative Research Group (VACURG) clinical trial, 61 men with clinically localized prostate cancer were randomized to radical prostatectomy and 50 men to expectant management; about half had cancers found at TURP and half palpable cancers. After seven years and again after 15 years, there is no statistically significant difference in survival between the two treatment strategies (54, 147). However, the trial's small sample size impedes detection of any real difference that may exist.[19]

The Risks of Prostatectomy

As indicated in table 4-2, Wasson's synthesis of the medical literature since 1981 indicates that the median risk of death associated with radical prostatectomy itself is about 1.1 percent; any incontinence, 27 percent; complete incontinence, 7 percent; impotence, 85 percent (31 percent in two studies of the never-sparing procedure); and stricture (obstruction or narrowing of the urethra) requiring long-term treatment, 12 percent. However, the definitions of adverse outcomes vary considerably among the studies, and as with radiation therapy, the likelihood of these outcomes are likely to vary with the experience and skill of the surgeon and hospital (50, 69, 276). On the other hand, these may be a lower-bound of the risks faced by typical patients since publication bias may lead to underestimates (27). Furthermore, Medicare patients may face higher risks because of age and comorbidities.

A recent survey that used Medicare claims data to choose a national probability sample of men who have received radical prostatectomy provides more generalizable estimates of the risks associated with this procedure for Medicare beneficiaries (127).[20] The results are presented in table 4-3 and stand in contrast to the less frequent adverse outcomes suggested by the preliminary analysis mentioned earlier of a similar survey of Medicare-age men (albeit older ones) who underwent radiation therapy. Within this cohort of men over 65, the risk of these complications was not related to age at surgery.

FOLLOWUP TREATMENT AFTER CURATIVE THERAPY

After initial treatment by radiation or radical prostatectomy, clinicians often consider additional therapy if

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[18]The attributable benefit is that portion of the total observed benefit in the treated population (i.e., extra years of life) actually due to radical prostatectomy as opposed to other causes.

[19]After seven years, patients undergoing radical prostatectomy had a probability of death 0.01 higher than those receiving expectant management. However, calculation of a 95-percent confidence interval around this figure indicates that the data are actually consistent with a probability of death with radical prostatectomy as much as 0.07 *lower* than that for expectant management as well as a probability as much as 0.09 *higher* than that for expectant management.

[20]The researchers analyzed Medicare claims data and performed a survey based on a national probability sample of 1,070 men who had radical prostatectomies under Medicare between 1988 and 1990; they oversampled Massachusetts for a subexperiment to determine whether mode of interview (personal, mail, or phone) gave different results. The method of interview did not affect any of the data presented in this paper (127).

TABLE 4-3: ADVERSE OUTCOMES OF RADICAL PROSTATECTOMY AMONG MEDICARE BENEFICIARIES

Condition	Percent of men reporting
Attributable 30-day post-operative mortality[a]	0.6%
Cardiopulmonary complications[b]	4.0-5.0
Incontinence	
▪ Wore pads or other devices for incontinence[c]	31.0
▪ Dripped more than a few drops daily	23.0
▪ Underwent surgical treatment for incontinence	6.0
▪ Had a catheter	2.0
Impotence	
▪ Had ability to have erections prior to surgery	90.0
▪ No full or partial erections since surgery	61.0
▪ Had erections firm enough for intercourse in previous month	11.0
Underwent medical/surgical treatment for stricture, 2-4 years after surgery	20.0

[a] Total 30-day post-operative mortality (1%) minus probability of death for other causes.

[b] Congestive heart failure, myocardial infection, pulmonary embolism, or respiratory failure.

[c] Over 80% of these men reported dripping every day, indicating these pads and devices were not just used prophylactically.

SOURCE: Office of Technology Assessment 1995. Data from F.J. Fowler, M.S. Barry, A. Roman, et al. "Patient-Reported Complications and Follow-up Treatment After Radical Prostatectomy, The National Medicare Experience: 1988-1990 (Updated June 1993), " *Urology* 42(6):622-629, 1993.

there is evidence of recurrence, spread, or indications that the patients are at high risk of such problems. For men who have had radiation treatment, the clinician can consider "salvage" radical prostatectomy with evidence of local progression (297, 370), but the results are usually disappointing (67).

After initial treatment by radical prostatectomy, clinicians often consider adjuvant radiation or androgen deprivation therapy for men at higher risk of harboring residual cancer, particularly those with positive surgical margins or PSA test values that do not fall to female levels, although it is controversial whether these adjuvant treatments improve survival (77, 373). Furthermore, clinicians follow patients closely for evidence of recurrent disease with periodic DRE and PSA testing (35, 289). Men with evidence of recurrence are often considered for additional treatment with radiation. As is the case for men treated expectantly, androgen deprivation therapy may be instituted for men with locally symptomatic cancer recurrence, for men who develop distant metastases, or for some men without symptoms but a progressive abnormality on DRE or a rising PSA.

In the survey of Medicare-age men who underwent radical prostatectomy between 1988 and 1990 discussed above, 5 percent reported followup radiation therapy within the first year (probably for residual disease), and another 13 percent underwent radiation therapy between the beginning of the second and the end of the fourth year of followup (probably for evidence of recurrence). Ten percent of men had hormonal therapy prescribed in the four years following their operation, and 15 percent had an orchiectomy.

CHAPTER

5

Benefits, Risks, and Costs of Screening

This chapter draws from the literature reviewed in the previous three chapters to analyze the impact of a hypothetical prostate cancer screening program for Medicare-age men. In addition, it uses data on Medicare reimbursements to examine some of the economic implications of early detection in this age group. As explained below, the screening benefit analyzed is designed to be illustrative of the difficulties in drawing unambiguous conclusions about the value of screening, rather than to predict the impacts of a screening benefit as it actually would likely be implemented as part of Medicare.

A number of decision models have been published or presented dealing with prostate cancer screening or treatment (58, 124, 195, 196, 217, 316). These models have yielded different results, due to widely different "base case" assumptions about the probabilities and values of the various outcomes of these clinical policies. The lack of definitive data on which to base such assumption, particularly for the effectiveness of treating localized prostate cancer, and the different values different patients may place on potential outcomes make it possible to support analyses of screening that use divergent sets of assumptions.[1]

This paper only considers a one-time screening of men at ages 65, 70, and 75. Realistically, a Medicare benefit would most likely cover periodic screening for example, a digital rectal examination (DRE) and prostate-specific antigen (PSA) every year as the American Cancer Society (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 birthdays. However, as this analysis will demonstrate, 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.

[1]For example, a recently published paper (30) used one of the decision analyses cited here (124) together with newer, life expectancy data that are more optimistic than those used in the original decision analysis. The authors of the more recent paper conclude that their reanalysis leads to conclusions different from those drawn by Fleming and colleagues. Beck and colleagues, the authors of the newer paper, suggest that radical prostatectomy for localized prostate cancer may actually increase quality-adjusted life-years. These authors also endorse the continuation of randomized clinical trials to resolve issues of cancer progression rates and the ultimate effectiveness of prostate cancer treatment, the two greatest unknowns in the decision about whether to screen for prostate cancer (30).

The analysis is presented in three stages:

- The first stage models the health outcomes of a one-time screening program for three cohorts of 100,000 men 65, 70, and 75 years old respectively using a baseline set of assumptions.
- The second stage adds in the costs of screening, treatment, and associated procedures to estimate the cost-effectiveness of this illustrative one-time screening in terms of dollars life-years gained compared with not screening at all.
- The third stage examines how much these measures of cost-effectiveness change with changes in the assumptions about the effectiveness of treating prostate cancer and other assumptions important to screening.

MODELING THE HEALTH OUTCOMES OF SCREENING

To estimate the health outcomes of a one-time screening program for each of the three age groups, the model follows a hypothetical cohort of 100,000 men. It assumes a certain underlying distribution of prostate cancers of different types. It subjects the men to a combined DRE/PSA screening program (using a 4 ng/mL PSA cutpoint) and follows them with assumptions about diagnostic and treatment strategies as well as the probabilities of the different outcomes of these strategies.

Rather than assign different "values," or "utilities," to nonfatal outcomes such as postsurgical incontinence or metastatic disease, which will be valued differently by different patients (317), the analysis simply records the number of patients with these problems and the life-years over which these problems must be endured, allowing the reader to weigh the risks and benefits of the decision whether to screen. At this stage, the analysis does not downvalue (discount) future years of life, or account for future life-years that would be of lower quality due to disability, loss of independence, or other health problems (225).[2]

The discussion that follows outlines the assumptions used in this model and ties them to the literature review in the preceding chapters. Table 5-1 summarizes these assumptions for 65- and 75-year-old men. All age-specific probabilities for 70-year-old men are the average of the probabilities for those 65 and 75.

Assumptions in the Model

The model employs a Markov process that extends one developed for a published study of the outcomes of treating clinically localized prostate cancer (124).[3] It simulates the clinical course of each cohort of men by allowing them to make transitions from one health state to another in increments of six months. During any six month period, men who harbor prostate cancer in the cohort may present with either local obstruction requiring therapy or develop new metastatic disease. Grade-specific rates of developing metastases come from a patient-level meta-analysis recently conducted by Chodak and colleagues (83).

Probabilities of Prostate Cancer

The model distinguishes among three types of cancer by size: 1) <0.5 mL, all assumed to be contained with the prostate capsule; 2) >0.5 mL with <1 cm of capsular penetration; and, 3) >0.5 mL with >1cm of capsular pen-

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[2]However, the section on cost-effectiveness analysis below appropriately discounts both future years of life and future costs.

[3] A Markov model is a quantitative tool useful in understanding how people move through different states of the world (in this case, states of health) over time when: 1) there are a finite number of states, 2) any individual can fall into only one state in any given time period, 3) the probability of moving from one state to the next over any two periods of time is known, and 4) the periods of time are uniform in length (335). In this analysis, the Markov model describes how many members of each cohort of men experience different types of cancer, treatment complications, other symptoms, and death, when they experience each event, and (as seen later) what costs they incur for Medicare along the way.

TABLE 5-1: BASELINE ASSUMPTIONS USED TO MODEL HEALTH OUTCOMES OF PROSTATE CANCER SCREENING OF MEN AGE 65 AND 75 WITH DIGITAL RECTAL EXAM AND PROSTATE-SPECIFIC ANTIGEN

Assumption	Probability	
	65-year-old men	75-year-old men
Derivation of poor probabilities of prostate cancer		
1. Probability of any cancer = (A)	0.22	0.39
2. Probability of cancer being < 0.5 mL (insignificant, assume all confined) = (B)	0.60	0.60
3. Probability of cancer being > 0.5 mL (significant) with < 1 cm of capsular penetration (intracapsular) = (C)	0.4x0.73=.29	0.4x0.73=.29
4. Probability of cancer being > 0.5 mL (significant) with > 1 cm of capsular penetration (extracapsular) = (D)	0.4x0.27=.11	0.4x0.27=.11
5. Derived prior probability of insignificant (< 0.5 mL) cancer = (AxB)	0.132	0.234
6. Derived prior probability of significant cancer (>0.5 mL), intracapsular = (AxC)	0.064	0.114
7. Derived prior probability of significant cancer (>0.5 mL), extracapsular = (AxD)	0.024	0.042
Probabilities of cancers having different grades		
Insignificant cancers (<0.5 mL)		
8. Well differentiated	0.65	0.65
9. Moderately differentiated	0.26	0.26
10. Poorly differentiated	0.09	0.09
Significant (>0.5 mL) intracapsular cancer		
11. Well differentiated	0.33	0.33
12. Moderately differentiated	0.56	0.56
13. Poorly differentiated	0.11	0.11
Significant (>0.5 mL) extracapsular cancers		
14. Well differentiated	0.04	0.04
15. Moderately differentiated	0.70	0.70
16. Poorly differentiated	0.26	0.26
Derivation of screening results		
17. Probability of a suspicious DRE or PSA requiring biopsy = (E)	0.28	0.40
18. Overall probability of detection of cancer (actual yield) = (F)	0.042	0.072
19. Proportion of detected cancers with insignificant (< 0.5 mL) volume = (G)	0.11	0.11
20. Derived probability of finding an insignificant cancer among men who harbor them = (FxG)/(AxB)	0.035	0.034
21. Probability that screen detected cancers are extracapsular = (H)	0.24	0.40
22. Derived probability of detecting extracapsular cancers among men who harbor them = (FxH)/(AxD)	0.42	0.69
23. Derived probability of detecting significant, intracapsular cancers among men who harbor them =Fx(1-G-H)/(AxC)	0.43	0.31
Probabilities of biopsy complications (with antibiotic prophylaxis)		
24. Urinary tract infection	0.056	0.056
25. Urosepsis	0.005	0.005

CONTINUED

TABLE 5-1: BASELINE ASSUMPTIONS USED TO MODEL HEALTH OUTCOMES OF PROSTATE CANCER SCREENING OF MEN AGE 65 AND 75 WITH DIGITAL RECTAL EXAM AND PROSTATE-SPECIFIC ANTIGEN CONTINUED

Assumption	Probability	
	65-year-old men	75-year-old men
Treatment compliance		
26. Probability of men with confirmed cancer receiving treatment	0.70	0.48
Probabilities of radical prostatectomy complications:		
28. Attributable surgical mortality	0.006	0.006
29. Nonfatal serious cardiopulmonary complications	0.04	0.08
30. Probability of incontinence	0.23	0.23
31. Probability of impotence	0.61	0.61

Assumption	Expected remaining years of life	
	65-year-old men	75-year-old men
Life expectancy (in years)[a]		
32. Without cancer	14.45	8.95
33. With untreated, well-differentiated cancer, < 0.5 mL	14.45	8.95
34. With untreated, well-differentiated cancer, > 0.5 mL	12.64	8.26
35. With untreated, moderately differentiated cancer	12.64	8.26
36. With untreated, poorly differentiated cancer	7.57	6.01
37. With treated intracapsular cancer (< 0.5 mL and > 0.5 mL, all grades)	14.45	8.95
38. With treated extracapsular, well differentiated cancer	12.64	8.26
39. With treated extracapsular, moderately differentiated cancer	12.64	8.26
40. With treated extracapsular, poorly differentiated cancer	7.57	6.01

[a] Metastatic rates for well (> 0.5 mL), moderately, and poorly differentiated cancers derived from G.W. Chodak, R.A. Thisted, G.S. Gerber, et al., "Results of Conservative Management of Clinically Localized Prostate Cancer," *New England Journal of Medicine* 330:242-248, 1994. Metastatic rates for these cancers are assumed not to vary by volume or capsular status (i.e., only by grade), except for well-differentiated cancers < 0.5 mL, which are assumed not to metastasize. See text for details.

SOURCE: Office of Technology Assessment, 1995. Based on data from M.J. Barry, C.M. Coley, C. Fleming, et al., "The Safety, Effectiveness, and Cost of Early Detection and Treatment of Prostate Cancer Among Older Men: A Report to the Congressional Office of Technology Assessment," OTA contract paper no, K3-0546.0. Massachusetts General Hospital, June 30, 1994.

etration. The underlying prevalence of each of these cancers in the population is derived from autopsy data presented in table 2-5 and explained in appendix A. Pathological data from Oesterling's study (263) of 208 nonpalpable, PSA-detected, Stage T1c prostate cancers provide the probabilities of each size of cancer being well differentiated (Gleason Score of 2 to 4), moderately differentiated (Gleason Score of 5 to 6), or poorly differentiated (Gleason Score of 7 to 10) (256).

Screening and Biopsy

The probabilities that screening yields a suspicious DRE or PSA requiring biopsy (table 5-1, line 17) comes from Richie and colleagues' community-based screen-

ing study (279),[4] as do the overall probabilities that screenees will have a cancer detected and the probabilities that cancers detected through screening will not be confined to the prostate gland (table 5-1, lines 18 and 21).[5] The analysis assumes that transrectal needle biopsy (TRNB) is the "gold standard" for confirming or rejecting suspicious DRE/PSA results. In the Richie study, only 69 percent of men ages 60 to 69 with suspicious PSA or DRE results actually received biopsy. For men ages 70 to 79, the biopsy compliance rate is 68 percent. These compliance rates are implicit in the probabilities that screening will detect cancer in both the Richie study and the analysis in this chapter (table 5-1, line 18). The probabilities that detected cancers will be of small volume (< 0.5 mL) come from Oesterling and colleagues' study of the pathology of nonpalpable T1c cancers described above.[6]

Combining these data on screening results with the data on the prior probabilities of harboring cancers allow the estimation of age- and volume-specific sensitivities for a one-time combined DRE and PSA screening (table 5-1, lines 20, 22, and 23).[7]

As indicated in chapter 3, biopsy itself can result in infection even with antibiotic prophylaxis. Assumptions about the rates of infections confined to the urinary tract (16, 89,) and urosepsis (91) are taken from the literature.

Treatment Strategies and Cure Rates

Because biopsy cannot determine the volume, grade, and extent of spread of discovered cancers, this analysis assumes all men found to have cancer are offered aggressive treatment. Based on data from Richie (279), 70 percent of 65-year-old men are assumed to accept that recommended treatment; the analysis assumes a 48-percent compliance rate for 75-year-old men.

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[4]It is interesting to note that the proportion of Medicare-age screenees who would have suspicious results on DRE and PSA testing (28 to 40 percent depending on age) is much higher than for mammography (up to 6 percent) (351), fecal occult blood testing (2 to 5 percent) (348), or Pap smears (1 to 13 percent) (347). Thus, the level of intrusiveness of a strategy of early detection of prostate cancer, with recommendations for biopsy being generated in over a quarter of screenees, is much greater than among other commonly used cancer screening strategies.

[5]These estimates of the age-specific yield of combined DRE and PSA screening, which come from the study by Richie (72, 279), favor screening since the volunteers who participated in the study may have had an enriched prevalence of cancer. As previously noted in chapter 3, a community-based study using the same screening strategy among men ages 40 to 79 found cancer in 5 out of 537 (<1%) screenees (261).

[6]Among prostate-confined cancers, the Richie study (279) does not distinguish between the volume categories used in this analysis (<0.5 mL and >0.5 mL). Hence, this analysis uses Oesterling's 11 percent probability that detected cancers are <0.5 mL (263) even though the Oesterling data are not age-specific. The resulting mix of cancers discovered by screening and coming to radical prostatectomy predicted by the model at age 65 are as follows: <0.5 mL, 11 percent; >0.5 mL and intracapsular, 65 percent; and .05mL and extracapsular, 24 percent. This distribution is actually considerably more favorable than the distribution of T1c cancers coming to radical prostatectomy recently described by investigators at Johns Hopkins University (52, 119): insignificant or "minimal" (<0.5 mL), 26 percent; "moderate" (includes some cancers with capsular penetration if well or moderately differentiated), 40 percent; and "advanced," 34 percent. However, those investigators felt that only tumors less than 0.2 mL with a Gleason grade less than seven were truly "insignificant," and candidates for expectant management; this category comprised 16 percent of their T1c tumors. Oesterling (263), on the other hand, found that only 11 percent of his series of T1c cancers were less than 0.5 mL in volume, and Richie (279) reported that only 24 percent of screen-detected cancers in men this age were unconfined; as indicated, this model reflects Oesterling and Richie's more favorable probabilities.

[7]The model-estimated sensitivities of combined PSA/DRE/biopsy are lower than many clinicians would predict. For example, at age 65, 3.5 percent of cancers less than 0.5 mL, 42 percent of intracapsular cancers >0.5 mL, and 43 percent of extracapsular cancers >0.5 mL would be detected. However, if one assumes full compliance with biopsy for suspicious screening results (instead of 69 percent), the estimated sensitivities of DRE/PSA/biopsy would increase to 5, 60, and 62 percent, respectively. These estimated sensitivities reflect the assumption that cancers are distributed by volume according to the autopsy study by McNeal (233) described in table 2-5 and appendix A. Assuming different distributions of cancers by volume would affect the estimated sensitivities, but would not affect the estimated benefits of screening, which are based on the post-test distributions of cancer reported in screening studies. For example, if only 20 percent, (rather than 40 percent) of prevalent cancers are greater than 0.5 mL in size, as reported in some cystoprostatectomy series (328), the sensitivity of screening at age 65 for cancers less than 0.5 mL would drop to 4 percent, and the predicted sensitivities of DRE/PSA/biopsy (assuming perfect compliance) for intracapsular and extracapsular cancers >0.5 mL would both be over 100 percent. In other words, the yield of cancers >0.5 mL described by Richie (279) would actually be greater than the predicted prevalence of these lesions.

Because there is no evidence from controlled studies that aggressive treatment (by either radical prostatectomy or radiation therapy) reduces the risk of death compared with expectant management, this analysis assumes that men with cancers confined to the prostatic capsule (absence of *complete* capsular penetration *of more than 1 cm*^{2}) are *cured* by aggressive treatment, regardless of other prognostic factors, such as degree of tumor differentiation. This assumption, which is favorable to screening (all else being held equal) is based on the work of Epstein (118), who has documented a worse prognosis for tumors with established, complete capsular penetration, as opposed to partial capsular penetration.[8]

Although there are two strategies for aggressive treatment (radical prostatectomy and radiation therapy), the baseline analysis examines only radical prostatectomy. This initial assumption seems reasonable despite older data that radiotherapy has been more commonly used, as the urologic literature now strongly endorses radical prostatectomy as the best treatment for localized prostate cancer, and because men with suspicious screening tests would almost always see a urologist for TRUS and biopsy. The rapidly rising rates of radical prostatectomy in the United States also support this initial assumption. Assuming equal effectiveness for radiation therapy (in the absence of strong evidence to the contrary) would result in similar estimated benefits; however, estimated risks would be much lower.[9]

Patients who are found to have distant metastases are assumed to receive hormonal therapy. Patients receiving such therapy are assumed to be responsive to it for a period of time, but then enter a "refractory" period characterized by no further benefit as well as pain or other discomfort before dying from the cancer or, infrequently, from some other cause.

All patients with intracapsular cancers (whether >0.5 mL or <0.5 mL in volume) who undergo and survive treatment are assumed to have the same life expectancy they would have had if they never had cancer (14.45 years for 65-year-old men and 8.95 years for 75-year-old men). In addition to the extra years of life they gain, these patients also avoid years of both hormone-responsive and refractory disease and associated morbidity. At the same time, though, they do risk the complications of aggressive treatment as outlined in the next section. Treated patients whose cancers are found to have spread beyond the prostate capsule at time of surgery have the same life expectancy as untreated patients with extracapsular cancer.

Finally, the analysis assumes that following radical prostatectomy, no additional cancer treatment is administered unless patients develop documented metastatic disease (as described below). In fact, in a survey of Medicare beneficiaries, 18 percent of men without metastatic disease reported followup radiation therapy within four years of radical prostatectomy, 10 percent reported hormonal therapy, and 15 percent reported orchiectomy (124). As is the case for primary aggressive treatment, there is no evidence from controlled studies that any such interventions (in the absence of documented metastases, at least) improve patient outcomes. Exclusion of

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[8]Although some men with established capsular penetration and no evidence of the tumor on the outside of tissue removed during prostatectomy (negative surgical margins) may be cured as well, these cases are balanced by Epstein's observation that roughly 25 percent of men with only partial capsular penetration had in fact demonstrated evidence of progression after eight years.

[9]Estimates of the treatment complications that would accrue if all patients were treated with radiotherapy, rather than radical prostatectomy, are presented later.

the costs associated with these additional treatments in the cost-effectiveness analysis later in this chapter reduces the total costs associated with screening, thus generating more favorable cost-effectiveness ratios.

Treatment Complications

Assumptions about the rate of complications following prostatectomy come from the survey of Medicare beneficiaries by Fowler and colleagues (124) since these are the most generalizable data available (see table 4-3). Among these risks, the model uses relatively conservative definitions for incontinence and impotence. Only men who drip more than a few drops of urine every day are considered incontinent[10]; while only preoperatively sexually active men who have had *no* partial or full erections since surgery are considered impotent.[11]

Although pelvic lymphadenectomy has its own complications (229), we assume no complications for this procedure as some clinicians question whether it is necessary at all. The analysis disregards other, less frequent complications of surgery and radiotherapy, such as rectal injury (230).

Prognosis and Life Expectancy

The analysis assumes that prognosis is determined entirely by grade, rather than extent of tumor; that is, a moderately differentiated cancer has the same prognostic impact whether it is intracapsular or extracapsular. The only exception is for well-differentiated tumors less than 0.5 mL in volume, which are assumed not to have potential for metastasis, and hence, equivalent to not having cancer at all.

Table 5-1 details life expectancies for untreated cancers.[12] Age-specific probabilities of death from causes other than prostate cancer used in the model were derived from U.S. life tables (350). Grade-specific rates of developing metastatic cancer come from an individual patient level meta-analysis by Chodak and colleagues (83). These data also generated grade-specific estimates of life expectancy for men with untreated cancers. The impact of treatment on rates of metastasis and these life expectancies are described above.

To model the progression from hormonally-responsive to hormonally-refractory metastatic cancer and the excess mortality associated with advanced prostate cancer, the model incorporates data from a randomized trial of hormonal treatment of late-stage disease (93). The data yield a progression rate to refractory prostate cancer of 36 cases per 100 patient years, and an excess mortality rate from hormonally-refractory metastatic cancer of 80 deaths per 100 patient years.[13]

Men who have prostate cancer are susceptible not only to metastatic disease, but to complications from local progression as well. Obstructive symptoms or bleeding from progression in the prostate may require transurethral resection of cancer tissue for palliation. Men who still have a prostate in place may also eventually re-

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[10]If wearing pads is used to define incontinence, the risk would be higher; see table 4-3.

[11]Excluding consideration of all treatment-related complications other than the two most common ones, impotence and incontinence, is another assumption that favors screening in this analysis.

[12]The analysis incorporates relatively high rates of grade-specific metastatic and cancer-specific death rates in this model; these rates are calibrated to the 10-year cancer-specific survivals reported in Chodak's (83) individual-patient-level meta-analysis, which excluded studies of Stage A1 cancers, which may well be treated aggressively in some patients in the current environment. These metastatic and death rates are favorable to screening. As a result of these assumptions, the model predicts that a 65-year-old man has a cumulative probability of eventually dying of prostate cancer of 4.1 percent, while the empirical epidemiologic evidence documents this risk is 3 percent or less (308, 314). Higher metastatic rates or assignment of metastatic potential to small volume, well-differentiated tumors would cause even greater divergence between the predicted and observed cumulative incidences of prostate cancer mortality.

[13]Median survival in this trial once the disease became hormonally refractory was 0.9 years.

quire transrectal resection of the prostate (TURP) for progressive benign prostatic hyperplasia (BPH). This analysis assumes that radical prostatectomy completely eliminates these risks and their associated costs. Assumptions used to calculate costs of transurethral resection for those men with cancer who do not receive radical prostatectomy are reviewed in the section on costs later in this chapter.

The assumptions about prognosis and cure rates from treatment are particularly favorable to screening; to the extent that relatively more future morbidity and mortality result from cancers that have already spread beyond the prostate (a likely scenario), the benefits of screening will be less impressive. Another way of viewing the impact of these assumptions is through the reduction in the rate of metastases through the treatment patients receive. For well-differentiated cancers, the model predicts a 97 percent decrease in the metastatic rate compared with 70 percent for moderately differentiated, and 56 percent for poorly differentiated cancers.

Net Impact of Assumptions

As indicated in the sections above, many of the assumptions made in this baseline analysis of the health outcomes of a one-time screening benefit are favorable to screening. These include relatively high yields of screening itself, high rates of metastasis and cancer-specific death with untreated cancers, and 100 percent cure rates for treated intracapsular cancers.[14] Given these assumptions, the estimated health outcomes for screening with subsequent aggressive treatment in this baseline analysis probably represent the *maximally attainable* benefits of one-time screening.

Results

Tables 5-2 through 5-4 provide "balance sheets" with baseline estimates of the risks and maximal benefits of a one-time screening of 100,000 men ages 65, 70, and 75 with DRE and PSA. Table 5-5 presents estimates of treatment complications that would accrue if all patients undergoing treatment received radiation therapy instead of radical prostatectomy. These estimates are based on rates of complications reported in the literature and summarized in chapter 4 (362).

The model indicates that a one-time screening would result in a very large number of prostatic biopsies (19,330 to 27,200 per 100,000, depending on age), a small number of surgical deaths (18 to 23 per 100,000), and a larger number of men rendered incontinent (260 to 311 per 100,000), impotent (1,357 to 1,622 per 100,000), or both (405 to 483 per 100,000) as a result of surgical treatment. Because these complications must be endured from the start, a very large number of life-years with these complications are generated by early detection efforts. Over time, using the optimistic assumptions about the efficacy of treatment, 653 men age 65, 570 men age 70, and 427 men age 75 who would otherwise have developed metastatic prostate cancer (542, 449, and 314 of whom would become hormone-refractory and die, respectively) would die of something else first in each of these cohorts of 100,000 screenees. The *net* benefit of

[14]The fact that this part of the analysis does not "discount" future life-years relative to current life-years also favors screening as risks of treatment. Discounting accounts for the fact that future costs and benefits are valued less than the same outcomes encountered in the present. It is particularly significant in the case of prostate cancer screening and treatment since the benefits of treatment (and risks of cancer) are faced in the future, while the risks of screening and treatment are faced in the present. Hence, discounting would diminish the estimated life-years gained through screening. The analysis does discount future health benefits subsequently when examining the costs and cost-effectiveness of screening.

TABLE 5-2: HEALTH OUTCOMES OF A ONE–TIME PROSTATE CANCER SCREENING OF 100,000 65-YEAR-OLD MEN WITH DRE/PSA

			Cancer > 0.5 mL				
	No cancer	Cancer < 0.5 mL	Intracapsular	Extracapsular	Total number	LY lost	LY morbidity
Number screened	78,000	13,200	6,424	2,376	100,000		
Estimated harm							
CA missed by DRE/PSA/biopsy (compliance with biopsy 69%)		12,744	3,743	1,363	17,850		
CA detected by DRE/PSA/biopsy		456	2,681	1,013	4,150		
Suspicious DRE/PSA					28,000		
TRUS/biopsy (compliance with biopsy 69%)					19,330		
Urinary tract infections from biopsy					1,083		
Urosepsis from biopsy					96		
Death from urosepsis					1	(14)[a]	
Radical prostatectomy (compliance with RPX 70%)		320	1,877	709	2,906		
Deaths from radical prostatectomy		2	12	4	18		
Life-years lost from radical prostatectomy deaths		(28)	(167)	(50)		(245)	
Morbidity from radical prostatectomy							
Incontinence:	n affected						
	life-years affected						
Impotence:	n affected						
	life-years affected						
Both incontinence and impotence	n affected						
	life-years affected						
Total harm from screening (life–years)						(259)	(27,510)
Total harm per patient screened (days)						(1)	(100)
Total harm per patient treated (days)						(33)	(3,455)

CONTINUED

TABLE 5-2: HEALTH OUTCOMES OF A ONE–TIME PROSTATE CANCER SCREENING OF 100,000 65-YEAR-OLD MEN WITH DRE/PSA CONTINUED

			Cancer > 0.5 mL				
	No cancer	**Cancer < 0.5 mL**	**Intracapsular**	**Extracapsular**	**Total number**	**LY saved**	**LY improved**
Estimated maximal benefit							
Survive radical prostatectomy		318	1,865	705	2,888		
Hormonally–responsive metastatic cancer							
Number *spared* by treatment		45	608	0	653[b]		
Life–years affected		72	731	0			803
Hormonally–refractory metastatic cancer							
Number *spared* by treatment		38	504	0	542[b]		
Life–years affected		27	260	0			287
Cancer deaths *prevented*		38	504	0	542[b]		
Additional years of life attained		338	4,274	0		4,612	
		Total benefit from screening (life-years)				4,612	1,090
		Total benefit per patient screened (days)				174	
		Total benefit per patient treated (days)				579	137

[a] Life-years and days *lost* through screening are presented in parenthesis.

[b] Six additional cases of hormonally–responsive metastatic disease leading to five cases of hormonally refractory metastatic disease and death are averted through immediate operative deaths; these cases are not counted as benefits.

KEY: CA: cancer; DRE = digital rectal examination; LY = life-years; PSA = prostate-specific antigen; RPX = radical prostatectomy; TRUS = transrectal ultrasound.

SOURCE: Office of Technology Assessment, 1995. Based on data from M.J. Barry, C.M. Coley, C. Fleming, et al., "The Safety, Effectiveness, and Cost of Early Detection and Treatment of Prostate Cancer Among Older Men: A Report to the Congressional Office of Technology Assessment," OTA contract paper no. K3–0546.0, Boston, MA: Massachusetts General Hospital, June 30, 1994.

TABLE 5-3: HEALTH OUTCOMES OF A ONE–TIME PROSTATE CANCER SCREENING OF 100,000 70-YEAR-OLD MEN WITH DRE/PSA

				Cancer > 0.5 mL				
		No cancer	Cancer < 0.5 mL	Intracapsular	Extracapsular	Total number	LY lost	LY morbidity
Number screened		69,500	18,300	8,906	3,294	100,000		
Estimated harm								
CA missed by DRE/PSA/biopsy (compliance with biopsy 69%)			17,674	5,671	1,460	24,805		
CA detected by DRE/PSA/biopsy			626	3,235	1,834	5,695		
Suspicious DRE/PSA						34,000		
TRUS/biopsy (compliance with biopsy 69%)						23,460		
Urinary tract infections from biopsy						1,314		
Urosepsis from biopsy						117		
Death from urosepsis						1	(12)	
Radical prostatectomy (compliance with RPX 59%)			369	1,909	1,082	3,360		
Deaths from radical prostatectomy			2	12	7	21		
Life-years lost from radical prostatectomy deaths			(27)	(140)	(66)		(233)	
Morbidity from radical prostatectomy								
Incontinence:	n affected					301		
	life-years affected							(3,229)
Impotence:	n affected					1,569		
	life-years affected							(16,908)
Both incontinence and impotence	n affected					467		
	life-years affected							(5,050)
			Total harm from screening (life–years)				(245)	(25,187)
			Total harm per patient screened (days)				(1)	(92)
			Total harm per patient treated (days)				(27)	(2,736)

CONTINUED

TABLE 5-3: HEALTH OUTCOMES OF A ONE–TIME PROSTATE CANCER SCREENING OF 100,000 70-YEAR-OLD MEN WITH DRE/PSA CONTINUED

			Cancer > 0.5 mL				
	No cancer	Cancer < 0.5 mL	Intracapsular	Extracapsular	Total number	LY saved	LY improved
Estimated maximal benefit							
Survive radical prostatectomy		367	1,897	1,075	3,339		
Hormonally–responsive metastatic cancer							
Number *spared* by treatment		46	524	0	570[a]		
Life–years affected		67	560	0			627
Hormonally–refractory metastatic cancer							
Number *spared* by treatment		37	412	0	449[a]		
Life–years affected		22	180	0			202
Cancer deaths *prevented*		37	412	0	449[a]		
Additional years of life attained		254	2,765	0		3,019	
		Total benefit from screening (life-years)				3,019	829
		Total benefit per patient screened (days)				113	
		Total benefit per patient treated (days)				328	90

[a] Six additional cases of hormonally–responsive metastatic disease leading to five cases of hormonally refractory metastatic disease and death are averted through immediate operative deaths; these cases are not counted as benefits.

KEY: CA: cancer; DRE = digital rectal examination; LY = life-years; PSA = prostate-specific antigen; RPX = radical prostatectomy; TRUS = transrectal ultrasound.

SOURCE: Office of Technology Assessment, 1995. Based on data from M.J. Barry, C.M. Coley, C. Fleming, et al., "The Safety, Effectiveness, and Cost of Early Detection and Treatment of Prostate Cancer Among Older Men: A Report to the Congressional Office of Technology Assessment," OTA contract paper no. K3–0546.0, Boston, MA, Massachusetts General Hospital, June 30, 1994.

TABLE 5-4: HEALTH OUTCOMES OF A ONE–TIME PROSTATE CANCER SCREENING OF 100,000 75-YEAR-OLD MEN WITH DRE/PSA

				Cancer > 0.5 mL				
		No cancer	Cancer < 0.5 mL	Intracapsular	Extracapsular	Total number	LY lost	LY morbidity
Number screened		61,000	23,400	11,388	4,212	100,000		
Estimated harm								
CA missed by DRE/PSA/biopsy (compliance with biopsy 68%)			22,604	7,843	1,318	31,765		
CA detected by DRE/PSA/biopsy			796	3,545	2,894	7,235		
Suspicious DRE/PSA						40,000		
TRUS/biopsy (compliance with biopsy 68%)						27,200		
Urinary tract infections from biopsy						1,523		
Urosepsis from biopsy						136		
Death from urosepsis						1	(9)	
Radical prostatectomy (compliance with RPX 48%)			382	1,702	1,389	3,473		
Deaths from radical prostatectomy			3	11	9	23		
Life-years lost from radical prostatectomy deaths			(23)	(100)	(71)		(194)	
Morbidity from radical prostatectomy								
Incontinence:	n affected					311		
	life-years affected							(2,597)
Impotence:	n affected					1,622		
	life-years affected							(13,598)
Both incontinence and impotence	n affected					483		
	life-years affected							(4,062)
			Total harm from screening (life–years)				(203)	(20,257)
			Total harm per patient screened (days)				(1)	(74)
			Total harm per patient treated (days)				(21)	(2,129)

CONTINUED

TABLE 5-4: HEALTH OUTCOMES OF A ONE–TIME PROSTATE CANCER SCREENING OF 100,000 75-YEAR-OLD MEN WITH DRE/PSA CONTINUED

			Cancer > 0.5 mL				
	No cancer	Cancer < 0.5 mL	Intracapsular	Extracapsular	Total number	LY saved	LY improved
Estimated maximal benefit							
Survive radical prostatectomy		379	1,691	1,380	3,450		
Hormonally–responsive metastatic cancer							
Number *spared* by treatment		40	387	0	427[a]		
Life–years affected		63	417	0			480
Hormonally–refractory metastatic cancer							
Number *spared* by treatment		30	284	0	314[a]		
Life–years affected		3	38	0			41
Cancer deaths *prevented*		30	284	0	314[a]		
Additional years of life attained		159	1,459	0		1,618	
		Total benefit from screening (life-years)				1,618	521
		Total benefit per patient screened (days)				62	
		Total benefit per patient treated (days)				170	55

[a] Six additional cases of hormonally–responsive metastatic disease leading to five cases of hormonally refractory metastatic disease and death are averted through immediate operative deaths; these cases are not counted as benefits.

KEY: CA = cancer; DRE = digital rectal examination; LY = life-years; PSA = prostate-specific antigen; RPX = radical prostatectomy; TRUS = transrectal ultrasound.

SOURCE: Office of Technology Assessment, 1995. Based on data from M.J. Barry, C.M. Coley, C. Fleming, et al., "The Safety, Effectiveness, and Cost of Early Detection and Treatment of Prostate Cancer Among Older Men: A Report to the congressional Office of Technology Assessment," OTA contract paper no. K3–0546.0, Boston, MA, Massachusetts General Hospital, June 30, 1994.

TABLE 5-5: EXPECTED HARM FROM A ONE-TIME PROSTATE CANCER SCREENING (DRE/PSA) OF 100,000 MEN, AGES 65, 70, OR 75, FOR CURATIVE RADIATION THERAPY

Morbidity	Life-years of morbidity
Age 65	
Incontinence	1,385
Impotence	11,275
Both incontinence and impotence	593
Total harm from screening	13,253
Total harm per patient screened (days)	48
Total harm per patient treated (days)	1,664
Age 70	
Incontinence	1,269
Impotence	10,337
Both incontinence and impotence	544
Total harm from screening	12,150
Total harm per patient screened (days)	45
Total harm per patient treated (days)	1,321
Age 75	
Incontinence	1,023
Impotence	8,329
Both incontinence and impotence	438
Total harm from screening	9,790
Total harm per patient screened (days)	36
Total harm per patient treated (days)	1,029

SOURCE: Office of Technology Assessment, 1995. Based on data from M.J. Barry, C.M. Coley, C. Fleming, et al., "The Safety, Effectiveness, and Cost of Early Detection and Treatment of Prostate Cancer Among Older Men: A Report to the Congressional Office of Technology Assessment." OTA contract paper no. K3-0546.0, Massachusetts General Hospital, Boston, MA, June 30, 1994.

screening in each cohort would be 4,353, 2,774, and 1,415 life-years saved (without discounting) for the 100,000 men ages 65, 70, and 75; or 16, 10, and 5 days per man screened, respectively.

If, in fact, contrary to our initial, "best case" assumptions, aggressive treatment of prostate cancer is ineffective at reducing the rate of distant metastases and death, these cohorts would loose about 200 life-years due to operative mortality and endure over 20,000 life-years with incontinence, impotence, or both. The net benefit predicted by the model is very sensitive to the assumptions regarding the efficacy of treatment. For example, if in this undiscounted analysis the proportion of intracapsular prostate cancers that are cured by aggressive treatment is decreased from 100 to 50 percent, the net days of life saved per patient screened at ages 65, 70, and 75 drops to seven, four, and two days, respectively.

DRE/PSA Together Versus DRE Alone

Many physicians already perform DREs in older men to seek evidence of both prostate and colorectal cancer. What is the *marginal value* of adding PSA to the

DRE? In the recent combined screening described by Richie and colleagues (279), DRE, which was suspicious in 16 percent of men ages 60-69, had a predictive value of 21 percent, yielding cancer in 2.4 percent of the screenees. Adding PSA increased the detection rate to 4.2 percent. Therefore, since the ratio of intracapsular to extracapsular disease was roughly equal (at 3:1) between the DRE-detected cancers and the cancers detected by combination screening, one can assume that roughly 60 percent of the risks and maximal benefits presented in table 5-2 would be accrued by screening with DRE alone. However, such results would only be seen if DRE were performed with a very low threshold to proceed to systematic biopsies for any minor palpable abnormality, an approach not common in current clinical practice. Again, roughly half the cancers detected using this DRE-alone strategy would actually be found in palpably normal areas of the prostate as a result of the systematic biopsies. For men ages 70 to 79 in the Richie study, DRE detected cancer in 3.5 percent of screenees versus 7.2 percent for combined DRE/PSA screening, but a lower proportion of DRE-detected cancers was intracapsular compared with all cancers found by combined DRE/PSA screening (45 percent versus 60 percent). Therefore, about half the risks presented in table 5-4 would be expected to accumulate with DRE screening, accompanied by less than half the maximal benefits.

MODELING THE COST-EFFECTIVENESS OF ONE-TIME SCREENING

The overall costs of a screening program would comprise the upfront costs of the screening tests themselves, subsequent ultrasound (TRUS) exams and biopsies, staging tests, early treatment, and therapy for treatment complications. To the extent that early detection and treatment are effective, savings accrue from averting costs of subsequent treatment of local cancer progression, metastatic disease, and end-stage cancer. Appropriate discounting diminishes the value of these later savings since policymakers or patients in the present would rather realize benefits now than in the future. Moreover, older men treated for prostate cancer, on average, extend their lives an average of 6 (age 75) to 19 (age 65) months (see tables 5-2 through 5-4), given their risks of death from other causes.[15]

Beyond whether or not a prostate cancer screening benefit would result in net costs or savings for Medicare, one can also consider whether the health benefit realized for each extra dollar spent for prostate cancer screening (and subsequent treatment) is more or less than those of screening programs or other services already covered by Medicare. This ratio of a benefit per dollar spent is the "cost effectiveness" of the screening program. This section models the cost-effectiveness of the illustrative, one-time screening benefit examined in the previous section. As indicated earlier, the actual estimates produced in this analysis are unlikely to be the same as those for an actual Medicare benefit since Medicare would most likely cover multiple, periodic screenings rather than a one-time benefit. However, as will be seen, this simplified analysis does illustrate how sensitive the cost-effectiveness of screening is to assumptions about the effectiveness of treating prostate cancer.

Cost Assumptions

The Cost of Specific Resources

To estimate the costs of an early detection program with DRE and PSA among our hypothetical cohorts of

[15]Epidemiologically, cardiovascular disease and other cancers are by far the most likely causes (table 2-1). The costs of these alternative scenarios for death further blunt any savings from averting terminal care costs for prostate cancer.

100,000 men ages 65, 70, and 75, this analysis adopts the perspective of the Medicare program and considers only direct medical care costs.[16] Cost estimates for resource inputs are based on the 1992 Medicare fee schedule and diagnosis-related groups (DRG) reimbursements for relevant hospitalizations.[17] Appendix G details these cost estimates. Tables 5-6 through 5-8 combine these costs for individual resource inputs into low, medium, and high estimates of the costs of different steps in the process of early detection and treatment, respectively. The low, medium, and high estimates reflect uncertainty about how resources would be utilized and billed in actual practice.[18] The analysis discounts all future health care costs and health benefits are both discounted at an annual rate of 5 percent.

Other Cost Assumptions

The analysis assumes the marginal costs for the care of hormonally refractory prostate cancer, compared with all other causes of death, to be $6,260 in the last year of life (in 1992 dollars), based on the work of Riley and colleagues (282).

As indicated earlier, men who have prostate cancer but do not receive a radical prostatectomy are susceptible not only to metastatic disease, but to complications from local progression as well. To estimate the costs associated with transrectal resection (TURP) to treat local cancer progression or BPH, the analysis used the weighted average of the only two empirical estimates of the probability of this phenomenon currently available (176, 366).[19]

Also as explained in a previous section, the analysis excludes the cost of any additional cancer treatment (radiation therapy, hormonal therapy, or orchiectomy) unless patients have evidence of metastatic cancer. This assumption again favors early detection and treatment.

In estimating the costs of treating complications of radical prostatectomy (or radiation therapy), the analysis again makes assumptions favoring early detection and treatment. For patients with sexual dysfunction, we ignore all costs other than for penile implants, and assume that no additional patients require surgery for impotence more than four years after surgery.[20] For men with incon-

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[16]Beyond the costs to the federal government through Medicare, patients also bear the direct and indirect nonmedical costs associated with screening and any detected disease such as travel costs to receive medical care, lost wages, and the anxiety associated with being told they may have cancer on the basis of a suspicious screening test result. In addition, patients or third-party private insurers would bear medical care costs not covered by Medicare.

[17]Continuing changes in Medicare reimbursements for procedures associated with prostate cancer screening and treatment may make these 1992 costs inaccurate predictors of costs in 1995 or in subsequent years (13a).

[18]For example, it is unknown exactly what percentage of men would get a pelvic CT scan or bone scan as part of a staging evaluation, or what percentage of men undergoing radical prostatectomy would be billed under DRG 335 (without comorbidity/complications) versus DRG 334 (with comorbidity/complication). An October 1993 publication by the American Urological Association entitled, "Coding Tips for the Urologist's Office," was helpful in preparing the ambulatory component of these estimates.

[19]Johansson (176) recently updated the outcomes in his Scandinavian series of "watchful waiters" at an annual American Urological Association meeting in San Antonio. At 12.5 years of average followup, 30 untreated cancer patients had required TURP over approximately 1,610 person-years (a rate of 0.019 TURPs per person-year); in 16 men the pathology report showed cancer, while in 14 the diagnosis was BPH. Whitmore (366), on the other hand, found that among men with T2 cancers treated expectantly, 23 patients required 37 TURPs in approximately 803 person-years of followup (a rate of 0.046 per person year); 27 men had cancer in their resected specimens while 10 had only BPH. We use an average of these two rates (a weighted average based on person-years of followup would be closer to that of the larger Johansson study) to calculate the costs of treatment for local progression of cancer and for BPH among men with cancer.

[20]For men treated with radical prostatectomy, the survey of Medicare prostatectomy patients by Fowler and colleagues (127) found that actually 15-percent report postoperative treatment for sexual dysfunction within two to four years after surgery: eight percent with a vacuum device, 7 percent with pharmacologic erection therapy, and 3 percent with a penile implant.

TABLE 5-6: MEDICARE COST ESTIMATES FOR EARLY DETECTION AND STAGING OF PROSTATE CANCER USING DIGITAL RECTAL EXAMS AND PROSTATIC-SPECIFIC ANTIGEN

	Low estimate	Mediumestimate	High estimate
Initial testing			
PSA	$30	$45[a]	$60[a]
DRE	$0	$3	$28[b]
Total	$30	$48	$88
Work-up for suspicious results			
Consult (urology)	$47	$47	$47
TRUS (diagnostic)	$0	$85	$85
TRUS-guided biopsy	$189	$189	$189
Pathology (level IV)	$208[c]	$312[d]	$312[d]
Total	$444	$633	$633
Staging for men with cancer			
Pelvic CT scan[e]	$71 (25%)	$142 (50%)	$213 (75%)
Bone scan[e]	$46 (25%)	$92 (50%)	$138 (75%)
Lymphadenectomy[e]	$0 (0%)	$164[f] (25%)	$328[f] (50%)
Visit to discuss results	$28	$28	$28
Total	$145	$426	$707

[a] Assumes some repeat testing necessary.
[b] Assumes brief office visit specifically for a prostate evaluation.
[c] Four cores examined.
[d] Six cores examined.
[e] Not all patients get pelvic CT scan with contrast (cost $284), bone scan ($184), or lymphadenectomy ($656); figures in parentheses indicate percentage of men who get these studies.
[f] Includes pathology fee (level IV, two sets of nodes).
KEY: CT = computed tomography; DRE = digital rectal exam; PSA = prostate-specific antigen; TRUS = transrectal ultrasound.

SOURCE: Office of Technology Assessment, 1995. Based on information presented in M.J. Barry, C.M. Coley, C. Fleming, et. al, "The Safety, Effectiveness, and Cost of Early Detection and Treatment of Prostate Cancer Among Older Men: A Report to the Congressional Office of Technology Assessment," OTA contract paper no. K3-0546.0, Massachusetts General Hospital, Boston, MA, June 30, 1994.

tinence, the analysis includes only the costs of an artificial sphincter implantation for the six percent of men who reported corrective surgery for incontinence, ignoring the costs of pads for the 31 percent of prostatectomy patients who report using them (124). While some of these men may have had less aggressive and expensive corrective surgery for incontinence (such as collagen injections), the other cost assumptions make the overall approach to estimating costs of treatment complications conservative.

For men with urethral strictures following radical prostatectomy, the analysis assumes that 95 percent are treated with a simple stricture dilation in the office, while only 5 percent need in-hospital operative repair. We assume no additional treatments are required beyond

TABLE 5-7: MEDICARE COST ESTIMATES FOR PROSTATE CANCER TREATMENT

Treatment	Low estimate	Medium estimate	High estimate
Radical prostatectomy			
Hospital[a]	$5,867	$6,271	$6,675
Surgeon	$1,497	$1,497	$1,497
Anesthesia	$194	$194	$194
Pathology[b]	$125	$125	$125
Total	$7,680	$8,084	$8,488
External beam radiotherapy			
Course	$3,604	$3,604	$3,604
Monitoring post-treatment (annual cost)			
Office visit and PSA	$59	$59	$59
Bone scan[c]	$0	$46	$92
Total	$59	$105	$151
Diagnosis and treatment:			
Metastatic disease			
Bone scan	$184	$184	$184
Orchiectomy	$4,406	$4,406	$4,406
Hormonal therapy[d]	$4,224	$5,748	$6,953

[a] Low estimate: 0% diagnosis-related groups 334 (complications) at $7,483 and 100% DRG 335 (no complications) at $5,867; medium estimate: 25% DRG 334 and 75% DRG 335; high estimate 50% DRG 334 and 50% DRG 335.

[b] Level VI.

[c] Low estimate: 0% get bone scan each year at $184, medium estimate: 25% get bone scan each year; high estimate: 50% get bone scan each year.

[d] Annual cost; low estimate: 100% GnRH agonist and 0% flutamide; medium estimate: 100% GnRH agonist and 50% flutamide; high estimate: 100% GnRH agonist and 100% flutamide; includes monthly fees for an office visit ($29) with chemotherapy injection ($4).

KEY: DRG = diagnosis-related groups; PSA = prostate-specific antigen.

SOURCE: Office of Technology Assessment, 1995. Based on information presented in M.J. Barry, C.M. Coley, C. Fleming, et. al, "The Safety, Effectiveness, and Cost of Early Detection and Treatment of Prostate Cancer Among Older Men: A Report to the Congressional Office of Technology Assessment," OTA contract paper no. K3-0546.0, Massachusetts General Hospital, Boston, MA, June 30, 1994.

four years after surgery,[21] and ignore costs related to the diagnosis of strictures, such as for cystourethroscopy.[22]

Incorporation of Costs in the Screening Model

The analysis estimates cost-effectiveness by incorporating the costs for early detection, staging, treatment of clinically localized cancer, diagnosis of metastatic disease, and treatment of metastatic disease by orchiectomy, into the Markov model of prognosis described earlier in the chapter. The model accumulates these costs (with appropriate discounting) as each intervention is

[21] Since strictures are often recurrent, this assumption is particularly conservative.

[22] In Medicare survey (127), 20 percent of men reported at least one dilation or surgical procedure for what they believed to be strictures two to four years following radical prostatectomy; 11 percent required treatment at least twice.

TABLE 5-8: MEDICARE COST ESTIMATES FOR THERAPY OF PROSTATE CANCER TREATMENT COMPLICATIONS

	Low estimate	Medium estimate	High estimate
TURP for BPH or local progression of cancer			
Hospital[a]	$2,778	$3,069	$3,361
Surgeon	$898	$898	$898
Anesthesia	$147	$147	$147
Pathology	$92	$92	$92
Total	$3,915	$4,206	$4,498
Treatment for cancer therapy complications			
Incontinence			
(Artificial sphincter)	—	$8,080	—
Impotence			
(Penile implant)	—	$11,350	—
Stricture			
(Dilation)	—	$51	—
(Urethroplasty)	—	$5,259	—

[a] Low estimate: 0% DRG 336 (complications) at $3,943 and 100% DRG 337 (no complications) at $2,778; medium estimate: 25% DRG 336 and 75% DRG 337; high estimate 50% DRG 336 and 50% DRG 337.

KEY: BPH = benign prostatic hypertrophy; DRG = diagnosis-related group; TURP = transurethral resection of the prostate.

SOURCE: Office of Technology Assessment, 1995. Based on data from M.J. Barry, C.M. Coley, C. Fleming, et al., "The Safety, Effectiveness, and Cost of Early Detection and Treatment of Prostate Cancer Among Older Men: A Report to the congressional Office of Technology Assessment," OTA contract paper no. K3-0546.0, Massachusetts General Hospital, Boston, MA, June 30, 1994.

encountered. The model accumulates ongoing costs, such as post-treatment surveillance and androgen deprivation therapy for metastatic disease, continuously with each Markov cycle patients spend in a particular state.

Cost-Effectiveness Results

Tables 5-9 through 5-11 present estimates of discounted costs (in dollars), discounted effectiveness (in life-years saved), and cost per life year saved for cohorts of 100,000 men ages 65, 70, and 75 receiving a hypothetical, one-time screening under the baseline assumptions described in this chapter. Using the medium set of assumptions about costs, the cost per year of life saved (compared with doing no screening) would be $14,200 at age 65, $25,290 at age 70, and $51,290 at age 75.

Sensitivity of the Results

These results are extremely sensitive to the assumption about the effectiveness of prostate cancer treatment and, to a somewhat lesser degree, the assumption about the rate at which cancers of different grades metastasize. As indicated earlier, the actual effectiveness of treatment is unknown because of the lack of randomized controlled trials. Similarly, the true rates of future metastasis and prostate cancer death from tumors currently discovered by early detection are also unknown. The assumptions about both treatment and metastasis used in the baseline

TABLE 5-9: MARGINAL COST-EFFECTIVENESS OF ONE-TIME HYPOTHETICAL DRE/PSA SCREENING VERSUS NOT SCREENING (100,000 men, age 65)[a]

Marginal cost	Low Estimates	Medium Estimates	High Estimates
	Cost estimate (millions of dollars)		
Initial costs			
Initial testing	3.000	4.800	8.800
TRUS/biopsy	3.045	4.341	4.341
Staging	0.602	1.087	1.573
Treatment	22.578	23.751	24.924
Delayed costs			
Monitoring	2.509	4.457	6.383
Future treatment[b]	-5.929	-9.128	-14.808
Total	$25.804	$29.308	$31.214
	Discounted life-years saved		
Marginal effectiveness	2064	2064	2064
	Dollars per life-year		
Marginal cost-effectiveness	$12,502	$14,200	$15,123

[a] Both future costs and health benefits are discounted at 5% annually.
[b] Future treatment for local progression of prostate cancer, benign prostatic hyperplasia (BPH), metastatic prostate cancer, and therapy complications.
KEY: TRUS = transrectal ultrasound.

SOURCE: Office of Technology Assessment, 1995. Based on data from M.J. Barry, C.M. Coley, C. Fleming, et al., "The Safety, Effectiveness, and Cost of Early Detection and Treatment of Prostate Cancer Among Older Men: A Report to the Congressional Office of Technology Assessment," OTA contract paper no. K3-0546.0, Massachusetts General Hospital, Boston, MA, June 30, 1994.

analysis are favorable to screening. What happens when these assumptions are relaxed?

- Reducing the grade-specific metastatic rates in this model[23] to those used in the previously published analysis of prostate cancer treatment by Fleming and colleagues (124), the estimate of cost per year of life saved (discount rate 5 percent) ranges from $42,590 at age 65 to $177,094 at age 75.
- Alternatively, assuming only half (rather than all) intracapsular cancers >0.5 mL are cured by radical prostatectomy, the cost per year of life saved ranges from $30,524 at age 65 to $109,721 at age 75 (same discount rate).
- Assuming that both the lower metastatic rates from the Fleming analysis and the lower proportion of cures represent the true state of affairs, the cost per year of life saved would range from $94,458 at age 65 to $506,909 at age 75.

[23] As mentioned earlier, the rates used in this analysis result in a lifetime cumulative risk of prostate cancer death more than a third higher than the risk actually observed in the literature.

TABLE 5-10: MARGINAL COST-EFFECTIVENESS OF ONE-TIME HYPOTHETICAL DRE/PSA SCREENING VERSUS NOT SCREENING (100,000 men, age 70)[a]

Marginal cost	Low Estimates	Medium Estimates	High Estimates
	Cost estimate (millions of dollars)		
Initial costs			
Initial testing	3.000	4.800	8.800
TRUS/biopsy	4.462	6.362	6.362
Staging	0.826	1.492	2.158
Treatment	26.114	27.472	28.829
Delayed costs			
Monitoring	2.522	4.478	6.407
Future treatment[b]	-5.596	-6.165	-10.531
Total	$31.765	$36.467	$39.042
	Discounted life-years saved		
Marginal effectiveness	1,442	1,442	1,442
	Dollars per life-year		
Marginal cost-effectiveness	$22,059	$25,290	$27,076

[a] Both future costs and health benefits are discounted at 5% annually.
[b] Future treatment for local progression of prostate cancer, benign prostatic hyperplasia, metastatic prostate cancer, and therapy complications.
KEY: DRE = digital rectal exam; PSA = prostate-specific antigen; TRUS = transrectal ultrasound.

SOURCE: Office of Technology Assessment, 1995. Based on data from M.J. Barry, C.M. Coley, C. Fleming, et al., "The Safety, Effectiveness, and Cost of Early Detection and Treatment of Prostate Cancer Among Older Men: A Report to the Congressional Office of Technology Assessment," OTA contract paper no. K3-0546.0, Massachusetts General Hospital, Boston, MA, June 30, 1994.

To emphasize the sensitivity of the results to these key assumptions, figures 5-1 through 5-3 display the estimated cost per year of life saved for men ages 65, 70, and 75, using higher (83) and lower (362, 124) metastatic rates, and different assumptions about the proportion of intracapsular cancers (of all grades) cured by aggressive treatment.[24]

Another assumption in the baseline analysis is that the metastatic rate is the same for each grade of tumor (except for well-differentiated cancers less than 0.5 mL in volume), regardless of whether the tumor is intracapsular or extracapsular. If, however, future metastatic events are *preferentially* generated from extracapsular cancers, a likely scenario, the estimated effectiveness of treatment and screening would diminish considerably. For example, if intracapsular cancers have the grade-specific prostate cancer mortality rates described by Fleming (124), while extracapsular cancers have the

[24]The costs per year of life saved are displayed on a log scale because of the steep escalation in costs as the favorable initial assumptions are relaxed.

TABLE 5-11: MARGINAL COST-EFFECTIVENESS OF ONE-TIME HYPOTHETICAL DRE/PSA SCREENING VERSUS NOT SCREENING (100,000 men, age 75)[a]

Marginal cost	Low Estimates	Medium Estimates	High Estimates
	Cost estimate (millions of dollars)		
Initial costs			
Initial testing	3.000	4.800	8.800
TRUS/biopsy	6.019	8.581	8.581
Staging	1.049	1.896	2.742
Treatment	26.991	28.394	29.797
Delayed costs			
Monitoring	2.208	3.919	5.601
Future treatment[b]	-5.596	-6.165	-10.531
Total	$33.671	$41.424	$44.990
	Discounted life-years saved		
Marginal effectiveness	808	808	808
	Dollars per life-years saved		
Marginal cost-effectiveness	$41.690	$51.290	$55.705

[a] Both future costs and health benefits are discounted at 5 % annually.

[b] Future treatment for local progression of prostate cancer, benign prostatic hyperplasia, metastatic prostate cancer, and therapy complications.

KEY: DRE = digital rectal exam; PSA = prostate-specific antigen; TRUS = transrectal ultrasound.

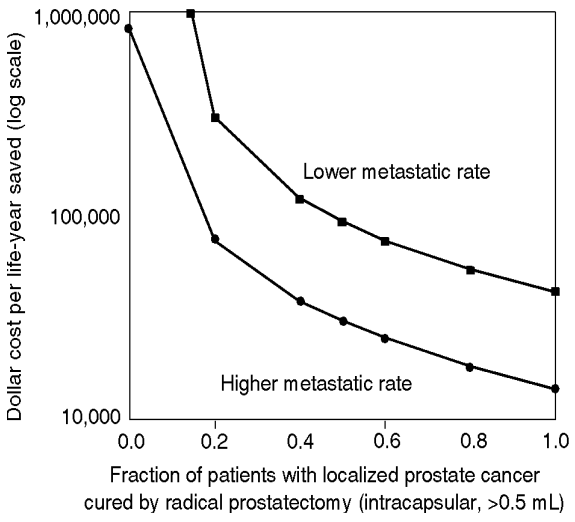
SOURCE: Office of Technology Assessment, 1995. Based on data from M.J. Barry, C.M. Coley, C. Fleming, et al., "The Safety, Effectiveness, and Cost of Early Detection and Treatment of Prostate Cancer Among Older Men: A Report to the congressional Office of Technology Assessment," OTA contract paper no. K3-0546.0, Massachusetts General Hospital, Boston, MA, June 30, 1994.

mortality rates described by Chodak (83), the cost-effectiveness estimates for early detection (which are based on the curability of the *intracapsular* lesions) would follow the higher curves in figures 5-1 through 5-3.[25]

Finally, a substantial component of the estimated net benefits come from the early detection and treatment of well-differentiated prostate cancers greater than 0.5 mL in volume. This finding is due to well differentiated cancers having had the same cancer-specific death rates as moderately differentiated cancers in the Chodak (83) meta-analysis. However, Kolon (194) has recently found that men with well-differentiated cancers treated expectantly among cases reported to the Connecticut tumor registry had the same life expectancy as age-matched men in the general state population. If, in fact, well-differentiated prostate cancers do not result in a higher-than-expected future mortality for men diagnosed at age 65 or above, the estimated number of deaths averted per

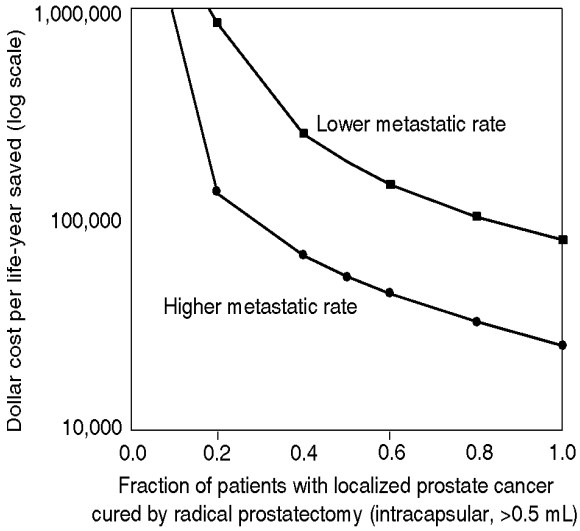
[25]This set of assumptions actually results in a prediction of the cumulative probability of a prostate cancer death for men age 65 of 2.5 percent, within the empirically observed probability range of 2.5 to 3 percent.

FIGURE 5-1: COST-EFFECTIVENESS OF ONE-TIME DRE/PSA SCREENING OF 65-YEAR-OLD MEN FOR PROSTATE CANCER: SENSITIVITY ANALYSIS



SOURCE: Office of Technology Assessment, 1995. Based on data from M.J. Barry, C.M. Coley, C. Fleming, et al., "The Safety, Effectiveness, and Cost of Early Detection and Treatment of Prostate Cancer Among Older Men: A Report to the Congressional Office of Technology Assessment," OTA Contract Paper No. K3–0546.0, Massachusetts General Hospital, Boston, MA, June 30, 1994.

FIGURE 5-2: COST-EFFECTIVENESS OF ONE-TIME DRE/PSA SCREENING OF 70-YEAR-OLD MEN FOR PROSTATE CANCER: SENSITIVITY ANALYSIS



SOURCE: Office of Technology Assessment, 1995. Based on data from M.J. Barry, C.M. Coley, C. Fleming, et al., "The Safety, Effectiveness, and Cost of Early Detection and Treatment of Prostate Cancer Among Older Men: A Report to the Congressional Office of Technology Assessment," OTA Contract Paper No. K3–0546.0, Massachusetts General Hospital, Boston, MA, June 30, 1994.

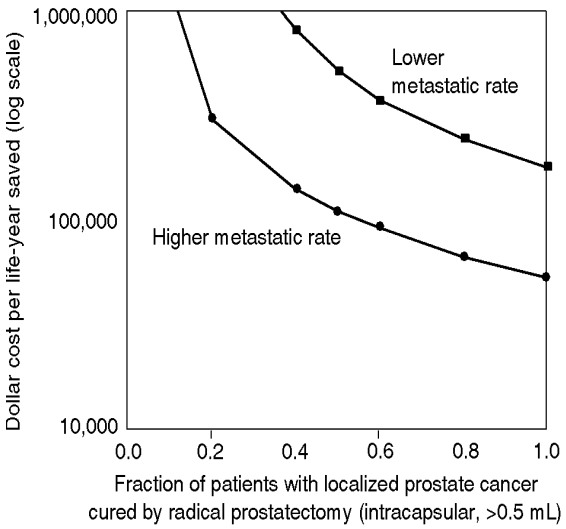
100,000 by screening and treatment (as presented in tables 5-2 through 5-4) would drop from 547 to 414 at age 65, from 431 to 325 at age 70, and from 294 to 224 at age 75. This would result in a parallel increase in the cost per life-year saved by screening.

Turning from effectiveness to cost, how would changes in the cost assumptions affect the cost-effectiveness ratios? Each increase of $10,000 in the costs of caring for terminal prostate cancer above the baseline estimate reduces the present value per person cost of prostate cancer screening only by about $30. This relatively small effect on the analysis is due in large part to the discounting of these future expenses.

Comparisons to Other Medicare Disease Screening

How do these estimates for the cost-effectiveness of one-time screening for prostate cancer compare with previously published estimates for other cancer screening maneuvers among Medicare patients? Such comparisons are problematic since most cost-effectiveness analyses of disease screening for Medicare beneficiaries examine periodic screening rather than only a one-time benefit. However, as part of a previous analysis by the Office of Technology Assessment (OTA), Muller and colleagues (347) found that a one-time screening with cervical Pap smears at age 65 would cost $1,666 per life-

FIGURE 5-3: COST-EFFECTIVENESS OF ONE-TIME DRE/PSA SCREENING OF 75-YEAR-OLD MEN FOR PROSTATE CANCER: SENSITIVITY ANALYSIS



SOURCE: Office of Technology Assessment, 1995. Based on data from M.J. Barry, C.M. Coley, C. Fleming, et al., "The Safety, Effectiveness, and Cost of Early Detection and Treatment of Prostate Cancer Among Older Men: A Report to the Congressional Office of Technology Assessment," OTA Contract Paper No. K3–0546.0, Massachusetts General Hospital, Boston, MA, June 30, 1994.

year saved.[26] Among previous OTA analyses of disease screening for Medicare beneficiaries that examined periodic screening (as opposed to one-time screening) are two that make estimates for colorectal and breast cancer screening. The breast cancer study concluded that annual mammography would cost Medicare $13,200 per year of life saved (346), and the colorectal cancer study estimated that annual occult blood testing beginning at age 65 would cost $35,054 per year of life (348).[27] Medicare currently covers both cervical and breast cancer screening as periodic benefits.

IMPLICATIONS FOR MEDICARE

What information does the analysis in this background paper yield for policymakers considering coverage of prostate cancer screening as a Medicare benefit?

Although the quantitative analysis in this chapter focused on a hypothetical one-time benefit instead of the periodic benefit more likely to be considered by the Medicare program, it does offer important information for policymakers. Most importantly, the cost-effectiveness of any Medicare prostate cancer benefit is extremely sensitive to whether or not treatment of tumors that have not yet spread extends life or not. The analysis suggests that prostate cancer screening could prove to be as cost effective as other disease screening services already covered by Medicare.

On the other hand, if treatment proves to be less than 100 percent effective (or if rates of metastasis turn out to be less than those assumed in our baseline analysis), prostate cancer screening could end up costing much more per life-year saved than other Medicare disease screenings. At the same time, however, screening carries significant risks of complications. These include the possibility of surgical death in at least six out of 1,000 cases, urinary stricture, heart and lung disease, and years of impotence and incontinence in substantial portions of treated patients.

[26]This study also found that the cost per life-year rose as the screening frequency increased. It was $1,453 for screening every five years compared with no screening, was $5,956 per life-year saved when moving from a five-year to a three-year screening cycle, and was $39,693 for annual screening compared with screening for every 3 years.

[27]A more recent analysis of breast cancer screening found that a one-time mammography for Medicare-age women cost $23,212 per year of life saved at ages 65 to 69 and $27,983 per year of life saved at age 70 to 74 (224).

The evidence of effectiveness and cost-effectiveness of other preventive services already covered by Medicare (e.g.. breast and cervical cancer screening, influenza and pneumococcal vaccines) is substantially stronger than for prostate cancer screening. Although scientific knowledge is currently limited as we await the completion of well-controlled clinical trials, the consequences of prostate cancer and its treatment remain serious. Under such circumstances, an informed and reasonable patient could equally well decide to have screening or forgo it. Patient preferences are also a major component in deciding what to do when screening uncovers a localized cancer. 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 reactions that may result from treating those localized cancers discovered through 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 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 it 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 uncovered by screening. When data from well-controlled trials (including those described in appendix H) tell us if treating prostate cancer is effective, science will be able to provide more definitive guidance in facilitating clinical decisionmaking for patients and in establishing or continuing a screening benefit under Medicare.

APPENDIX

A

Derivation of Prostate Cancer Prevalence by Age and Tumor Volume

This appendix describes the derivation of age-specific prevalence rates of latent prostate cancer (overall and by tumor volume) presented in table 2-5. Overall prevalence data for each age strata were derived by Office of Technology Assessment contractors from eight available autopsy series that specifically excluded cases where prostate cancer had been clinically suspected, and that provided complete age-specific prevalence by decade (24, 113, 128, 134, 159, 222, 293, 305). All eight were consecutive unselected autopsy series; seven were U.S. hospital-based, one (Lundberg) was a community-based Swedish series. All eight used serial step-sectioning (usually 4 mm slices) of the entire gland.

The estimates for each prostate cancer volume and capsular status stratum were derived by applying volume data from McNeal (233) to the derived age-specific prevalences. McNeal and colleagues performed morphometric autopsy analyses on 100 consecutive unselected prostates with adenocarcinoma. For all ages, 60 percent of all cancers are assumed to be 0.5 mL or less even though cancers in men below age 70 years were somewhat more likely to be less than 0.5 mL in volume than for men 70 years and older (68 percent vs. 56 percent).

The remaining 40 percent were assumed to be greater than 0.5 mL in volume. In deriving the distribution of intracapsular and extracapsular tumors for these larger cancers, extracapsular spread was required to be greater than 1 cm beyond capsule, although half of tumors with volume above 0.5 mL in the McNeal study showed some lesser degree of capsular penetration.[1] Although McNeal's and other's (180, 244) data suggest the proportion of cancers above 0.5 mL that are extracapsular increases for men over 70 years, the wide confidence intervals around these estimates lead us to apply a uniform 27 percent probability for all ages. Hence, we assume that of all cancers more than 0.5 mL, 27 percent are extracapsular and 73 percent are intracapsular.

Several studies of incidental prostate cancer among patients undergoing cystoprostatectomy for bladder cancer (180, 244, 328) suggest that only 20 percent of unrecognized prostate cancers exceed 0.5 mL. However, a recent autopsy series of 105 patients without history of prostate cancer and with recent normal rectal exams

[1] See figure 5 in the study by McNeal and colleagues (233).

(mean age 66, not stratified) found a 35 percent prevalence of prostate cancer with 41 percent >0.5 mL; two-thirds of these larger cancers were intracapsular (49).

Looking only at men over age 50 as a single group from the eight autopsy studies yields an overall prevalence of prostate cancer of 30 percent. Breaking these cancers down by volume for all men over age 50, the estimated weighted prevalence of cancers less than 0.5 mL is 18 percent, the prevalence of intracapsular cancers exceeding 0.5 mL is 8.8 percent, and the prevalence of extracapsular cancer exceeding 0.5 mL is 3.2 percent.

APPENDIX

B

Methods Used To Estimate Likelihoods of Cancer for Particular DRE And PSA Results

This appendix describes the derivation of likelihood ratios of different types of cancer for various digital rectal examination (DRE) and prostate-specific antigen (PSA) measurement results presented in tables 3-1 and 3-3 and discussed in the accompanying text. The likelihood ratios are estimates of how many times more likely a patient with a particular test result is to have a given type of cancer than if the patient did not have the test. The probabilities of cancer with no test are the prevalence estimates found in table 2-5. For each test, the likelihood ratios were estimated using the following method:

- Studies of screening tests that provided predictive values for a population of men with a *specified* age distribution were selected; these predictive values were converted into post-test odds of disease.
- Next, the true underlying prevalence of prostate cancer in the general population derived from autopsy studies, displayed in table 2-5, was assumed to be applicable to the populations in these studies of positive predictive values.
- Finally, the post-test odds were divided by the pretest odds of disease (and nondisease) to estimate likelihood ratios.

LIKELIHOOD RATIOS FOR DRE RESULTS

The calculations for DRE results (table 3-1) use data from two studies (79, 279) that provided detailed age distributions of study patients and to which we could apply the estimates of prostate cancer prevalence by tumor volume as presented in table 2-5. Calculations are performed using data for all men ages 50 years and up. "Suspicious" DRE results are defined as palpable asymmetries, nodules, or induration (hardness).

In the Chodak study, although 125 of the 2,131 men ages 45 to 80 in the initial screen group had an abnormal DRE and received a DRE-directed biopsy, the number of men ages 45 to 50 with abnormal DRE is not provided since no cancers were found in this subgroup. Calculations were done using the 1,894 men over 50 years (31 cancers detected in the first year of screening). Systematic biopsies were not performed and volume data for detected cancers were not provided. All were clinically Stage B or higher by the Whitmore staging system (see table 2-3), and it appears safe to assume none were below 0.5 mL.

Subjects in the Richie study (279) with abnormal DRE received systematic and TRUS-guided biopsies in addition to DRE-directed biopsies. Specific volume dis-

tributions are not provided. The 8 percent of detected cancers that were "organ-confined, well-differentiated, and involved only one quadrant" is not necessarily tantamount to a volume below 0.5 mL. We assume 11 percent of detected cancers are below 0.5 mL using data from 208 Stage T1c cancers reported by Oesterling (263). The proportion of cancers in this volume category for T1c tumors (using the TNM staging system described in table 2-3) has been as high as 26 percent (119). Although only 70 percent of patients with abnormal DRE in the Richie study (279) consented to biopsy, and only 63 percent of cancers were surgically staged, our derivations of the post-test odds and likelihood ratios assume perfect biopsy compliance and a comparable proportion of organ-confined cancers in those not receiving radical prostatectomy.

LIKELIHOOD RATIOS FOR PSA RESULTS

Likelihood ratios for PSA results are based on data from four studies: pooled results from studies by Catalona (66) and Brawer (44), results from a study by Richie (279), and results from another study by Catalona (70).

The values derived from pooling data from Catalona (66) and Brawer (44) are probably overestimates for the likelihood ratios for PSA testing alone since only patients who had either abnormal DRE or TRUS in the presence of PSA >4 ng/mL received biopsy. In addition to DRE- and TRUS-guided biopsies, when appropriate, systematic biopsies were performed in willing patients who met these criteria.

Specific volume distributions are not provided by any of the four studies. We again assume 11 percent of the detected cancers are below 0.5 mL based on the study by Oesterling (263). Eleven percent of all PSA 4 to 10 ng/ml detected cancers (presumed to be <0.5 mL) are subtracted from organ-confined cancers to derive the post-test odds for intracapsular cancers >0.5 mL. These likelihood ratios reflect "best case" values because we assume perfect compliance with biopsy (compared with the actual compliance rate of 70 percent in the Oesterling study (263) and a comparable proportion of intracapsular cancers above 0.5 mL in patients not receiving surgery. These "adjustments" were made for data from all four studies in table 3-3.

Patients in the Richie study (279) received both DRE and PSA independently, and the data are presented in a way that allows derivation of the likelihood ratio for PSA alone. However, separate pre- and post-test odds for PSA results of 4.1 to 9.9 ng/mL or PSA > 10 ng/mL cannot be derived from data reported in this study.

The later (and larger) study by Catalona (70) used a protocol similar to his earlier study (66). The derivations of the likelihood ratios used only the data reported for the initial screening of 9,629 volunteers. There is a major discrepancy between the likelihood of intracapsular cancer given a PSA result of greater than 10 ng/ml (3.0) in this study and the corresponding value (0.4) from the earlier pooled studies. This is explained by the observed difference in probability of pathologically localization for cancers (>0.5 mL) detected by PSA >10 ng/mL (32 percent vs. 5 percent).

APPENDIX

C

Studies of Digital Rectal Examination for Prostate Cancer Screening

APPENDIX C: STUDIES OF DIGITAL RECTAL EXAMINATION FOR PROSTATE CANCER SCREENING

Author	Biases/ methodologic weaknesses[a]	Setting	Time frame (year)	Number of patients	Age (Y) range (mean)	Abnormal criterion No. patients (%) No. patients biopsied (%)	Overall detection yield[b]	Proportion detected cancers (%) clinically localized	Positive predictive value (%)	Proportion surgically staged[c] (%)	Long-term followup
Chadwick et al., 1991[d]	3,4,6,7,8	British population-based	1 time	814 eligible 472 recruited (58%) 407 DRE	55-69	Nodule or Induration 13/407(3.2%) not specified if all 13 biopsied (only if TRUS lesion also)	1/472 (0.2%)	1/1 (100%)	1/13 (8%)	1/1 (100%) pathologic localized	NA
Chodak et al., 1984[e]	2,3,4,6,7,8	Urology screening (invitational)	1 time	811	45-80	Nodule or induration 43/811(5.3%) but only 38 complied with biopsy (88%)	11/811(1.4%)	5/11(45%)	11/38(29%) [5/38 (13%)]	2/11(18%)	
Chodak et al., 1989[f]	2,3,4,6,7,8	Urology screening (invitational)	6-year serial average 2 exams/man	2,131	45-86	Nodule Induration or asym 144/2131 (6.8%) 143/144 (99%) biopsied.	36/2131 (1.7%) (1.5% initial)	25/36 (69%)	36/144(25%)[g] 25/144(17%)	18/25(72%) 9/18(50%) path loc.	See Gerber et al., 1993[f]
Drago et al., 1992	1,2,3,5,6,7,8	Academic Urology Clinic	U.S. year with annual followup. Exact no. men enrolled each year not provided.	1940 "asymptomatic" Recruitment process not well described	55-70 (64)	Not specified ("abnormal"). No blinding 147(7.6%) Implied all were biopsied [260 others biopsied for TRUS abn].	39/1940 (2%)	Not provided for DRE-detected cancers.	39/147 (27%) [not provided]	Not provided for DRE-detected cancers.	NA
Faul, 1982	2,3,4,6,7,8	German screening	1 time 1978	9,000,000 eligible 1,500,000 recruited 17% participated	>45	Induration or nodule	0.1%	NA	1951/21,308(9%)	NA	NA
Frohmuller, 1991	2,3,4,6,7,8	German screening. Government insurance sponsored (same program as Faul et al. report, 1982).	1987 data 1 time	1,341,833 participants (approx 15% of 60 yr eligible, 8% of 45 year old eligible)	>45	Nodule or Induration exact % prostate abn not given 1.7% suspicious prostate or genitalia	0.12% (1638 cases)	NA	1638/22,590 (7%)	NA	NA
Gilbertson, 1971	2,3,4,6,7,8	University invitational (general)	Serial exams, 16-year study, average 5 exams/man	5,856	Over 45	Nodule % abnormal not given	75/5856 (1.3%) cumulative 20/5856 (0.34%) initial	Unknown (22/75 detected received radical surgery)	Unable to derive	NA	(5-year survival 91% for surgery 72% for others)[h]

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APPENDIX C: STUDIES OF DIGITAL RECTAL EXAMINATION FOR PROSTATE CANCER SCREENING CONTINUED

Author	Biases/ methodologic weaknesses[a]	Setting	Time frame (year)	Number of patients	Age (Y) range (mean)	Abnormal criterion No. patients (%) No. patients biopsied (%)	Overall detection yield[b]	Proportion detected cancers (%) clinically localized	Positive predictive value (%)	Proportion surgically staged[c] (%)	Long-term followup
Guinan et al., 1980[i]	1,2,3.	Inpatient Academic Urology Service All symptomatic with varying levels of prostatism. Study described as multiple "screening" test evaluation, but population highly enriched with prostate cancer. Not generalizable to office-based DRE screening situation. Selection bias.	1 time	300 (consecutive admissions to urology service; not known to have prostate cancer previously)	50-90 (no data on mean or distribution)	Gross Asymmetry, Induration or Nodule (blinded assessment). All patients received DRE, as well as *prospective* determination of acid phosphatase, urine cytology (pre- and post-massage), and several other antiquated tests. All patients biopsied.	69/300 (23%)	Not provided.	48/72 (67%) [Sensitivity - 69% Specificity - 89%]	Not provided	NA
Guinan et al., 1987	1,2,3.	Inpatient Urology Service Comparative study of 5 studies, including TRUS, PSA. All symptomatic selection bias Not generalizable to office-based population.	1 time convenience sample (incomplete testing)	280 (imply consecutive admissions no known cancer)	(68)	Gross Asymmetry, Induration or Nodule 96/258 (37%)	78/280 (28%)	Not specified.	51/96 (53%) [Sensitivity 51/70 (73%) Specificity 143/188 (77%)]	not specified	NA
Gustafsson et al., 1992[j]	6,8	Swedish screening population-based	1 time	2400 eligible 1788 recruited (74%)	55-70	Nodule or induration asymmetry 195/1782 (11%) Implied all biopsied.	42/1782 (2.4%)	22/42 (52%) 6 patients not biopsied.	42/195 (22%) [22/195 (11%)]	NA	NA
Imai et al., 1988[k]	2,3,4,5,6,7,8	Japanese mass screening	1 time	35,055 eligible 5302 screened (15%)	>60	Not specified (minimal change) 551 Abn by first urologist, 202 biopsied.	54/5302(1%)	28/54 (52%) stage B	54/202(27%) 28/202(14%)	NA	NA

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APPENDIX C: STUDIES OF DIGITAL RECTAL EXAMINATION FOR PROSTATE CANCER SCREENING CONTINUED

Author	Biases/ methodologic weaknesses[a]	Setting	Time frame (year)	Number of patients	Age (Y) range (mean)	Abnormal criterion No. patients (%) No. patients biopsied (%)	Overall detection yield[b]	Proportion detected cancers (%) clinically localized	Positive predictive value (%)	Proportion surgically staged[c] (%)	Long-term followup
Jenson, 1960	2,3,4,6,7,8	University Invitational (General) asymptomatic	Serial exams, 11-year study, average 7.6 exam/man	4,367	Over 45	Nodule or In duration	37/4367 (0.8%) cumulative (0.32% initial exam)	NA	NA	NA	Overall survival 57% for cancers detected first exam, 86% subsequent exams
Lee et al., 1988[l]	1,2,3,5,6,8	Screening invitational/ referral	1 time	784	60-86 (65)	NA	10/784 (1.3%)	Unknown for DRE itself	10/29 (34%) [not provided]	NA	NA
Mettlin et al., 1991 ACS-NPCDP	2,3,6,7,8	10 Centers in U.S./Canada Hospital/Clinic Invitational	Initial Screen	2,425	55-70 (63)	Nodule, Induration or Asymmetry 153/2425 (6.3%) 118/2425 (4.9%)	33/2425 (1.4%)	27/32 (84%) [missing data]	33/118 (28%) Among patient biopsied [27/118 (23%]	20/30 (66%) Radical Surgery-20 (missing data in 9 of 57 total cancers detected but not specified which were DRE detected.)	NA
Mettlin et al., 1993 ACS-NPCDP	2,3,6,7,8	10 Centers US/ Canada Hospital/Clinic Invitational	5-year annual followup. Report on 1972 men with 2 sequential exams with complete data.	2,999 enrolled overall Data provided for 1972 initial exam 1899 second exam.	55-70 entry (63)	Nodule, Induration of Asymmetry Initial exam. 139/1972 (7%) 117/1972 (6%) Second Exam 82/1899 (4.3%) 75/1899 (4%)	38/1972 (1.9%) initial exam 16/1899 (0.8%) Second exam.	32/37 (86%) initial[l],/missing 13/13 (100%) second, 3 missing.	38/117 (32%) [32/117 (27%)] initial 16/75 (21%) [13/75 (17%)] Second	18/32 (56%) resurg. 7/32 (22%) XRT 6 missing data initial 12/13 (92%) surgery 1/13 (8%) XRT 3 missing data.	NA
Moon et al., 1991	2,3,4,5,6,7,8	University/ Veterans Administration Urology Clinic Invitational	1 time	417 3 patients not biopsied.	40-59	Not specified	30/414 (7%) overall abnormal gland (0/190 40-49 years) 29/30 (97%) implied biopsied	1/414 (0.24%) overall 1/224 (0.45%) for age 50-59 year.	1/1 (100%)	1/30 (3.3%)	1/1 (100%) Stage C pathologic.
Mueller et al., 1988	1,2,3,4,5,6,7,	Military Urology Clinic Retrospective of ongoing study; used years 1979-85.	7-year serial average 2-4 exams/year	4,843	40-79	Nodule 312/4843 (6.4%) imply 100% biopsy late	122/4843 (2.5%) (1.7% initial exam 0.63% per subsequent exam	77/122 (63%) 58% initial 74% subsequent exam	122/312 (39%)	73% (46% initial pathologic local, 58% subsequent exam)	NA

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APPENDIX C: STUDIES OF DIGITAL RECTAL EXAMINATION FOR PROSTATE CANCER SCREENING CONTINUED

Author	Biases/ methodologic weaknesses[a]	Setting	Time frame (year)	Number of patients	Age (Y) range (mean)	Abnormal criterion No. patients (%) No. patients biopsied (%)	Overall detection yield[b]	Proportion detected cancers (%) clinically localized	Positive predictive value (%)	Proportion surgically staged[c] (%)	Long-term followup
Muschenheim et al., 1991	2,3,4,5,6,7,8	Invitational Free Screen. Prostate Cancer Awareness break Madison County New York 2 Sites 2 urologists.	1 time	565 incomplete followup	not provided	Not specified 83/565 (19.6%) Abnormal DRE 37/565 (6.5%) biopsied. Patients not all biopsied at Central study sites.	16/565 (2.8%) 5/16 (31%) grade "poorly diff" (Gleason grade not performed)	13/16 (81%) although insufficient detail provided	16/37 (43%) of those biopsied.	Insufficient detail 11/16 surgical treatment (3 RT) All 11 surgically staged had no lymph node disease.	Treatment: RP 11 RT 3 Orchiectomy 2 No. Tx 1.
Naito, 1988	1,2,3,4,5,7	Japanese Urology Clinic Cooperative referrals for variety untreated prostate symptoms Highly selected all received DRE (unclear if blinded assessment) and TRUS (blinded) 3.5 $_{m}$ H_2	1 time	109	35-89 (70)	Poorly specified 2 levels of Abnormal "malig. cancer not ruled out" 19/109 (17%) "malig. cancer highly suggestive" 19/109 (17%) All patients biopsied but technique not specified	22/109 (20%)	NA No data provided on clinical/path stage or grade	22/38 (69%) if lump both levels of abnormal DRE (not provided) 'sensitivity'= 22/32 (69%) 'specificity'= 61/77 (79%)	NA	NA
Pederson et al., 1990[m]	4,6,8	Swedish population screening random selection.	1 time	1494 (1163 participate (78%)	50-69	Nodule Induration	13/1163 (1.1%)	12/13 (92%)	13/44 (30%) 12/44 (27%)GP 15/44 (35%) Urology	10/13 (77%) 10 surgeries (7 extracap. by pathology 1xRT	NA
Perrin et al., 1991[n]	1,2,3,4,6,7,8	French urology clinic asymptomatic health check	1 time	863	50-60	Nodule or induration	0.35%, 1.9% adjusted	NA	3/11 (27%)	NA	NA
Richie	2,3,6,7,8	6 Urology clinics. General public recruited.	Initial screen data	6630	50-96 (63)	DRE: Asymmetry, In duration or Nodule All patients had PSA; biopsy received if PSA > 4 Abnormal DRE in 982/6630 (15%) 683/982 (70%) biopsied	146/6630 (2.2%) Cancer on basis DRE alone	143/146 (98%)	146/683 (21%)	92/146 (63%) 64/92 (70%) pathologic, confined	NA

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APPENDIX C: STUDIES OF DIGITAL RECTAL EXAMINATION FOR PROSTATE CANCER SCREENING CONTINUED

Author	Biases/ methodologic weaknesses[a]	Setting	Time frame (year)	Number of patients	Age (Y) range (mean)	Abnormal criterion No. patients (%) No. patients biopsied (%)	Overall detection yield[b]	Proportion detected cancers (%) clinically localized	Positive predictive value (%)	Proportion surgically staged[c] (%)	Long-term followup
Thompson, 1984	1,2,3,4,6,7	Military Urology Clinic retrospective random review of ongoing screening study, from 1979-83. Data likely part of Mueller 1988 study.	4 year serial 1.3 exam/ patient	2005 part of routine exam 43% patients with negative biopsy had urologic symptoms.	40-92 (58)	Nodule both lobes biopsied routinely # per patient not specified	17/2005 (0.8%) 0.55% initial 0.25% second	15/17 (88%)	[17/65 (26%)] [15/65 (22%)]		NA See Gerber et al 1993.[f]
Varenhorst et al., 1992[o]	4,6,8	Swedish population invitational screening random selection. 9,026 males eligible from geographic area. Only general practitioners involved with second round.	Second follow up to Pederson et al study.	1994 invitational initially; 1,163 participating first screen (78%) 1363 invited second screen 953 participating second (70%).	50-69	Nodule or Induration (similar FNA biopsy technique as in first screening).	7/953(0.7%)	5/7(71%) not specified whether 2 advanced cancers were the 2 not screened first cycle.	7/42 (17%) [5/42 (12%)]	3/7 (43%)	NA
Vihko	1,2,3,4,5,6,7,8	Veteran's Rehabilitation Urology clinic	4 year serial	771 imply full compliance biopsy if tests abn.	54-76	Not specified 27/771 (3.5%) DRE abnormal	6/771 (0.89%)	4/6 (67%)	6/27 (22%) [4/27 (15%)]	NA	NA
Waaler	1,2,3,4,5,6,7,8	German Occupational Health Program screening	1 time	480	45-67	Not specified; Abnormal did not include "adenomatous enlargement" 26/480 (5.4%) referred to urology, 9/26 specifically suspicious for PC in first screen. Urologists suspected PC in 10/26 referred. 16 patients biopsied.	1/480 (0.2%)	0/1 (0%)	1/16 (6%) [0/16 (0%)]	0	NA

[a] Legend for study bias/methodological weaknesses: 1) not population-based community setting; 2) selection/referral bias; 3) nonrandomly sampled study group; 4) explicit inclusion/exclusion criteria not provided; 5) abnormal test criterion not described; 6) incomplete application of appropriate reference (gold) standard (work-up bias); 7) lack of proper blinding in test interpretation; 8) failure to account completely for all enrolled subjects (include biopsy of all abnormal tests and reporting of clinical and pathologic staging information). Note that for each study listed, the presence of one or more of these methodologic deficiencies will be devoted with the particular number (1-8) in the proper cell. We chose not to grade or weigh to degree to which a study bias was present.

[b] Detection yield = number of patients with prostate cancer detected/number patients screened. Numbers in parenthesis refer to yield of each individual examination.

[c] Refers to proportion of patients clinically localized who receive surgical staging.

APPENDIX C: STUDIES OF DIGITAL RECTAL EXAMINATION FOR PROSTATE CANCER SCREENING CONTINUED

[d] No apparent selection bias. 407 of 472 recruited patients who agreed to at least part of the "health screen" received DRE by general physician. Total of 7 cancers detected but only 1 had an abnormal DRE; remaining 6 had elevated PSA (see table 11). Work-up bias. Only 68 of 472 received TRUS, based on either abnormal PSA or DRE. 29 patients were biopsied based on hypoechoic TRUS lesion and/or abnormal DRE.

[e] The 811 patients in this invitation screening study are also included in the subsequent study of 2,131 patients by Chodak (1989).

[f] Detection rate for initial screen 1.5% (32/2131), 0.2% for second-year exam (3/1321). Long-term disease-specific survival for patients in this cohort and the similar design of Thompson et al. (1984) are reported in Gerber et al. (1993). 56 men (mean age 65 years) were followed for median of 75 months; 3/56 men were not reported in the 2 original reports. Clinically localized cancer diagnosed in 73% on initial screen and for 83% of cancers detected in subsequent examinations. Patients were treated by variety of strategies initially but in general aggressive treatment (surgery or radiation) used for those clinically localized. However, 10-year disease-specific survival was 86% for men diagnosed during first screen and only 57% for subsequent exams (p=.02). This data suggest presence of length bias. Only 63% and 22% of patients in Chodak (1989) cohort returned for second and third examinations, respectively.

[g] Overall PV + for entire period of study; PV + for initial exam abnormalities versus subsequent ones not provided.

[h] Unable to assess effect of lead-time and length bias.

[i] This is the single study available that is not flawed by work-up bias. All patients received transrectal biopsies, using a modification of the Vim-Silverman needle. However, the population studied is very atypical of men without suspected prostate cancers being followed in a routine office-based primary care setting. All men were symptomatic inpatients on urology service. The high prevalence of detected cancers, 10 to 20 fold higher than typical screening studies of DRE, suggests significant selection biases. Although the comprehensive biopsy protocol explains some of this discrepancy, the prevalence is still nearly twice as high as an earlier hospital-based study employing routine "wedge" biopsy in a population enriched with prostatism but no suspected cancer (Hudson, 1954).

[j] The study cohort was derived from 2,400 patients in this age group randomly selected from a defined catchment area of the study hospital. All cases in group with prior history of prostate cancer were excluded. Patients were invited to participate in multiphasic 1 time screening program. All 1,788 recruited patients received DRE, TRUS, and PSA with proper blinding performed. A preliminary report of this data was published by Norming et al. (1991). Biopsy performed selectivity for DRE positive and/or TRUS positive patients (small unspecified number for elevated PSA above 10ng/ml). Clinical staging performed by TNM system. 11/42 DRE positive cancers were T2A, 11 were T2B.

[k] "Mass screening" study organized between 1981 and 1985 by the urology department at Gunma Cancer Center Hospital. Intervention involved questionnaire, acid phosphatic (PAP), and DRE in a "field" type approach. "Any small change" in DRE led to "suspicious" categorization (N=551), however, only 202/551 (37%) were biopsied after second evaluation by urologist. Thus, actual PV+ for patients receiving biopsy was 54/202 (27%) for all cancer. The mean age of patients with detected cancer was 73 years (63-87 range). The average cost of detecting each case was calculated to be equivalent to $5,358. Authors compared clinical stage distribution in study group (52% stage B) with 93 patients diagnosed in outpatient clinic ("controls") over same time period (16% stage B). Crude survival curves of patients (by stage) in both groups indicate no differences at mean followup of 3 years. However, only 3/28 (11%) of stage B patients in the study agreed to surgery.

[l] Bias against DRE (vs. transrectal ultrasound comparison); 50% of patients reportedly had normal DRE within 1 year of study.

[m] From a population of 9,026 men ages 50 through 69 in a defined catchment area in Sweden, 1,494 were randomly selected and invited to receive DRE by both a general practitioner and a urologist, performed independently. These data were also presented, in virtual identical fashion, in E. Varenhorst, et al. Biopsy technique included fine needle aspiration (FNA) of suspected area and 3 samples from each lobe, using cytologic analysis. It is not specified whether a "geographic" approach to FNA of nonsuspected areas is used.

[n] This study has significant methodologic flaws. The 863 patients receiving a "screening" DRE represent one subgroup receiving different interventions. The men are reportedly asymptomatic. No description of how these men are selected for study. 61 (7%) had suspicious DRE but only 11 got biopsied revealing cancer in 3. Assuming same PV+ would apply if all 61 received biopsy, the estimated "adjusted" yield of DRE is 1.9%. Because of potential uncharacterizable selection bias, the study population cannot be considered a screening cohort.

[o] This publication presents the second screening yield from the original study of Pederson et al. (1990). Thirteen cancers were detected in the initial round and 7 cancers during the second round 3 years later. Six other cancers were diagnosed through routine care (4 incidentally at TURP) between screening cycles for this population. Of the combined 20 cases detected by screening, 14 (70%) had PSA > 4ng/mL, although PSA was routinely performed in this protocol. Of the 7 cancers detected in the second round, 5 had normal DRE in the first round and 2 had not participated in first round.

APPENDIX

D

Studies of Prostate-Specific Antigen for Prostate Cancer Screening and Early Detection

APPENDIX D: STUDIES OF PROSTATE SPECIFIC ANTIGEN FOR PROSTATE CANCER SCREENING AND EARLY DETECTION: RESEARCH DESIGN AND FINDINGS

Author	Biases and methodologic weaknesses[a]	Setting	Age (year) (mean)	Number patients enrolled (%)	Abnormal PSA criterion (%)	Biopsy criteria	No. patients (%) with criteria No. patients (5) biopsied	No. (%) PC detected	No. (%) PC clinically localized	No. (%) PC pathologically localized	PPV %[b] PSA	Treatment
Babaian et al., 1992 ACS-NPCDP[c]	2,3,6,7,8	10 sites in U.S./Canada, hospital/ clinic-based public invited	55-70 (63)	2425 over 3.5 years (PSA in 2,227)	> 4 ng/mL (not provided)	Abnormal DRE and/or TRUS (11 additional biopsies for abn PSA, most > 10 ng/mL) blinding not specified	Not provided 520/2425 (21%) year 1 - 395 year 2 - 102 year 3 - 23	88/2,425 (3.6%) no data on grade/volume	Not provided	Not provided	59/137 (43%)	Not provided
Babaian et al., 1991	1,2,3,4,6,7,8	Urology Clinic Cancer (most symptomatic) referral and selection biases	50-75 (63 median)	362 (75 MD referral recorded)	> 4 ng/mL 90/362 (25%)	Abnormal DRE and/or TRUS, or PSA > 20 No blinding	120/362 (33%) 109/362 (30%)	37/362 (10%) 27/75 (36%) MD referred; 10/287 (3%) self referred	23/37 (62%)	Not provided	30/90 (33%)	Not provided
Brawer et al., 1992	2,3,6,7,8	U.S. Urology Clinic Public recruited	>50 (67)	1249	> 4 ng/mL 187/1,249 (15%)	If PSA > 4, then DRE/TRUS with systematic biopsy adjunct blinding not specified	187/1249 (15%) 105/1249 (8.4%)	32/1249 (2.6%) no data on grade/ volume	30/32 (94%)	9/32 (28%) 4 of the 9 capsule penetration without perforation 16 surgical staging	32/105 (30%)	RP - 15 PL - 1 RT - 10 No TX - 6
Catalona et al., 1991	2,3,6,7,8	U.S. Urology Clinic Public recruited	50-89	1653	< 4 ng/mL 137/1653 (8.3%)	If PSA > 4 on initial or 6 month re-test, then DRE and TRUS, biopsy if either abn blinding not specified	137/1653 (8.3%) 112/1653 (6.8%)	37/1653 (2.2%)[d] no data on grade/volume	36/37 (97%)	12/37 (32%) 33 surgical staging	37/112 (33%) if PSA 4-9.9 19/85 (22%) if PSA ≥ 10 18/27 (67%)	Not provided (at least 19 had RP)
Catalona et al., 1993	2,3,6,7,8	U.S. Urology Clinic Public recruited	50-90 (63)	10,251 (but 622 "protocol violations") 9,629 initial screen 9,333 serial screen (up to 37 month followup)	> 4 ng/mL 902/9629 (9.4%) initial 873/9333 (9.4%) serial	If PSA > 4 twice initially, or on any 6 month serial check then DRE an TRUS. If either abn, biopsy. No systematic biopsy	902/9629 (9.4%) 860/9629 (8.9%) initial 873/9333 (9.4%) 465/9333(5%) serial	296/9629 (3.1%) initial 195/9333 (2.0%) serial 491/9629 (5.1%) total	277/296 (94%) initial 170/175 (97%) serial, but missing data	153/262 (58%) initiate, but 27 clinically localized did not get surg stage 92/129 (71%) serial, but missing data in 46 patients	296/860 (34%) overall initial 174/652 (27%) PSA 4 - 9.9 initial 122/208 (59%) PSA > 10, initial	Of total 491: RP - 348 RT - 68 HT - 27 No TX - 16 Pending - 32
Chadwick et al., 1991	3,4,6,7,8	British population-based general practice recruitment	55-69	863 eligible 814 recruited 472 screened 437 got PSA 407 got DRE	> 4 ng/mL 63/472 (13%)	If PSA > 4 and/or DRE abnormal, TRUS recommended. If TRUS abn, biopsy recommend	75/472 (16%) 12 of 75 for abn DRE alone 29/472 (6%) biopsied	7/472 (1.5%) (mean PSA 17) No data on size/volume	7/7 (100%)	5/7 (71%) 5 surgical staging	7/63 (11%)	RP - 5 No TX - 2

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APPENDIX D: STUDIES OF PROSTATE SPECIFIC ANTIGEN FOR PROSTATE CANCER SCREENING AND EARLY DETECTION: RESEARCH DESIGN AND FINDINGS CONTINUED

Author	Biases and methodologic weaknesses[a]	Setting	Age (year) (mean)	Number patients enrolled (%)	Abnormal PSA criterion (%)	Biopsy criteria	No. patients (%) with criteria No. patients (5) biopsied	No. (%) PC detected	No. (%) PC clinically localized	No. (%) PC pathologically localized	PPV %[b] PSA	Treatment
Cooner et al., 1990	1,2,3,4,6,7,8	U.S. Group Urology Practice referral bias [selected population many symptomatic with prostatism of varyinge gree]	50-89	1,807	> 4 ng/mL 602/1,807 (33%) 4-10 ng/mL 366/1,807 (20%) > 10 ng/mL 236/1,807 (13%)	Abnormal TRUS (hypoechoic) No systematic biopsy. DRE, PSA performed but not basis for biopsy No blinding.	835/1,807 (46%) all biopsied	263/1,807 (14.5%) < 3.0 cc vol 172/263 (65%) > 3.0 cc vol 91/263 (35%)	136/242 (56%) of data available	43/263 (16%) 60 patients surgically staged	263/835 (32%)	RP - 57
Drago et al., 1992[e]	1,2,3,5,6,7,8	U.S. Academic Urology Clinic	55-70 (64)	1940 "asymptomatic" No clear description of recruitment process. Annual followup over 4.5 years.	> 4 ng/mL 989/1,940 (51%)	Abnormal DRE and/or TRUS systematic biopsy not used 27 of patients biopsied on basis Abn PSA but level not specified.	Not provided. 416/1940 (21%) biopsied Initial, 320 biopsied 2nd, 80 biopsied 3rd, 16 biopsied	79/1940 (4.1%) cumulative yield No data on grade/tumor [57/79 (72%) of PC had PSA >4]	64/79 (81%)	Not provided.	57/137 (42%) of the 989 patients with PSA > 4 not biopsied.	Not provided.
Guinan et al., 1987	1,2,3	Inpatient Urology Service Comparative study of 5 studies, including TRUS, PSA. All symptomatic selection bias. Not generalizable to office-based population.	Mean 68	280	Not specified "Mean plus 1 S.D." Hybritech 102/280 got PSA (36%)	Unknown for entire group: only 46/102 (45%) PSA 'pos' All 280 biopsied	Actual prevalence 78/280 (28%) of PSA tested 42/102 (41%)	Not specified.	Not specified.	31/46 (67%) sensitivity = 31/42 (74%) specificity = 45/60 (75%)	Not provided.	
Gustafsson et al., 1992	6,8	Swedish Urology Clinic Random selection population-based	55-70	2400 eligible (census database) 1,782 recruited No data on number of patients with urologic symptoms or evidence of BPH.	> 4 ng/mL 306/1782 (17%)	Abnormal DRE, TRUS or PSA > 10 ng/mL (systematic biopsy if PSA >10). Patients received all 3 tests Abn DRE (nodule, induration, asymmetry) TRUS (hypo or asymmetry).	Not provided 371/1782 (21%) biopsied Average 3 fine needle aspirates/ patient and 2-4 core biopsy/ patient.	65/1782 (3.6%) If age 55-59 7/481 (1.5%) age 60-64 26/585 (4.4%) age 65-70 32/716 (4.5%) Overall PSA alone 52/1782 (2.9%)	40/65 (62%) (2.2% of 1782) T2A or less - 22 T2B - 18 63/65 in peripheral zone	Not provided.	52/306 (17%)	Not provided.

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APPENDIX D: STUDIES OF PROSTATE SPECIFIC ANTIGEN FOR PROSTATE CANCER SCREENING AND EARLY DETECTION: RESEARCH DESIGN AND FINDINGS CONTINUED

Author	Biases and methodologic weaknesses[a]	Setting	Age (year) (mean)	Number patients enrolled (%)	Abnormal PSA criterion (%)	Biopsy criteria	No. patients (%) with criteria No. patients (5) biopsied	No. (%) PC detected	No. (%) PC clinically localized	No. (%) PC pathologically localized	PPV %[b] PSA	Treatment
Labrie et al., 1992	6,8	Canadian University Center Random selection, population-based from electoral roles	45-80	1002 (number initially invited not provided)	> 4 ng/mL 124/1,002 (12.4%) >3 ng/mL 191/1,002 (19%)	Abnormal DRE and/or TRUS (PSA test for all but not biopsy for PSA alone) If abnormal DRE but TRUS neg. six random biopsies	Not Provided. Not provided.	Overall 57/1,002 (5.7%) For PSA > 4, 41/1,002 (4.1%) For PSA > 3, 46/1,002 (4.6%) No data on volume or grade	Not provided.	Not provided.	For PSA > 4, 41/124 (33%) For PSA > 3, 46/191 (24%)	Not provided.
Mettlin et al., ACS-NPCDP, 1991[f]	2,3,6,7,8	10 sites in U.S./ Canada Hospital/Clinic Public invited	55-70 (63)	2,425 over 3.5 years (PSA in 2,227) Report on initial screen	> 4 ng/mL 312/2,227 (14%)	Abnormal DRE and/or TRUS (unknown number biopsy recommended for PSA > 10 ng/mL) Blinding of tests not specified	396/2425 (16.3%) 330/2425 (13.6%) 70/312 (22%) with PSA > 4 were biopsied	57/2,425 (2.4%) 5 of 57 on basis of PSA > 10 ng/mL alone	46/51 (90%) 6 others missing stage data	21/31 (68%) 3 missing surgical stage data, 23 not staged pathologically < 1.0 cm - 10 > 1.0 cm - 40 No size data - 7 No volume data Grade: Gleason 4-6: 43 Gleason 7-8: 9 No data: 5	34/312 (11%) (5 of the 34 cancers had PSA >10) 242/312 (78%) patient with PSA > 4 were not biopsied.	RP - 34 RT - 10 HT - 3 Orchiectomy - 1 No TX - 4
Mettlin et al., ACS-NPCDP, 1993[g]	2,3,6,7,8	10 sites in U.S./Canada Hospital/ Clinic Public invited	55-70 on entry (63)	2,999 enrolled Annual evaluation up to 5 years Reporting on 1972 men with 2 sequential exams with complete data for primary variables.	> 4 nl/mL 271/1972 (21%) initial exam 248/1899 (22%) follow-up exam	71/271 (26%) with PSA >4 biopsied initial 49/248 (20%) with PSA >4 biopsied on follow-up	326/1972 (16.5%) Initial exam 216/1899 (11.4%) follow-up exam 285/1972 (14.5%) Initial 196/1899 (10%) Follow-up	73/1972 (3.7%) Initial exam 33/1899 (1.7%) Follow-up exam	79/85 (93%) No data for 21 56/61 (92%) Initial 23/24 (96%) Follow-up	Not provided 67/88 (76%) Gleason grade provided were grade 4-5.	49/271 (18%) Initial Exam 22/248 (9%) Follow-up Exam Explicit number cancer with PSA > 4 in initial and follow-up groups not provided overall 71/106 (67%) cancers had PSA >4.	RP - 59 RT - 17 No TX - 6 HT - 2 Orchiectomy - 3\ No data provided - 19

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APPENDIX D: STUDIES OF PROSTATE SPECIFIC ANTIGEN FOR PROSTATE CANCER SCREENING AND EARLY DETECTION: RESEARCH DESIGN AND FINDINGS CONTINUED

Author	Biases and methodologic weaknesses[a]	Setting	Age (year) (mean)	Number patients enrolled (%)	Abnormal PSA criterion (%)	Biopsy criteria	No. patients (%) with criteria No. patients (5) biopsied	No. (%) PC detected	No. (%) PC clinically localized	No. (%) PC pathologically localized	PPV %[b] PSA	Treatment
Moon et al., 1991	2,3,4,5,6,7,8	University/ Veterans Administration Urology Clinic General public recruited	40-59	414	> 4 ng/mL 10/414 (2.4%) Age 40-49 4/190 (2%) Age 50-59 10/224 (4.5%)	Not provided Implied that all patients received both PSA and DRE with TRUS if either positive (not specified)	Not provided 11/414 (2.7%)	Overall 5/414 (1.2%) If 40-49: 0/190 (0%) If 50-59: 5/224 (2.2%) white 2/153 (1.3%) black 3/71 (4.2%)	4/5 (80%) Little detail provided	2/5 (40%) However, no uniform whole mount histologic technique 2 organ-confined may have been understaged No data on grade/volume	5/10 (50%)	RP - 4
Muschenheim et al., 1991	2,3,4,5,6,7,8	Free screening General public recruited (Prostate Cancer Awareness Week)	not provided	565	> 4 ng/mL 59/565 (10.4%) 6 biopsies/ patient	Abn DRE (not specified) and/or PSA elevated. No independent blinding specified	118/565 (21%) 54/565 (9.6%) 34/59 (58%) Abn. PSA biopsied	20/565 (3.5%) 5/20 grade "poorly diff"	17/20 (85%) although insufficient detail provided	Not provided in sufficient detail. All 12 surgically staged had no lymph node disease. 9/12 (75%) presumed localized.	15/59 (25%) For DRE alone: 16/83 (19%)	RP - 12 RT - 4 Orchiectomy - 3 No TX - 1
Perrin et al., 1991[h]	1,2,3,4,6,7,8	French Urology Clinic Recruited within clinic men attending for "routine" of 4-year checkup	50-60	863	> 4 ng/mL 38/863 (4.4%)	If DRE Abn. for those with PSA > 4	Not provided. Not provided.	3/863 (0.3%)	Not provided.	Not provided.	3/38 (8%).	Not provided.
Powell et al., 1989	1,2,3,4,6,7,8	Single British Urology Clinic Referral population All men had prostatism symptoms prospective accrual, patients invited to "prescreen" most later got TURP	50-88 (68)	287 referred 211 enrolled	> 10 ng/mL (Hybritech) 37/211 (17.5%)	PSA > 10 DRE not uniformly performed (not available for 23%) No TRUS used	37/211 (17.5%) 36/37 (97%)	17/211 (8%)	8/17 (47%)	Not provided.	17/37 (46%)	Not provided.

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APPENDIX D: STUDIES OF PROSTATE SPECIFIC ANTIGEN FOR PROSTATE CANCER SCREENING AND EARLY DETECTION: RESEARCH DESIGN AND FINDINGS CONTINUED

Author	Biases and methodologic weaknesses[a]	Setting	Age (year) (mean)	Number patients enrolled (%)	Abnormal PSA criterion (%)	Biopsy criteria	No. patients (%) with criteria No. patients (5) biopsied	No. (%) PC detected	No. (%) PC clinically localized	No. (%) PC pathologically localized	PPV %[b] PSA	Treatment
Richie et al., 1993[i]	2,3,6,7,8	6 University sites Public invited	50-96 (63)	6630 [White - 6,098 Black - 194 (3%) Other - 338 (5.1%)] Symptoms of BPH: Yes - 3,500 (53%) No - 3,130 (47%)	> 4 ng/mL 983/6630 (14.8j%) PSA ABN stratified by age: 50-59: 150/2381 (6%) 60-69: 487/2959 (17%) 70-79: 311/1161 (27%) 80+: 35/129 (27%)	Abnormal DRE (asymmetry, induration or nodule) and/or PSA elevated. If either abnormal, TRUS performed with guided biopsy if abnormal and systemic quadrant biopsies for all patients with elevated PSA even if TRUS or DRE normal	Overall 1710/6630 (26%) 1167/6630 (17.6%) Number of patients meeting criteria by age: 50-59: 364/2381 (15%) 60-69: 828/2959 (28%) 70-79: 463/1161 (40%) 80+: 55/129 (43%)	Overall 264/6630 (4%) By age: 50-59: 48/2381 (2%) 6-69: 123/2959 (4.2%) 70-79: 84/1161 (7.2%) 80+: 9/129 (7%) Not stratified by presence of symptoms	261/264 (99%)	114/160 (71%) of those received surgical staging 101 of the 261 patients with clinically localized cancers elected not to have surgery. 17/160 (11%) had poorly differentiated grade For PSA > 10 ng/mL 40% organ-confined	Among patients biopsied: Overall 216/686 (31%) By age: 50-59: 36/113 (32%) 60-69: 99/336 (29%) 70-79: 73/216 (34%) Combined Abn PSA or DRE PPV: Overall 264/1167 (23%)	RP - 160 No other data provided.

[a] Legend for study biases and methodologic weaknesses: 1) not population-based or community setting; 2) selection (including self) and/or referral biases; 3) nonrandom study group accrual; 4) explicit inclusion/exclusion criteria not provided; 5) abnormal test criteria not described; 6) incomplete application of appropriate reference (gold) standard (work-up bias); 7) lack of proper blinding in test interpretation; 8) failure to account completely for all enrolled subjects (including biopsy of all abnormal tests and reporting of clinical and pathologic stage data). For each study listed in this appendix, the presence of one or more of these deficiencies is denoted with the corresponding number (1-8). We chose not to qualify weight to the extent of each particular methodologic weakness.

[a] BPA = benign prostate hypertrophy; PC = prostate cancer; PL = pelvic lymph node dissection (metastasis); PPV = positive predictive value; RP = radical prostatectomy; RT = radiation therapy; No TX = No treatment.

[b] ACS-NPCDP = American Cancer Society National Prostate Cancer Direction Project. The ACS-NPCDP used DRE abnormality (asymmetry, induration, or nodule) and/or TRUS abnormality (hypoechoic area greater than 5-7 mean not due to cyst, vascular structure, or artifact). Although 2,227 of 2,425 patients received PSA during first examination (with DRE and TRUS), no patient was biopsied for PSA > 4 ng/mL alone.

[c] 12 of 37 cancers detected had "non suspicious" DRE but 8 of the 12 had asymmetry or DRE that would have prompted biopsy elsewhere (Stamey). 14 of 16 cancers "missed" by TRUS had "abnormal but benign" findings (e.g., asymmetry) that would have been biopsied elsewhere. Routine systematic biopsy of PSA > 4 not recommended.

[d] This study enrolled 1940 purportedly asymptomatic men over a 4 1/2 year period and followed them with annual DRE, TRUS, and PSA. No data on exact number of men followed per year are provided, nor is it clear how many cancers were detected in each examination (apparent maximum of 3). It is also not clear whether all men received each test with each iteration. The data are presented in a confusing manner with multiple textual errors and miscalculations. PSA is not a major determinant of biopsy and less that one-half of those with PSA > 4 received biopsy.

[e] DRE detected 33 of 57 cancers found (detection rate 33/2425 = 1.4%). TRUS detected 44 of 57 cancers found (detection rate 44/2425 = 1.8%).

[f] The ACS-NPCDP continued to rely on DRE and/or TRUS abnormalities as the main determinants for recommending biopsy, although subsequent evaluations incorporated PSA testing. For 144 of the 1972 men reported here PSA data are unavailable. For clinical staging, this study uses a modification of Whitmore's classification: A1 defined here as TRUS-measured tumor volume < 0.2 cm3 (average diameter less than 0.7 cm). An unknown number of patients had biopsy within the study on the basis of PSA > 10 ng/mL, although 11 of the 106 detected cancers resulted from this effort. Patients with PSA > 10 ng/mL who had a negative set of systematic biopsies were re-evaluated with repeated TRUS and DRE in 12 months. It is not specified how many patients were rebiopsied if these studies remained negative. Six other detected cancers were found through non-protocol means (e.g., TURP in men who were not previously recommended for biopsy). Positive Predictive Value (PPV) of DRE was 22% initially and only 14% follow-up examination. The PPV for TRUS were 14% and 8%, respectively (combined DRE/TRUS PPV 37% and 32%).

[g] Overall study design and mode of data presentation is poor. Description of patient cohort and method of recruitment scant. Only patients with elevated PSA who then had abnormal DRE were eligible for biopsy. Actual number who meet criteria and then received biopsy were not reported. This study precludes fair comparison of DRE and PSA, as only patients with elevated PSA received DRE. Proper blinding was not specified. Their results have little usefulness and are not generalizable to an office-based screening population.

[h] Overall 68% compliance with biopsy performance for either/both DRE, PSA abnormal. The cancer detection rates and positive predictive values reported in the paper ignore noncompliance and assume same proportion of positive biopsies would occur if all men meeting biopsy criteria actually received systematic biopsies. Unfortunately, although 53% of study group reported symptoms of prostatism, the data for predictive values of each test and detection are not stratified by symptoms or race. PPV for abnormal DRE among those patients biopsied is 146/683 (21%).

APPENDIX

E

Studies of Repeat/Serial Prostate-Specific Antigen Testing Yield for Prostate Cancer Screening and Early Detection

APPENDIX E: STUDIES OF REPEAT/SERIAL[a] PROSTATE-SPECIFIC ANTIGEN TESTING YIELD FOR PROSTATE CANCER SCREENING AND EARLY DETECTION: RESEARCH DESIGN AND FINDINGS

Author	Biases and methodologic weaknesses[b]	Setting	Age (year) (mean)	Number patients enrolled (%)	Abnormal PSA criterion (%)	Biopsy criteria	No. patients (%) with criteria No. patients (%) biopsied	No. (%) PC detected	No. (%) PC clinically localized	No. (%) PC pathologically localized	Positive predictive value of criteria	Treatment
Brawer et al., 1993[c]	2,3,6,7,8	U.S. Urology Clinic Public recruited Second year of screening study Includes only patients whose year 1 PSA was < 4 ng/mL Many men were evaluated at non–study sites but these data not included Blinding methods not specified	> 50 (67) Similar age distribution to original cohort (Brawer 1992)	701 Reflects 66% of original cohort with PSA < 4 None of these had DRE/TRUS in year 1 of study	20% increase in PSA above year 1 level; Absolute PSA > 1.5 also used as criterion for biopsy recommendation 75/701 (11%) had PSA > 4 at year 2, but only 19/75 (25%) received biopsy Presumably all of the 75 were recommended to get biopsy, but reasons for noncompliance not specified.	If 20% increase PSA, then DRE with biopsy if positive If absolute PSA > 1.5 ng/mL, systematic biopsy with TRUS guidance regardless of DRE Abnormal DRE included asymmetry, induration, nodule Abnormal TRUS included hypoechoic peripheral zone lesion	260/701 (37%) had 20% increase PSA 82/701 (12%) biopsied overall 159/260 (61%) had PSA > 1.5; and 71/159 (45%) agreed to DRE biopsy; 50/71 (70%) had abnormal DRE; 101/260 (39%) had PSA < 1.5; 31/101 (31%) agreed to DRE; 11/31 (36%) had abnormal DRE and got biopsy	14/701 (2.0%) overall Among 260 with 20% increase in PSA over 1 year, 14/260 (5.4%) yield 5/14 cancers had only asymmetry or a benign gland on DRE 2/14 cancers (14%) had PSA > 4 17/68 benign biopsies (25%) had PSA >4	13/14 (93%)	Not known 7/8 who received surgical staging were organ–confined or had negative margins No data on prostate cancer volumes at surgery provided	14/82 (17%)	RP–8 No data for other 6
Catalona et al., 1993	2,3,6,7,8	U.S. Urology Clinic Public recruited Original cohort 10,251 men	50–90 (63)	9,333 serial screenees (up to 37 months after initial screening PSA) Actual number of patients who received multiple serial biopsies (mean, range) not specified	Overall > 4 ng/mL 873/9333 (9.4%) if age ≤ 70 years 693/8320 (8.3%) if age > 70 years 180/1013 (17.8%) PSA 4.1–9.9 ng/mL 743/9333 (8%) PSA ≥ 10 ng/mL 130/9333 (1.4%)	PSA > 4 ng/mL twice on any of 6 month serial checks, then DRE and TRUS. If either abnormal biopsy recommended No systemic biopsies on PSA alone If biopsy neg. repeat PSA at 6 month intervals and repeat DRE/TRUS, with biopsy if indicated, if PSA > 4 again	873/9,333 (9.4%) 465/9,333 (5%)	195/9,333 (2.0%) overall If age ≤ 70 years, 153/8320 (1.8%) If age > 70 years, 42/1013 (4.1%) Number Cancers detected: First biopsy 90 Second biopsy 84 Third biopsy 17 Fourth biopsy 4 Denominators not provided	170/175 (97%); missing data in 20	92/129 (71%); missing data in 46 If age ≤ 70 years, 84/111 (76%) If age > 70 years, 8/18 (44%)	195/465 (42%), overall 165/392 (42%) if PSA 4.1–9.9 ng/mL 30/73 (41%) if PSA ≥ 10 ng/mL If age < 70 years, 153/363 (42%). if age > 70 years, 42/102 (42%)	Results not stratified by initial screening or serial screening. See Appendix D for aggregated treatment outcomes for the total 491 cancers detected in both cohorts. No long–term outcome data.

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APPENDIX E: STUDIES OF REPEAT/SERIAL[a] PROSTATE-SPECIFIC ANTIGEN TESTING YIELD FOR PROSTATE CANCER SCREENING AND EARLY DETECTION: RESEARCH DESIGN AND FINDINGS CONTINUED

Author	Biases and methodologic weaknesses[b]	Setting	Age (year) (mean)	Number patients enrolled (%)	Abnormal PSA criterion (%)	Biopsy criteria	No. patients (%) with criteria No. patients (%) biopsied	No. (%) PC detected	No. (%) PC clinically localized	No. (%) PC pathologically localized	Positive predictive value of criteria	Treatment
Mettlin et al ACS–NPCDP, 1993	2,3,6,7,8	10 sites in U.S./ Canada Hospital/ Clinic Public recruited Annual evaluation up to 5 years	55–70 on entry (63) 2,999 original enrollees	1899 men reported with 2 sequential exams with complete data, no cancer on first exam. Only results of followup testing reported here.	> 4 ng/mL 248/1899 (22%) follow–up PSA abnormal Patients not biopsied for PSA results alone Only 1783/1899 (94%) of patients in follow–up group received PSA test	Abnormal DRE and/or abnormal TRUS (unknown number biopsies recommended for PSA > 10 ng/mL) 49/248 (20%) biopsied with PSA > 4 in follow–up	216/1899 (11%) on follow–up testing 196/1899 (10%) biopsied on basis follow–up testing	33/1899 (1.7%) on follow–up testing If initially 55–59 years, 1% detection rate, If 60–64 years, 1.1% detection rate, If 65–70 years, 3.1% detection rate	23/24 (96%) missing data in 9 cases	Not provided for follow–up testing group	For PSA > 4, 22/248 (9%) with follow–up testing 11/33 cancers detected in follow–up testing group had PSA < 4	Not stratified by followup testing group, See Appendix D for treatment choices for overall cohort

[a] Refers to followup with PSA but in the case of Mettlin, (1993) PSA is not used as a primary criterion for biopsy. The criteria for biopsy in all 3 of these papers are different. However, we specifically do not include papers that evaluate PSA or velocity as principal issue (see Carter, 1992). Rather, serial PSA refers to the detection rate and predictive value of repeated measures of PSA testing. However, use of PSA and protocol in the 3 studies differ significantly.

[b] Legend for study biases and methodologic weaknesses: 1) not population–based or community setting; 2) selection (including self) and/or referral biases; 3) nonrandom study group accrual, 4. Explicit inclusion/exclusion criteria not provided; 5) abnormal test criteria not described; 6) incomplete application of appropriate reference (gold) standard (work–up bias); 7) lack of proper blinding in test interpretation; 8) failure to account completely for all enrolled subjects (including biopsy of all abnormal tests and reporting of clinical and pathologic stage data). For each study listed in this appendix, the presence of one or more of these deficiencies is denoted with the corresponding number (1–8). We chose not to qualify weight to the extent of each particular methodologic weaknesses.

[c] In the Brawer study, the use of the arbitrary PSA increase of 20% serially actually constitutes a form of PSA velocity. Unlike the Catalona (1993) study that followed all patients in the original cohort regardless of initial PSA and performed DRE/TRUS and biopsy on those with persistent or newly developed PSA, the Brawer followup study evaluates only those patients who had an original PSA < 4 ng/mL.

APPENDIX

F

Studies of Transrectal Ultrasound for Prostate Cancer Screening and Early Detection

APPENDIX F: STUDIES OF TRANSRECTAL ULTRASOUND FOR PROSTATE CANCER SCREENING AND EARLY DETECTION: RESEARCH DESIGN AND FINDINGS

Author	Biases and methodologic weaknesses[a]	Setting	Time frame (years)	Number patients (N)	Age (Y) range (mean)	Criteria for positive TRUS	Biopsy method	Proportion BPH	TRUS lesion-Diameter (cm) Range (mean)	Overall detection yield (%)[b]	Proportion detected cancers clinically localized (%)	Positive predictive value[c] (clinically localized)	Proportion detected cancer pathologically localized (%)
Carter et al. (1989)	1,2,3,7	Retrospective All patients with abnormal DRE who got TRUS before surg for known cancer 1 lobe.	—	59 highly selected	not provided	peripheral hypoechoic in contralateral lobe	en bloc surgical specimen	Not specified.	0.5-4.5 cm (1.7 mean)	25/59 patient cancer in other lobe	NA Sensitivity 13/25 (52%) Specificity 23/34 (68%)	13/24 (66%)	NA Sensitivity 10/20 (50%) if diameter 0.5-2.0 cm
Coffield et al. (1992)	1,2,3,7	Consecutive autopsy no history prostate cancer; all non-suspicious DRE within 1 year	—	63 (7 others excluded, insufficient information)	37-87 (64)	Broad, any echo suggesting space occupying lesion	en bloc autopsy	Not specified.	diameter not specified, volume range .009-6.3 ml (1.62 ml mean)	19/63 cancer (30%)	Sensitivity 6/19 (32%) for hypoechoic Specificity 7/44 (39%) for hypoechoic	6/33 (18%) overall Half TRUS isoechoic	Surgical state not specified Proportion extracapsular not given. Histologic grade distribution not given.
Cooner et al. (1990)	1,2,3,4,6,7,8	Urology continuity clinic (42% new) work-up bias no patient with suspected PC referral bias	—	1807 varying levels of symptoms	50-89	Peripheral hypoechoic	TRUS, DRE no blind biopsy 46% biopsied	Not specified.	Not provided volume range 0.5-41 ml (mean 2.2) if DRE neg. 0.5-5.5 (1.2)	263/1807 (14.6%) all cancers; 136/1807 (7.5%) clinically localized	136/242 (56%)	263/835 (31%) all cancer	43/60 (72%) only 23% detected cancer surgically staged
Cooner et al. (1988)	1,2,3,4,6,7,8	Urology Continuity Clinic referral bias	1 time	255 (all benign DRE)	50-89	Peripheral hypoechoic (≥ 5 mm)	TRUS 43% biopsied	Not specified.	5-6 mm diameter lowest, no data (all lesions/Prostate Cancer in peripheral)	incomplete clinical staging 28/225 (12.4%)	—	28/96 (29%) overall cancer	8/28 got surgical staging (7/8 pathologically localized)
Dahnert (1986)	1,2,3,7	Known cancer (presurgery)	—	52	47-73 (61)	Hypoechoic 5.0 mHz	en bloc surgery specimens	85% pathologically evident	—	NA	100% (preselected for surgery)	NA, Sensitivity 64% (Unilateral) 81% (Bilateral)	NA, 24/52 (46%) upstaged to extracapsular at surgery
Devonac et al. (1990)	1,2,3,4,6,7,8	Urology Symptomatic (most BPH prospective)	1 time	666	Not provided	Peripheral hypoechoic (no size threshold) 7.0 or 7.5 mHz 226/666 (34%) abnormal TRUS	TRUS or DRE Imply all abnormal TRUS biopsied	Not specified	—	45/666 (6.7%) (34/45 detected DRE[c])	24/45 (53%)	24/225 (11%) 45/246 (19%) all cancer	unknown (no data on histologic grade)

CONTINUED

APPENDIX F: STUDIES OF TRANSRECTAL ULTRASOUND FOR PROSTATE CANCER SCREENING AND EARLY DETECTION: RESEARCH DESIGN AND FINDINGS CONTINUED

Author	Biases and methodologic weaknesses[a]	Setting	Time frame (years)	Number patients (N)	Age (Y) range (mean)	Criteria for positive TRUS	Biopsy method	Proportion BPH	TRUS lesion Diameter (cm) Range (mean)	Overall detection yield (%)[b]	Proportion detected cancers clinically localized (%)	Positive predictive value[c] (clinically localized)	Proportion detected cancer pathologically localized (%)
Drago et al. (1992)	1,2,3,5,6,7,8	Urology unknown prostate disease-not true screening population	Serial 4.5 year annual follow-up	1940 recruitment not well described	55-70 (64)	Hypoechoic 352/1940 (18%) abnormal test	TRUS guided abnormal DRE PSA alone in 2% of biopsies	Not specified	—	70/1940 (3.6%)	Not specified for TRUS detected, overall 64/79 cancers (81%) in study clinically localized when discovered by any method.	70/352 (20%) all cancers	—
Guinan et al. (1987)	1,2,3	Inpatient Urology Service Comparative study of 5 studies, including TRUS, PSA. All symptomatic selection bias Not generalizable to office-based population	1 time	280	68 (mean)	3.5 mHz scanner not specified 3 "independent" reviewers 84/280 (30%) had TRUS 37/84 (44%) TRUS positive	All patients biopsied	129/280 (46%) on pathology biopsy spec.	—	78/280 (28%) overall prevalence of TRUS received 22/84 (26%) cancers	—	NA 22/37 (59%) Sensitivity = 22/31 (71%) Specificity = 38/53 (72%)	—
Gustafsson et al. (1992)	6,8	Swedish screening population-based randomly selected	1 time	2,400 eligible 1,780 recruited (74%)	55-70	Any hypoechoic area (non cyst) or asymmetry	TRUS guided and/or DRE guided if PSA > 10 blind bx (21% biopsied)	Not specified.	—	58/1780 (3.3%)	34/58 (59%)	34/244 (14%) 58/244 (24%) all cancer	—
Hammerer et al. (1992)	1,2,3,7,8	Urology all cancers at other site no prostate symptoms	—	73	54-70 (65)	Hypoechoic	TRUS, DRE and systematic 100% biopsied	Not specified.	—	17/73 (23%) cancers (13/17 TRUS[c]) (15/17 DRE[c])	Not specified (implied all clinically localized)	13/30 (43%) overall; if DRE 1/14 (7%)	Not provided.
Lee et al. (1988)[d]	1,2,3,6	Screening invitational/ referral	1 time	784 Half normal DRE < 1 yr.	60-86 (65)	Peripheral hypoechoic > 5 mm 64/784 (8%) TRUS abnormal	DRE or TRUS (2-fold greater # biopsies for TRUS DX cases than DRE 10%	Not specified.	0.7-3.0 (1.3)	20/784 (2.6) 20/22 cancers TRUS[c]	Unknown for TRUS alone 17/22 (77%) overall DRE and TRUS.	Unknown 20/64 (31%) for all cancers by TRUS.	16/22 (73%)

CONTINUED

APPENDIX F: STUDIES OF TRANSRECTAL ULTRASOUND FOR PROSTATE CANCER SCREENING AND EARLY DETECTION: RESEARCH DESIGN AND FINDINGS CONTINUED

Author	Biases and methodologic weaknesses[a]	Setting	Time frame (years)	Number patients (N)	Age (Y) range (mean)	Criteria for positive TRUS	Biopsy method	Proportion BPH	TRUS lesion-Diameter (cm) Range (mean)	Overall detection yield (%)[b]	Proportion detected cancers clinically localized (%)	Positive predictive value[c] (clinically localized)	Proportion detected cancer pathologically localized (%)
Mettlin et al. (1991)	2,3,6,7,8	Screening invitation	1st year of serial study	2425	55-70 (63)	Peripheral hypoechoic > 0.5 cm	TRUS, DRE few if PSA elevated 14% biopsied)	135/330 biopsied (41%)	10/50 < 1.0 cm 40/50 > 1.0 cm	44/2425 (1.8%) for TRUS 44/57 detected ca. for TRUS[b]	unknown for clinical loc. for TRUS only 39/51 (76%) stage A,B for available data	44/290 (15%) all cancer. if < 1.0 cm 6/135 (7%); if ≥ 1.0 cm 30/136 (22%)	Unknown for TRUS only 21/31 (68%) overall study for available data
Naito, 1988	1,2,3,4,7	see Appendix C	1 time	109	35-89 (70)	Proposed by Japanese Urological Association including disarranged forms, asymmetry, discontinuity in capsule, irregular echogenicity of parenchyma (especially hypoechoic). Do not specificity if discrete hypoechoic included 46/109 (42%) Abnormal	All patients biopsied but technique not detailed		Not provided.	28/109 (25.6%)	Not specified.	28/46 (61%) 'sensitivity' = 28/32 (88%) 'specificity' = 59/77 (77%)	Not specified.
Nesbitt et al. (1989)	1,2,3,4,6,7,8	Urology Not pure screening	1 time	240 asymptomatic self-selected or referral for unrelated problem	55-70	Peripheral anechoic hypoechoic 5.5 or 7.0 mHz scan	TRUS, DRE (unclear if PSA influenced) 19% biopsied	Not specified.	1.0-1.5 approximate only	19/240 (7.9%)	17/19 (89%) (11/19 DRE[b])	17/45 (38%)	15/19 (79%)
Norming et al. (1991)	6,8	Swedish Population Screening (75% compliance)	1 time	1,788	50-70	Hypoechoic Asymmetry (no size) 246/1788 (14%) TRUS abnormal	TRUS, DRE or PSA > 10 365/1788 (20%) biopsied overall proportion of TRUS abn. biopsied not specified	Not specified.	—	62/1788 (3.5%)	Not specified for TRUS alone overall 26/62 cancers T1 or T2A.	Not specified 56/246 (23%) all cancers.	Unknown (no surgical staging).

CONTINUED

APPENDIX F: STUDIES OF TRANSRECTAL ULTRASOUND FOR PROSTATE CANCER SCREENING AND EARLY DETECTION: RESEARCH DESIGN AND FINDINGS CONTINUED

Author	Biases and methodologic weaknesses[a]	Setting	Time frame (years)	Number patients (N)	Age (Y) range (mean)	Criteria for positive TRUS	Biopsy method	Proportion BPH	TRUS lesion Diameter (cm) Range (mean)	Overall detection yield (%)[b]	Proportion detected cancers clinically localized (%)	Positive predictive value[c] (clinically localized)	Proportion detected cancer pathologically localized (%)
Palken et al. (1991)	1,2,3,5,6,8	Urology invitational referral	1 time	315	50-86	2 classes "high" suspicious "low"	DRE, TRUS systematic if negative first time 28 biopsied	Not specified.	—	14/315 (4.4%)	Unknown 14/23 (61%) cancers TRUS[b].	Unknown 14/52 (27%) all cancers.	—
Perrin et al. (1989)	1,2,3,4,6,7,8	Screening invitation	1 time	666 (602 DRE)		Hypoechoic	TRUS	Not specified.	—	11/666 (1.7%)	—	11/162 (6.8%) all cancers	—
Perrin et al. (1992)	1,2,3,4,6,7,8	French urology referral population	1 time	481	(67)	Not specified.	'Abnormal' TRUS and/or abnormal DRE[e]	—	—	83/481 (17%)	24/83 (29%)	8/233 (3%) 65/233 (28%) all cancers	—
Ragde et al. (1989)	1,2,3,4,6,7,8	Radiology screening invitational	1 time	1,051	over 50	Hypoechoic	TRUS (some DRE pos. not biopsied)	Not specified.	—	50/1051 (4.8%) all cancers	—	50/138 (36%) all cancers	—
Rifkin (1988)	1,2,3,4,6,7,8	Radiology prospective referral population	1 time "all comers" to USG clinic since 1986	329 heteroge-nous none with known PC include symptom-atic "mild" Abn DRE (180)	45-91 (64)	Peripheral hypoechoic Used 5, 6.5, or 7.5 mHz scanner 80/329 (24%) abn. TRUS	TRUS or DRE 79/329 (24%) biopsied only 56/180 "mild DRE" Abnormal were biopsied	Not specified.	0.5-1.5	5.2% (17/329)	—	Unknown, overall 17/79 (22%) all can-cers	—
Shinohara et al. (1989)	1,2,3,7,8	Preopera-tive TRUS known clinically localized cancer (pre-sur-gery TRUS)	—	70	48-78 (63)	Hypoechoic (42) Hyperechoic (1) Isoechoic (27)	en bloc surgical specimen	Not specified.	Smallest lesion seen by TRUS (hypoechoic) 4.5 mm (actual tumor size)	Overall 42/70 (60%) hypoecho-ic abnor-mal 3/17 (18%) cancers were < 1.0 cm were hypoecho-ic 40/52 (77%) cancers > 1.0 cm were hypo-echoic	NA	9/25 (36%) cancers with DRE normal had hypo-echoic abn. 34/45 (79%) cancer with DRE pos itive were hypo-echoic	

CONTINUED

APPENDIX F: STUDIES OF TRANSRECTAL ULTRASOUND FOR PROSTATE CANCER SCREENING AND EARLY DETECTION: RESEARCH DESIGN AND FINDINGS CONTINUED

Author	Biases and methodologic weaknesses[a]	Setting	Time frame (years)	Number patients (N)	Age (Y) range (mean)	Criteria for positive TRUS	Biopsy method	Proportion BPH	TRUS lesion Diameter (cm) Range (mean)	Overall detection yield (%)[b]	Proportion detected cancers clinically localized (%)	Positive predictive value[c] (clinically localized)	Proportion detected cancer pathologically localized (%)
Simak (1993)	1,2,3,7	Prospective Urology Clinic Consecutive patients with nonsuspicious DRE who received TRUS and PSA prior to TURP	1 time	288 All scheduled for TURP for BPH	55-84 (68)	Hypoechoic (near capsule) 32/288 (11%) TRUS Abnormal	TRUS-guided (no apparent systematic)		Not provided Histologic grade: Moderate (6) Poor (8)	14/288 (4.9%) by TRUS total of 46/288 (16%) cancers at TURP 1/231 patients with PSA < 7 had TRUS detected cancer (0.4% yield)	13/14 (93%) total 45/46 cancers at TURP were clinically localized	14/32 (44%) [13/32 (41%)] for 13/14 TRUS detected cancers, PSA > 7 57/288 (20%) PSA > 7	12/14 (86%) Overall, post TURP 44/46 (96%) were pathologically localized of 32 cancers missed by TRUS, 7 stage A_2 25 stage A_1
Terris et al. (1991)	1,2,3,7	Preoperative Cystoprostatectomy for Bladder cancer	—	51 (no known prostate cancer)	31-79 (64)	Hypoechoic	en bloc surgical specimen	Not specified.	volume .001-5.3 ml (0.8 mL mean)	NA, 15/51 (29%) prevalence prostate cancer	8/17 (47%) both clinical and pathologically localized	overall sensitivity 53% specificity 75%	Peripheral zone sens. = 70% spec. = 81% PV+ = 64% Transition sens. = 20% spec. = 64% PV+ = 17%
Watanabe et al. (1991)	2,3,4,6,7,8	Japanese mass screening	1 time	7235 asymptomatic	> 55	Hypoechoic	TRUS guided (small minority of patients got DRE)	—	—	48/7235 (0.7%)	25/48 (52%)	not provided	—

[a] Legend for study biases/methodologic weaknesses: 1) Not population-based/community setting, 2) Selection/referral bias, 3) Non-randomly sampled study group, 4) Explicit inclusion/exclusion criteria not provided, 5) Abnormal test criterion and type and TRUS equipment (e.g., 3.5, 5.0, 7.5 mHz) not described, 6) Incomplete application of appropriate reference (gold) standard work-up bias, 7) Lack of proper blinding in test interpretation, 8. Failure to account completely for all enrolled subjects (including biopsy of all abnormal tests and reporting of clinical and pathologic staging information). For each listed study the presence or absence of one or more of these methodologic deficiencies is denoted with the corresponding number (above). Further grading of the degree to which these biases/deficiencies are present was not performed.

[b] Detection yield = number of patients prostate cancer detected/number patients screened (for TRUS only).

[c] Positive predictive value = proportion of patients with abnormal test (TRUS) who have clinically localized prostate cancer.

[d] Potential bias against DRE comparison (with TRUS); solo men had "normal" DRE within 1 year prior.

[e] This study has significant weaknesses both in terms of potential selection and work-up bias as well as sloppy presentation of data and apparent contradictions. For example, patients are said to have received biopsy only if DRE or TRUS was abnormal (criterion for each not specified), but 16 of the 83 cancers detected were both DRE and TRUS negative. PSA testing was not used to also select patients for biopsy, nor was a systematic biopsy applied according to the brief selection. Nor was it clearly stated that all "test positive" patients actually received a biopsy. Only 8/135 (6%) patients with a normal DRE but an abnormal TRUS had prostate cancer detected. Of the 24 Stage T1-T2 (A,B) cancers found among the 83 overall detected, 16 of these patients (66%) had both normal DRE and TRUS.

KEY: NA = not applicable.

APPENDIX

G

Methods for Estimating the Medicare Costs of Resources Used in Detection and Care of Prostate Cancer

This appendix presents microlevel Medicare cost information on the components of screening, diagnosis, and treatment for prostate cancer.[1] As described in chapter 5, these data are incorporated into a mathematical Markov model to estimate the total costs and the cost-effectiveness of an illustrative hypothetical Medicare benefit for prostate cancer screening. All cost data are in 1992 dollars.[2]

The analysis collected and sorted Physicians' *Current Procedural Terminology*, Fourth Edition (CPT-4) codes for procedures (e.g., diagnostic tests, hospitalizations) by urological and radiation oncology billing departments at the Massachusetts General Hospital and the Mayo Clinic. A clinical advisory panel from these institutions and outside reviewers then reviewed these codes for completeness and accuracy.

Tables G-1, G-2, G-3, and G-5 present cost information for components of treatment for prostate cancer grouped by general treatment category: screening and staging, radical prostatectomy, transurethral resection of prostate, and hormone therapy. Table G-4 differs from the others in that it presents an episode of care for external beam radiation therapy for localized prostate cancer. Table G-6 includes information on the cost of procedures/treatments related to complications associated with prostate cancer (impotence, incontinence, etc.). Table G-7 organizes the cost data by CPT-4 code or Diagnosis-related Group (DRG), allowing easy development of cost estimates based on complete treatment protocols.

SPECIFIC ISSUES

Cost Information

We present cost information in terms of both Medicare average allowable charge data for 1992 and the 1992 Medicare fee schedule (tables G-1 through G-7). Average allowable charges are percentages of regionally determined "usual, customary, and reasonable" (UCR) physician fees determined on a service-by-service basis. The physician fee schedule is based on a resource-based relative-value scale (RBRVS) point system to which a monetary conversion factor is applied.

Cost-effectiveness research has historically used allowable charges for physician services. However,

[1]Information in this appendix is based on an OTA contract paper by Fahs and colleagues. (121).

[2]Continuing changes in Medicare reimbursements for procedures associated with prostate cancer screening and treatment may make these 1992 costs inaccurate predictors of costs in 1995 or in subsequent years (13a).

TABLE G-1: ESTIMATED COSTS OF SERVICES RELATED TO SCREENING AND STAGING OF PROSTATE CANCER

Description	CPT-4 code	Medicare average allowable charge, 1992[a] ($)	Medicare fee schedule ($)
PSA	86316	$29.56	not included
DRE			
▪ Office visit with primary care physician/urologist[b]	99213	3.79	4.12
TRUS	76872	76.14	84.94
▪ Office consult with urologist	99214	45.71	47.12
TRNB			
▪ TRUS guidance for biopsy	76942	67.95	84.07
▪ Prostatic needle biopsy (single/multiple)	55700	120.54	105.09
Osseus survey for metastases	76061	32.00	54.87
Radionuclide bone scan	78306	81.02	184.14
Pelvic CT scan	72170	15.67	25.11
▪ with contrast	72193	93.77	283.66
Pelvic MRI	72196	247.60	450.13
Limited lymphadenectomy for staging	38562	639.55	672.11
▪ anesthesia	00860	203.63	194.04

[a] The majority of the surgical allowable charges have two components: one for the surgeon and one for surgical assistance. Composite charges are reported.

[b] DRE is estimated to take 13.3% of a 99213 office visit. The entire office visit average allowable charge is $28.52 and under the fee schedule is $31.

SOURCE: Office of Technology Assessment, 1995. Data are HCFA's unpublished Medicare Average Allowable Charge data from NCH/Best system. Other categories are unpublished data from the HCFA Office of Research provided by W.J. Sobaski, HCFA, Baltimore, MD, personal communication, 1993.

TABLE G-2: ESTIMATED COSTS FOR RADICAL PROSTATECTOMY SERVICES

Description	CPT-4 code/DRG	Medicare average allowable charge, 1992[a] ($)	Medicare fee schedule[b] ($)
Retropubic radical prostatectomy	55840	$1,450.34	1,493.82
▪ with lymph node biopsies	55862	1,041.51	1,135.37
▪ with bilateral pelvic lymphadenectomy	55845	2,097.83	2,056.62
▪ anesthesia	00860	203.63	194.04
Hospitalization for radical prostatectomy and pelvic node excision			
▪ with complications	334	NA	7,483.00
▪ without complications	335	NA	5,867.00

[a] The majority of the surgical allowable charges have two components: one for the surgeon and one for the surgical assistance. Composite charges are reported.

[b] For DRGs, the figures represent average expenditures per beneficiary, including Medicare reimbursement and beneficiary deductible.

KEY: NA = not applicable.

SOURCE: Office of Technology Assessment, 1995. Data are HCFA's unpublished Medicare Average Allowable Charge data from NCH/Best system. Other categories are unpublished data from HCFA Office of Research provided by W.J. Sobaski, Health Care Financing Administration, Baltimore, MD, personal communication, 1993.

TABLE G-3: ESTIMATED COSTS FOR TRANSURETHRAL RESECTION OF THE PROSTATE

Description	CPT-4 code/DRG	Medicare average allowable charge, 1992[a] ($)	Medicare fee schedule[b] ($)
Transurethral resection of prostate (TURP)	52601	$948.10[b]	897.96
▪ anesthesia	00914	139.69	146.51
Hospitalization for TURP			
▪ with complications	336	NA	3,943.00
▪ without complications	337	NA	2,778.00

[a] The majority of the surgical allowable charges have two components: one for the surgeon and one for surgical assistance. Composite charges are reported.
[b] For DRGs, the figures represent average expenditures per beneficiary, including Medicare reimbursement and beneficiary deductible.

KEY: NA = not applicable.
SOURCE: Office of Technology Assessment, 1995. 1992 HCFA data from Part B Medicare Annual Data System and Part A Medicare Annual Data System for short-stay hospitals provided by W.J. Sobaski, Office of Research, HCFA, Baltimore, MD, personal communication, 1993.

starting in 1992, Medicare began paying physicians using a fee schedule based on RBRVS. The fee schedule attempts to measure the costs of providing services based on resources consumed. In this way, it may be a more accurate input for cost-effectiveness analysis if that analysis attempts to relate resource use (monetary and otherwise) to benefits.

However, there has been much debate over two components of the fee schedule: the monetary conversion factor that is applied to the RBRVS and the allocation of true practice costs. In a recent study, Hsiao and colleagues (170) concluded that the practice-expense component of the Medicare fee schedule was incorrectly legislated. It is based on historical charges instead of resource costs and, thus, the Medicare fee schedule "continues to provide an overly generous rate of payment for invasive services" (170). The authors also conclude that the conversion factor is too low to yield sufficient net income to most physicians and warn that in the short run this may cause access problems for Medicare beneficiaries and in the long run may discourage an adequate supply of qualified medical personnel.

One other caution on the fee schedule is in order. The fee schedule is in transition and will not be fully implemented until 1996. This means that fees actually paid to providers are a weighted blend of allowable charges and the fee schedule rate (in each of 230 payment localities) (e.g., 56 FR 59502). Despite these anomalies, the 1992 fee schedule is preferable to average allowable fees for cost-effectiveness research both because of its more explicit relationship to resource use and because it will be how providers are reimbursed for Medicare patients in 1996.

One must use caution in interpreting and applying any "cost" information for medical care (122). The "cost" of a procedure may bear little resemblance to the charge submitted, which will probably only be paid on a percentage basis anyway. In attempting to provide inputs for a cost-effectiveness analysis for the addition of a screening benefit for prostate cancer to the Medicare program, we present the reimbursement amounts that Medicare pays out, not the submitted charge or an estimated "cost" of the procedure.

TABLE G-4: ESTIMATED COSTS OF SERVICES FOR TREATING LOCALIZED[a] PROSTATE CANCER BY RADIATION THERAPY (based on Medicare fee schedule)

Description	Calculation of total cost ($)
Radiation treatment	$3,604.41
Hospital	
Simple (77406) 19 @ $58.59 = $1,113.21	
Complex (77416) 19 @ $76.88 = $1,460.72	
Radiation oncologist	
Simple (77420) 4 @ $79.67 = $318.68	
Complex (77430) 4 @ $177.95 = $711.80	
Complex treatment planning (77263)	154.69
Complex treatment simulation (77263)	154.69
Dosimetry calculation (77300)	75.02
Weekly evaluation of dosage (77336) 7 evaluations @ $123.09	861.63
Isodose plan for teletherapy (77315)	185.89
Radiation oncologist Consult (99244)	113.46

[a] Stage A and B cancers.

SOURCE: Office of Technology Assessment, 1995. Data are HCFA's unpublished Medicare Average Allowable Charge data from NCH/Best system. Other categories are unpublished data from HCFA Office of Research provided by W.J. Sobaski, HCFA, Baltimore, MD, personal communication, 1993.

This caution in using "cost" information may be particularly relevant for services provided to elderly men, regardless of the source of the "cost" information. The disease processes, as well as the psychosocial, environmental and financial attributes of geriatric patients have been suggested to be out of sync with payment structures derived from acute care services for younger populations (120). In other words, payment structures may not adequately reflect the additional resources required by geriatric patients as compared with younger patients, including longer time spent dressing and undressing, or in communication with the physician on the risks and benefits of clinical choices.

Digital Rectal Examination

One of the standard screening procedures for prostate cancer examined in this analysis is the digital rectal examination (DRE). This procedure is considered to be part of a routine physical exam (349). It is estimated that this procedure requires two minutes to perform (265). This analysis assumes the cost of this procedure is 13.3 percent of a standard 15-minute (CPT-4 code 99213) office visit. It is worth noting that if this DRE were found abnormal, it would likely be repeated by a urologist.

Treatment Costs

We present the cost of drugs for hormone therapy at specified dosages. The total will depend on the combination of drugs and the length of treatment/research that is ongoing (107, 319). Some drugs for hormone therapy require implantation. Cost data for this procedure are not available. An estimate for the cost of implantation can perhaps be imputed using implantation fees for related procedures. This estimate will be added to the drug costs, pending physician consultation.

Surgical Procedures

Costs for surgical procedures include both surgeon and surgical assistance fees.

Diagnostic Radiology

Diagnostic radiology is composed of two components: technical and professional. Oftentimes the two components are billed by the same provider, who receives a composite payment. Sometimes different providers are involved and each is paid according to the component provided. However, the composite payment for each CPT-4 code is not necessarily the sum of the components for a variety of reasons (i.e., different localities, different modifiers, etc.). We advise using the com-

TABLE G-5: ESTIMATED COSTS OF HORMONE THERAPY SERVICES FOR PROSTATE CANCER

Description	CPT-4 code/DRG	Medicare average allowable charge, 1992[a] ($)	Medicare fee schedule[b] ($)
GnRH agonist (does not include fees for monthly implantation)			
▪ Zoladex @ 3.6 mg/month	NA	$318.75/month	NA
▪ Lupron @ 7.5 mg/month	NA	437.50/month	NA
Flutamide (Eulexin) @ 250 mg	NA	135.42/100	NA
Diethylstilbesterol (DES) tablets @ 1 mg/day	NA	9.14/100	NA
Orchiectomy	54520	516.16	408.16
▪ anesthesia	00920	97.93	105.25
Hospitalization for bilateral orchiectomy	338	NA	3,893.00

[a] The majority of the surgical allowable charges have two components: one for the surgeon and one for surgical assistance. Composite charges are reported.
[b] For DRGs, the figures represent average expenditures per beneficiary, including Medicare reimbursement and beneficiary deductible.

KEY: NA = not applicable.

SOURCE: Office of Technology Assessment, 1995. Data are HCFA's unpublished Medicare Average Allowable Charge data from NCH/Best system. Other categories are unpublished data from HCFA Office of Research provided by W.J. Sobaski, HCFA, Baltimore, MD, personal communication, 1993. Pharmaceutical costs are wholesale prices as reported in the 1993 *Red Book* published by Medical Economics Data, Montvale, NJ.

posite payment, rather than adding the two components together for two reasons: predominantly, one provider performs both components and, thus, it is the composite rate that is most commonly paid; and because Medicare is moving toward a fee structure where the components add to the composite rate (320).

Anesthesia Services

Costs for anesthesia services are provided for the P1, P2, and P3 severity of illness categories as well as both with and without CPT-4 code 99100 (an adjustment for patients over age 70). However, there are many other modifiers that could be applied, and they may or may not affect reimbursement. For some time, the Health Care Financing Administration (HCFA) has not incorporated many of these modifiers into their reimbursement amounts (231). The cost figures presented are calculated based on the average time associated with each CPT-4 code. Time is the most significant component of the cost of anesthesia, overshadowing the application of modifiers (320).

Courses of Treatment

The analysis uses the total costs for a six-week episode of external beam radiotherapy treatment for localized (T1/T2) cancer (26). The costs associated with complications (proctitis, incontinence, etc.) are presented separately (313, 363), as well as average allowable charges and Medicare fee schedule amounts for the entire range of related radiotherapy procedures (that are to be organized into treatment protocols relevant to T3 cancer).

The course of medical treatment for advanced, hormone-sensitive prostate cancer is difficult to specify. There are numerous clinical trials incorporating a significant number of drugs both singly and in combination (107, 319). This analysis estimates costs for related drugs (27l) using the *Red Book* of wholesale drug prices for 1993.

TABLE G-6: ESTIMATED COSTS OF LOCAL SYMPTOMS/TREATMENTS/COMPLICATIONS FOR PROSTATE CANCER

Description	CPT-4 code/DRG	Medicare average allowable charge, 1992[a] ($)	Medicare fee schedule[b] ($)
Dilation of urethral stricture	53600	$31.86	$51.15
▪ under anesthesia	53605	33.62	58.59
▪ anesthesia	00910	85.20	97.16
Hospitalization for urethral stricture dilation			
▪ with complications	312	NA	3,800.00
▪ without complications	323	NA	2,281.00
Urethroplasty (stricture repair)	53415	1,084.57	1,077.76
▪ anesthesia	00910	85.20	97.16
Hospitalization for major stricture repair			
▪ with complications	312	NA	3,800.00
▪ without complications	313	NA	2,281.00
Artificial sphincter placement	53445	1,780.34	1,352.14
▪ anesthesia	00860	203.63	194.04
Hospitalization for artificial urinary sphincter			
▪ with complications	308	NA	6,534.00
▪ without complications	309	NA	3,439.00
Penile prosthesis			
▪ non-inflatable	54400	1,173.30	868.81
▪ inflatable, self-contained	54401	1,494.56	1,107.60
▪ inflatable, multi-component	54405	1,812.29	1,375.52
▪ anesthesia	00938	162.46	170.34
Hospitalization for penile prosthesis insertion	315	NA	10,072.00

[a] The majority of the surgical allowable charges have two components: one for the surgeon and one for the surgical assistance. Composite charges are reported.
[b] For DRGs, the figures represent average expenditures per beneficiary, including Medicare reimbursement and beneficiary deductible.

KEY: NA = not applicable.

SOURCE: Office of Technology Assessment, 1995. Data are HCFA's unpublished Medicare Average Allowable Charge data from NCH/Best system. Other categories are unpublished data from HCFA Office of Research provided by W.J. Sobaski, HCFA, Baltimore, MD, personal communication, 1993.

TABLE G-7: ESTIMATED COST OF SERVICES RELATED TO PROSTATE CANCER

CPT–4 or DRG	Description	Charge[a] ($)	Fee schedule or DRG[b] ($)
Medical			
99213	Office visit with primary care physician or urologist	28.52	31.00
Surgical			
38562	Limited lymphadenectomy for staging (anesthesia code 00914)	639.55	672.11
52601	Transurethral resection of prostate (anesthesia code 00914)	948.10	897.96
53415	Urethroplasty (stricture repair) (anesthesia code 00910)	1084.57	1077.76
53445	Artificial sphincter placement for incontinence (anesthesia 00860)	1780.34	1352.14
53600	Dilation of urethral stricture	31.86	51.15
53605	Dilation of urethral stricture under anesthesia (anesthesia code 00910)	33.62	58.59
	Insertion of penile prosthesis for impotence (anesthesia code 00938)		
54400	non-inflatable	1173.36	868.81
54401	inflatable, self-contained	1494.56	1107.60
54405	inflatable, multi-component	1812.29	1375.52
54520	Orchiectomy (anesthesia code 00920)	516.22	408.16
55700	Prostatic needle biopsy (single or multiple)	120.54	105.09
55840	Retropubic radical prostatectomy (anesthesia code 00860)	1450.34	1493.82
55845	with lymph node biopsies	1041.51	1136.37
55862	with bilateral pelvic lymphadenectomy	2097.83	2056.62
Consults			
99214	Office consultation with urologist	28.52	31.00
99244	Office consultation with radiation oncologist	106.42	113.46
Diagnostic radiology			
76061	Osseus survey for metastases	32.00	54.87
76872	Transrectal ultrasound	76.14	84.94
78306	Radionuclide bone scan	81.02	184.14
72170	Pelvic CT scan	15.67	25.11
72193	with contrast	93.77	283.66
72196	Pelvic MRI	247.60	450.13
76942	Transrectal ultrasound guidance for prostatic biopsy	67.95	84.07
Diagnostic laboratory			
84060	Phosphatase, acid; total	10.61	NA
84075	Prostates, alkaline	7.64	NA
84403	Testosterone, total	37.86	NA
86316	Prostate-specific antigen	29.56	NA
Radiation therapy			
	External beam radiation clinical treatment planning		
77261	simple	78.32	68.02
77262	intermediate	119.60	103.85
77263	complex	177.78	154.69
77300	Dosimetry calculation	72.67	75.02
77315	Isodose plan for teletherapy	160.48	145.89

CONTINUED

TABLE G-7: ESTIMATED COST OF SERVICES RELATED TO PROSTATE CANCER CONTINUED

CPT–4 or DRG	Description	Charge[a] ($)	Fee schedule or DRG[b] ($)
77336	Weekly evaluation of delivered dose	87.04	123.09
	External beam radiation treatment delivery		
77401	treatment delivery	49.13	58.59
88402	single, ≤ 5 MeV	57.62	58.59
77403	single area, 6–10 MeV	58.08	58.59
77404	single area, 11–19 MeV	71.60	58.59
77406	single area, ≥ 20 MeV	55.44	58.59
77407	2 areas, ≤ 5 MeV	66.99	69.13
77408	2 areas, 6–10 MeV	70.10	69.13
77409	2 areas, 11–19 MeV	77.59	69.13
77411	2 areas, ≥ 20 MeV	65.67	69.13
77412	3 or more areas, ≤ 5 MeV	74.87	76.88
77413	3 or more areas, 6–10 MeV	78.22	76.88
77414	3 or more areas, 11–19 MeV	82.85	76.88
77416	3 or more areas, ≥ 20 MeV	75.64	76.88
Diagnostic radiology			
76061	Osseus survey for metastases	32.00	54.87
76872	Transrectal ultrasound	76.14	84.94
78306	Radionuclide bone scan	81.02	184.14
72170	Pelvic CT scan	15.67	25.11
72193	with contrast	93.77	283.66
72196	Pelvic MRI	247.60	450.13
76942	Transrectal ultrasound guidance for prostatic biopsy	67.95	84.07
Diagnostic laboratory			
84060	Phosphatase, acid; total	10.61	NA
84075	Phosphatase, alkaline	7.64	NA
84403	Testosterone, total	37.86	NA
86316	Prostate specific antigen (PSA)	29.56	NA
Anesthesia[c]			
00914	P1	201.00	
	P2	222.50	
	P3	157.00	
	All	139.69	146.51
00860	P1	271.00	
	P2	NA	
	P3	181.00	
	All	203.63	194.04
00910	P1	28.52	
	P2	103.80	
	P3	NA	
	All	85.20	97.16

CONTINUED

TABLE G-7: ESTIMATED COST OF SERVICES RELATED TO PROSTATE CANCER CONTINUED

CPT–4 or DRG	Description	Charge[a] ($)	Fee schedule or DRG[b] ($)
00938	P1	NA	
	P2	NA	
	P3	NA	
	All	162.46	170.34
00920	P1	NA	
	P2	158.00	
	P3	17.00	
	All	97.93	105.25
Hospitalizations			
	Implantation, artificial urinary sphincter (58.93)		
308	with complications		6,534
309	without complications		3,439
	Release, urethral stricture (58.5) or		
	Repair, urethra (58.4)		
312	with complications		3,800
313	without complications		2,281
315	Penile prosthesis insertion		10,072
	non-inflatable (64.95)		
	inflatable (64.97)		
	Pelvic lymph node excision (59.00) or		
	Prostatectomy, radical (60.5)		
334	with complications		7,483
335	without complications		5,867
	Prostatectomy, transurethral (60.2)		
336	with complications		3,943
337	without complications		2,778
338	Orchiectomy, bilateral (62.4)		3,893
Pharmaceuticals[d]			
	GnRH agonist		
	▪ Goserelin acetate implant (Zoladex) @ 3.6 mg monthly	318.75	
	▪ Leuprolide acetate depot (Lupron) @ 7.5 mg monthly	437.50	
	Flutamide (Eulexin) @ 250 mg	135.42/100	
	Diethylstilbesterol (DES) @ 1 mg	9.14/100	
	Macrodantin @ 50 mg (cystitis)	66.13/100	
	Prednisone @ 10 mg	3.30/100	
	Methylprednisolone acetate @ 10 ml	6.00	

NOTES:
[a] Medicare Average Allowable Charge, 1992.
[b] Medicare Fee Schedule, 1992 and Average Expenditure per Beneficiary (DRG), 1992.
[c] Medicare fee schedule anesthesia costs are not adjusted for supervision of more than one patient.
[d] Pharmaceutical prices are wholesale costs as found in the 1993 *Red Book*, Montvale, NJ.

KEY: NA = not included in fee schedule.
SOURCE: Office of Technology Assessment, 1995. Data are HCFA's unpublished Medicare Average Allowable Charge data from NCH/Best system. Other categories are unpublished data from HCFA Office of Research provided by W.J. Sobaski, HCFA, Baltimore, MD, personal communication, 1993.

APPENDIX

H

Current Research Efforts To Resolve the Effectiveness of Prostate Cancer Screening and Treatment

Most evidence-based criteria for evaluating screening maneuvers demand evidence from controlled studies on which to base recommendations. Randomized controlled trials (RCTs) are the best studies on which to base such recommendations. In the absence of RCTs, researchers and policymakers often examine less desirable cohort studies with concurrent nonrandomized controls and case-control studies. Unfortunately, in the area of early detection and treatment of prostate cancer, little controlled data are available, regardless of study design. A single case-control study has shown no evidence of benefit from digital rectal examination (DRE), in terms of lower exposure odds to DRE within the prior 10-year period among men with metastatic prostate cancer compared to controls (129). The point estimate of the DRE exposure odds ratio among men with metastatic cancer compared with controls in this study was 0.9, with a 95-percent confidence interval of 0.5 to 1.7. Similarly, a single small, underpowered randomized trial of radical prostatectomy versus expectant management showed no evidence of benefit from more aggressive treatment (54, 147), as discussed in detail earlier in this report.

TRIALS OF TREATMENT FOR CLINICALLY LOCALIZED PROSTATE CANCER

However, researchers are now planning or have already initiated clinical trials to address this lack of data. In terms of determining the optimal treatment for localized prostate cancer, the Scandinavian Prostate Cancer Group began a randomized trial of radical prostatectomy versus deferred treatment in 1989. Men less than age 75 with well or moderately differentiated (but not Stage T1a) cancer are eligible for the trial. Men randomized to surgery undergo a pelvic lymph node dissection, and proceed to radical prostatectomy if the nodes are uninvolved. However, an "intention to treat" analysis is planned to avoid biasing the results in favor of surgical treatment. The investigators plan to randomize 520 men and follow them for a minimum of 10 years to have adequate power to "rule out" a true improvement in 10-year cancer-specific survival from 85 to 95 percent, which represents a two-thirds reduction in cancer-specific mortality. This trial is more than halfway to its accrual target.

In the United Kingdom, the Medical Research Council has just opened a trial comparing the strategies of no immediate treatment, external beam radiotherapy, and radical prostatectomy for men with T1b/T1c/T2 N0 M0 prostate cancer (Trial PRO6). As part of the design, patients can be randomized among all three or any two of the treatment strategies, at the discretion of the physician and patient. Primary endpoints will be the development of documented metastases and survival time. The PRO6 protocol calls for the randomization of 400 men into each treatment arm over three years to achieve 90 percent power to detect a 10 percent difference in survival between any two arms.

Another large trial has been initiated in the United States. The Prostate Cancer Intervention Versus Observation Trial (PIVOT) is to be conducted as a collaboration between the Veterans Administration Cooperative Studies Program and the National Cancer Institute. The investigators plan to enroll about 2,000 men up to age 75 with clinically localized prostate cancer of all grades. Men who provide consent would be randomized to a strategy of immediate radical prostatectomy with additional aggressive treatment for evidence of residual or recurrent disease, or a strategy of expectant management with treatment for symptomatic local progression or metastases. PIVOT started late in 1994, and will accrue patients over three years with an additional 12 years of followup. PIVOT is powered to detect a 15 percent decrease in overall mortality with radical prostatectomy, or roughly a one-third reduction in cancer-specific mortality.

TRIALS OF EARLY DETECTION OF PROSTATE CANCER

Randomized trials of early detection of prostate cancer are also being planned and initiated. The National Cancer Institute's Prostate, Lung, Colorectal, and Ovarian (PLCO) Screening Trial is a ten-center study designed to measure the net benefit of screening for a number of common malignancies. For the prostate cancer component, 74,000 men ages 60 to 74 will be randomized to four annual screens with PSA and DRE, versus "usual care." The study was initiated in 1993, and may need to continue as long as 16 years to have adequate power to detect a 20 percent reduction in prostate cancer mortality, allowing for some "dilution" in the intervention group (due to incomplete compliance with followup of suspicious screening studies) and "contamination" in the control group (due to DREs and prostate-specific antigen tests that may be done as part of usual care).

Finally, a European screening study is currently being planned, and a number of preparatory pilot studies have been conducted in Belgium and the Netherlands. The main study is currently envisioned as involving about 50,000 men in a number of European countries. Details of the design are still being finalized.

Despite many reasonable individual concerns about the designs of the PLCO and PIVOT studies, support for these trials was recently expressed by a group of U.S. prostate cancer experts at a meeting cosponsored by the American Urological Association and the American Cancer Society (253). As Kaufman (186) has recently reminded the medical community, well-designed clinical trials, even in the controversial area of cancer treatment, are "good medicine."

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