CHAPTER

2

Prostate Cancer in Older Men

*p*rostate 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 common-sense 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

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[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

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[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, inconti-

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

Age	Life expectancy	
	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).

nence, and a small chance of surgical death, must be weighed against evidence of reductions in mortality to make screening worthwhile.

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

FIGURE 2-1: CROSS-SECTIONAL ILLUSTRATION OF NORMAL MALE PELVIC REGION
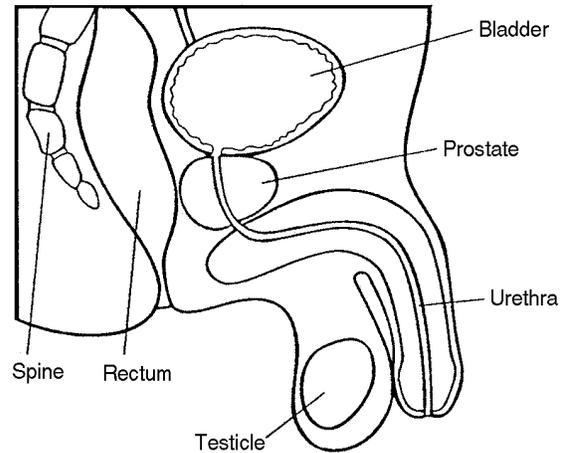
SOURCE: The American Prostate Society, Inc.

detection, none of the guidelines described above directly took these costs into account.

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.

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[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		Definition
Whitmore (A-D)	**TNM system[a]**	**Definition**
1. Clinically nonpalpable cancers		
A_1	T_{1a}	Incidental finding of cancer in $\leq$ 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	Metastasis in a single lymph node 2 cm, metastasis single
	N_2	nodes 2-5 cm, or multiple nodes (all $\geq$5 cm), metastasis in
	N_3	node $\geq$ 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.

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.