CHAPTER 3

Prostate Cancer

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INTRODUCTION

Prostate cancer is the most common solid tumor found in American men. One in approximately every 6 American men over the age of 50 will be diagnosed with prostate cancer in his lifetime (1). This astonishing statistic underscores the significance of this cancer not only as a urologic disease, but also as a general public health burden. It should be noted that the lifetime risk of prostate cancer has increased considerably in the past 15 years, following the introduction of prostate-specific antigen (PSA) testing. Although the risk of being diagnosed with prostate cancer is high, the risk of dying of the disease is much lower: Roughly one in every 33 American men over the age of 50 actually dies of prostate cancer. In this respect, there is truth in the clinical adage, "More men die with prostate cancer than of it." While the mortality burden associated with prostate cancer is less than might be expected, the physical, psychological, and economic burdens are considerable.

DEFINITION AND DIAGNOSIS

Unlike malignant neoplasms arising in other organs, of which there are numerous pathologic subtypes, the overwhelming majority of malignant prostate tumors are primary adenocarcinomas arising from the glandular tissue within the prostate. Roughly 85% of these tumors occur in the periphery of the gland and are multifocal in nature. In addition to adenocarcinoma, rare pathologic variants also arise in the prostate, including mucinous adenocarcinoma, small cell (neuroendocrine) carcinoma, squamous cell carcinoma, rhabdomyosarcoma, and leiomyosarcoma. Finally, the prostate can be invaded by malignant neoplasms from other organs, including transitional cell carcinoma of the bladder and lymphoma (2). While these rare pathologic variants are of academic importance, we refer exclusively to primary adenocarcinoma in this discussion. Table 1 presents the diagnosis and procedure codes associated with prostate cancer.

Prior to the 1980s, men with prostate cancer usually presented in one of three ways: (1) they had lower urinary tract symptoms, which the doctor believed were due to benign prostatic hyperplasia (BPH), and then underwent transuretheral resection of the prostate (TURP) and were incidentally found to have prostate cancer on pathologic analysis of the TURP specimen; (2) they presented with advanced prostate cancer causing bony pain and/or severe local symptoms, a biopsy then confirmed the suspected diagnosis, and treatment was initiated; and (3) a digital rectal exam revealed an abnormality that led to a prostate biopsy.

Patterns of care in prostate cancer have changed tremendously in the past 20 years, altering the way patients with this tumor present and how they are evaluated before and after diagnosis. To understand current trends in prostate cancer, it is necessary to be familiar with three important scientific/clinical advances that have impacted the care of older men with prostate disease in North America and Western Europe. The first of these three "turning points" was the introduction of nerve-sparing radical retropubic

Table 1. Codes used in the diagnosis and management of prostate cancer

Males 40 years or older with one or more of the following:	
ICD-9 diagnosis codes	
185	Malignant neoplasm of prostate
233.4	Carcinoma in situ of prostate
236.5	Neoplasm of uncertain behavior of prostate
ICD-9 procedure codes	
60.13	Closed [percutaneous] biopsy of seminal vesicles
60.5	Radical prostatectomy
60.62	Perineal prostatectomy
CPT procedure codes	
55810	Prostatectomy, perineal radical
55812	Prostatectomy, perineal radical; with lymph node biopsy(s) (limited pelvic lymphadenectomy)
55815	Prostatectomy, perineal radical; with bilateral pelvic lymphadenectomy, including external iliac, hypogastric and obturator nodes
55840	Prostatectomy, retropubic radical, with or without nerve sparing
55842	Prostatectomy, retropubic radical, with or without nerve sparing; with lymph node biopsy(s) (limited pelvic lymphadenectomy)
55845	Prostatectomy, retropubic radical, with or without nerve sparing; with bilateral pelvic lymphadenectomy, including external iliac, hypogastric, and obturator nodes
55859	Transperineal placement of needles or catheters into prostate for interstitial radioelement application, with or without cystoscopy
55860	Exposure of prostate, any approach, for insertion of radioactive substance
55862	Exposure of prostate, any approach, for insertion of radioactive substance; with lymph node biopsy(s) (limited pelvic lymphadenectomy)
55865	Exposure of prostate, any approach, for insertion of radioactive substance; with bilateral pelvic lymphadenectomy, including external iliac, hypogastric and obturator nodes
55866	Laparoscopy, surgical prostatectomy, retropubic radical, including nerve sparing
55873	Cryosurgical ablation of the prostate (includes ultrasonic guidance for interstitial cryosurgical probe placement)
J9217[a]	Leuprolide acetate (for depot suspension), 7.5 mg
J9218[a]	Leuprolide acetate, per 1 mg
J9219[a]	Leuprolide acetate implant, 65 mg
J9202[a]	Goserelin acetate implant, per 3.6 mg

[a]Included in definition of outpatient and physician office visits only.

prostatectomy in 1982 (3). This surgical technique allowed the urologic surgeon to preserve during prostatectomy the neurovascular bundles that course lateral to the prostate. This preserved erectile function after surgery, making the operation more palatable to patients. This surgical innovation was a driving force behind the increasing utilization of surgery to treat prostate cancer in the late 1980s and early 1990s (discussed later in this chapter). It also removed some of the stigma of a prostate cancer diagnosis and increased public awareness of the disease. The second turning point was the development of effective oral therapies for lower urinary tract symptoms (LUTS) caused by benign prostatic hyperplasia (BPH). Although BPH is discussed elsewhere in greater detail in this compendium, it deserves mention here as well, since most men with prostate cancer have pathologic evidence of BPH. Prior to the introduction and widespread use of alpha-blocker therapy for the treatment of LUTS/BPH in the early 1990s, the

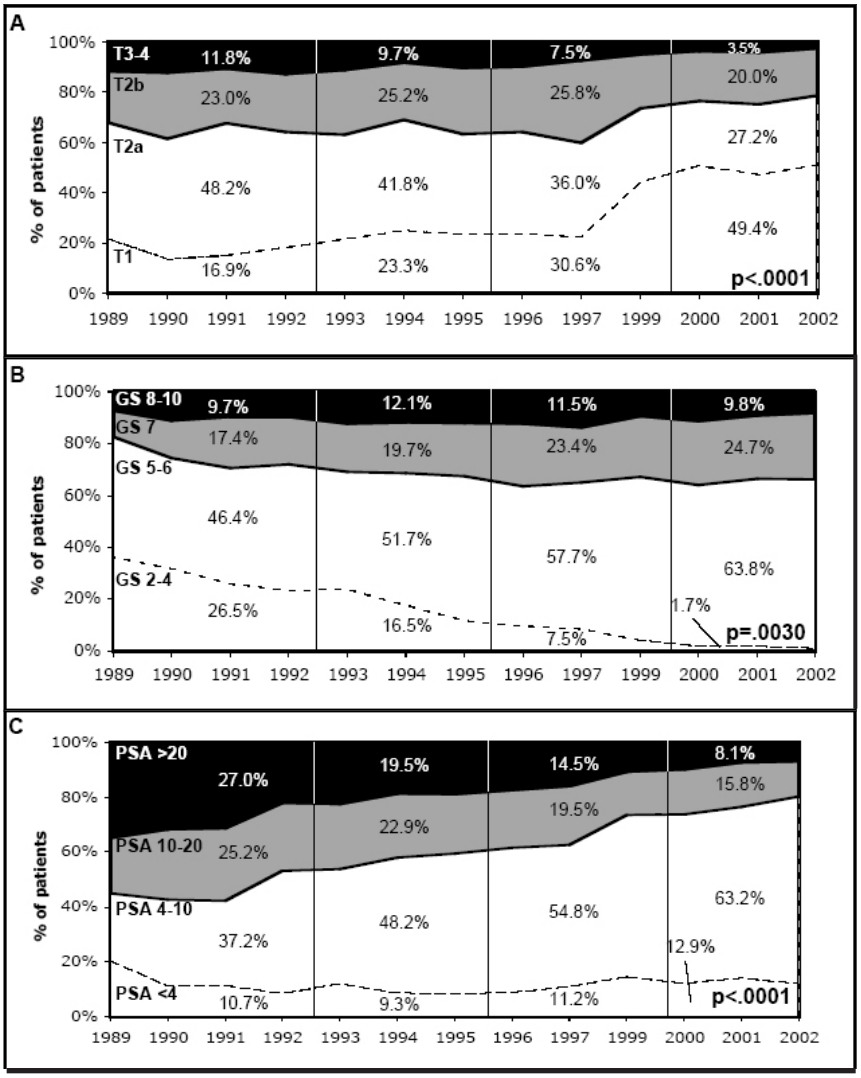

Figure 1. Time trends in individual risk characteristics for prostate cancer.

A: clinical T stage; B: Gleason score; C: serum PSA levels. Characteristic levels defining low, intermediate, and high risk are shaded white, gray, and black, respectively.

SOURCE: Reprinted from Journal of Urology, 170, Cooperberg MR, Lubeck DP, Mehta SS, Carroll PR. Time trends in clinical risk stratification for prostate cancer: implications for outcomes (data from CaPSURE), S21–S27, Copyright 2003, with permission from American Urological Association.

Table 2. Use of prostate needle biopsy with and without transrectal ultrasound (TRUS) among Medicare beneficiaries, count[a], rate[b], age-adjusted rate[c]

	1992					1995				
	Count	Rate		Age-Adjusted Rate	% with ultrasound guidance	Count	Rate		Age-Adjusted Rate	% with ultrasound guidance
Total[d]	450,200	2,935	(2,897–2,973)		49	330,460	2,035	(2,005–2,066)		67
A ge										
40–49	380	68	(38–99)		37	180	25	(8.7–41.5)		33
50–59	2,920	418	(350–485)		43	3,420	405	(345–466)		77
60–69	119,720	2,088	(2,036–2,141)		51	99,700	1,739	(1,691–1,787)		69
70–79	248,000	4,135	(4,064–4,207)		50	177,240	2,789	(2,732–2,846)		68
80+	79,180	3,362	(3,260–3,465)		44	49,920	1,929	(1,854–2,004)		59
Race/ethnicity										
White	391,820	3,005	(2,963–3,046	2,991	50	285,480	2,039	(2,006–2,073)	2,039	67
Black	33,500	2,737	(2,607–2,866)	2,715	41	30,460	2,231	(2,120–2,342)	2,189	64
Hispanic	…	...		…	…	3,540	1,795	(1,533–2,057)	1,896	66
Asian	...	...		...	...	1,440	1,804	(1,391–2,216)	1,703	53
Region										
Midwest	112,440	3,037	(2,959–3,115)	3,061	48	79,780	2,074	(2,010–2,137)	2,084	66
Northeast	99,620	3,116	(3,031–3,201)	3,092	31	75,500	2,275	(2,203–2,346)	2,245	53
South	169,840	3,252	(3,184–3,320)	3,256	58	125,940	2,249	(2,194–2,303)	2,256	74
West	65,020	2,268	(2,191–2,345)	2,262	56	45,360	1,463	(1,404–1,523)	1,469	74

	1998					2001				
	Count	Rate		Age-Adjusted Rate	% with ultrasound guidance	Count	Rate		Age-Adjusted Rate	% with ultrasound guidance
Total[d]	275,060	1,630	(1,603–1,657)		70	282,640	1,601	(1,575–1,627)		78
Age										
40–49	380	47	(26–68)		68	420	48	(27–68)		67
50–59	3,960	401	(345–456)		64	4,660	406	(354–458)		71
60–69	78,780	1,401	(1,358–1,445)		73	84,600	1,467	(1,423–1,511)		80
70–79	150,080	2,258	(2,208–2,309)		71	150,100	2,206	(2,157–2,256)		78
80+	41,860	1,494	(1,430–1,557)		63	42,860	1,403	(1,344–1,462)		73
Race/ethnicity										
White	238,960	1,662	(1,632–1,691)	1,646	71	240,040	1,594	(1,566–1,622)	1,580	79
Black	23,740	1,644	(1,551–1,737)	1,751	66	27,480	1,752	(1,660–1,844)	1,851	72
Hispanic	5,180	1,342	(1,180–1,504)	1,342	69	5,400	1,268	(1,118–1,419)	1,226	69
Asian	2,700	1,507	(1,255–1,760)	1,373	70	2,740	1,090	(908–1,272)	955	65
Region										
Midwest	72,080	1,840	(1,780–1,899)	1,841	67	71,560	1,777	(1,719–1,835)	1,774	78
Northeast	58,400	1,725	(1,663–1,787)	1,680	62	53,820	1,546	(1,488–1,604)	1,502	72
South	103,200	1,748	(1,701–1,796)	1,765	75	111,700	1,789	(1,742–1,835)	1,821	81
West	38,060	1,161	(1,109–1,213)	1,172	76	41,620	1,193	(1,142–1,243)	1,180	80

…data not available.

[a]Unweighted counts multiplied by 20 to arrive at values in the table.

[b]Rate per 100,000 male Medicare beneficiaries age 40 and above in the same demographic stratum.

[c]Age-adjusted to the US Census-derived age distribution of the year under analysis.

[d]Persons of other races, unknown race and ethnicity, and other region are included in the totals.

NOTE: Counts less than 600 should be interpreted with caution.

SOURCE: Centers for Medicare and Medicaid Services, 1992, 1995, 1998, 2001.

primary therapy for this condition was TURP (4). As mentioned above, patients undergoing TURP for LUTS were sometimes found to have prostate cancer upon pathologic analysis of the surgical specimen. Therefore, as TURP rates dropped in the late 1980s and early 1990s (4), the number of men who had prostate cancer diagnosed in this way dropped as well. The third and perhaps most important of the three landmark events was the introduction of PSA testing. First described in the general medical literature in 1987, PSA, a serine protease, was purported to be a reliable screening test for the presence of occult prostate cancer and an accurate tumor marker after the diagnosis was established and treatment rendered (5). The use of prostate cancer screening, in the form of a PSA test and a digital rectal examination (DRE), increased exponentially in the early 1990s, changing the primary method by which prostate cancer was detected and the way in which men presented with the disease.

The majority of patients with prostate cancer now present with asymptomatic localized disease detected either by an elevated PSA test or an abnormal DRE. Data from Cooperberg and colleagues (6) document that nearly half of patients with newly diagnosed prostate cancer presented with clinical stage T1 disease in 2000, as shown in Figure 1. Patients who present with symptoms tend to have LUTS, such as nocturia, hesitancy, and intermittency. Patients presenting with a large, bulky tumor causing bilateral ureteral obstruction or painful bony metastases, fairly common prior to the introduction of PSA testing, are now quite rare.

The primary method of determining whether prostate cancer is present is the transrectal prostate needle biopsy. Historically, prostate biopsies were

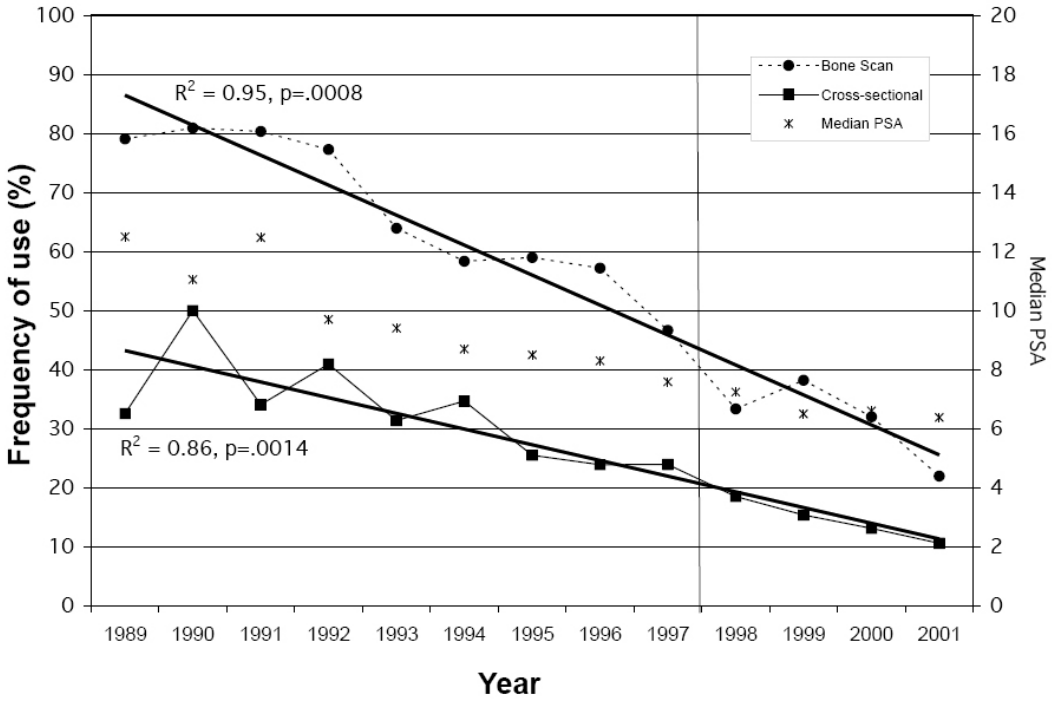

Figure 2. Time trends in imaging test utilization rates in patients at low and intermediate risk for prostate cancer showing percent that underwent bone scan or cross-sectional imaging per year of diagnosis.

SOURCE: Reprinted from Journal of Urology, 168, Cooperberg MR, Lubeck DP, Grossfeld GD, Mehta SS, Carroll PR, Contemporary trends in imaging test utilization for prostate cancer staging: data from the cancer of the prostate strategic urologic research endeavor, 491–495, Copyright 2002, with permission from American Urological Association.

performed transperineally, often with fine-needle aspiration techniques. Advances in ultrasound technology and improvements in spring-loaded needle designs led to the widespread adoption of the transrectal ultrasound-guided prostate needle biopsy as the primary diagnostic approach. As illustrated in Table 2, data from a 5% Medicare sample indicate that biopsy rates were highest in 1992 (2,935 biopsies per 100,000 male Medicare beneficiaries), then declined and stabilized by 2001 (1,601 per 100,000). This decline and stabilization represent the exhaustion of the "prevalent pool" of prostate cancer patients who were diagnosed soon after the introduction of PSA testing. The relatively stable but high rate between 1998 (1,630 per 100,000) and 2001 documents the considerable burden that prostate cancer screening places on healthcare resources. The positive biopsy rate within the 5% Medicare sample for 2001 was 40.3%, indicating that more than half of the men undergoing biopsy were not immediately found to have prostate cancer. The positive biopsy rate was approximated by identifying new ICD-9 coding of prostate cancer in the 6-month period that followed the biopsy. The Medicare biopsy data also revealed interesting regional and ethnic variation. The age-adjusted biopsy rate was highest in the South and lowest in the West. The exact reasons for the disparities are unclear, but it is difficult to ascribe them to clinical differences among older men in the different regions. In addition, the percentage of biopsies performed using ultrasound guidance increased from 49% in 1992 to 78% in 2001. While this is consistent with clinical guidelines and the diffusion of advanced ultrasound technologies into the community, it should be noted that the Northeast region consistently had lower rates of ultrasound utilization than other geographic areas. In addition, African American men were less likely to undergo an ultrasound-guided biopsy than were

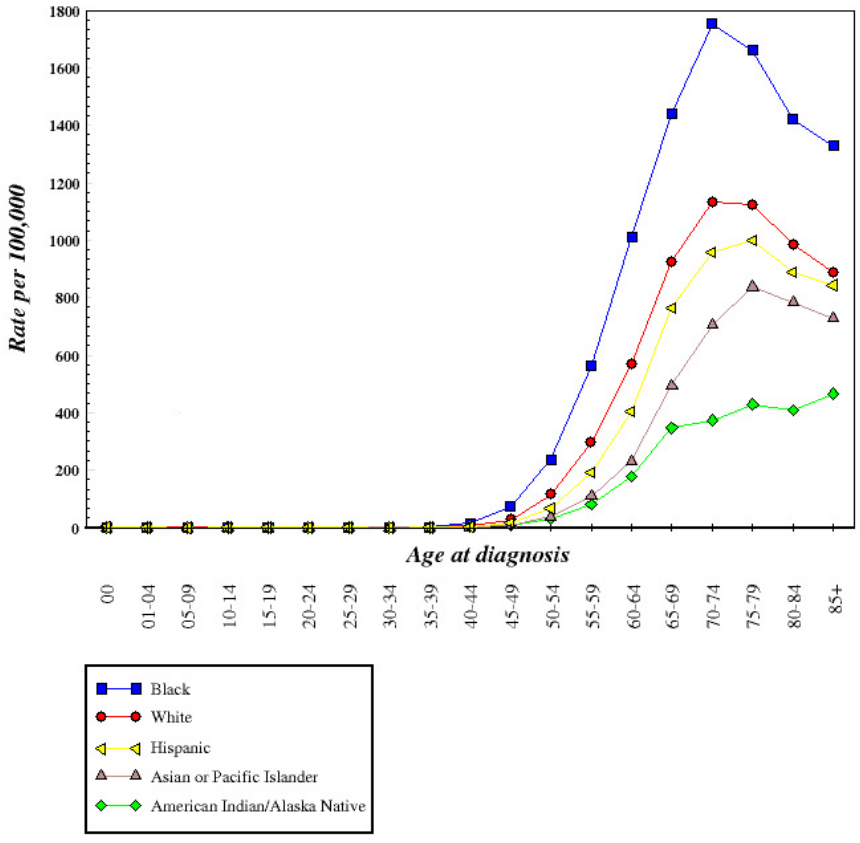

Figure 3. Crude incidence rates for prostate cancer, by race/ethnicity.

SOURCE: Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov).

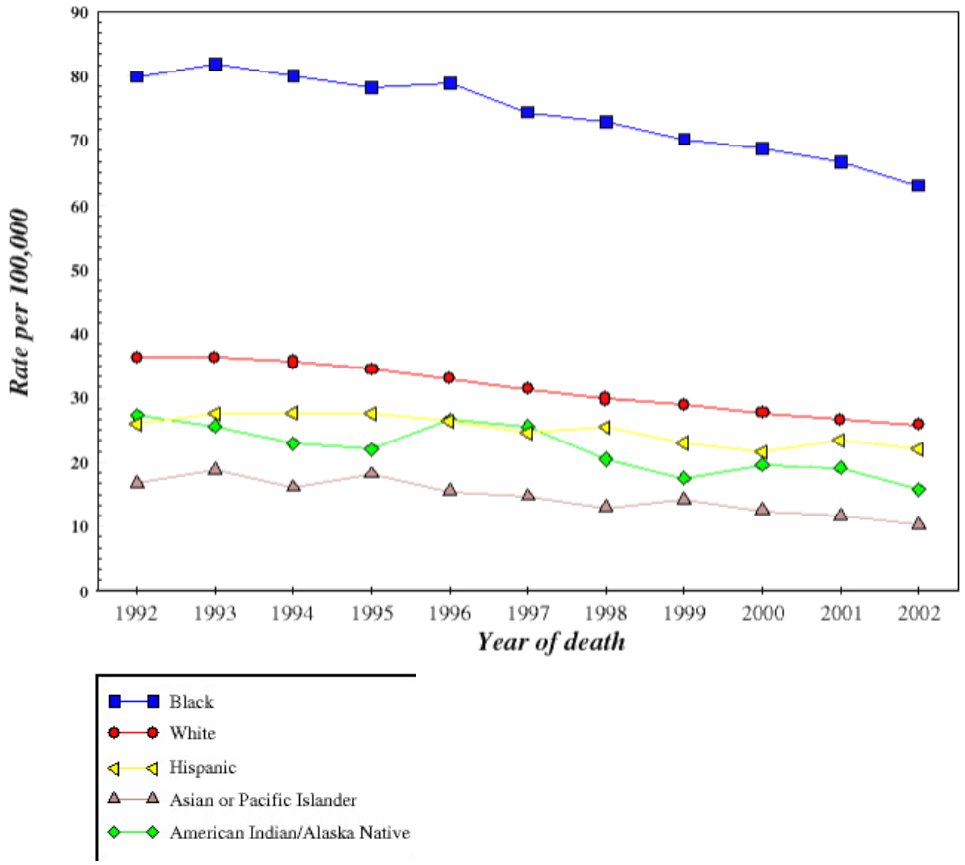

Figure 4. Mortality rates for prostate cancer, 1992–2002, age-adjusted, all ages, by race/ethnicity.

SOURCE: Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov).

Caucasian men at all time points. These regional and ethnic differences in patterns of care merit further study, as they may represent correctable differences in access to care.

Once the diagnosis of prostate cancer is established, the workup depends upon the suspected stage at presentation. Patients with higher PSA levels, more pathologically undifferentiated tumors, and/or suspected metastatic disease routinely undergo nuclear medicine scans to determine if the cancer is present in the bone. The use of routine bone scans in newly diagnosed prostate cancer has steadily declined in recent years as patients have presented with earlier-stage disease (7). Routine computed tomography (CT) and/or magnetic resonance imaging (MRI) add little to the staging of prostate cancer. Neither CT nor routine MRI is particularly helpful in accurately identifying nodal involvement (8-10). Some researchers have suggested that MRI imaging with an endorectal coil can identify extracapsular extension of prostate cancer and aid in decision-making (11). However, the ability to perform these procedures is generally limited to selected academic centers; hence, MRI has a minimal role in the staging of prostate cancer in the community. It is important to note that although their use has declined, these imaging studies are still probably employed more often than needed. The CaPSURE™ database, a large observational disease registry of prostate cancer survivors, documents that despite guidelines recommending limited imaging for patients presenting with lower-stage disease, in 2001 roughly 25% of low- and intermediate-risk patients underwent bone scan, and 10% underwent CT or MRI (Figure 2) (7).

RISK FACTORS

Age, Race, and Family History

Age, race, and family history are well-established and often-quoted risk factors for prostate cancer incidence. The incidence of prostate cancer rises dramatically with age, as shown in Figure 3, peaking at age 70–74 at 1,134 per 100,000 for Caucasians and 1,753 per 100,000 for African Americans (12). Figure 3 also illustrates the trend in prostate cancer incidence by racial/ethnic group in the United States. African American men have an incidence rate persistently higher than that of any other racial-ethnic group—for each age group, their rate of developing prostate cancer is roughly 1.5 to 2 times higher than the rate for Caucasians. The rate of prostate cancer mortality among African American men is also approximately twice that of Caucasians (Figure 4). In contrast, American Indian/Alaskan Natives have the lowest incidence of prostate cancer in the United States, and Asians/Pacific Islanders have the lowest mortality rate from it (12). Although the data are equivocal, it appears that Hispanic men may have a somewhat lower risk of developing prostate cancer than Caucasian men. Further research regarding this important topic is necessary, as the number of Hispanic men in the US population is increasing.

As shown in Figure 5, the incidence of prostate cancer worldwide varies dramatically, with men in China and parts of Southeast Asia having incidence rates of less than 5 to 10 per 100,000, (13) compared with African American men in the United States, who have a rate of 265 per 100,000 (age-standardized 2002 rates) (13). These dramatic differences by racial/ethnic group have led researchers to examine risk factors for prostate cancer that may vary by race or culture. Another explanation for worldwide regional variations may be differing use of PSA screening in different countries.

Family history is also an important risk factor. A man with a history of prostate cancer in a first-degree relative has approximately two to three times the risk of a man without such a family history. This association appears to be consistent across African Americans, Caucasians, and Asians (14). At least one study reported a higher prevalence of familial

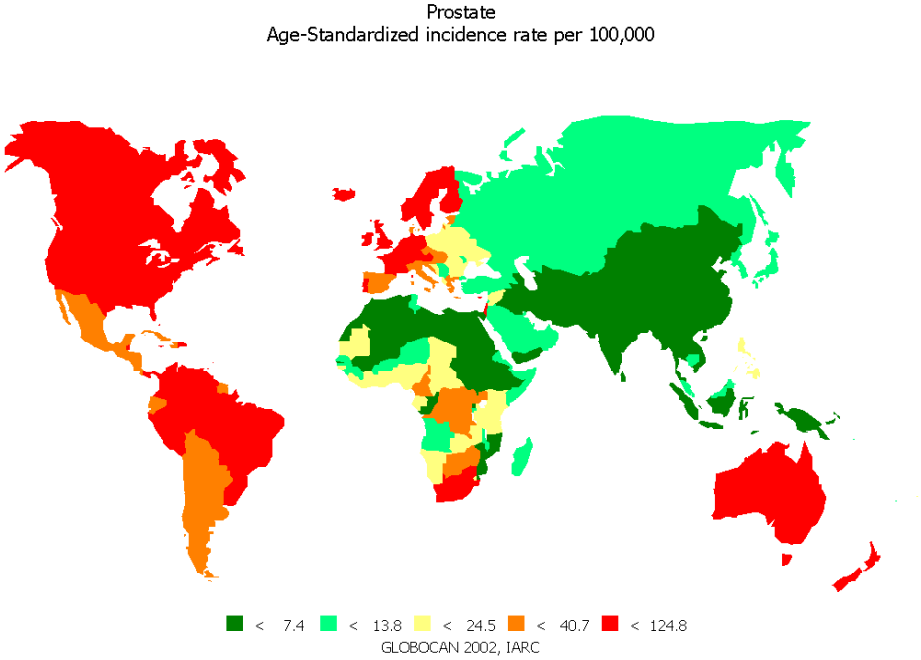

Figure 5. Worldwide incidence of prostate cancer.

SOURCE: Globocan 2002, International Agency for Research on Cancer.

prostate cancer among African Americans than in Caucasians (31% vs 22%) (15). These associations suggest that there may be an important hereditary genetic component to prostate cancer etiology. Based on a large study of twins from several Scandinavian countries, it has been estimated that 42% (95% CI, 29–50%) of the variation in prostate cancer occurrence may be due to hereditary factors (16). However, this estimate does not take into account the potential effects of gene/environment interactions on the risk of developing prostate cancer.

Diet

The dramatic differences in prostate cancer incidence worldwide have led researchers to examine several environmental risk factors that vary by culture, especially diet. The majority of the evidence for diet and prostate cancer focuses on relationships with incidence of the disease, not with progression or mortality. The epidemiology of diet and prostate cancer was recently reviewed in detail (17) and is summarized below and in Table 3.

Vegetables, Fruits, and Related Micronutrients

Although the data are mixed, it is likely that vegetables and soy/legumes impart some protective benefit against risk of developing prostate cancer (18-25). Tomatoes, tomato products, and lycopene (the primary carotenoid in tomatoes) have been consistently linked to a reduced risk of incident prostate

Table 3. Nutritional risk factors for prostate cancer incidence, recurrence, and mortality

Food or nutrient	Direction of Association with Risk of Prostate Cancer Incidence	Direction of Association with Prostate Cancer Recurrence or Mortality	Overall Quality of Evidence
Selenium	Inverse		Strong
Tomatoes and lycopene	Inverse	Inverse[a] (possible postdiagnostic effect on recurrence)	Good
Other carotenoids (e.g., Beta-carotene)	Inverse, esp. among those low in other carotenoids	Inverse[a] (prediagnostic supplemental beta-carotene effect on mortality, by MnSOD status)	Good[a]
Vitamin E	Inverse (effect seen mainly among smokers)	Inverse[a] (possible prediagnostic effect for mortality)	Good
Vitamin D	Inverse		Good
Calcium and dairy	Null to positive (inverse for calcium supplements and early-stage disease[a])		Good
Red meat	Positive		Good
Fish/marine omega-3 fatty acids	Inverse	Inverse[a] (possible prediagnostic effect for mortality; possible pre- and postdiagnostic effects for recurrence)	Fair to good
Soy/isoflavones	Null to inverse	Null for PSA recurrence after treatmenta	Fair[a]
Tea/polyphenols	Null to inverse		Fair[a]
Zinc	Positive		Fair[a]
Heterocyclic amines	Positive		Fair[a]

[a]Limited data available

SOURCE: Chan JM, Gann PH, Giovannucci EL, Role of diet in prostate cancer development and progression, J Clin Oncol, 2005, 23(32):8,152-8,160. Reprinted with permission from the American Society of Clinical Oncology.

cancer. While fewer data exist on other carotenoids, some studies have observed inverse associations with intake or levels of plasma lutein, beta-cryptoxanthin, and zeaxanthin (24, 26-36)

Soy consumption is fairly low in most Western populations, where many of the largest epidemiologic studies with the most follow-up have been conducted, making its effects difficult to study. In a few epidemiologic studies that have examined soy or its primary phytochemicals (genistein, daidzein, and equol), inverse associations have been observed, (32, 37-40) although they have not always been statistically significant (41, 42).

Vitamin E has been associated with a reduction of up to 40% in the risk of prostate cancer incidence and mortality (43-47) and is the focus of an ongoing primary prevention study, the Selenium and Vitamin E Cancer Prevention Trial (SELECT). The Alpha-Tocopherol Beta-Carotene (ATBC) Cancer Prevention Trial found a statistically significant 30–40% reduction in prostate cancer incidence and mortality among men randomized to daily 50 IU supplements of alpha-tocopherol (a common supplement form of vitamin E) vs placebo (48). Interestingly, all participants in this trial, which was originally focused on lung cancer as an outcome, had a substantial smoking history; and in the Health Professionals Follow-Up Study (HPFS), greater supplemental vitamin E intake was associated with decreased risk of advanced prostate cancer only among smokers (46). Some studies (46, 49-53) have observed no association between prostate cancer and vitamin E.

Selenium may have pro-apoptotic, antiangiogenic, antiproliferative, or antioxidant properties to protect against prostate cancer (54-69). The Nutrition Prevention of Cancer Trial (59) reported a halving of risk of prostate cancer incidence among men randomized to selenium supplements vs placebo; several prospective studies have observed 50–65% reductions in prostate cancer associated with greater physiologic measures of selenium (54, 60, 64).

Milk, Dairy, and Calcium

Several studies (70-72) have found milk, calcium, and dairy products to be associated with a greater risk of prostate cancer. In the HPFS, for example, men who consumed > 2000 mg vs < 500 mg of calcium daily had almost five times the risk of developing advanced prostate cancer (73). However, secondary results from a randomized clinical trial on calcium supplements and colorectal adenomas reported a null to inverse association between prostate cancer and calcium supplements. The majority of cases observed in that trial were early-stage PSA-detected cancers, whereas many observational studies have reported elevated risks from milk, dairy, or calcium for advanced or metastatic prostate cancer. It has been hypothesized that this apparent discrepancy between trial and observational studies' results may be due to calcium having different actions on prostate cancer development depending on tumor stage, phenotype, or timing within the disease course. The leading hypothesized mechanism by which dairy or milk intake may affect prostate cancer risk involves the effects of calcium intake on circulating levels of 1,25(OH)2,D3, the most biologically active form of vitamin D, which has been shown to inhibit growth of prostate cancer cells (18, 74).

Meat and Fat

Several studies suggest that total and specific fats and meat intake may be associated with prostate cancer. While results are mixed, saturated and alpha-linolenic fatty acids have been positively associated with prostate cancer risk, while long-chain marine omega-3 fatty acids may impart some protection. Saturated fatty acids or meat may affect prostate cancer through the insulin-like growth factor-I (IGF-I) and androgen pathways (75-82).

There is suggestive epidemiologic evidence that fish or the marine omega-3 fatty acids may afford some protection against prostate cancer (83-87). It is hypothesized that they or their ratio to omega-6 fatty acids may influence inflammatory pathways by inhibiting production of prostaglandins (i.e., PGE2) or modulating COX-2 expression and may thereby potentially affect prostate cancer development (88-96). Further evidence of a role for inflammation in prostate cancer comes from data suggesting that non-steroidal anti-inflammatory drugs may be inversely associated with prostate cancer risk (97-99).

Gene-Diet Interactions

Recent studies have identified potential gene-diet interactions associated with prostate cancer risk, adding support to the evidence of involvement

of vegetables and related micronutrients in prostate cancer. Manganese-superoxide dismutase (MnSOD) is an antioxidant enzyme that has been identified as a potential tumor-suppressor gene in prostate cancer (100, 101). A few studies have found that a specific MnSOD variant is related to a greater risk of prostate cancer (28, 102). In the Physicians' Health Study (PHS), men with the MnSOD Ala/Ala genotype had a 50% *lower* risk of prostate cancer if they had high serum levels of antioxidants (i.e., selenium, vitamin E, and lycopene combined) but a twofold *increased* risk if they were low in antioxidants, compared with men who did not have the Ala/Ala genotype and who had low antioxidant levels (p-value for interaction = 0.02) (28, 103). A similar interaction effect was observed for beta-carotene randomization vs placebo (the PHS was also a randomized clinical trial for heart disease and cancer): men with the Ala/Ala variant who were assigned beta-carotene had a 63% lower risk of fatal prostate cancer than those assigned to placebo (p-value for interaction = 0.03).

All of the studies discussed above address the relationship between various dietary risk factors and prostate cancer incidence. There are also limited data on the effect of diet after diagnosis, specifically the effect of diet on recurrence and/or survival. Several studies of diet and prostate cancer incidence observed stronger associations with risk of advanced, metastatic, or fatal prostate cancer (e.g., for lycopene/tomatoes, vitamin E, selenium, milk/calcium, zinc, meat/saturated and alpha-linolenic fatty acid, fish) (17). In the HPFS, higher tomato sauce and fish intake *after* diagnosis were associated with reduced risks of prostate cancer recurrence and progression in a cohort of prostate cancer survivors (104). A few studies of men with prostate cancer reported that lycopene or tomato sauce may decrease PSA or tumor volume; these results must be interpreted cautiously, however, as the studies were small, some did not have a control group, (105) and some had unbalanced randomization (106). One study reported a greater risk of prostate cancer death associated with higher saturated fat intake after diagnosis (107)

Hormonal Risk Factors

Insulin-like growth factor-I (IGF-I), sex hormones, and their associated binding proteins have also been examined for their potential biological roles in prostate cancer development and progression. IGF-I has been consistently positively associated with the development of prostate cancer (80, 81). The recently completed Prostate Cancer Prevention Trial (PCPT) (108) specifically studied the 5-alpha reductase inhibitor, finasteride, as a preventive agent. While the study found that finasteride substantially reduced prostate cancer risk, the results were controversial and further study is needed.

Body Size and Physical Activity

The evidence for an association between body size and risk of prostate cancer remains equivocal, with some studies reporting small to moderate positive associations, (109-114) the majority of studies observing no association, (14, 115-122), and a few reporting inverse associations (115, 123-125). Overall, studies have not reported any strong relationships between adult body size and the risk of prostate cancer. A few prospective studies suggest that body mass index (BMI) is slightly positively associated with risk of prostate cancer mortality (126, 127). This is consistent with additional findings that obesity at the time at diagnosis and plasma leptin correlate positively with worse tumor features (128-131).

Studies on physical activity have had conflicting results, (14, 111, 113, 120, 132-151) but some suggest an inverse association (74, 120, 132, 136, 137, 140-143, 145-147, 150, 152-154). A review by Torti et al. (154) in 2004 reported that among 27 studies published between 1976 and 2002 examining physical activity and prostate cancer, 16 observed a reduced risk associated with greater activity levels, and nine of these had statistically significant results.

PREVALENCE AND INCIDENCE

In the United States, prostate cancer has an estimated annual incidence of 176 cases per 100,000 men (Table 4). According to the American Cancer Society, in 2006, 234,460 men in the United States will develop prostate cancer and 27,350 men will die of it (Table 4) (155). While prostate cancer is the third leading cause of cancer in men, after lung/bronchus and colorectal, and is estimated to cause 118,200 deaths in 2006, (155) it is also clear that many more men are diagnosed with prostate cancer than will die from the disease each year. The prevalence of prostate cancer,

Table 4. Incidence[a], mortality[a], estimated new cases, and deaths for the most common cancer sites among men in the United States, 2006

	Cancer Site					
	Incidence	Mortality	Estimated new cases		Estimated new deaths	
Lung/bronchus	77.8	73.5	92,700	(13%)	90,330	(31%)
Colon & Rectum	42.1	19.9	72,800	(10%)	27,870	(10%)
Prostate	176.3	28.1	234,460	(33%)	27,351	(9%)
Urinary Bladder	35.9	7.5	44,690	(6%)	8,990	(3%)

[a]Rate per 100,000, age-adjusted to the US standard population.

SOURCE: Cancer Statistics, 2006. American Cancer Society Surveillance Research.

by age category, is 3% for men aged 60–64; 6% for men 65–69; 10% for men 70–74; 13% for men 75–79; 15% for men 80–84; and 14% for men over 85. More than 1.8 million men are estimated to live with the disease in the United States (156).

Recent trends in prostate cancer incidence in the United States reflect the increasing use of serum-based PSA testing to screen for the disease (Figure 6) (157). During the past two decades, incidence rates peaked in 1992 at 237 per 100,000 (age-adjusted, all races and ages) (12), declined steeply until 1995, and then rose at approximately 1.7% per year through 2000. In 2000, 2001, and 2002, the annual age-adjusted incidence rates were 180, 181, and 176 per 100,000, respectively (Table 5). In contrast, mortality rates have been steadily declining at approximately 4% per year since 1994 (157). It is speculated that this decline reflects the beneficial effects of early diagnosis with

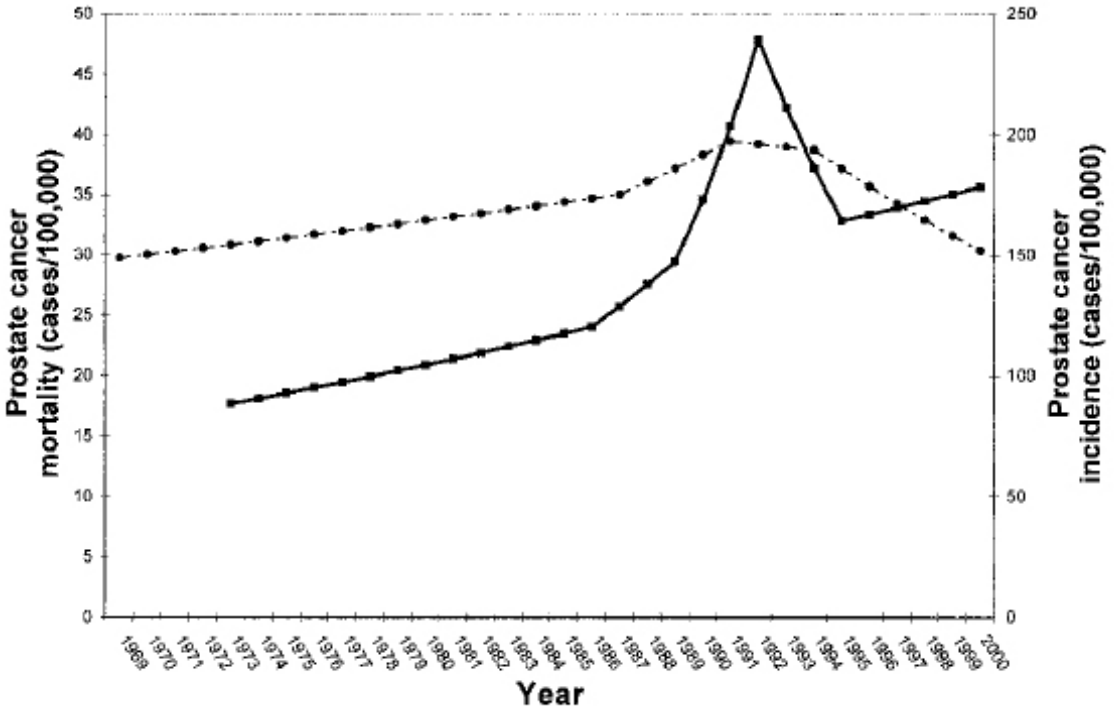

Figure 6. Prostate cancer incidence (solid line) and mortality (broken line).

SOURCE: Reprinted from Journal of Urology, 172, Chan JM, Jou RM, Carroll PR, The relative impact and future burden of prostate cancer in the United States, S13–S17, Copyright 2004, with permission from American Urological Association..

Table 5. Incidence rates for prostate cancer, by race/ethnicity and age, age-adjusted[a]

	All Males			White Males			Black Males		
	All	< 65	≥ 65	All	< 65	≥ 65	All	< 65	≥ 65
Year of Diagnosis									
1975	94	14	650	92	13	640	141	27	929
1976	98	15	674	97	14	674	141	29	911
1977	100	15	691	99	14	681	159	29	1,057
1978	99	15	681	98	15	671	148	27	985
1979	103	15	715	102	15	708	162	26	1,100
1980	106	15	731	105	15	728	161	34	1,040
1981	109	17	745	108	16	743	162	34	1,042
1982	108	16	743	107	16	740	168	32	1,110
1983	112	17	764	111	17	762	171	34	1,117
1984	112	17	764	110	16	758	179	37	1,158
1985	115	18	790	115	18	785	170	32	1,126
1986	119	19	813	119	18	815	168	34	1,093
1987	134	22	908	134	21	917	189	36	1,244
1988	137	22	934	139	22	942	191	35	1,267
1989	145	24	983	146	24	989	192	37	1,261
1990	171	29	1,152	172	29	1,165	222	44	1,449
1991	215	39	1,429	216	39	1,439	288	57	1,883
1992	237	49	1,535	238	49	1,540	327	77	2,051
1993	209	51	1,306	204	49	1,275	342	94	2,063
1994	180	49	1,088	174	47	1,052	311	94	1,806
1995	169	50	989	163	48	961	279	97	1,531
1996	168	53	965	164	52	938	280	99	1,526
1997	173	55	985	169	54	962	278	96	1,537
1998	169	55	964	165	53	946	280	101	1,519
1999	181	61	1,017	176	58	989	286	110	1,499
2000	180	61	1,001	176	59	982	284	112	1,478
2001	181	63	993	178	61	987	261	112	1,291
2002	176	64	954	172	62	935	276	114	1,396

[a]Rates are per 100,000 and are age-adjusted to the 2000 United States standard population.

SOURCE: Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) Public-Use Data (1973–2002), National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2005, based on the November 2004 submission.

PSA screening or improved treatments. However, it has also been noted that declines in mortality may be attributable to other causes, such as earlier and widespread use of androgen deprivation therapy. Specifically, Lu-Yao and colleagues (158) compared prostate-cancer-specific mortality between two population-based cohorts of men with prostate cancer from King County, Washington, and the state of Connecticut. Although PSA utilization rates and treatment patterns differed widely between the two populations, prostate cancer mortality was comparable, implying that more-intensive screening was not associated with the drop in mortality. Formal, randomized, clinical-trial data on PSA screening in the general population are anticipated from the European Randomized Screening for Prostate Cancer Trial and the Prostate, Lung, Colorectal, and Ovary cancer trial within the next several years. These data should provide a better understanding of the value of prostate cancer screening in reducing mortality. When considering epidemiologic data, it is important to recognize the difference between mortality, the deaths in the general population due to the specific disease, and survival, which is limited to the patient cohort with the disease.

Survival rates, median age at diagnosis, and stage at diagnosis have also changed drastically over the past 20 years due to the effects of PSA screening (Table 6). During the intervals 1975–1979 and 1985–1989, 73% of prostate cancer diagnoses were localized or regional. In contrast, during 1995–2001, 91% of diagnoses were localized or regional (Table 7). Across the same three

Table 6. Survival rates for prostate cancer, by race/ethnicity, diagnosis year, stage, and age

	All Males			White Males			Black Males		
	All	< 50	≥ 50	All	< 50	≥ 50	All	< 50	≥ 50
5-Year Survival Rates									
Year of Diagnosis									
1960–1963[a]	…	…	…	50.0	…	…	35.0	…	…
1970–1973[a]	…	…	…	63.0	…	…	55.0	…	…
1974–1976[b]	67.1	71.5	65.5	68.1	73.0	66.4	58.4	60.7	57.0
1977–1979[b]	71.1	75.8	69.4	72.2	77.5	70.3	62.6	64.4	61.7
1980–1982[b]	73.4	76.4	72.3	74.5	78.0	73.3	64.8	66.7	63.8
1983–1985[b]	74.8	75.7	74.5	76.2	77.5	75.8	63.9	64.6	63.5
1986–1988[b]	81.2	81.3	81.2	82.7	83.1	82.6	69.3	69.8	69.1
1989–1991[b]	90.7	90.2	90.8	92.0	91.3	92.2	80.8	82.3	80.2
1992–1994[b]	97.3	96.3	97.7	98.1	97.0	98.6	92.4	93.4	91.9
1995–2000[b]	99.3[c]	99.1	99.7	100[c]	99.5	100	96.0[c]	98.1	95.1c
1995–2000[b]									
All Stages	99.3	99.1	99.7	100	99.5	100	96.0	98.1	95.1
Localized/Regional	100	100	100	100	100	100	100	100	100
Distant	33.5	30.5	34.6	32.7	30.3	33.6	29.0	31.1	28.0
Unstaged	81.4	89.3	79.4	82.8	91.3	80.9	75.5	82.6	72.4
5-Year Survival Rates, 1995–2000[b]									
Age at Diagnosis									
< 45	91.7	…	…	91.3	…	…	95.4	…	…
45–54	97.2	…	…	97.5	…	…	96.8	…	…
55–64	99.7	…	…	100	…	…	98.4	…	…
65–74	100	…	…	100	…	…	98.1	…	…
75+	94.8	…	…	96.5	…	…	87.5	…	…
< 65	99.1	…	…	99.5	…	…	98.1	…	…
65+	99.7	…	…	100	…	…	95.1	…	…

…data unavailable

[a]Rates are based on End Results data from a series of hospital registries and one population-based registry.

[b]Rates are from SEER 9 areas. They are based on data from population-based registries in Connecticut, Puerto Rico, Utah, Iowa, Hawaii, Atlanta, Detroit,Seattle-Puget Sound, and San Francisco-Oakland. Rates are based on follow up of patients into 2001.

[c]The difference in rates between 1974–1976 and 1995–2000 is statistically significant ($p < 0.05$).

SOURCE: Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence-SEER 9 Regs Public-Use (1973–2002), National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2005, based on the November 2004 submission.

Table 7. Stage distribution by race/ethncity for prostate cancer patients, all ages, 1975–79, 1985–89, and 1995–2001

	1975–1979			1985–1989			1995–2001		
	All	White	Black	All	White	Black	All	White	Black
Localized	73%	73%	66%	73%	74%	65%	91%	91%	89%
Regional	0%	0%	0%	0%	0%	0%	0%	0%	0%
Distant	20%	19%	28%	16%	15%	25%	5%	5%	7%
Unstaged	7%	8%	5%	11%	11%	11%	4%	4%	5%

SOURCE: Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence-SEER 9 Regs Public-Use (1973–2002), National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2005, based on the November 2004 submission.

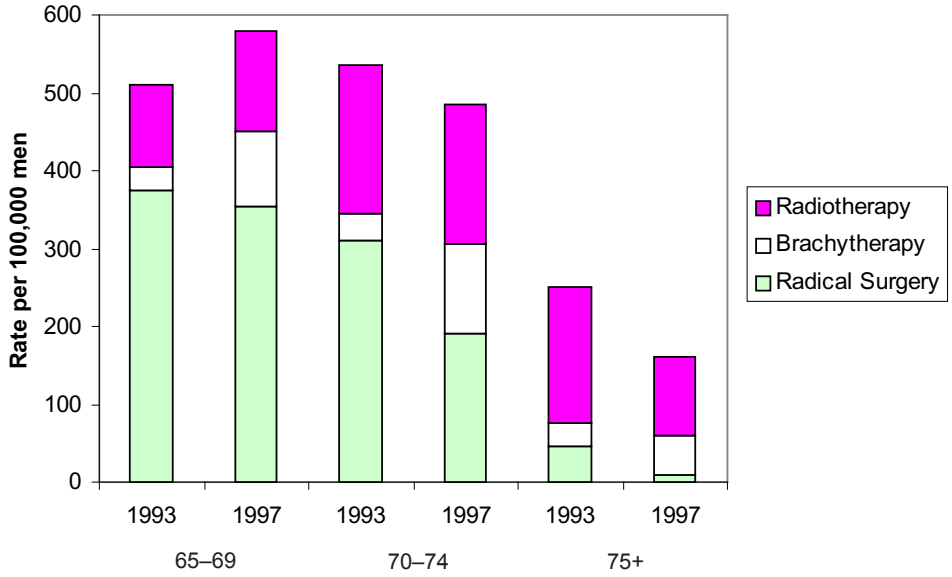

Figure 7. Patterns of treatment use for prostate cancer, 1993–1997.

SOURCE: Adapted from Urology, 58, Bubolz T, Wasson JH, Lu-Yao G, Barry MJ, Treatments for prostate cancer in older men: 1984–1997,Urol, 58: 977–982, Copyright 2001, with permission from Elsevier.

time intervals, the percentage with distant disease at diagnosis decreased from 20% to 16% to 5% (Table 7). This shift in disease stage at diagnosis has been accompanied by an increase in five-year survival rates. Of the men diagnosed with local or regional prostate cancer in 1973, 61% survived 5 years. For men diagnosed in 1981, the survival rate increased to 74%; for those diagnosed in 1989, it rose to 87%; and of those diagnosed in 1995–2000, 100% survived 5 years (155, 159). With PSA screening, men are also being diagnosed at earlier ages. In 1980, the median ages at diagnosis for Caucasian men and African American men were 72 and 70 years, respectively (159). During 1998–2002, the median ages at diagnosis were 68 and 65 years for Caucasian and African American men, respectively (160). These shifts are expected with the introduction of a new screening technology that effectively increases lead-time bias and increases the number of overdetected cases. The key question is whether discovering prostate cancer cases earlier in the disease course will make it possible to alter the natural history of the illness. Further research and additional follow-up will shed more light on this important issue.

TREATMENT

Localized Disease

There are numerous therapeutic options for men with newly diagnosed localized prostate cancer. Unfortunately, there is little level I evidence (i.e., from randomized clinical trials) that one particular therapy is superior to another in terms of survival. In fact, the only adequately sized randomized clinical trial completed to date compared radical surgery to conservative management (watchful waiting) and found that surgery did afford an overall survival advantage, although it required nearly 10 years of follow-up for the difference to become statistically significant (161). The lack of conclusive evidence leads to wide variation in the use of the various therapies and may ultimately impact quality of care. The four most common treatment modalities in localized prostate cancer are radical prostatectomy, external beam radiotherapy, interstitial brachytherapy, and watchful waiting. There is also limited utilization of cryosurgery, proton-beam radiotherapy, and other technologies.

Radical Prostatectomy

Surgery is the most common treatment modality for localized prostate cancer, particularly in younger men. Bubolz et al. (162) reviewed rates of surgery, radiotherapy, and brachytherapy from 1984 to 1997 in a 20% sample of the Medicare part A dataset. As shown in Figure 7, utilization rates for surgery were much higher than the rates for the two other treatment modalities in men aged 65–69. In all three age groups shown in Figure 7, the utilization of interstitial brachytherapy increased from 1993 to 1997; for men aged 70–74, utilization rates for surgery and external beam radiotherapy were similar by 1997. In the oldest age group, surgery rates were much lower, which is to be expected, as available guidelines (163) for prostate cancer state that surgery is not appropriate in men with a life expectancy of less than 10 years.

Utilization rates for radical prostatectomy are notably higher in men younger than 65. Ellison et al. (164), using data from the SEER program to assess utilization rates for radical prostatectomy from 1989 to 1995, found that the rate more than doubled between 1989 and 1992 (from 78 men per 100,000 men to 206 per 100,000), likely due to the introduction of PSA testing and the rapid increase in the number of men newly diagnosed with prostate cancer. The rate then decreased by one-third between 1992 and 1995 (to 146 per 100,000 men). During this time period, as shown in Figure 8, radical prostatectomy rates dropped off significantly in older patients (decreasing 51% in men aged 70–74 and 71% in men 75 or older). However, rates in younger men continued to increase between 1992 and 1995, rising 42% in men 45–49 years of age and 18% in men aged 50–54. These temporal trends mirror changes in detection rates and widespread realization by clinicians that aggressive surgical treatment of localized prostate cancer in elderly men (who have relatively short life expectancies) is not clinically indicated in most cases.

Data from the Healthcare Cost and Utilization Project (HCUP) confirm these findings and provide us with a more recent assessment of trends in

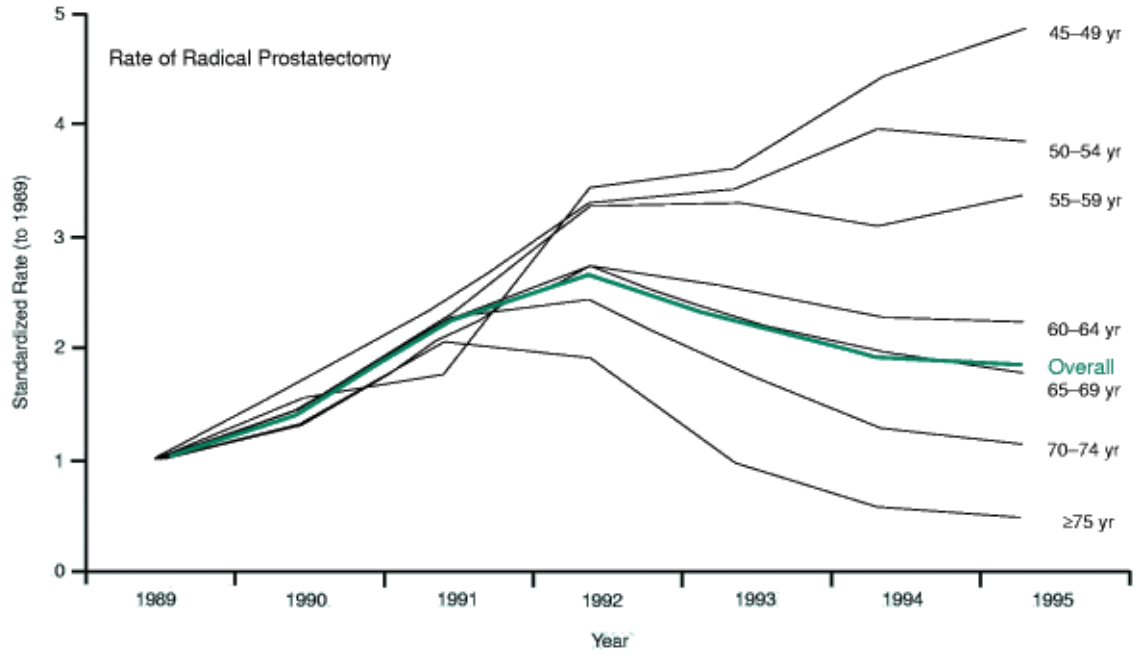

Figure 8. Rate of radical prostatectomy, age-stratified annual rates, standardized to 1989.

SOURCE: Reprinted from Effective Clinical Practice, 2, Ellison LM., Heaney JA, Birkmeyer JD, Trends in the use of radical prostatectomy for treatment of prostate cancer, 228–233, Copyright 1999, with permission from American College of Physicians.

Table 8. Radical prostatectomy in men hospitalized for a primary diagnosis of prostate cancer, count, rate[a] (95% CI), rate per 100,000 prostate cancer hosptializations[b] (95% CI)

	1994					1996				
	Count		Rate	Rate per 100,000 hospitalizations for primary diagnosis of Prostate Cancer		Count		Rate	Rate per 100,000 hospitalizations for primary diagnosis of Prostate Cancer	
Total[c]	58,254	128	(128–128)	50,553	(50,440–50,666)	61,952	127	(126–127)	57,851	(57,710–57,992)
Age										
40–54	5,467	23	(23–24)	4,744	(4,721–4,768)	7,573	29	(29–30)	7,072	(7,039–7,104)
55–64	22,683	236	(235–237)	19,684	(19,621–19,749)	25,288	254	(254–255)	23,614	(23,552–23,676)
65–74	28,444	361	(360–362)	24,684	(24,612–24,756)	27,861	341	(340–342)	26,017	(25,938–26,095)
75–84	1,649	43	(42–45)	1,431	(1,395–1,467)	1,220	29	(28–30)	1,139	(1,086–1,193)
85+	*	*		*		*	*		*	
Race/ethnicity										
White	39,405	107	(106–107)	34,196	(34,103–34,288)	42,773	108	(108–109)	39,942	(39,828–40,056)
Black	4,218	105	(102–103)	3,660	(3,640–3,680))	5,188	116	(116–116)	4,845	(4,832–4,857)
Hispanic	1,529	50	(50–51)	1,327	(1,313–1,342	1,626	20	(49–50)	1,518	(1,503–1,533)
Region										
Midwest	14,167	133	(132–134)	12,294	(12,233–12,357)	16,212	139	(138–139)	15,139	(15,092–15,187)
Northeast	9,287	96	(95–96)	8,059	(8,014–8,104)	12,237	124	(124–125)	11,427	(11,384–11,470)
South	23,509	153	(152–153)	20,401	(20,317–20,485)	23,450	137	(136–137)	21,898	(21,793–22,002)
West	11,291	116	(115–116)	9,798	(9,766–9,831)	10,052	98	(98–99)	9,387	(9,317–9,458)
MSA										
Rural	6,255	50	50 (50–51)	5,428	(5,401–5,456)	5,898	50	(49–50)	5,508	(5,455–5,559)
Urban	51,768	157	(156–157)	44,924	(44,814–45,034)	55,883	151	(151–151)	52,184	(52,054–52,314)

	1998					2000				
	Count		Rate	Rate per 100,000 hospitalizations for primary diagnosis of Prostate Cancer		Count		Rate	Rate per 100,000 hospitalizations for primary diagnosis of Prostate Cancer	
Total[c]	50,943	99	(99–99)	57,861	(57,744–57,978)	58,191	108	(108–108)	61,949	(61,825–62,073)
Age										
40–54	7,439	27	(27–27)	8,449	(8,416–8,483)	10,198	35	(35–35)	10,856	(10,821–10,892)
55–64	21,267	201	(200–201)	24,155	(24,090–24,218)	26,135	234	(234–235)	27,822	(27,755–27,888)
65–74	21,161	263	(262–264)	24,034	(23,959–24,109)	20,815	259	(258–260)	22,159	(22,076–22,242)
75–84	1,076	24	(23–25)	1,222	(1,176–1,270)	1,026	21	(20–22)	1,092	(1,045–1,139)
85+	*	*		*		*	*		*	
Race/ethnicity										
White	32,845	80	(80–81)	37,305	(37,211–37,399)	35,009	82	(82–82)	37,269	(37,177–37,362)
Black	4,307	90	(89–90)	4,892	(4,859–4,925)	4,784	94	(93–94)	5,093	(5,065–5,121)
Hispanic	2,117	55	(55–56)	2,404	(2,383–2,426)	2,210	55	(54–55)	2,353	(2,329–2,377)
Region										
Midwest	11,749	99	(98–99)	13,344	(13,285–13,403)	13,853	110	(110–111)	14,747	(14,698–14,796)
Northeast	10,994	108	(107–108)	12,487	(12,427–12,548)	12,924	123	(123–124)	13,758	(13,696–13,821)
South	17,307	95	(95–95)	19,657	(19,582–19,731)	20,758	108	(108–108)	22,098	(22,016–22,180)
West	10,893	98	(97–98)	12,372	(12,337–12,408)	10,657	92	(92–92)	11,345	(11,298–11,392)
MSA										
Rural	5,183	42	(42–42)	5,887	(5,855–5,919)	5,888	45	(45–46)	6,268	(6,237–6,298)
Urban	45,599	117	(116–117)	51,791	(51,678–51,904)	52,245	128	(127–128)	55,615	(55,498–55,737)

*Figure does not meet standard for reliability or precision.

MSA, metropolitan statistical area.

[a]Rate per 100,000 is based on 1994–2000 population estimates from Current Population Survey (CPS), CPS Utilities, Unicon Research Corporation, for relevant demographic categories of US adult male 40+ civilian non-institutionalized population.

[b]Rate per 100,000 male 40+ visits with radical prostatectomy performed is based on estimated number of visits for prostate cancer in HCUP_NIS 1994–2000.

[c]Persons of other races, missing or unavailable race and ethnicity, and missing MSA are included in the totals.

NOTE:Counts may not sum to totals due to rounding.

SOURCE: Healthcare Cost and Utilization Project Nationwide Inpatient Sample, 1994, 1996, 1998, 2000.

radical prostatectomy. As shown in Table 8, radical prostatectomy rates were relatively stable in 1994 and 1996 (128 and 127, respectively, per 100,000 men over the age of 40), but they decreased in 1998 to 99 per 100,000 and then increased again in 2000 to 108 per 100,000. One could hypothesize that the decline in 1998 was due to the increasing use of brachytherapy (which was "reintroduced" in the mid-1990s), and the moderate increase in 2000 was related to increased awareness that brachytherapy monotherapy was best reserved for men with low-risk disease (i.e., Gleason 6 or less and PSA <10 ng/ml) (165). Similar declines were seen in the Veterans Affairs (VA) population (Table 9) between 1998 and 2003, although the rates seemed to stabilize slightly later in this population. This may be related to the fact that brachytherapy was not as readily available at VA facilities. Importantly, when prostatectomy rates were stratified by age, rates dropped consistently in older patients (over age 65), while there were consistent increases in the rates for younger patients (40–54 years of age). In summary, there have been significant changes in the utilization of radical prostatectomy in the last 15 years, with the overall rate of use decreasing in older men but increasing in younger men. There is also considerable ethnic and geographic variation, which is to be expected in the absence of conclusive level I evidence to guide therapy.

Table 9. VA users with radical prostatectomy for prostate cancer patients,1998–2003, count, age-adjusted rate[a]

	1998		1999		2000		2001		2002		2003	
	Count	Rate	Count	Rate	Count	Rate	Count	Rate	Count	Rate	Count	Rate
Total	1,508	1,539	1,625	1,491	1,815	1,467	1,880	1,254	2,005	1,154	2,168	1,132
Age	1,705	1,378	1,742	1,408			1,633	1,320	1,547	1,251	1,498	1,211
40–44	7	2,525	12	4,808	8	3,089	9	3,524	24	9,137	14	5,236
45–54	244	5,431	279	6,224	322	7,173	313	6,977	332	7,397	330	7,349
55–64	656	4,435	743	5,025	800	5,409	719	4,864	686	4,639	684	4,626
65–74	764	1,480	681	1,319	671	1,301	577	1,118	491	952	459	889
75–84	32	66	25	53	14	29	14	29	14	29	12	24
85+	3	68	1	29	0	0	1	18	0	0	0	0
Gender												
Male	1,508	1,539	1,625	1,491	1,815	1,467	1,880	1,254	2,005	1,154	2,168	1,132
Female	0	0	0	0	0	0	0	0	0	0	0	0
Race/ethnicity												
White	1,037	1,463	1,079	1,330	1,184	1,260	1,248	1,070	1,303	958	1,089	742
Black	392	1,827	460	2,016	498	2,084	490	1,912	422	1,551	390	1,384
Hispanic	44	2,013	32	1,413	42	1,730	37	1,376	70	2,392	48	1,546
Other	17	1,595	23	1,973	23	1,801	21	1,472	25	1,529	16	920
Unknown	18	755	31	1,935	68	3,128	84	2,368	185	3,111	625	5,377
Insurance Status												
No insurance/ self-pay	1,123	1,980	1,269	2,045	1,338	2,153	1,315	1,983	1,368	1,934	1,482	2,120
Medicare	94	621	119	510	198	504	264	432	307	390	355	368
Medicaid	1	1,724	0	0	3	5,357	3	2,290	3	1,493	3	1,282
Private Insurance/HMO	284	1,102	229	984	265	1,219	272	1,257	312	1,330	313	1,301
Other Insurance	6	2,390	8	2,540	11	2,296	26	4,586	14	2,226	15	1,935
Unknown	0	0	0	0	0	0	0	0	1	0	0	0
Region												
Eastern	174	1,159	194	1,107	196	941	183	655	236	695	267	718
Central	265	1,671	304	1,670	352	1,736	337	1,332	423	1,227	478	1,174
Southern	614	1,579	660	1,543	705	1,451	821	1,377	821	1,193	897	1,162
Western	455	1,613	467	1,532	562	1,652	539	1,457	525	1,439	526	1,444

[a]Rate per 100,000 veterans using the VA system, age-adjusted to 2000.
SOURCE: Inpatient and Outpatient Files, VA Information Resource Center (VIReC), Veterans Affairs Health Services Research and Development Service Resource Center.

Table 10. Distribution (%) of treatments for prostate cancer, by year of diagnosis

	1992 (N=103,979)	1995 (N=72,337)
Radical prostatectomy	31.6	34.1
External beam radiation	30.1	26.3
Radiation implant	1.4	2.2
Hormone	12.0	11.7
Other treatment	4.9	4.1
No treatment	20.0	21.6

SOURCE: Reprinted from Cancer, 83, Mettlin CJ, Murphy GP, Rosenthal DS, Menck HR, The National Cancer Data Base report on prostate carcinoma after the peak in incidence rates in the U.S., 1,679–1,684, Copyright 1998, with permission from Wiley.

External Beam Radiation Therapy

Radiation therapy can be delivered to the prostate for cancer control and cure through a number of different modalities, including external beam radiation (in the form of three-dimensional conformal beam therapy or intensity-modulated radiotherapy), permanent implantation of radioactive seeds (interstitial brachytherapy), and temporary transperineal implantation of radiation sources to deliver higher treatment doses (so-called high dose rate, HDR). These modalities can be used alone or in combination. There is little epidemiologic data on HDR treatment or other forms of radiation, such as proton-beam therapy, however, so we will not address these relatively uncommon modalities.

External beam radiotherapy (EBRT) is the most commonly used form of radiotherapy for prostate cancer. A review of the Medicare part A dataset by Bubolz et al. (145, 162), shown in Figure 7, documented that EBRT rates were relatively stable for all prostate cancer patients, except those over age 75, from 1993 to 1997. In the older patients, EBRT utilization dropped, reflecting the general realization by providers that many of these patients did not require any treatment, given their relatively short life expectancy.

While the data from the Medicare population are informative, most Medicare recipients are over the age of 65 and may not be representative of the entire population of men with prostate cancer, since the average age at diagnosis has dropped in the past decade. Therefore, it is helpful to review information from other data sources that include younger men. Mettlin and colleagues (166) reviewed data from

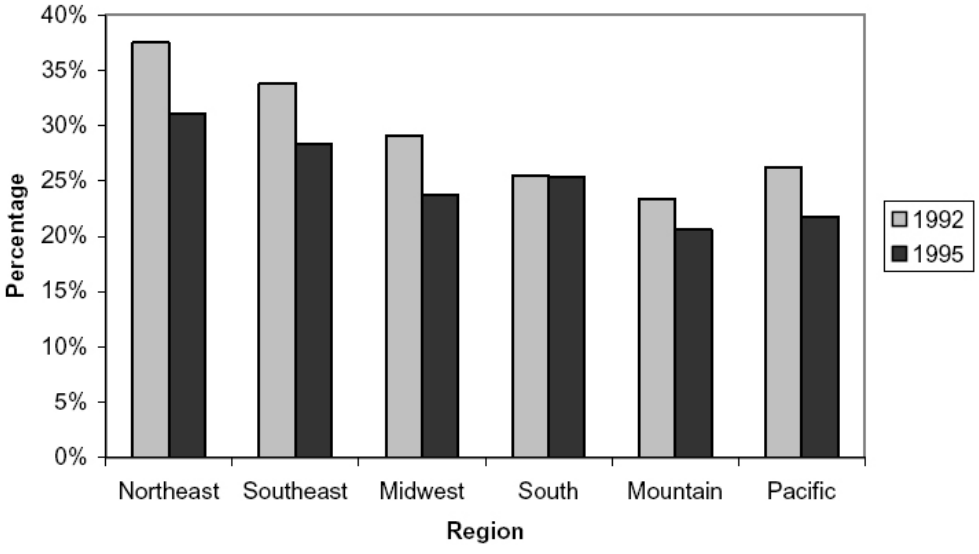

Figure 9. Proportions of patients treated for prostate cancer by external beam radiation therapy, 1992–1995, by region.

SOURCE: Adapted from Cancer, 83, Mettlin CJ, Murphy GP, Rosenthal DS, Menck HR, The National Cancer Data Base report on prostate carcinoma after the peak in incidence rates in the U.S., 1,679–1,684, Copyright 1998, with permission from Wiley.

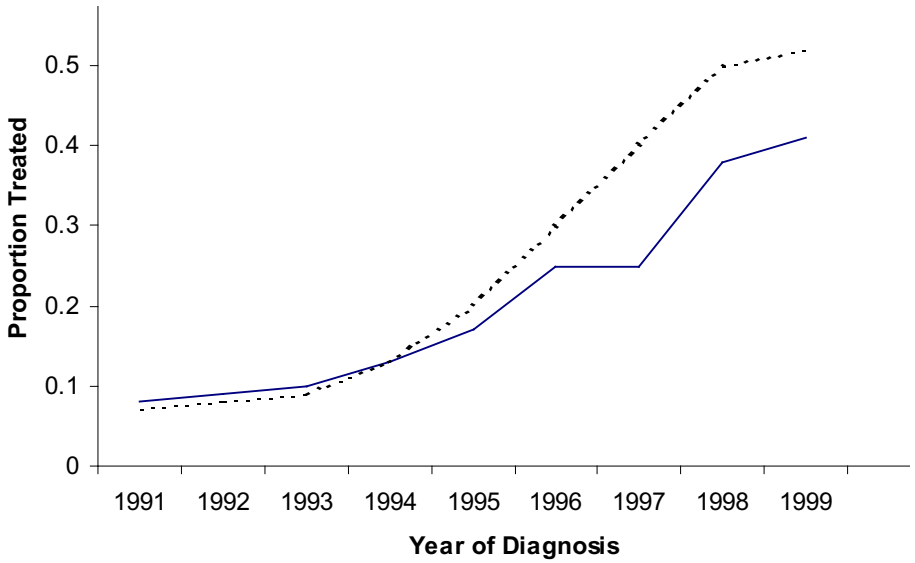

Figure 10. Trends in androgen deprivation therapy (ADT) with external beam radiation therapy (EBRT) at diagnosis for prostate cancer patients, age-standardized, in African American (solid line) and Caucasian (dashed line) men.

SOURCE: Adapted from Urology, 64, Zeliadt SB, Potosky AL, Etzioni R, Ramsey SD, Penson DF. Racial disparity in primary and adjuvant treatment for nonmetastatic prostate cancer: SEER-Medicare trends 1991 to 1999, 1,171–1,176, Copyright 2004, with permission from Elsevier.

the American College of Surgeons National Cancer Database (NCDB), which includes information from 1,114 hospitals in the United States. As shown in Table 10, 30% of patients diagnosed in 1992 and 26% of those in 1995 received EBRT as treatment for prostate cancer. This decrease in the use of EBRT was accompanied by an increase in the use of radical prostatectomy. As shown in Figure 9, there was considerable geographic variation in the use of EBRT. It was used more commonly in the Northeast, where 31% of patients received EBRT in 1995; it was used least commonly in the Pacific region (for only 22% of patients).

In patients of all ages, EBRT was often accompanied by the use of androgen ablation therapy, Zeliadt and colleagues (167) studied the use of adjuvant hormone ablation therapy with EBRT in the SEER-Medicare dataset and found that the use of this combined therapy increased steadily in the past decade. As shown in Figure 10, approximately 40% of African American and 50% of Caucasian men in the SEER-Medicare dataset who received EBRT had adjuvant hormone ablation therapy. Although this practice is supported by level I evidence in intermediate- and high-risk patients (168, 169), there are no data to support its use in low-risk patients. Given the increasing number of patients presenting with low-risk disease (6), it is likely that increasing numbers of them are receiving adjuvant hormone ablation, although there are currently no data to support this practice.

Interstitial Brachytherapy

Permanent radioactive seed implantation was originally described in the 1970s. The technique was performed using an open surgical approach, but it was associated with a high complication rate and fell out of favor. With advances in ultrasonography and computed tomography, interstitial brachytherapy (IB) performed using a transperineal approach gained popularity in the mid 1990s. Data from the NCDB document that while the overall proportion of prostate cancer patients treated with IB was small, it increased steadily throughout the 1990s (170). As shown in Figure 11, the proportion of stage I patients treated with IB increased from 2.0% in 1992

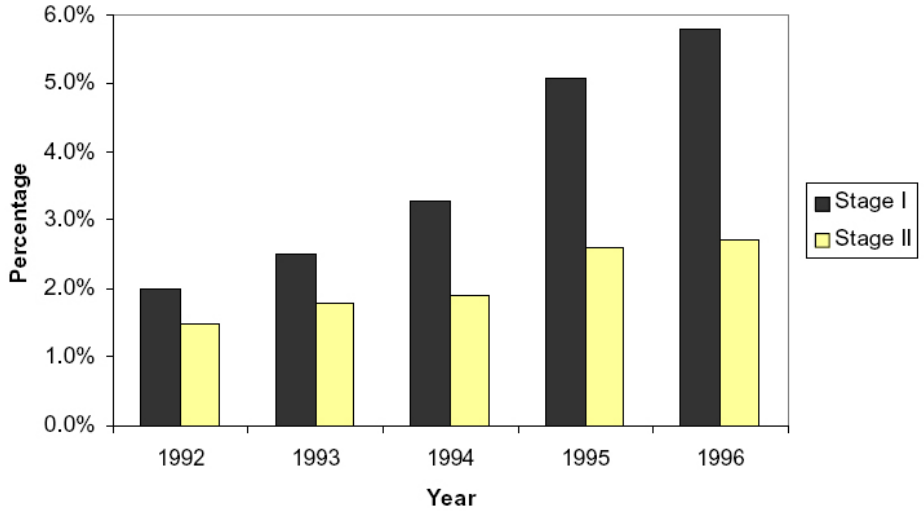

Figure 11. Proportions of 89,060 American Joint Committee on Cancer Stage I and 185,407 Stage II prostate cancer patients treated by radiation implant, by year.

Source: Adapted from Cancer, 86, Mettlin CJ, Murphy GP, McDonald CJ, Menck HR, The National Cancer Data base Report on increased use of brachytherapy for the treatment of patients with prostate carcinoma in the U.S., 1,877–1,882, Copyright 1999, with permission from Wiley.

to 5.8% in 1996, and the proportion of stage II patients increased from 1.5% in 1992 to 2.7% in 1996. It is likely that a number of generally recognized high-volume centers were driving this trend, as is reflected in the geographic variation in utilization shown in Figure 12. Enthusiasm for IB may be declining, however, as the treatment often must be accompanied by a boost of external beam radiotherapy or adjuvant hormone therapy. Many patients electing IB cite the lack of sexual side effects and the short time away from work as reasons for choosing this treatment (171), but if IB must be combined with other treatment modalities, these advantages may be lost. This underscores the need for more data on outcomes following IB and treatment decision making in prostate cancer.

Watchful Waiting/Conservative Management

It is clear that PSA screening has led to an increase in the number of "overdetected" prostate cancers (172). Some patients likely do not require any treatment, as the disease will not progress quickly enough to be clinically meaningful. The challenge for providers is to determine which patients have indolent disease and which require therapy. A population-based study of men in Connecticut who initially elected conservative management for prostate cancer in the 1970s indicated that those with lower Gleason scores (6 or less) and older men are much less likely to die of prostate cancer than of other unrelated causes (152). Clearly, these data and others (173) document that watchful waiting is a reasonable treatment option for some men with prostate cancer.

From an epidemiologic perspective, it is difficult to estimate accurately the number of men with prostate cancer who are treated with conservative management. In men with suspected prostate cancer and other comorbid conditions, doctors often do not aggressively pursue the diagnosis of prostate cancer, because they would not actively treat the malignancy if the diagnosis were made. Therefore, any estimates of the use of watchful waiting are likely to underestimate true utilization. In addition, many patients who initially elect watchful waiting have difficulty with the psychological burden of a cancer diagnosis and later opt for aggressive therapy, although it may not be clinically indicated. This can lead to differing definitions of conservative management in different publications.

Zeliadt and colleagues (167) examined the use of conservative management in men with localized

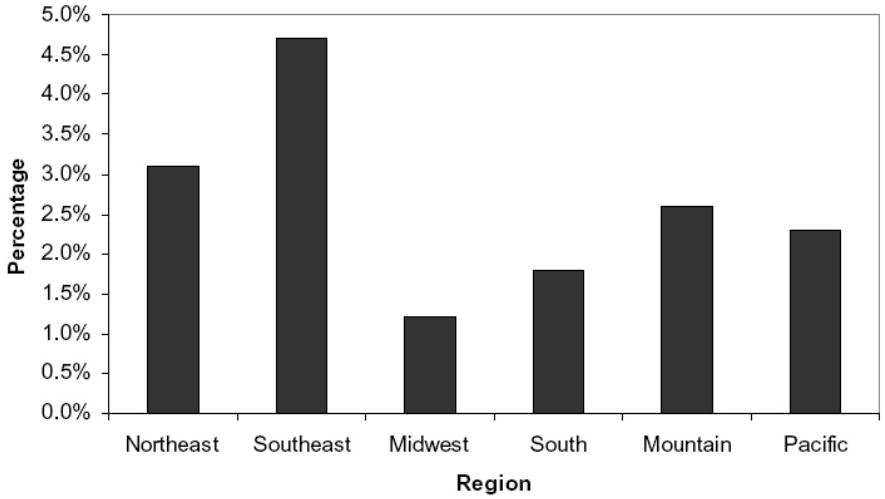

Figure 12. Proportion of 274,188 American Joint Committee on Cancer Stage I and II prostate cancer patients treated with brachytherapy, by region, 1992–1996.

SOURCE: Adapted from Cancer, 86, Mettlin CJ, Murphy GP, McDonald CJ, Menck HR, The National Cancer Data base Report on increased use of brachytherapy for the treatment of patients with prostate carcinoma in the U.S., 1,877–1,882, Copyright 1999, with permission from Wiley.

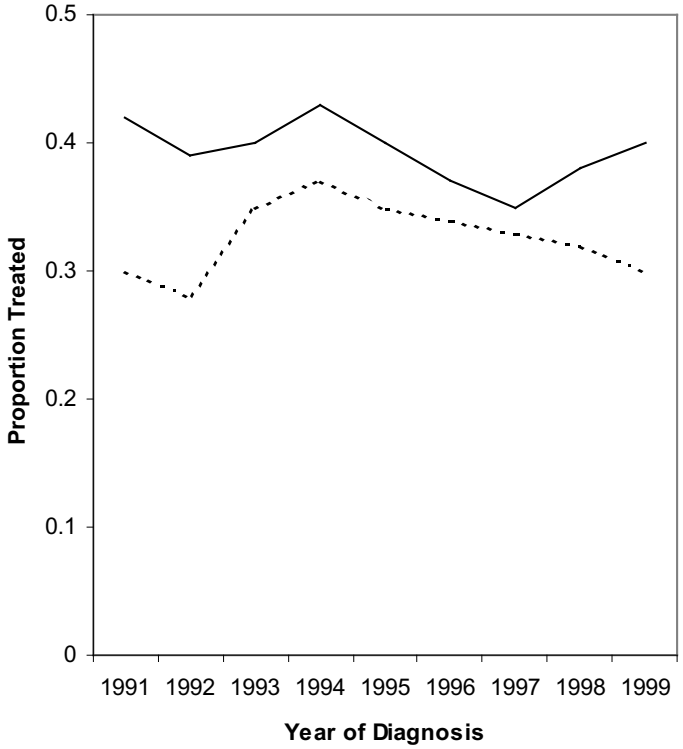

Figure 13. Proportion of men with prostate cancer selecting conservative management, age-standardized, in African American (solid line) and Caucasian (dashed line) men.

SOURCE: Adapted from Urology, 64, Zeliadt SB, Potosky AL, Etzioni R, Ramsey SD, Penson DF. Racial disparity in primary and adjuvant treatment for nonmetastatic prostate cancer: SEER-Medicare trends 1991 to 1999, 1,171–1,176, Copyright 2004, with permission from Elsevier.

prostate cancer in the SEER-Medicare dataset. They defined conservative management as either no treatment or treatment with primary hormone ablation therapy. As shown in Figure 13, 35–44% of African American men with localized prostate cancer and 27–36% of Caucasian men received conservative management. Within this group, roughly 30–40% received some form of hormone ablation therapy, while the remaining 60–70% received no other therapy. It is worth noting that there was considerable racial/ethnic variation in utilization rates, although there is no clinical evidence to support these differences. In addition, numerous studies have noted racial/ethnic differences in PSA surveillance among men electing watchful waiting or aggressive therapies (167, 174). However, as noted earlier, the SEER-Medicare dataset comprises primarily patients over the age of 65 and may not be representative of the general population of men with localized prostate cancer. Nevertheless, the data underscore the need for additional research in the epidemiology of conservative management of prostate cancer, with particular focus on racial disparities in access to and quality of care.

Metastatic Prostate Cancer

The cornerstone of treatment for advanced prostate cancer is hormone ablation therapy. Hormone ablation can be achieved with a number of medications that inhibit the production of or block the effect of testosterone. Alternatively, testosterone production can be halted by the surgical removal of the testicles (orchiectomy). In 1994, the total Medicare expenditure for medical androgen suppression therapy in the treatment of prostate cancer was $477,851,000, which was 34% of the total Medicare expenditure for the disease that year (175). As shown in Figure 14, the use of such medications increased greatly in the 1990s, contributing to higher Medicare expenditures for treatment of the disease. To some degree, the increasing use of hormone ablation therapy may be associated with the fact that in the past it was a fairly lucrative practice for healthcare providers.

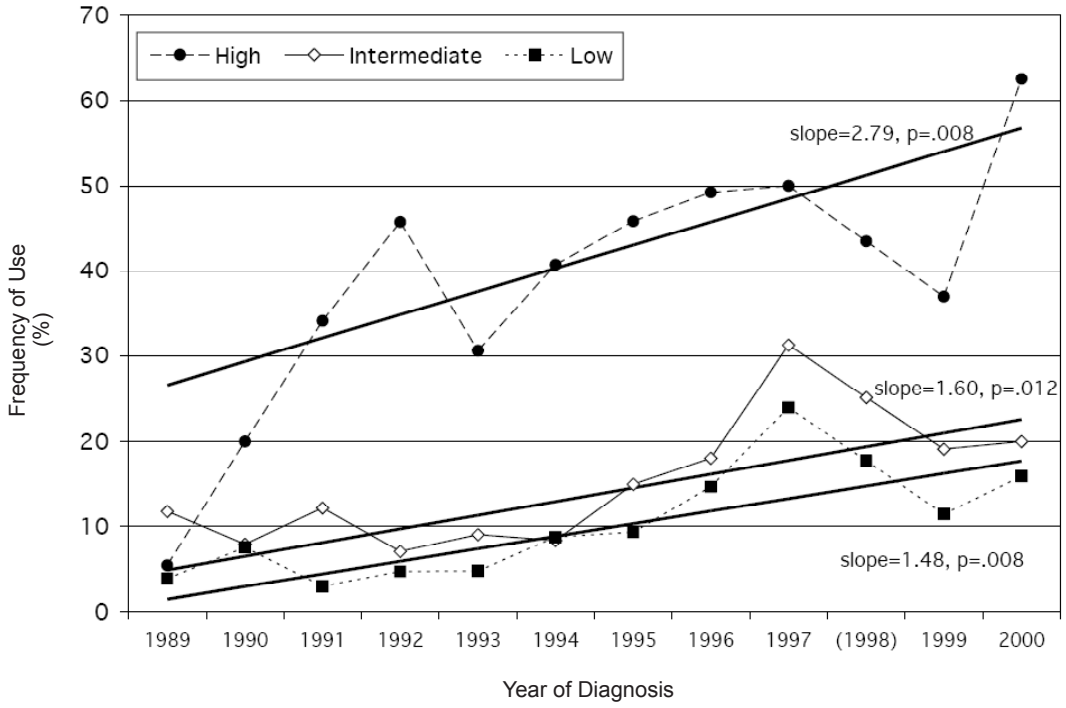

Figure 14. Time trends in the use of primary hormonal ablation therapy, by risk group.

SOURCE: Reprinted from Cooperberg MR, Grossfeld GD, Lubeck DP, Carroll PR. National practice patterns and time trends in androgen ablation for localized prostate cancer. Journal of the National Cancer Institute, 2003, 95(13):981–989, by permission of Oxford University Press.

Table 11. Hormonal therapy for men with prostate cancer, age-adjusted rate[a]

	1999			2000			2001		
	Count	Rate		Count	Rate		Count	Rate	
Total	15,243	13,985	(13,763–14,207)	16,918	13,674	(13,468–13,880)	19,099	12,744	(12,563–12,924)
Age	17,433	14,090	(13,881-14,300)				15,644	12,645	(12,447–12,843)
40–44	2	641	(0–1,529)	11	4,247	(1,737–6,757)	11	4,405	(1,675–7,136)
45–54	320	7,140	(6,337–7,942)	317	7,062	(6,284–7,839)	317	7,055	(6,328–7,782)
55–64	1,575	10,651	(10,109–11,192)	1,501	10,149	(9,636–10,663)	1,420	9,599	(9,133–10,065)
65–74	7,241	14,037	(13,699–14,376)	6,930	13,434	(13,118–13,750)	6,232	12,080	(11,801–12,359)
75–84	7,634	15,798	(15,408–16,188)	7,468	15,454	(15,104–15,805)	6,959	14,400	(14,102–14,699)
85+	660	15,446	(14,141–16,752)	691	16,160	(14,955–17,365)	706	16,516	(15,454–17,577)
Race/ethnicity									
White	10,487	12,944	(12,696–13,191)	11,880	12,682	(12,454–12,910)	13,609	11,724	(11,527–11,921)
Black	4,209	18,490	(17,931–19,048)	4,364	18,327	(17,783–18,871)	4,649	18,244	(17,719–18,768)
Hispanic	218	9,499	(8,238–10,760)	281	11,317	(9,994–12,640)	319	11,520	(10,256–12,785)
Other	173	15,017	(12,780–17,255)	191	15,317	(13,145–17,489)	200	14,378	(12,385–16,371)
Unknown	156	8,844	(7,456–10,231)	202	8,074	(6,960–9,187)	322	7,761	(6,913–8,609)
Region									
Eastern	1,946	11,105	(10,611–11,598)	2,136	10,256	(9,821–10,691)	2,575	9,213	(8,857–9,569)
Central	2,869	15,758	(15,181–16,334)	3,137	15,469	(14,928–16,011)	3,653	14,443	(13,974–14,911)
Southern	6,251	14,614	(14,251–14,976)	7,036	14,479	(14,141–14,817)	8,034	13,474	(13,180–13,769)
Western	4,177	13,700	(13,284–14,115)	4,609	13,546	(13,155–13,937)	4,837	13,072	(12,703–13,440)

	2002			2003		
	Count	Rate		Count	Rate	
Total	21,106	12,147	(11,983–12,311)	21,472	11,212	(11,062-11,362)
Age	14,803	11,965	(11,722–12,157)	13,563	10,963	(10,778-11,147)
40–44	14	5,584	(2,284–8,884)	9	3,665	(950-6,380)
45–54	323	7,201	(6,500–7,903)	279	6,208	(5,555-6,860)
55–64	1,327	8,971	(8,555–9,387)	1,180	7,980	(7,623-8,337)
65–74	5,732	11,111	(10,856–11,366)	5,100	9,887	(9,653-10,122)
75–84	6,725	13,916	(13,649–14,183)	6,313	13,065	(12,819-13,310)
85+	682	15,950	(15,039–16,860)	681	15,928	(15,119-16,736)
Race/ethnicity						
White	14,713	11,283	(11,101-11,466)	13,554	10,504	(10,327–10,681)
Black	4,840	18,110	(17,600-186,20)	4,675	17,382	(16,884–17,881)
Hispanic	369	12,142	(10,903-13,381)	365	11,471	(10,294–12,648)
Other	235	15,280	(13,326-17,233)	237	15,430	(13,465–17,394)
Unknown	949	7,874	(7,373-8,375)	2,641	8,557	(8,231–8,884)
Region						
Eastern	2,970	8,749	(8,435-9,064)	2,991	8,046	(7,757–8,334)
Central	4,526	13,126	(12,743-13,508)	5,061	12,434	(12,091–12,776)
Southern	8,932	12,977	(12,708-13,246)	9,112	11,802	(11,559–12,044)
Western	4,678	12,819	(12,452-13,186)	4,308	11,827	(11,474–12,181)

[a]Rate per 100,000 veterans using the VA system, age-adjusted to 2000.

SOURCE: Pharmacy Benefits Management Version 3.0 (PBM), Department of Veterans Affairs.

Table 12. Inpatient hospital stays by male Medicare beneficiaries with prostate cancer listed as primary diagnosis, counta, rateb (95% CI), age-adjusted ratec

	1992			1995			1998			2001		
	Count	Rate	Age-Adjusted Rate	Count	Rate	Age-Adjusted Rate	Count	Rate	Age-Adjusted Rate	Count	Rate	Age-Adjusted Rate
Total[d]	87,540	588 (570–605)		50,620	333 (320–346)		38,840	268 (256–280)		37,840	245 (234–256)	
Total < 65	1,720	55 (43–67)		1,740	51 (40–61)		1,460	42 (33–52)		1,860	49 (39–59)	
Total 65+	85,820	729 (707–751)	729	48,880	415 (399–432)	410	37,380	339 (323–354)	337	35,980	310 (295–324)	309
Age												
65–69	27,620	679 (643–714)		17,260	448 (418–478)		12,680	376 (346–405)		12,340	349 (321–376)	
70–74	27,720	853 (808–897)		15,240	457 (425–489)		11,500	377 (346–408)		10,520	342 (313–371)	
75–79	16,580	732 (683–782)		7,360	324 (291–358)		5,700	250 (221–279)		5,820	237 (210–264)	
80–84	8,720	666 (603–728)		5,300	381 (336–427)		3,800	276 (237–315)		3,540	237 (202–271)	
85–89	3,780	634 (544–724)		2,340	367 (301–434)		2,580	397 (328–465)		2,500	346 (285–406)	
90–94	1,200	592 (443–742)		1,060	501 (367–636)		920	428 (304–551)		1,040	449 (327–571)	
95–97	160	396 (121–671)		200	531 (202–859)		180	455 (159–750)		140	364 (94–635)	
98+	40	105 (0–250)		120	271 (54–488)		20	42 (0–123)		80	147 (3.7–291)	
Race/ethnicity												
White	74,280	591 (572–610)	592	42,800	329 (315–343)	330	32,200	263 (250–276)	263	31,400	240 (228–252)	240
Black	8,600	674 (611–737)	646	5,860	423 (375–472)	412	4,880	366 (320–411)	355	4,680	319 (278–360)	315
Asian	…	…	…	100	137 (16–258)	137	160	117 (36–198)	131	140	68 (18–119)	68
Hispanic	…	…	…	560	282 (178–386)	282	740	220 (150–291)	215	640	170 (111–229)	160
N. American Native	…	…	…	40	199 (0–472)	298	60	215 (0–458)	143	100	300 (36–565)	240
Region												
Midwest	20,840	562 (528–596)	566	11,700	304 (279–328)	300	10,220	276 (252–300)	279	9,620	253 (231–276)	259
Northeast	18,620	587 (550–625)	573	11,760	370 (340–400)	360	7,420	267 (240–294)	270	6,720	230 (205–255)	221
South	32,260	616 (586–646)	616	19,360	353 (331–375)	357	14,960	279 (259–299)	277	15,180	261 (243–280)	262
West	14,720	609 (566–653)	622	7,200	310 (278–343)	322	5,700	255 (225–284)	251	5,660	229 (202–255)	231

…data not available.

[a]Unweighted counts multiplied by 20 to arrive at values in the table.

[b]Rate per 100,000 male Medicare beneficiaries in the same demographic stratum.

[c]Age-adjusted to the US Census-derived age distribution of the year under analysis.

[d]Persons of other races, unknown race and ethnicity, and other region are included in the totals.

NOTE: Counts less than 600 should be interpreted with caution.

SOURCE: Centers for Medicare and Medicaid Services, MedPAR Files, 1992, 1995, 1998, 2001.

Table 13. Most common procedures during inpatient hospital stays for prostate cancer listed as primary diagnosis, count, rate[a] (95% CI), rate per visits[b] (95% CI)

	1994			1996		
	Count	Rate per 100,000 population	Rate per 100,000 hospitalizations for Prostate Cancer	Count	Rate per 100,000 population	Rate per 100,000 hospitalizations for Prostate Cancer
Radical Prostatectomy	58,254	128 (128–128)	50,553 (50,440–50,666)	61,952	127 (126–127)	57,851 (57,710–57,992)
Regional Lymph Node Excision	29,677	65 (63–67)	25,753 (24,880–26,627)	33,667	69 (65–73)	31,439 (29,549–33,329)
Transurethral Prostatectomy[c]	30,822	68 (65–70)	26,747 (25,810–27,684)	...	...	...
Other Transurethral Prostatectomy	...	...	...	23,045	47 (45–49)	21,520 (20,664–22,376)

	1998			2000		
	Count	Rate per 100,000 population	Rate per 100,000 hospitalizations for Prostate Cancer	Count	Rate per 100,000 population	Rate per 100,000 hospitalizations for Prostate Cancer
Radical Prostatectomy	50,943	99 (99–99)	57,861 (57,744–57,978)	58,191	108 (108–109)	61,949 (61,825–62,073)
Regional Lymph Node Excision	26,458	51 (45–58)	30,050 (26,074–34,027)	28,487	53 (50–55)	30,326 (28,946–31,705)
Transurethral Prostatectomy[c]	...	...	...	...	...	...
Other Transurethral Prostatectomy	18,605	36 (35–38)	21,131 (20,222–22,040)	16,738	31 (30–32)	17,819 (17,035–18,603)

[a]Rate per 100,000 is based on 1994–2000 population estimates from Current Population Survey (CPS), CPS Utilities, Unicon Research Corporation, for relevant demographic categories of U.S. adult male 40+ civilian noninstitutional population.

[b]Rate per 100,000 male 40+ visits is based on estimated number of visits for prostate cancer in HCUP_NIS 1994–2000.

[c]Transurethral prostatectomy only made the top three procedure list in 1994.

SOURCE: Healthcare Cost and Utilization Project Nationwide Inpatient Sample, 1994–2000.

Data from the VA pharmacy-benefits-management dataset indicate that in a closed healthcare system in which there is no financial incentive to use these medications, medical hormone ablation use actually decreased from a peak rate of 13,985 per 100,000 male veterans over the age of 40 with a diagnosis of prostate cancer in 1999 to 11,212 per 100,000 in 2003 (Table 11). It should be noted that there are numerous other possible explanations for the increase in the use of hormone ablation therapy in the 1990s, including patient preference over orchiectomy, increased use as primary therapy for localized disease, and increased use in the adjuvant setting following radiotherapy, although it would be hard for any one of these factors alone to explain the marked increase. It is possible that recent changes in Medicare reimbursement for outpatient administration of chemotherapeutic agents may affect hormone ablation utilization rates, particularly in men with asymptomatic recurrent or metastatic disease.

There are limited options for patients who fail to respond to hormone ablation therapy. Few effective chemotherapeutic agents exist for men with hormone-resistant prostate cancer, and the survival advantage afforded by these drugs is minimal. There is little epidemiologic data on the use of chemotherapeutic agents in the treatment of prostate cancer. Nevertheless, recent data from the Southwest Oncology Group document a clear survival advantage for men with metastatic diseases treated with docetaxel-based therapy (176, 177).

TRENDS IN HEALTHCARE RESOURCE UTILZATION

Inpatient Care

Table 12 shows the total number of inpatient stays by male Medicare beneficiaries with a primary diagnosis of prostate cancer during 1992 and 2001. Almost 86,000 were hospitalized with a primary diagnosis of prostate cancer in 1992. In contrast, fewer than 36,000 had hospital stays in 2001. The age-adjusted rate of inpatient stays declined from 729 per 100,000 to 309 per 100,000 between 1992 and 2001. It is likely that inpatient care utilization rates are related to changes in treatment patterns—specifically, radical prostatectomy rates, since this is the most common inpatient procedure among prostate cancer patients in the HCUP dataset (Table 13). Therefore, the decrease in inpatient hospitalization likely reflects the decline in prostatectomy utilization rates discussed earlier (Figure 8). The decrease in inpatient hospitalization rates also likely reflects the marked lowering of age at diagnosis that resulted from the introduction of PSA screening in the 1990s. As men started being diagnosed at younger ages, treatments that required hospitalization (i.e., surgery) also occurred earlier in life. Hence, fewer men 65 or older (the population eligible for Medicare) were experiencing their initial diagnosis of and treatment for prostate cancer.

Table 14. Inpatient hospital stays for prostate cancer listed as primary diagnosis for 1994–2000 (merged), count, rate[a] (95% CI), annualized rate[b]

	1994–2000			
	Count	4-year Rate		Rate
Total[c]	407,042	815	(780–851)	204
Age				
40–44	1,651	16	(13–19)	4.0
45–54	33,749	211	(189–234)	53
55–64	118,051	1,143	(1,064–1,223)	286
65–74	161,183	2,006	(1,929–2,084)	502
75–84	69,400	1,598	(1,544–1,652)	400
85+	23,009	2,441	(2,338–2,544)	610
Race/ethnicity				
White	260,321	651	(614–687)	163
Black	37,954	821	(769–872)	205
Hispanic	14,584	412	(368–456)	103
Region				
Midwest	96,752	827	(766–887)	207
Northeast	89,190	887	(817–956)	222
South	148,779	851	(772–929)	213
West	72,322	677	(626–728)	169
MSA				
Urban	352,310	939	(893–985)	235
Rural	53,269	429	(397–461)	107

MSA, metropolitan statistical area.

[a]Rate per 100,000 is based on 1994, 1996, 1998, 2000 population estimates from Current Population Survey (CPS), CPS Utilities, Unicon Research Corporation, for relevant demographic categories of US adult male 40+ civilian non-institutionalized population.

[b]Average annualized rate per year.

[c]Persons of other races, missing or unavailable race and ethnicity, and missing MSA are included in the total.

NOTE: Counts may not sum to total due to rounding.

SOURCE: Healthcare Cost and Utilization Project Nationwide Inpatient Sample, 1994, 1996, 1998, 2000.

Table 15. Length of stay (LOS) for primary diagnosis for prostate cancer

	1994				1996			
	Count	LOS (Mean)	LOS (Median)	LOS (Max)	Count	LOS (Mean)	LOS (Median)	LOS (Max)
Total[a]	116,018	5.4	5	216	107,776	4.5	4	1,426
Age								
40–44	265	5.3	4	30	463	4.1	4	8
45–54	6,407	5.1	5	48	8,273	4.1	4	57
55–64	29,746	5.4	5	88	31,054	4.1	4	79
65–74	50,380	5.3	5	191	43,878	4.3	4	231
75–84	22,663	5.3	3	216	18,333	4.8	3	1,233
85+	6,558	6.2	4	70	5,775	7.5	4	1,426
Race/ethnicity								
White	76,077	5.3	5	122	72,557	4.5	4	1,426
Black	10,246	6.5	5	216	10,485	4.8	4	79
Hispanic	3,608	5.6	5	85	3,336	4.9	4	67
Region								
Midwest	27,488	5.4	5	100	26,674	4.3	4	61
Northeast	22,822	6.6	5	216	23,982	4.7	4	112
South	45,639	5.2	5	99	39,419	4.2	4	115
West	20,069	4.4	4	191	17,702	4.9	3	1,426
MSA								
Rural	16,755	5.6	5	191	13,704	4.7	4	57
Urban	98,610	5.4	5	216	93,723	4.4	4	1,426

	1998				2000			
	Count	LOS (Mean)	LOS (Median)	LOS (Max)	Count	LOS (Mean)	LOS (Median)	LOS (Max)
Total[a]	88,628	4	3	162	94,620	3.7	3	133
Age								
40–44	373	3.9	3	19	550	3.1	3	8
45–54	8,060	3.7	3	84	11,009	3.4	3	79
55–64	25,814	3.7	3	111	31,437	3.4	3	72
65–74	34,142	3.8	3	81	32,783	3.6	3	118
75–84	14,958	4.2	3	65	13,446	4.4	3	133
85+	5,281	5.7	3	162	5,394	5.2	3	111
Race/ethnicity								
White	55,679	3.8	3	162	56,009	3.6	3	118
Black	8,540	4.6	3	84	8,683	4.8	3	133
Hispanic	3,825	4.8	4	65	3,814	4.5	3	104
Region								
Midwest	20,405	4.0	3	73	22,184	3.7	3	111
Northeast	19,941	4.3	3	81	22,445	4.2	3	133
South	31,024	3.8	3	111	32,697	3.7	3	113
West	17,258	3.7	3	162	17,293	3.3	3	79
MSA								
Rural	11,408	4.1	3	162	11,402	3.9	3	111
Urban	76,833	3.9	3	111	83,144	3.7	3	133

MSA, metropolitan statistical area.

US adult male 40+ civilian non-institutionalized population.

[a]Persons of other races, missing or unavailable race and ethnicity, and missing MSA are included in the totals.

NOTE: Counts may not sum to totals due to rounding.

SOURCE: Healthcare Cost and Utilization Project Nationwide Inpatient Sample, 1994, 1996, 1998, 2000.

Table 12 also indicates that the inpatient hospitalization rate was greater for African Americans than for Caucasians at all time points, likely reflecting the increasing incidence of the disease in this racial group. Trends in geographical variation in inpatient utilization are also interesting. Although there was a marked decrease in inpatient hospitalization in all geographic regions, the decrease between 1992 and 2001 was most striking in the West and the Northeast. The reasons for this are unclear but may reflect geographical trends in screening and treatment practices during this time period.

Data from the HCUP nationwide inpatient sample indicate similar rates (Table 14). Not surprisingly, hospitalization rates for prostate cancer in rural regions were less than half the rates in urban areas during 1994–2000. There was also geographic variation, with the West having the lowest hospitalization rates in the country.

As inpatient hospitalization rates dropped, length of stay associated with hospitalization dropped as well (Table 15). Across age and racial groups and geographic regions, the median length of stay declined between 1994 and 2000. Patients were hospitalized for the least amount of time (mean of 3.3–4.4 days) in the West in all the time periods examined and hospitalized longest in the Northeast (mean of 4.2–6.6 days). While hospitalization rates tended to be lower in rural than in urban areas, the average length of stay in rural hospitals was slightly longer than that in urban hospitals. African Americans and Hispanics tended to have slightly longer hospital stays than Caucasians during each of the years examined. This trend may underlie or be driven by geographic differences as well.

Outpatient Care

Most radiation therapy is delivered in the outpatient hospital setting. In fact, with the exception of the immediate period surrounding surgery, most prostate cancer survivors access the healthcare system as outpatients. We focus here on three aspects of outpatient care: physician office visits, hospital outpatient visits, and ambulatory surgery visits.

Physician Office Visits

Data from the National Ambulatory Medical Care Survey (NAMCS) document that the average annual age-adjusted rate of physician office visits for prostate cancer in 1992–2000 was 5,001 per 100,000 American males over the age of 40 (Table 16). The rate was 5,449 per 100,000 in 1992, and it declined to a low of 3,870 per 100,000 in 1998. It then jumped to 5,828 per 100,000 in 2000. The exact reasons for these shifts are unclear. In this time period, men aged 75–84 had the highest rate of office visits, 112,069 per 100,000, as compared with 54,445 per 100,000 for men 65–74 and 5,930 per 100,000 for men 40–64. This may be explained by the fact that older patients are least likely to undergo aggressive therapy for localized disease and most likely to elect conservative management. Therefore, they may be seen more often by their providers and may require more outpatient care.

Data from the Medicare sample do not show the same decline between 1992 and 1998. Rather, as shown in Table 17, they indicate that the rate of physician office visits increased from 1992 to 1995 and remained relatively stable after that, reflecting changes in the age-adjusted incidence rate of prostate cancer. Differences between the NAMCS and Medicare data may be explained by the fact that the Medicare patients are older and likely have somewhat different patterns of care than the younger patients in the NAMCS sample. Also, the NAMCS is primarily a research database, while the Medicare dataset is an administrative database, which may explain some of the difference. There is considerable geographic variation in physician office visit rates in both the NAMCS and Medicare samples, although the differences are not consistent between the two datasets. It is likely that physician office visits are related to patterns of care in primary treatment choice. The relation of primary treatment to geographic region and patient age would explain the differing patterns of geographic variation between the two samples.

It is often assumed that most outpatient office visits for prostate cancer are to urologists, and NAMCS data confirm this. In 1992–2000, 12,236,564 office visits for prostate cancer were reported in NAMCS (Table 16). Of these, 8,662,617 were to urologists, and 3,573,947 were to non-urologists (Table 18). The overall annualized rate was 5,001 visits per 100,000 men, while the annualized office visit rate to urologists was 3,540 per 100,000 and to all other specialists was 1,461 per 100,000. Effectively, 71% of all annual office visits

Table 16. Physician office visits for prostate cancer listed as primary diagnosis, count, rate[a] (95% CI), annualized rate[b], age-adjusted rate[c]

	1992–2000				
	Count	Rate		Annualized Rate	Age-Adjusted Rate
Total[d]	12,236,564	25,004	(22,810–27,198)	5,001	25,034
Age					
40–64	2,118,240	5,930	(4,647–7,212)	1,186	
65–74	4,399,702	54,445	(46,664–62,226)	10,889	
75–84	4,739,092	112,069	(95,718–128,421)	22,414	
85+	979,530	108,031	(79,820–136,242)	21,606	
Race/ethnicity					
White	10,498,163	26,644	(24,119–29,170)	5,329	25,313
Other	1,738,401	18,227	(14,001–22,452)	3,645	23,366
Region					
Midwest	2,906,931	25,262	(20,840–29,683)	5,052	25,086
Northeast	3,718,177	37,425	(31,362–43,488)	7,485	36,556
South	3,187,693	18,669	(15,599–21,740)	3,734	18,435
West	2,423,763	23,256	(18,398–28,114)	4,651	24,738
MSA					
MSA	10,498,173	28,760	(25,998–31,522)	5,752	28,935
Non-MSA	1,738,391	13,979	(11,014–16,943)	2,796	13,835

	1992				1994			
	Count	Rate		Age-Adjusted Rate	Count	Rate		Age-Adjusted Rate
Total[d]	2,450,034	5,449	(4,410–6,487)	5,449	2,234,586	4,910	(4,112–5,709)	4,910
Age								
40–64	*	*			301,211	914	(515–1,314)	
65–74	832,868	10,070	(6,717–13,423)		783,398	9,946	(7,212–12,681)	
75–84	1,007,893	26,753	(18,874–34,632)		993,754	26,205	(19,613–32,796)	
85+	*	*			*	*		
Race/ethnicity								
White	2,217,258	5,998	(4,799–7,197)	5,730	1,893,654	5,120	(4,222–6,018)	4,881
Other	*	*		*	340,932	4,000	(2,270–5,730)	5,109
Region								
Midwest	*	*		*	595,052	5,590	(3,971–7,209)	5,649
Northeast	817,237	8,649	(6,016–11,282)	8,360	695,338	7,164	(4,685–9,643)	7,018
South	647,909	4,207	(2,690–5,723)	4,139	595,211	3,868	(2,760–4,976)	3,868
West	614,662	6,544	(3,718–9,369)	6,885	348,985	3,573	(2,303–4,843)	3,687
MSA								
MSA	2,156,249	6,651	(5,305–7,997)	6,922	1,838,675	5,559	(4,557–6,561)	5,781
Non-MSA	*	*		*	395,911	3,184	(1,985–4,384)	2,843

Continued on next page

Table 16 (continued). Physician office visits for prostate cancer listed as primary diagnosis, count, rate[a] (95% CI), annualized rate[b], age-adjusted rate[c]

	1996				1998				2000			
	Count	Rate		Age-Adjusted Rate	Count	Rate		Age-Adjusted Rate	Count	Rate		Age-Adjusted Rate
Total[d]	2,420,055	4,951	(3,924–5,978)	4,951	1,991,798	3,870	(2,971–4,770)	3,870	3,140,091	5,828	(4,751–6,906)	5,828
Age												
40–64	*	*			*	*			616,205	1,541	(863–2,219)	
65–74	964,667	1,798	(8,159–15,436)		765,200	9,508	(6,360–12,656)		1,053,569	13,115	(8,809–17,421)	
75–84	826,418	19,600	(11,962–27,239)		655,783	14,461	(7,774–21,148)		1,255,244	25,974	(18,418–33,531)	
85+	*	*			*	*			*	*		
Race/ethnicity												
White	2,159,471	5,475	(4,239–6,712)	5,232	1,667,407	4,077	(3,028–5,125)	3,891	2,560,373	5,994	(4,797–7,192)	5,712
Other	*	*		*	*	*		*	579,718	5,193	(2,731–7,656)	6,402
Region												
Midwest	520,291	4,457	(2,604–6,310)	4,485	*	*		*	1,100,234	8,747	(5,931–11,563)	8,976
Northeast	665,572	6,753	(4,106–9,400)	6,523	784,053	7,689	(4,760–10,618)	7,622	755,977	7,223	(4,418–10,028)	6,982
South	670,950	3,915	(2,479–5,351)	3,878	*	*		*	806,504	4,193	(2,588–5,797)	4,162
West	563,242	5,516	(2,804–8,228)	5,787	*	*		*	477,376	4,116	(2,625–5,608)	4,341
MSA												
MSA	1,965,145	5,307	(4,114–6,500)	5,406	1,683,174	4,310	(3,172–5,447)	4,417	2,854,930	6,975	(5,585–8,365)	7,099
Non-MSA	*			*	*	*		*	285,161	2,203	(1,326–3,079)	2,068

*Figure does not meet standard for reliability or precision.

MSA, metropolitan statistical area.

[a]Rate per 100,000 is based on 1992, 1994, 1996, 1998, 2000 population estimates from Current Population Survey (CPS), CPS Utilities, Unicon Research Corporation, for relevant demographic categories of US male civilian non-institutionalized population, 40 years and older.

[b]Average annualized rate per year.

[c]Grouped years age-adjusted to the US Census-derived age distribution of the midpoint of years. Individual years age-adjusted to the US Census-derived age distribution of the year under analysis.

[d]Persons of missing or unavailable race and ethnicity, and missing MSA are included in the totals.

NOTE: Counts may not sum to totals due to rounding.

SOURCE: National Ambulatory Medical Care Survey, 1992, 1994, 1996, 1998, 2000.

Table 17. Physician office visits by male Medicare beneficiaries with prostate cancer listed as primary diagnosis, count[a], rate[b] (95% CI), age-adjusted rate[c]

	1992			1995		
	Count	Rate	Age-Adjusted Rate	Count	Rate	Age-Adjusted Rate
Total[d]	1,600,000	10,738 (10,668–10,808)		2,370,000	15,543 (15,462–15,625)	
Total < 65	19,220	615 (577–654)		36,040	1,046 (998–1,094)	
Total 65+	1,580,000	13,424 (13,337–13,511)	14,389	2,330,000	19,785 (19,684–19,887)	20,978
Age						
65–69	295,800	7,267 (7,155–7,380)		398,440	10,344 (10,208–10,480)	
70–74	422,160	12,984 (12,820–13,147)		614,140	18,417 (18,231–18,603)	
75–79	419,420	18,529 (18,303–18,755)		606,600	26,741 (26,484–26,999)	
80–84	284,660	21,728 (21,413–22,044)		444,260	31,975 (31,629–32,322)	
85–89	124,620	20,902 (20,440–21,363)		205,980	32,339 (31,825–32,853)	
90–94	29,480	14,555 (13,868–15,242)		52,520	24,846 (24,023–25,670)	
95–97	3,280	8,119 (6,928–9,309)		6,280	16,658 (14,976–18,340)	
98+	880	2,318 (1,641–2,995)		1,420	3,205 (2,472–3,939)	
Race/ethnicity						
White	1,390,000	11,047 (10,969–11,124)	10,991	2,070,000	15,961 (15,872–16,050)	15,882
Black	127,840	10,019 (9,786–10,252)	10,039	219,620	15,860 (15,588–16,133)	16,593
Asian	…	…	…	8,980	12,322 (11,254–13,389)	11,690
Hispanic	…	…	…	16,380	8,250 (7,709–8,792)	8,814
N. American Native	…	…	…	640	3,181 (2,097–4,264)	2,883
Region						
Midwest	362,260	9,766 (9,631–9,902)	9,826	531,420	13,786 (13,632–13,940)	13,942
Northeast	344,580	10,866 (10,713–11,019)	10,909	573,600	18,035 (17,846–18,224)	17,937
South	603,420	11,520 (11,398–11,642)	11,465	875,680	15,962 (15,825–16,099)	16,014
West	272,220	11,270 (11,091–11,448)	11,213	356,680	15,381 (15,173–15,589)	15,111

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Table 17 (continued). Physician office visits by male Medicare beneficiaries with prostate cancer listed as primary diagnosis, count[a], rate[b] (95% CI), age-adjusted rate[c]

	1998			2001		
	Count	Rate	Age-Adjusted Rate	Count	Rate	Age-Adjusted Rate
Total[d]	2,240,000	15,472 (15,388–15,555)		2,280,000	14,785 (14,705–14,864)	
Total < 65	42,720	1,243 (1,191–1,296)		46,820	1,230 (1,180–1,280)	
Total 65+	2,200,000	19,900 (19,795–20,005)	20,561	2,230,000	19,227 (19,126–19,328)	19,759
Age						
65–69	363,940	10,778 (10,630–10,926)		368,740	10,421 (10,278–10,563)	
70–74	573,240	18,792 (18,596–18,988)		545,520	17,721 (17,531–17,912)	
75–79	594,320	26,025 (25,771–26,280)		598,920	24,414 (24,174–24,655)	
80–84	414,980	30,115 (29,773–30,458)		433,660	28,977 (28,652–29,302)	
85–89	193,160	29,687 (29,190–30,183)		220,620	30,494 (30,020–30,969)	
90–94	50,180	23,327 (22,527–24,126)		57,380	24,765 (23,979–25,551)	
95–97	5,500	13,896 (12,372–15,419)		6,060	15,773 (14,144–17,402)	
98+	2,000	4,181 (3,378–4,983)		2,200	4,055 (3,312–4,797)	
Race/ethnicity						
White	1,950,000	15,951 (15,859–16,042)	15,865	1,960,000	15,008 (14,922–15,095)	14,919
Black	206,760	15,491 (15,216–15,765)	16,107	217,460	14,819 (14,561–15,076)	15,414
Asian	14,940	10,894 (10,157–11,631)	10,704	15,020	7,330 (6,825–7,834)	6,871
Hispanic	39,920	11,893 (11,403–12,383)	12,167	41,960	11,167 (10,717–11,618)	11,024
N. American Native	1,200	4,292 (3,230–5,354)	4,220	1,360	4,084 (3,132–5,036)	2,823
Region						
Midwest	505,180	13,661 (13,504–13,817)	13,708	495,440	13,044 (12,893–13,196)	13,056
Northeast	507,460	18,259 (18,056–18,462)	18,050	504,160	17,253 (17,060–17,447)	17,033
South	861,120	16,044 (15,905–16,183)	16,292	894,900	15,410 (15,279–15,541)	15,620
West	330,420	14,775 (14,567–14,983)	14,389	344,760	13,930 (13,737–14,123)	13,674

…data not available.

[a]Unweighted counts multiplied by 20 to arrive at values in the table.

[b]Rate per 100,000 male Medicare beneficiaries in the same demographic stratum.

[c]Age-adjusted to the US Census-derived age distribution of the year under analysis.

[d]Persons of other races, unknown race and ethnicity, and other region are included in the totals.

NOTE: Counts less than 600 should be interpreted with caution.

SOURCE: Centers for Medicare and Medicaid Services, 5% Carrier and Outpatient Files, 1992, 1995, 1998, 2001.

Table 18. Physician office visits by physician specialty for prostate cancer listed as primary diagnosis, 1992–2000 (merged), count, rate[a] (95% CI), annualized rate[b], rate per 100,000 visits[c] (95% CI)

Physician Specialty	Count	Rate	Annualized Rate	Rate Per 100,000 visitsfor Prostate Cancer
Total	12,236,564	25,004 (22,810–27,198)	5,001	100,000 (91,225–108,775)
Urology	8,662,617	17,701 (16,400–19,002)	3,540	70,793 (65,589–75,997)
All Other	3,573,947	7,303 (5,640–8,966)	1,461	29,207 (22,555–35,859)

[a]Rate per 100,000 is based on 1992–2000 population estimates from Current Population Survey (CPS), CPS Utilities, Unicon Research Corporation, for relevant demographic categories of US male 40+ civilian non-institutionalized population.

[b]Average annualized rate per year.

[c]Rate per 100,000 male 40+ visits is based on estimated number of visits for prostate cancer in NAMCS 1992–2000.

NOTE: Counts may not sum to totals due to rounding.

SOURCE: National Ambulatory Medical Care Survey, 1992, 1994, 1996, 1998, 2000.

for prostate cancer were to urologists, while 29% were to other physicians.

Hospital Outpatient Visits

Hospital outpatient visits by prostate cancer patients are driven by a number of factors, the most important being that radiation therapy, whether EBRT or IB, is usually given in the hospital outpatient setting. We would expect to see significant variation in outpatient visit rates by geographic region and by age, as these two factors are correlated with receipt of radiotherapy as primary treatment. This is, in fact, what the data show. Table 19 presents data from the Medicare sample which indicate that hospital outpatient visits remained relatively stable from 1992 to 2001, but they were higher for men 75–79 years of age and those who live in the Northeast. These men were also more likely to receive radiotherapy, as documented in Table 10 and Figure 7.

Ambulatory Surgery Visits

As with outpatient hospital visits, ambulatory surgery center (ASC) visits for prostate cancer are driven by a number of unique factors and procedures. In particular, interstitial brachytherapy can be performed in ASCs, as can bilateral simple orchiectomy and various palliative/diagnostic procedures such as cystoscopy with stent placement or other minor interventions. Thus, one would expect ASC visits to vary regionally and with age, as these factors predict the use of IB and surgical hormone ablation therapy. As shown in Table 20, data from the Medicare dataset confirm these trends, and data from the National Survey of Ambulatory Surgery (Table 21) are similar.

ECONOMIC IMPACT

Medical expenditures for the treatment of prostate cancer in the United States totaled $1.3 billion in 2000, nearly 30% more than in 1994 (Table 22). The growth in spending occurred despite a reduction in hospitalization costs as treatment shifted from inpatient to outpatient settings. Spending on treatment provided in physician offices more than tripled between 1994 and 2000, while expenditures for ambulatory surgery more than doubled over this period. By 2000, inpatient expenditures accounted for 48% of total spending on prostate cancer, down from 69% in 1994.

Because prostate cancer primarily affects older males, more than two-thirds of all spending on the condition was borne by the Medicare program. Medicare reimbursements for prostate cancer totaled $846 million in 1992 and $927 million in 2001 (Table 23). Medicare spending among beneficiaries under 65 rose from $16 million in 1992 to more than $38 million in 2001, largely due to increased screening.

Individual-level expenditures were estimated using risk-adjusted regression models controlling for age, work status, geographic location, and health plan characteristics. Among males 40 to 64 years of age with employer-provided insurance, average annual expenditures for prostate cancer totaled $11,445, compared with $4,426 for similar men without the condition (Table 24).

Table 19. Hospital outpatient visits by male Medicare beneficiaries with prostate cancer listed as primary diagnosis, count[a], rate[b] (95% CI), age-adjusted rate[c]

	1992				1995			
	Count	Rate		Age-Adjusted Rate	Count	Rate		Age-Adjusted Rate
Total[d]	258,420	1,735	(1,705–1,765)		235,760	1,549	(1,521–1,577)	
Total < 65	4,760	152	(133–172)		7,640	222	(200–244)	
Total 65+	253,660	2,155	(2,118–2,192)	2,235	228,120	1,937	(1,902–1,973)	1,973
Age								
65–69	50,920	1,251	(1,203–1,299)		57,640	1,496	(1,442–1,551)	
70–74	85,720	2,636	(2,559–2,714)		70,360	2,110	(2,041–2,179)	
75–79	72,300	3,194	(3,092–3,296)		54,480	2,402	(2,313–2,491)	
80–84	33,000	2,519	(2,399–2,639)		30,140	2,169	(2,061–2,278)	
85–89	10,060	1,687	(1,541–1,834)		11,020	1,730	(1,587–1,873)	
90–94	1,480	731	(565–897)		3,660	1,731	(1,483–1,980)	
95–97	140	347	(89–604)		580	1,538	(9,84–2,093)	
98+	40	105	(0–250)		240	542	(237–847)	
Race/ethnicity								
White	213,500	1,700	(1,668–1,732)	1,683	188,260	1,448	(1,419–1,477)	1,435
Black	32,540	2,550	(2,428–2,673)	2,596	38,380	2,772	(2,649–2,894)	2,858
Asian	…	...		…	1,320	1,811	(1,378–2,245)	1,894
Hispanic	…	...		…	3,220	1,622	(1,374–1,870)	1,672
N. American Native	…	...		…	140	696	(184–1,208)	895
Region								
Midwest	71,060	1,916	(1,853–1,978)	1,894	71,500	1,855	(1,795–1,915)	1,826
Northeast	84,300	2,658	(2,579–2,738)	2,673	66,960	2,105	(2,035–2,176)	2,126
South	65,060	1,242	(1,200–1,285)	1,258	65,400	1,192	(1,152–1,233)	1,209
West	35,960	1,489	(1,420–1,557)	1,480	29,100	1,255	(1,191–1,319)	1,241

	1998				2001			
	Count	Rate		Age-Adjusted Rate	Count	Rate		Age-Adjusted Rate
Total[d]	239,780	1,656	(1,627–1,686)		271,280	1,759	(1,730–1,789)	
Total < 65	8,080	235	(212–258)		10,500	276	(252–299)	
Total 65+	231,700	2,098	(2,061–2,136)	2,128	260,780	2,245	(2,207–2,283)	2,271
Age								
65–69	49,680	1,471	(1,414–1,529)		57,660	1,629	(1,570–1,689)	
70–74	72,260	2,369	(2,293–2,445)		77,660	2,523	(2,444–2,601)	
75–79	64,620	2,830	(2,734–2,926)		72,960	2,974	(2,879–3,069)	
80–84	29,680	2,154	(2,045–2,262)		35,800	2,392	(2,283–2,502)	
85–89	11,480	1,764	(1,621–1,907)		13,160	1,819	(1,681–1,957)	
90–94	3,660	1,701	(1,457–1,946)		3,060	1,321	(1,113–1,529)	
95–97	220	556	(227–884)		420	1,093	(627–1,559)	
98+	100	209	(25–393)		60	111	(0–236)	
Race/ethnicity								
White	193,820	1,585	(1,554–1,616)	1,576	219,800	1,681	(1,650–1,712)	1,674
Black	32,240	2,415	(2,299–2,532)	2,475	36,620	2,495	(2,383–2,608)	2,559
Asian	3,160	2,304	(1,949–2,659)	2,450	2,120	1,035	(839–1,230)	1,064
Hispanic	5,220	1,555	(1,368–1,742)	1,609	5,140	1,368	(1,202–1,534)	1,309
N. American Native	680	2,432	(1,624–3,240)	2,647	1,040	3,123	(2,288–3,958)	3,003
Region								
Midwest	69,220	1,872	(1,810–1,934)	1,838	77,920	2,051	(1,988–2,115)	2,051
Northeast	66,160	2,380	(2,300–2,461)	2,370	72,960	2,497	(2,417–2,577)	2,498
South	63,200	1,178	(1,137–1,218)	1,191	71,800	1,236	(1,196–1,277)	1,249
West	36,840	1,647	(1,573–1,722)	1,688	44,040	1,779	(1,706–1,853)	1,753

…data not available.

[a]Unweighted counts multiplied by 20 to arrive at values in the table.

[b]Rate per 100,000 male Medicare beneficiaries in the same demographic stratum.

[c]Age-adjusted to the US Census-derived age distribution of the year under analysis.

[d]Persons of other races, unknown race and ethnicity, and other region are included in the totals.

NOTE: Counts less than 600 should be interpreted with caution.

SOURCE: Centers for Medicare and Medicaid Services, 5% Carrier and Outpatient Files, 1992, 1995, 1998, 2001.

Table 20. Ambulatory surgery visits by male Medicare beneficiaries with prostate cancer listed as primary diagnosis, count[a], rate[b] (95% CI), age-adjusted rate[c]

	1992			1995			1998			2001		
	Count	Rate	Age-Adjusted Rate	Count	Rate	Age-Adjusted Rate	Count	Rate	Age-Adjusted Rate	Count	Rate	Age-Adjusted Rate
Total[d]	45,900	308 (296–321)		34,220	225 (214–235)		39,920	276 (264–288)		41,660	270 (259–282)	
Total < 65	600	19 (12–26)		500	15 (8.8–20)		1,280	37 (28–46)		1,820	48 (38–58)	
Total 65+	45,300	385 (369–401)	411	33,720	286 (273–300)	297	38,640	350 (334–366)	353	39,840	343 (328–358)	343
Age												
65–69	8,840	217 (197–237)		7,820	203 (183–223)		8,780	260 (236–284)		11,260	318 (292–344)	
70–74	12,320	379 (349–409)		9,040	271 (246–296)		13,000	426 (393–459)		13,100	426 (393–458)	
75–79	11,940	527 (485–570)		8,560	377 (342–413)		9,500	416 (379–453)		9,540	389 (354–424)	
80–84	7,880	601 (542–661)		5,380	387 (341–433)		4,700	341 (298–385)		4,020	269 (232–306)	
85–89	3,300	553 (469–638)		2,400	377 (309–444)		2,160	332 (269–395)		1,500	207 (160–254)	
90–94	920	454 (323–585)		460	218 (129–307)		460	214 (126–301)		380	164 (90–238)	
95–97	100	248 (30–465)		60	159 (0–340)		40	101 (0–240)		40	104 (0–247)	
98+	0	0		0	0		0	0		0	0	
Race/ethnicity												
White	39,120	311 (298–325)	308	29,100	224 (212–235)	224	35,000	286 (273–300)	285	35,960	275 (262–288)	274
Black	4,480	351 (305–397)	376	4,120	298 (257–338)	299	3,740	280 (240–320)	294	4,060	277 (239–315)	285
Asian	…	…	…	80	110 (2.7–217)	110	120	88 (18–158)	73	300	146 (72–221)	146
Hispanic	…	…	…	180	91 (31–150)	111	460	137 (81–193)	125	640	170 (111–229)	160
N. American Native	…	…	…	40	199 (0–472)	199	20	72 (0–211)	72	40	120 (0–285)	60
Region												
Midwest	14,580	393 (365–422)	386	10,940	284 (260–308)	292	11,240	304 (279–329)	300	11,420	301 (276–325)	299
Northeast	9,560	301 (274–328)	317	7,020	221 (198–244)	221	8,960	322 (293–352)	330	8,280	283 (256–311)	289
South	16,220	310 (288–331)	311	12,440	227 (209–245)	225	14,600	272 (252–292)	272	16,260	280 (261–299)	279
West	5,440	225 (198–252)	211	3,580	154 (132–177)	146	4,840	216 (189–244)	215	5,400	218 (192–244)	216

…data not available.

[a]Unweighted counts multiplied by 20 to arrive at values in the table.

[b]Rate per 100,000 male Medicare beneficiaries in the same demographic stratum.

[c]Age-adjusted to the US Census-derived age distribution of the year under analysis.

[d]Persons of other races, unknown race and ethnicity, and other region are included in the totals.

NOTE: Counts less than 600 should be interpreted with caution.

SOURCE: Centers for Medicare and Medicaid Services, 5% Carrier and Outpatient Files, 1992, 1995, 1998, 2001.

Table 21. Ambulatory surgery visits for prostate cancer listed as primary diagnosis, 1994–1996 (merged and by year), count, rate[a] (95% CI), annualized rate[b], age-adjusted rate[c]

	1994–1996			
	Count	Rate	Annualized Rate	Age-Adjusted Rate
Total	136,925	289 (257–321)	96	287
Age				
40–64	23,490	68 (48–89)	23	
65–74	48,819	606 (499–712)	202	
75–84	49,808	1,232 (1,005–1,459)	411	
85+	14,808	1,719 (1,152–2,286)	573	
Region				
Midwest	50,169	451 (376–526)	150	449
Northeast	24,667	252 (168–337)	84	246
South	42,872	261 (215–307)	87	265
West	19,217	192 (131–253)	64	192

	1994			1995			1996		
	Count	Rate	Age-Adjusted Rate	Count	Rate	Age-Adjusted Rate	Count	Rate	Age-Adjusted Rate
Total	50,328	111 (89–132)	111	39,964	84 (68–100)	84	46,633	95 (78–113)	95
Age									
40–64	*	*	*	5,820	17 (9.71–24)		9,671	27 (16–38)	
65–74	18,085	230 (158–301)		14,441	178 (121–234)		16,293	199 (144–255)	
75–84	19,743	521 (372–669)		13,976	340 (231–448)		16,089	382 (247–517)	
85+	*	*	*	*	*		*	*	
Region									
Midwest	17,995	169 (121–217)	170	18,046	169 (117–210)	161	14,128	121 (85–157)	121
Northeast	10,161	*	104	*	*	*	9,835	100 (51–148)	98
South	14,210	92 (68–117)	93	13,475	81 (53–108)	83	15,187	89 (61–116)	88
West	7,962	82 (37–126)	85	*	*	*	7,483	73 (39–108)	76

*Figure does not meet standard for reliability or precision.

[a]Rate per 100,000 is based on 1994, 1995, 1996 population estimates from Current Population Survey (CPS), CPS Utilities, Unicon Research Corporation, for relevant demographic categories of US male civilian non-institutionalized population, 40 years and older.

[b]Average annualized rate per year.

[c]Grouped years age-adjusted to the US Census-derived age distribution of the midpoint of years. Individual years age-adjusted to the US Census-derived age distribution of the year under analysis.

NOTE: Counts may not sum to totals due to rounding.

SOURCE: National Survey of Ambulatory Surgery, 1994, 1995, 1996.

Table 22. Expenditures for prostate cancer, by site of service (% of total)

Service Type	1994		1996		1998		2000	
Hospital Outpatient	$129,108,028	12.9%	$62,988,055	6.5%	$112,133,820	11.8%	$174,484,751	13.5%
Physician Office	$97,839,385	9.8%	$115,394,094	12.0%	$143,409,456	15.1%	$305,584,466	23.6%
Ambulatory Surgery	$76,645,818	7.6%	$77,341,725	8.0%	$141,018,192	14.9%	$179,080,421	13.8%
Emergency Room	$9,590,867	1.0%	$10,444,787	1.1%	$13,811,416	1.5%	$15,553,104	1.2%
Inpatient	$689,630,760	68.8%	$697,677,985	72.4%	$537,794,704	56.7%	$621,098,169	47.9%
TOTAL	$1,002,814,857		$963,846,646		$948,167,588		$1,295,800,912	

SOURCE: National Ambulatory and Medical Care Survey; National Hospital and Ambulatory Medical Care Survey; Healthcare Cost and Utilization Project; Medical Expenditure Panel Survey, 1994, 1996, 1998, 2000.

This suggests that the annual incremental costs associated with prostate cancer exceed $7,000 per person. Average spending was higher among younger men (aged 40–54) and in the West, although regional variation was modest.

In addition to direct costs of medical care, prostate cancer can result in productivity losses through work absences. Overall, 26% of privately insured men in treatment for prostate cancer missed some work because of the condition. The average work loss was 20.9 hours per year (Table 25). Employees hospitalized for prostate cancer missed an average of 10.5 additional days of work (Table 26). Work loss for outpatient visits was less (2 hours per visit, on average) but was cumulatively similar due to the higher volume of outpatient treatment.

Max and colleagues (178) estimated the indirect costs of prostate cancer in California by estimating patients' lost (lifetime) earnings, discounted at a 3% annual rate. They estimated that the indirect costs due to premature mortality totaled $180 million, equal to the direct medical costs of treating the condition.

Medicare expenditures for medical androgen suppression therapy amounted to $478 million in 1994, 34% of the total Medicare expenditure for prostate cancer (155). These figures are likely to have increased over the past decade as the use of drug therapy has increased rapidly. Medicare has recently decreased the reimbursement rates for outpatient hormonal ablation therapy, which will likely decrease the overall economic burden of this treatment in the future. Nevertheless, these treatments still contribute greatly to the overall cost of prostate cancer in the United States.

Table 23. Expenditures for Medicare beneficiaries for treatment of prostate cancer, by site of service (% of total)

			Age 65 and over					
Service Type	1992		1995		1998		2001	
Hospital Outpatient	$199,884,080	24.1%	$185,917,800	28.4%	$215,481,000	30.0%	$250,870,360	28.2%
Physician Office	$74,274,100	9.0%	$107,163,440	16.4%	$158,207,040	22.0%	$227,776,200	25.6%
Ambulatory Surgery	$53,091,600	6.4%	$53,952,000	8.2%	$116,847,360	16.2%	$160,356,000	18.0%
Emergency Room	$2,455,000	0.3%	$2,665,680	0.4%	$1,869,840	0.3%	$2,218,220	0.2%
Inpatient	$500,158,960	60.3%	$305,255,600	46.6%	$226,821,840	31.5%	$247,542,400	27.9%
TOTAL	$829,863,740		$654,954,520		$719,227,080		$888,763,180	

			Under 65					
Service Type	1992		1995		1998		2001	
Hospital Outpatient	$2,522,800	15.6%	$5,149,360	27.7%	$6,003,440	26.6%	$8,998,500	23.3%
Physician Office	$922,560	5.7%	$1,910,120	10.3%	$3,118,560	13.8%	$4,447,900	11.5%
Ambulatory Surgery	$805,200	5.0%	$0	0.0%	$3,526,400	15.6%	$8,342,880	21.6%
Emergency Room	---	0.0%	---	0.0%	---	0.0%	---	0.0%
Inpatient	$11,936,800	73.7%	$11,558,820	62.1%	$9,952,820	44.0%	$16,872,060	43.6%
TOTAL	$16,187,360		$18,618,300		$22,601,220		$38,661,340	

SOURCE: Centers for Medicare and Medicaid Services, 1992, 1995, 1998, 2001.

Table 24. Estimated annual expenditures for privately insured employees with and without a medical claim for prostate cancer in 2002[a]

	Annual Expenditures (per person)					
	Males Age 50–64 without Prostate Cancer (N=203,181)			Males Age 50–64 with Prostate Cancer (N=3,135)		
	Medical	Rx Drugs	Total	Medical	Rx Drugs	Total
Total	$3,182	$1,244	$4,426	$9,551	$1,894	$11,445
Age						
50–54	$3,302	$1,306	$4,608	$8,108	$1,797	$9,905
55–59	$3,460	$1,291	$4,751	$6,997	$1,768	$8,765
60–64	$3,302	$1,159	$4,461	$6,181	$1,859	$8,040
Region						
Midwest	$2,996	$1,232	$4,228	$8,989	$1,888	$10,877
Northeast	$3,110	$1,332	$4,442	$9,331	$2,033	$11,364
South	$3,322	$1,175	$4,497	$9,965	$1,782	$11,747
West	$3,439	$1,238	$4,677	$10,317	$1,908	$12,225

Rx, Prescription.

[a]The sample consists of primary beneficiaries ages 40 to 64 having employer-provided insurance who were continuously enrolled in 2002. Estimated annual expenditures were derived from multivariate models that control for age, gender, work status (active/retired), median household income (based on zip code), urban/rural residence, medical and drug plan characteristics (managed care, deductible, co-insurance/co-payments) and binary indicators for 28 chronic disease conditions. Predicted expenditures for males age 40 to 49 are omitted due to small sample size.

SOURCE: Ingenix, 2002.

Table 25. Average annual work loss of males treated for prostate cancer, 1999 (95%CI)

			Average Work Absence (hrs)		
	Number of Workers[a]	% Missing Work	Inpatient[b]	Outpatient[b]	Total
Total	315	26%	11.6 (5.2–18)	9.2 (4.9–13.6)	20.9 (13–28.8)
Age					
30–39	1	0%	0	0	0
40–49	24	21%	4.3 (0–10.4)	21.2 (0–57.7)	25.5 (0–68)
50–64	290	27%	12.3 (5.3–19.2)	8.3 (4.5–12.1)	20.6 (12.6–28.5)
Region					
Midwest	81	23%	4 (0–9.9)	4 (0.4–7.5)	8 (1.3–14.7)
Northeast	52	29%	19.2 (0–44.1)	6.8 (0.7–13)	26.1 (0.5–51.6)
South	110	25%	8.9 (2.5–15.2)	10.3 (1.9–18.7)	19.1 (7.4–30.8)
West	29	31%	29.9 (0–72.5)	7.8 (0–16)	37.7 (0–80.6)
Unknown	43	28%	11.5 (0–26.2)	20.3 (-1.3–41.9)	31.9 (6.2–57.5)

…data not available.

[a]Individuals with an inpatient or outpatient claim for prostate cancer and for whom absence data were collected. Work loss based on reported absences contiguous to the admission or discharge dates of each hospitalization or the date of the outpatient visit.

[b]Inpatient and outpatient include absences that start or stop the day before or after a visit.

Source: Marketscan Health and Productivity Management, 1999.

Table 26. Average work lossa associated with a hospital stay or an ambulatory care visit for prostate cancer (95% CI)

	Number of Inpatient Stays	Average Hours Missed for Inpatient Stays	Number of Outpatient Visits	Average Hours Missed for Outpatient Visits
Total	43	85.2 (44–127)	1324	2.2 (1–3)
Age				
30–39	…	…	1	0
40–49	4	25.5 (0–73)	116	4.4 (2–7)
50–64	39	91.4 (46–137)	1207	2.0 (1–3)
Region				
Midwest	5	65.6 (0–182)	339	0.9 (0–2)
Northeast	11	90.9 (0–214)	198	1.8 (0–3)
South	15	64.9 (26–103)	476	2.4 (1–3.)
West	5	173.5 (0–469)	118	1.9 (0–4)
Unknown	7	70.9 (0–162)	193	4.5 (2–4)

…data not available

[a]Work loss is based on reported absences contiguous to the admission and discharge dates of each hospitalization or the date of outpatient visit.

Source: Marketscan Health and Productivity Management, 1999.

CONCLUSIONS

Prostate cancer is the most common urologic malignancy and the most common solid cancer found in American men. Disease incidence and patterns of care for this condition have changed dramatically in the past 20 years, following the introduction of prostate-specific antigen testing, which has resulted in widespread screening for this cancer throughout the United States and Western Europe. Although a number of randomized clinical trials assessing the effectiveness of prostate cancer screening are currently underway, the value of this clinical practice remains unproven. Despite this, prostate cancer screening has been embraced by the clinical community and the general population and likely will continue to be widely used.

There are numerous risk factors for prostate cancer. Although some of these are immutable (e.g., age, race, and family history), others are modifiable and could be the target of interventions that would allow primary prevention of the condition. Changes in diet, obesity, and physical activity, if these factors are proven to be associated with the development and aggressiveness of prostate cancer, could impact incidence and outcomes. This is a fertile area for further research.

Patterns of care have also changed tremendously in the past 20 years. Some of these changes are directly related to the introduction of PSA testing, while other reflect improved understanding of prostate cancer by both clinicians and researchers. In particular, older men with short life expectancies are, on average, receiving less-aggressive therapy than in the past, reflecting clinicians' realization that older men are at decreased risk of prostate cancer mortality, due to competing comorbid diseases. In contrast, more men are being diagnosed at younger ages and with earlier-stage disease and are therefore undergoing more-aggressive therapies for their condition. Surgical rates have consistently increased in these younger patients. There is considerable racial and geographic variation in treatment utilization; however, this is probably the result of clinical uncertainty as to which treatment is best for men with localized prostate cancer. Additional clinical trial data are desperately needed to identify which patients are best served by which therapies. Level I evidence regarding clinical outcomes following various therapies for localized prostate cancer is needed to reduce the clinical uncertainty surrounding this condition and to ensure high-quality care for all men diagnosed with prostate cancer in the United States.

Finally, there is a tremendous economic burden associated with the diagnosis and treatment of prostate cancer in the United States. While some of the costs are unavoidable, it may be possible to reduce this economic burden by generating better clinical data

and removing certain financial incentives associated with various treatments. Specifically, hormone ablation therapy is probably overused in men with localized prostate cancer. Recent changes in Medicare reimbursement for these agents will likely affect their utilization and reduce the economic burden of the disease.

RECOMMENDATIONS

There is an abundance of administrative data sources and observational cohorts for prostate cancer research. While many of these resources have proven valuable in addressing research questions, a great deal of important work remains to be done, much of which cannot be completed with the existing datasets. New resources must be developed in order to answer pressing research questions. In general, recommendations for future work can be divided into three categories: primary prevention, screening issues, and identification of optimal treatment strategies.

Primary Prevention

Further research should be undertaken to examine the association of certain modifiable risk factors and the development of prostate cancer. If independent relationships are identified, appropriate interventions should be designed and studied as primary prevention strategies. Primary prevention of prostate cancer may represent the most cost-effective way to reduce the burden of the disease. The following specific issues in primary prevention require further study:

- Better understanding of gene-diet interactions. These interactions are modifiable and may be useful not only for prevention, but also for clinical trial stratification, as some of them may also predict more-aggressive cancers.
- Identification of specific therapeutic agents for primary prevention (i.e., anti-inflammatory agents or compounds that modify the hormonal milieu).

Prostate Cancer Screening

Randomized clinical trials to evaluate the effectiveness of prostate cancer screening are currently under way. Once these studies are completed, appropriate steps should quickly be taken to incorporate the findings into clinical practice. Specifically, if prostate cancer screening is found to reduce mortality in a cost-effective manner and ultimately result in greater benefit than harm, programs should be enacted to ensure population-wide access to screening and treatment. If the randomized studies indicate that prostate cancer screening is ineffective, is not cost-effective, or does more harm than good, appropriate policy steps should be taken to discourage screening in the general population.

Identification of Optimal Treatment Strategies

There is a pressing need to generate high-quality evidence regarding the effectiveness of the various therapies for localized prostate cancer. While randomized clinical trials are desperately needed, they may not be feasible in the current healthcare environment, and observational cohorts that extensively control for potentially confounding factors may be needed. Much of the racial/ethnic and geographic variation in prostate cancer care is likely related to clinical uncertainty surrounding the condition. New, high-quality data on the effectiveness of various therapies could be used to generate clinical treatment guidelines that would improve the quality of care. Specifically, the following important research areas should be addressed:

- Development of independent clinical biomarkers for indolent vs aggressive prostate cancers.
- Identification of the treatments that result in the best outcomes in different patient groups. Outcomes that should be addressed include mortality, health-related quality of life, and economic costs of treatment.
- Determination of which patients require adjuvant therapies for localized prostate cancer.
- Longer-term follow-up of prostate cancer cohorts to improve understanding of the survivorship experience and to optimize the treatment of this effectively chronic disease.
- Adoption of indicators of high-quality care.

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