Special Section: Prostate Cancer

Excluding skin cancer, prostate cancer is the most commonly diagnosed cancer among men in the US and the second most common cause of cancer death among men. It is estimated that about 1 in 6 men in the US will be diagnosed with prostate cancer during their lifetime and 1 in 36 will die from this disease. Despite the important burden of prostate cancer cases and deaths, and extensive research on its causes, prevention, early detection, and treatment, many uncertainties remain about this cancer. This Special Section contains information about what we know about prostate cancer, what we don't know, and the research that has been done to try to answer these questions. Information in this article may be helpful to clinicians, men who are concerned about their risk of prostate cancer, who are making decisions about prostate cancer screening or treatment, or who are undergoing treatment or follow-up, as well as to anyone interested in learning more about this type of cancer.

How Many Cases and Deaths Are Estimated to Occur in 2010?

- Prostate cancer accounts for about 1 in 4 newly diagnosed cancers each year among US men. In 2010, an estimated 217,730 new cases of prostate cancer will be diagnosed in the US.
- Prostate cancer is the second most common cause of cancer death in men. In 2010, approximately 32,050 men are expected to die from prostate cancer. Only lung cancer accounts for more cancer deaths in US men.

Table 1. Probability (%) of Developing Prostate Cancer Over Selected Age Intervals by Race, US, 2004-2006*

Age	White	African American
30 to 39	0.01 (1 in 12,288)	0.02 (1 in 4,379)
40 to 49	0.27 (1 in 375)	0.60 (1 in 168)
50 to 59	2.14 (1 in 47)	3.78 (1 in 26)
60 to 69	6.23 (1 in 16)	9.75 (1 in 10)
70 to 79	8.02 (1 in 12)	11.17 (1 in 9)
Lifetime risk	**15.39 (1 in 6)**	**18.32 (1 in 5)**

*For people free of cancer at beginning of age interval. Percentages and "1 in" numbers may not be equivalent due to rounding.

Source: DevCan: Probability of Developing or Dying of Cancer Software, Version 6.4.1. Statistical Research and Applications Branch, National Cancer Institute, 2009. srab.cancer.gov/devcan.

Who Gets Prostate Cancer?

Age

- Age is the most important risk factor for prostate cancer. Prostate cancer incidence rates increase in men until about age 70 and decline thereafter. During 2002-2006, men aged 70 to 74 had the highest incidence rate, 888.6 cases per 100,000 white men and 1279.1 cases per 100,000 African American men.
- During 2002-2006, the median age at the time of prostate cancer diagnosis was 68 years. This means that about half of the men who developed prostate cancer were age 68 or younger at the time of diagnosis.
- The probability of developing prostate cancer varies greatly by age (Table 1). For white men who are cancer free at age 50, the probability of developing prostate cancer in the next 10 years is 2.14% (1 in 47); this rises to 8.02% (1 in 12) for a man whose current age is 70. For African American men, the probabilities are substantially greater; 3.78% (1 in 26) at age 50 and 11.17% (1 in 9) at age 70.
- Death rates for prostate cancer increase with age. During 2002-2006, the median age of death from prostate cancer was 80 years.

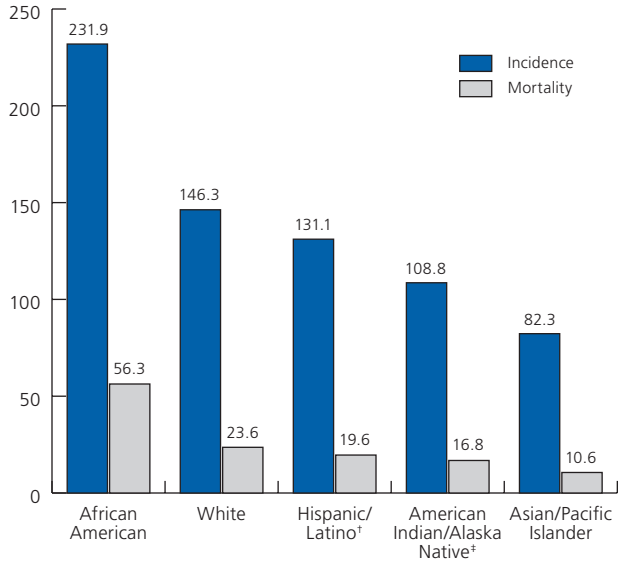
Race/Ethnicity

- African American men have a higher incidence of prostate cancer and are more likely to die from the disease than white men in every age group. In 2002-2006, the overall age-adjusted incidence rate for white men was 146.3 per 100,000, and for African American men it was 231.9 per 100,000. During the same time period, the mortality rate for white men was 23.6 per 100,000 and for African American men it was 56.3 per 100,000.[1]
- Incidence and death rates for prostate cancer are lower among men of other racial and ethnic groups than among white and African American men (Figure 1).

Socioeconomic position

- Prostate cancer death rates vary by years of education, especially among African American men. In a study of death rates among men aged 25 to 64 by level of education, American Cancer Society researchers found that the prostate cancer death rate for African American men with 12 or fewer years of education was twice that of men with more than 12 years of education.[2] In white men, the prostate cancer death rate for those with 12 or fewer years of education, was 1.5 times that of men with more than 12 years of education.
- Prostate cancer death rates declined markedly among African American and white men from 1993 to 2001. In both populations, declines were greater among men with 13 or more years of education.[3]

Figure 1. Prostate Cancer Incidence and Mortality Rates* by Race and Ethnicity, US, 2002-2006



*Per 100,000, age adjusted to the 2000 US standard population. †Persons of Hispanic/Latino origin may be of any race. ‡Data based on Contract Health Service Delivery Areas (CHSDA) counties.

Source: Edwards, et al.[1]

- A study linking data on socioeconomic factors from population surveys with cancer registries found that age-adjusted incidence rates (per 100,000) were highest among men with a college education or beyond (253.3) and lowest for men who did not complete high school (203.5). The higher incidence rates among the most educated men are likely due to higher rates of prostate-specific antigen (PSA) screening in this group. However, men with less than a high school education were significantly more likely to be diagnosed with distant-stage prostate cancer than men with a college education or beyond.[4]

Are There Geographical Differences in Prostate Cancer?

Geographical patterns within the US

- Figure 2 shows prostate cancer incidence and death rates per 100,000 men for white and African American men by state. Among white men, prostate cancer incidence rates tend to be highest in northern states, especially in the Midwest and Mountain States, while among African American men, incidence rates tend to be highest in the southeastern region. Mortality rates follow a similar pattern.
- In white men, prostate cancer incidence rates vary from 111.8 in Arizona to 184.7 in Utah. Among African American men, rates range from 113.6 in New Mexico to 277.9 in Delaware.
- Prostate cancer death rates among white men range from 19.3 in Florida to 28.4 in Idaho. Among African American men, death rates range from 35.2 in Arizona to 70.5 in Mississippi.
- A study of geographic variability in prostate cancer incidence, mortality, and PSA screening in US counties found that prostate cancer death rates were positively correlated with incidence rates of distant-stage disease for both African American and white men, suggesting a socioeconomic component to these disparities.[5]
- A study of the relationship between county-level poverty and distant-stage cancer in the US found that higher county poverty increased the odds of distant-stage prostate cancer (odds ratio = 1.7 for greater than or equal to 30% poverty compared to less than 10%).[6]

International variation

- Incidence rates vary by more than 50-fold worldwide, with the majority of cases diagnosed in economically developed countries.
- The highest incidence rates are observed in North America, Australia, and northern and central Europe.
- The lowest incidence rates are observed in southeastern and south central Asia and northern Africa.
- A 2002 study of prostate cancer incidence and mortality rates in 16 economically developed and 15 less developed countries found that incidence rates varied from < 5 per 100,000 in India, Egypt, China, and Bangladesh, to greater than 100 per 100,000 in the US and New Zealand. In the same study, the highest mortality rates were observed in Barbados (55.3 per 100,000), the Bahamas (35.6 per 100,00), Norway (28.4 per 100,000), and Sweden (27.7 per 100,000).[7] (International rates are adjusted to the 1960 world population and are not comparable to US rates presented in this publication, which are adjusted to the 2000 US population. For example, the current prostate cancer mortality rate in the US is 25.6 if age adjusted to the US standard population, but is 11.1 if age adjusted to the world standard population.)

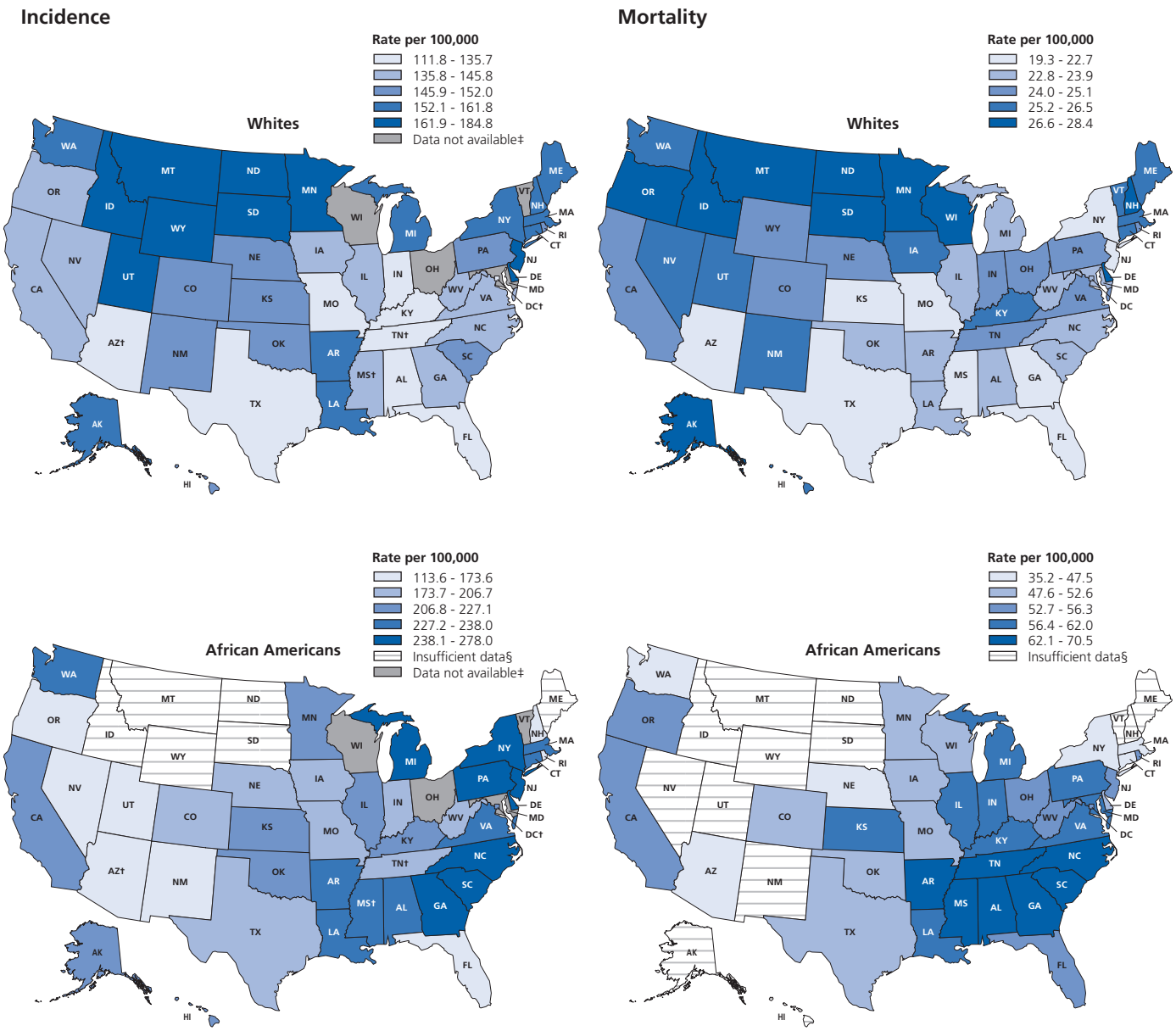
How Has the Occurrence of Prostate Cancer Changed Over Time?

Incidence trends

Incidence rates of prostate cancer for all races combined in the US show five distinct phases since 1975, when population-based surveillance of cancer began:

- Between 1975 and 1988, incidence increased by 2.6% per year.
- Between 1988 and 1992, incidence increased by 16.5% per year.
- Between 1992 and 1995, incidence decreased by 11.7% per year.
- Between 1995 and 2000, incidence was stable.
- Between 2000 and 2006, incidence rates decreased by 2.4% per year.[1]

Figure 2. Prostate Cancer Incidence and Death Rates* by State and Race, US, 2002-2006

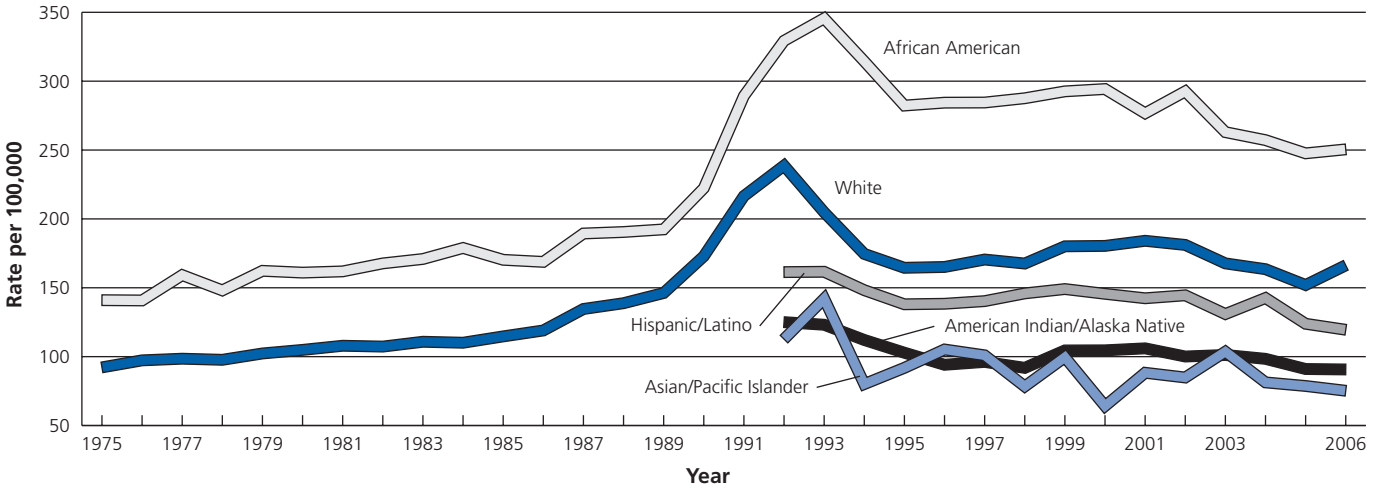


*Per 100,000 and age adjusted to the 2000 US Standard Population. †This state's registry did not achieve high-quality data standards for one or more years during 2002-2006, according to the North American Association of Central Cancer Registry (NAACCR) data quality indicators. ‡State did not submit incidence data to NAACCR for 2002-2006. §Statistic not displayed for states with fewer than 20 cases or deaths.

Source: Incidence: NAACCR, 2009. Deaths: National Center for Health Statistics, 2009.

In large part, changes in incidence rates of prostate cancer over the past 20 years reflect changes in prostate cancer detection, most importantly, the introduction of screening with the PSA blood test. PSA is a protein secreted by the prostate and normally present at low levels in blood. Elevated levels of PSA in blood can be a sign of prostate cancer, but can also be a sign of other conditions, such as benign prostatic hyperplasia (non-cancerous enlargement of the prostate) or prostatitis (inflammation of the prostate). Use of the PSA test for the diagnosis of prostate cancer increased dramatically in the US in the late 1980s, resulting in a rapid increase in prostate cancer incidence rates that peaked in 1992.[8-9] The rapid decline in prostate cancer incidence between 1992 and 1995 likely resulted from a decline in the number of men having their first PSA test (as opposed to subsequent) tests and from a reduced number of latent cases in the population due to the rapid dissemination of the test in the early 1990s. Factors associated with the more recent decline in incidence rates among men of all ages combined are less well understood. This

Figure 3. Trends in Prostate Cancer Incidence Rates* by and Race and Ethnicity, US, 1975-2006



*Rates are age adjusted to the 2000 US standard population

Data Source: Surveillance, Epidemiology, and End Results (SEER) Program, 1973-2006, Division of Cancer Control and Population Science, National Cancer Institute, 2009. Data for whites and African Americans are from the SEER 9 registries and are adjusted for delayed reporting. Data for other races/ethnicities are from the SEER 13 registries and are not adjusted for delayed reporting, and thus data for the most recent years are likely to bo underrepresented. For Hispanics, incidence data do not include cases from the Alaska Native Registry. Incidence data for American Indians/Alaska Natives are based on Contract Health Service Delivery Area (CHSDA) counties.

decline is evident among men aged 65 and older but not among younger men.

Although African American men have much higher incidence rates than whites, incidence trends have been similar for African American and white men since the 1970s (Figure 3). Incidence rates peaked in 1992 among white men (238.2 per 100,000) and in 1993 among African Americans (344.1 per 100,000). During the most recent time period (1997-2006), incidence rates decreased by 1.9% per year among African Americans and 1.7% per year among Hispanics, while remaining relatively stable among whites, Asian Americans/Pacific Islanders, and American Indians/Alaska Natives.

Mortality trends

Mortality rates for prostate cancer also show several distinct phases:

- Between 1975 and 1987, the death rate for all races combined increased by 0.9% annually.
- Between 1987 and 1991, the rate increased by 3.0% annually.
- Between 1991 and 1994, the rate remained level.
- Between 1994 and 2006, the rate decreased by 4.1% annually.

The increase in prostate cancer death rates between 1987 and 1991, coinciding with the introduction of PSA testing and rapidly rising incidence, is likely explained by attribution bias (increased likelihood of ascribing the cause of death to prostate cancer when multiple causes are present). After leveling off from 1991 to 1994, prostate cancer death rates declined in all racial/ethnic groups. From 1997 to 2006, prostate cancer death rates declined by a minimum of 3.5% per year in each major racial/ethnic group with the exception of American Indians and Alaska Natives, in which rates were stable.[1] Similar declines in prostate cancer mortality have been observed in Australia, Canada, and several countries in western Europe.[7] Some studies suggest that much of the decline in prostate cancer death rates is due to declines in the incidence of distant-stage disease due to early detection by PSA, while others suggest that improvements in prostate cancer treatment is responsible.[10-14] Improvements in surgery and radiation and the application of hormonal treatments for regional and metastatic disease may also have contributed to the decline.[15]

Can Prostate Cancer Be Prevented?

Although many epidemiological studies have been done to investigate the etiology (causes) of prostate cancer, few modifiable risk factors have been identified. Studies have investigated the role of family history, genetic factors, nutrition, dietary supplements, obesity, physical activity, infection, medication, and hormonal factors in prostate cancer risk.

Family history

Family history of prostate cancer has been widely studied, and is positively related to prostate cancer risk. Compared to men without a family history, men with one first-degree relative (a father or brother) with the disease are two to three times more likely to develop prostate cancer, and men with more than one affected first-degree relative are three to five times more likely to be diagnosed.[16]

Race/ethnicity

International variation in prostate cancer incidence and mortality, along with striking variations in incidence and mortality within the US, may in part reflect genetic factors that vary in populations originating in different parts of the world. A particularly high risk of prostate cancer is found in many populations with sub-Saharan African ancestry, while a low risk is found in many populations with Asian ancestry. Migration studies show that men of Asian heritage living in the US have a lower risk of prostate cancer than white Americans, but a higher risk than men of Asian heritage living in Asia.[16]

Genetic factors

A large number of studies have examined potential genetic factors associated with prostate cancer risk. Men with BRCA-2 mutations are at increased risk for prostate cancer that is more aggressive and develops at a younger age.[17-19] Consistent evidence from genetic studies has also identified locations on chromosome 8 (in a region called 8q24) that are associated with an increased risk of developing prostate cancer and with more aggressive prostate cancer.[20-21]

Nutrition and dietary supplements

A variety of nutritional factors have been suggested to alter the risk of prostate cancer in large prospective cohort studies, but results are inconsistent between studies. Some studies suggest that diets with very high levels of calcium (>1,500 mg/day) or consumption of red and processed meat may be associated with increased risk.[22-23] Some studies also suggest that consumption of diets high in milk and dairy products and high intake of animal and saturated fats may increase risk.[24] Factors found in some studies to decrease risk include diets high in lycopene (a substance found in tomatoes and watermelon), selenium (a nonmetallic element found in a variety of foods), and vitamin E.[24] However, a randomized, placebo-controlled trial of selenium and vitamin E supplementation found no evidence of decreased prostate cancer risk.[25] At the present time, the best dietary advice for reducing the risk of prostate cancer is to eat at least five servings of a wide variety of fruits and vegetables each day, limit intake of red meats, avoid excessive consumption (e.g. > 3 servings/day) of dairy products, maintain an active lifestyle, and consume foods that help maintain a healthy weight.[26]

Obesity and physical activity

Associations between obesity and prostate cancer vary by stage of disease. In the American Cancer Society Cancer Prevention Study-II (CPS-II) Nutrition Cohort, higher body mass index (BMI) was associated with lower risk of non-metastatic low-grade prostate cancer, but higher risk of high-grade, metastatic, and fatal prostate cancers.[27] An analysis of physical activity found no association with overall prostate cancer risk, but a 30% lower incidence of aggressive prostate cancer among the most physically active compared to inactive men.[28] Although results of studies are not completely consistent on the relationships among prostate cancer, obesity, and physical activity, the data suggest that following the American Cancer Society guidelines to maintain a healthy body weight and be physically active may reduce the risk of developing aggressive prostate cancer and improve outcomes following treatment.[29-30]

Infection

Some studies have shown associations between sexually transmitted diseases and clinical prostatitis with prostate cancer. However, most of the evidence comes from case-control studies in which information about risk factors is obtained from patients after diagnosis, raising the possibility that recall bias influences the results.[24]

Medications

Long-term use of aspirin was associated with lower risk of prostate cancer in the CPS-II Nutrition Cohort, as well as some other studies.[31-32] However, taking aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDS) for the prevention of prostate cancer is not recommended due to the potential side effects of these medications. Recent studies suggest that statins, which are prescribed to lower cholesterol levels and reduce the risk of cardiovascular disease, may reduce the risk of advanced prostate cancer.[33]

Hormonal factors

Androgens influence the maturation of the prostate and are believed to contribute to the development and progression of prostate cancer. However, studies of hormones and prostate cancer risk have been complicated by measurement issues and difficulties accounting for normal changes in hormone levels as men grow older. Thus, there is still uncertainty about how hormonal factors influence prostate cancer risk.[16]

Chemoprevention

The chemoprevention of prostate cancer is an active area of research. Two drugs of interest – finasteride and dutasteride – reduce the amount of certain male hormones in the body and are already used to treat the symptoms of an enlarged prostate. In the Prostate Cancer Prevention Trial, men who received finasteride had a 25% lower risk of developing prostate cancer than men who did not take the drug.[34] Side effects from finasteride experienced by some men in this study included erectile dysfunction, loss of libido, and breast enlargement. Recently published results from the Reduction by DUtasteride of Prostate Cancer Events (REDUCE) clinical trial found that men who received dutasteride had a 23% lower risk of developing prostate cancer than men who did not take the drug.[35] Men receiving the drug also had a lower rate of surgery for benign prostatic hypertrophy (non-malignant enlargement of the prostate) and fewer urinary problems; the risk of sexual and other side effects from dutasteride was modest.

Sunlight and vitamin D

Higher prostate cancer incidence and mortality among Caucasian populations living in more northern latitudes in the US and Europe suggest that exposure to ultraviolet radiation may be protective, possibly by increasing vitamin D synthesis. Although an ecologic study in the US found that prostate cancer mortality by county is inversely related to estimated UV radiation levels,[36] and some epidemiologic studies suggest that sun exposure may be protective, most studies examining individual blood levels of vitamin D and prostate cancer risk do not show an association.[37]

Can Prostate Cancer Be Detected Early?

Most prostate cancers are diagnosed before symptoms develop through PSA screening or a digital rectal exam (DRE). Early prostate cancer usually has no symptoms. With more advanced disease, individuals may experience weak or interrupted urine flow; inability to urinate or difficulty starting or stopping the urine flow; the need to urinate frequently, especially at night; blood in the urine; or pain or burning with urination. (It is important to note that these symptoms occur frequently as a result of non-cancerous conditions, such as prostate enlargement or infection and that none are specific for prostate cancer.) Advanced prostate cancer commonly spreads to the bones, which can cause pain in the hips, spine, ribs, or other areas.

PSA screening can usually detect prostate cancer years earlier than it would be detected by a DRE or the development of symptoms.[38] Although there is no absolute cutoff between a normal and an abnormal PSA level, screening programs in the US have commonly used >4 ng/mL to define a positive test. PSA screening has several limitations. Many men who do not have prostate cancer will screen positive and require a biopsy for diagnosis, and some men with prostate cancer do not have elevated PSA levels. In addition, because many prostate cancers grow so slowly that they may never threaten a patient's life, there is a danger of overtreatment. This is a particularly important issue since treatment for prostate cancer is often associated with significant side effects.

Two large randomized trials of prostate cancer screening with PSA testing have been completed. The US-based Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial did not observe a mortality benefit from screening, while the European Randomized Study of Screening for Prostate Cancer (ERSPC) demonstrated a 20% reduction in prostate cancer mortality among men in the group invited for screening compared to those not invited.[39-40] Differences in the methods used in the US and European screening trials and differences in screening practices in the general population of men in the US may have contributed to differences in the results of the two trials. Because of continued uncertainty about the balance of benefits and risks, the Society stresses the importance of involving men in the screening decision.

American Cancer Society Guidelines for Early Detection of Prostate Cancer

The American Cancer Society released updated prostate cancer screening guidelines in March 2010.[41] These guidelines recommend that asymptomatic men who have at least a 10-year life expectancy have an opportunity to make an informed decision with their health care provider about whether to be screened for prostate cancer after receiving information about the uncertainties, risks, and potential benefits associated with prostate cancer screening. Screening should not occur without an informed decision-making process. Men at average risk should receive this information beginning at age 50. Men at higher risk, including African American men and men with a first-degree relative (father or brother) diagnosed with prostate cancer before age 65, should receive this information beginning at age 45. Men at appreciably higher risk (multiple family members diagnosed with prostate cancer before age 65) should receive this information beginning at age 40. Men should either receive this information directly from their health care providers or be referred to reliable and culturally appropriate sources. Patient decision aids are helpful in preparing men to make a decision about whether to be tested (Table 2). For men who are unable to decide, the screening decision can be left to the discretion of the health care provider, who should factor into the decision his knowledge of the patient's general health preferences and values.

Asymptomatic men who have less than a 10-year life expectancy based on age and health status should not be offered prostate cancer screening. At age 75, only about half of men have a life expectancy of 10 years or more. Men in this age group with significant co-morbidities (additional unrelated health issues), as well as younger men with life-limiting conditions, are not likely to benefit from screening. Life-limiting conditions become more common as men age; thus, it is important to consider overall health status – not age alone – when making decisions about screening.

Core elements of the information to be provided to men to assist with their decision include:

- Prostate cancer is an important health concern for men.
- Screening with the PSA blood test alone or with both the PSA and the DRE detects cancer at an earlier stage than if no screening is performed.
- Prostate cancer screening may be associated with a reduction in the risk of dying from prostate cancer. However, evidence is conflicting, and experts disagree about the value of screening.
- For men whose prostate cancer is detected by screening, it is currently not possible to predict which men are likely to benefit from treatment. Some men who are treated may avoid disability and death from prostate cancer. Others who are treated would have died of unrelated causes before their cancer became serious enough to affect their health or shorten their lives.

Table 2. Decision Aids for Prostate Cancer Screening

Supporting organization	Type of decision aid	Title & online access
American Cancer Society	Downloadable Document (PDF)	"Testing for Prostate Cancer" Available at: cancer.org/downloads/PRO/Testing_Prostate.pdf
Foundation for Informed Medical Decision Making	Video and Online Interactive Resource	"Is a PSA Test Right For You?" Available through Health Dialog at healthdialog.com/
Centers for Disease Control and Prevention	Downloadable Document (PDF) Culturally targeted options	"Prostate Cancer Screening: A Decision Guide" Available at: cdc.gov/cancer/prostate/pdf/prosguide.pdf "Prostate Cancer Screening: A Decision Guide for African Americans" Available at: cdc.gov/cancer/prostate/pdf/aaprosguide.pdf "La Detección del Cáncer de Próstata: Una Guía para Hispanos en los Estados Unidos" Available at: cdc.gov/cancer/prostate/pdf/prostate_cancer_spanish.pdf
MayoClinic.com	Online Resource	"Prostate Cancer Screening: Should you get a PSA test?" Available at: mayoclinic.com/health/prostate-cancer/HQ01273
University of Cardiff, UK	Online Interactive Resource	"PROSDEX: A PSA Decision Aid" Available at: prosdex.com/

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- Treatment of prostate cancer can lead to urinary, bowel, sexual, and other health problems. These problems may be significant or minimal, permanent or temporary.
- The PSA and the DRE may have false-positive or false-negative results, meaning men without cancer may have abnormal results and get unnecessary additional testing, and clinically significant cancers may be missed. False-positive results can lead to sustained anxiety about prostate cancer risk.
- Abnormal results from screening with the PSA or the DRE require prostate biopsies to determine whether the abnormal findings are cancer. Biopsies can be painful, may lead to complications like infection or bleeding, and can miss clinically significant cancer.
- Not all men whose prostate cancer is detected through screening require immediate treatment, but they may require periodic blood tests and prostate biopsies to determine the need for future treatment.

In helping men to reach a screening decision based on their personal values, once they understand the uncertainties, risks, and potential benefits, it can be helpful to provide reasons why some men decide for or against undergoing screening. For example:

- A man who chooses to be screened might place a higher value on finding cancer early, might be willing to be treated without definite expectation of benefit, and might be willing to risk injury to urinary, sexual, and/or bowel function.
- A man who chooses not to be screened might place a higher value on avoiding the potential harms of screening and treatment, such as anxiety or risk of injury to urinary, sexual, or bowel function.

The screening decision is best made in partnership with a trusted source of regular care. Men who have no access to regular care should be tested only if high-quality, informed decision-making can be assured through community-based screening programs. Such programs also must assure that participants with abnormal screening results receive appropriate counseling and follow-up care if needed. Availability of follow-up care must not be an afterthought. Unless these program elements are in place, community-based screening should not be initiated.

Once a screening decision has been made, the decision should be readdressed when new research becomes available that significantly alters the balance between benefits and risks, as well as uncertainties regarding prostate cancer early detection. In the absence of new information, the decision should be readdressed periodically, as a man's health status, values, and preferences change over time.

For men who choose to be screened for prostate cancer after considering the possible benefits and risks:

- Screening is recommended with the PSA with or without the DRE.
- Screening should be conducted yearly for men whose PSA level is 2.5 ng/ml or higher.
- For men whose PSA is less than 2.5 ng/ml, screening intervals can be extended to every 2 years.
- A PSA level of 4.0 ng/ml or higher has historically been used to recommend referral for further evaluation or biopsy, which remains a reasonable approach for men at average risk for prostate cancer.

Table 3. Examples of Prostate Cancer Treatment Recommendations by Disease Characteristics and Life Expectancy

Risk of progression & recurrence	Clinical characteristics	Life expectancy	Recommended initial treatment options
Low	T1-T2a, and Gleason score 2-6, and Blood PSA level < 10 ng/mL	< 10 years	Active surveillance
		> 10 years	Active surveillance or radical prostatectomy or radiation therapy (external beam or brachytherapy)
Intermediate	T2b-T2c, or Gleason score 7 or PSA level 10-20 ng/mL	< 10 years	Active surveillance or radical prostatectomy or radiation therapy (external beam +/- brachytherapy) +/- ADT
		> 10 years	Radical prostatectomy or radiation therapy (external beam +/- brachytherapy) +/- ADT
High risk	T3a, or Gleason 8-10 or PSA level > 20 ng/mL	All	Radical prostatectomy (selected patients) or radiation therapy (external beam) + long-term ADT

ADT = androgen deprivation therapy

Source: Prostate Cancer. *NCCN Clinical Practice Guidelines in Oncology 2009.*[34]

For PSA levels between 2.5 and 4.0 ng/ml, health care providers should consider an individualized risk assessment that incorporates other risk factors for prostate cancer, particularly for high-grade cancer, which may be used for a biopsy recommendation. Factors that increase the risk of prostate cancer include African American race, family history of prostate cancer, increasing age, and an abnormal DRE. A prior negative biopsy lowers risk.

How is prostate cancer diagnosed?

When prostate cancer is suspected, a biopsy is performed. A biopsy is a procedure in which a sample of body tissue is removed and examined under a microscope. A core needle biopsy is the main method used to diagnose prostate cancer. Several biopsy samples are taken from the prostate and evaluated to determine whether cancer is present and what grade it is based on the degree of abnormality of the cells. Additional tests may be required to determine if the cancer has spread beyond the prostate.

What Factors Influence Prostate Cancer Survival?

Prostate cancer survival rates are strongly related to stage, with a 5-year relative survival rate approaching 100% among patients diagnosed with localized or regional disease and 31% among men diagnosed at distant stage.[42] However, prostate cancer survival rates in the US are strongly influenced by widespread screening. Most prostate cancer cases are diagnosed as the result of a PSA screening test, which advances the time by which they will be diagnosed (referred to as lead time) by as much as 5 to 7 years.[38] As a result, the majority of US men with prostate cancer are diagnosed with localized disease.[42]

Among patients with localized or regional stage disease, factors associated with disease recurrence and progression include PSA level and Gleason score.[43-44] These factors, along with tumor (T) stage, extent of lymph node involvement, and life expectancy, are used to estimate the risk of progression and recurrence and to assist with treatment decisions (Table 3).[44]

- **T stage** expresses the size and extension of the tumor. T1 tumors are so small that they can't be felt during a DRE or seen with imaging such as transrectal ultrasound. T2 tumors can be felt during a DRE but appear to be confined to the prostate gland. T3 tumors have begun to grow and spread outside the prostate and may involve the seminal vesicles. T4 tumors have grown into tissues next to the prostate (other than the seminal vesicles), such as the bladder sphincter (muscle that helps control urination), the rectum, and/or the wall of the pelvis. Patients with T3 tumors have AJCC Stage III (regional stage disease) and those with T4 tumors are considered to have AJCC Stage IV (distant stage disease).
- **PSA level** and velocity (rate of increrase over time) have been associated with the likelihood of recurrence or progression. PSA levels of less than 10 ng/mL are considered to be low risk; 10-20 ng/mL, intermediate risk; and greater than 20 ng/mL, high risk. A PSA velocity of greater than 2 ng/mL in the year prior to diagnosis is associated with both a greater risk of disease relapse and a higher risk of prostate cancer death following treatment.[45-46]
- **Gleason score** expresses the grade of the tumor, which is the degree to which it resembles normal prostate tissue. Higher Gleason scores indicate larger differences from normal tissue and more aggressive disease. Cancers with Gleason scores of 2 to 4 are sometimes called well differentiated or low grade; cancers with Gleason scores of 5 to 7 may be called moderately differentiated or intermediate grade; and cancers with Gleason scores of 8 to 10 may be called poorly differentiated or high grade.

Survival rates for prostate cancer differ by race and ethnicity. After controlling for age and stage at diagnosis, the risk of cancer death after diagnosis when compared to non-Hispanic whites is highest for American Indian and Alaska Native men (1.81), followed by African American (1.31) and Hispanic white men (1.12). Asian and Pacific Islander men are less likely than white men to die from prostate cancer (0.70).[47] Survival differences by race/ethnicity may be attributed to differences in prognostic factors and/or differences in access to care and treatment patterns. A study in the American Cancer Society Cancer Prevention Study-II (CPS-II) Nutrition Cohort found that men with at least a high school education were 50% less likely to die after prostate cancer diagnosis than those with less than a high school education, even after accounting for differences in age, race, stage, and grade.[48]

How Is Prostate Cancer Treated?

Most men with prostate cancer have several treatment options available to them and participate in treatment decisions along with their health care providers. Treatment recommendations vary by disease severity and life expectancy since the side effects of treatment may outweigh the potential benefits for men whose cancers are unlikely to progress in their lifetime (Table 3). The major treatments for clinically localized prostate cancer are active surveillance, radical prostatectomy, and radiation therapy, with active surveillance more likely to be recommended for men of any age with low risk cancer and for those with less than 10 years of life expectancy. Patients with locally advanced prostate cancer are generally recommended to receive external beam radiation along with androgen deprivation therapy (ADT); some may be eligible for radical prostatectomy as an alternative to external beam radiation. Patients with lymph node metastasis may receive ADT alone or a combination of external beam radiation and ADT, while those with metastatic disease will generally receive ADT alone.

Figure 4 shows the primary treatment selected among men diagnosed with localized prostate cancer in 2004-2006 in 17 areas covered by Surveillance, Epidemiology, and End Results (SEER) registries, by risk category and age at diagnosis. The category "no treatment" in this figure includes active surveillance, for which there is no specific treatment code, as well as ADT, which is not accurately coded in registry data and therefore not available for analysis in publically available SEER data. As would be expected when treatment recommendations are based on life expectancy, younger men (under 65) have the highest probability of receiving potentially curative treatment (radical prostatectomy or radiation therapy) across all risk categories, whereas older men (75+) are least likely to receive curative treatment.

Each type of treatment is associated with potential risks and benefits, which men should understand in order to choose treatment based on the factors most important to them.[49] The main benefit of active surveillance is that it may allow definitive treatment to be postponed indefinitely or for many years, during which time the man will not be affected by complications or side effects of treatment. On the other hand, there is a risk that if the cancer does progress, delayed treatment may make it more difficult to cure. Radical prostatectomy and radiation therapy with or without hormonal therapy are recommended for men for whom there is a reasonable chance of cure and who have a life expectancy greater than 10 years. Surgical and radiation treatment may result in urinary incontinence, problems in bowel function, and reduced ability to achieve and maintain an erection. Some of these problems may decline as time passes, but others may increase. Hormonal treatment may be offered as an adjunct (addition) to other forms of treatment, or may be used as primary treatment for advanced disease and for men with short life expectancy. Side effects of hormonal treatment may include loss of libido (interest in sex), hot flashes, osteoporosis (low bone density), and an increased risk of diabetes and cancer. The American Cancer Society recently collaborated with the American Heart Association and the American Urological Association to issue an advisory about the cardiovascular risks associated with ADT.[50]

Prostate Cancer Treament Options

Active surveillance involves monitoring the course of disease with the expectation to intervene if the cancer progresses. Active surveillance is often offered to men who have low-risk disease and/or limited life expectancy. Monitoring under active surveillance involves PSA testing every 3 to 6 months, DRE every 6 to 12 months, and may involve additional biopsies.

Radical prostatectomy involves surgical removal of the prostate along with nearby tissues. Regional lymph nodes may also be removed for examination to determine whether lymph node metastases are present. Several approaches can be used for radical prostatectomy, including conventional (open) surgery and several minimally invasive (laparoscopic) surgical techniques. Nerve-sparing surgery is done where possible to increase the likelihood that normal sexual function is preserved.

The two types of **radiation therapy** used for prostate cancer are **external beam radiation** and **brachytherapy**.

In **external beam radiation**, the patient receives radiation treatment from an external source, usually over an 8- to 9-week period. Patients with intermediate- or high-risk cancers may be recommended for pelvic lymph node irradiation and/or ADT in addition to external beam radiation to the prostate.

Brachytherapy involves placing small radioactive pellets, sometimes referred to as seeds, into the prostate tissue. Most centers use permanent, low-dose implants that gradually lose their radioactivity over time. Brachytherapy treatment alone may be recommended for low-risk cancers, and combined with external beam radiation therapy (with or without ADT) for intermediate-risk cancers.

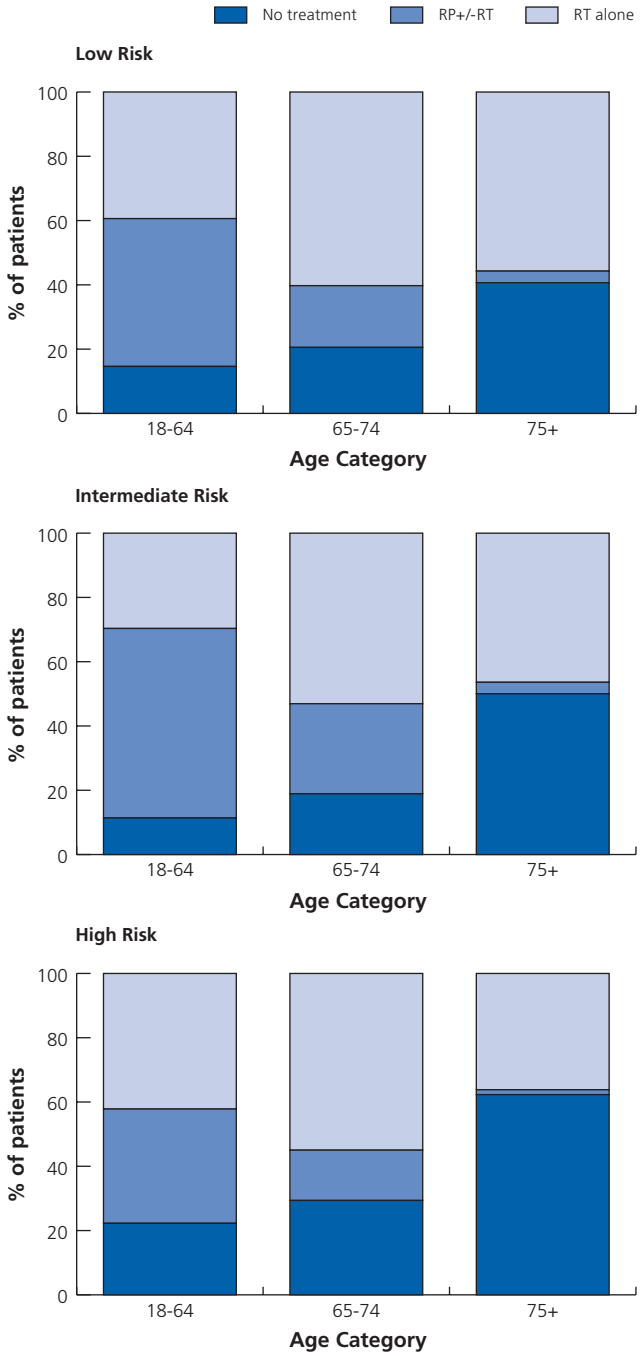
Androgen deprivation therapy (ADT), or hormone therapy, alters the effects of male hormones on the prostate through medical or surgical castration (elimination of testicular function) and/or administration of antiandrogen medications.

Men who receive curative-intent treatment with either radical prostatectomy or radiation therapy are usually monitored for cancer recurrence by measuring PSA levels every 6 to 12 months for the first 5 years and annually thereafter. Men who have radical prostatectomy are considered to have biochemical recurrence if their PSA level never falls to undetectable after surgery, or if they achieve an undetectable PSA after surgery, but have a subsequent detectable PSA that increases on two or more laboratory tests. Many men who do have a biochemical recurrence do not develop detectable metastases for many years. For example, one study found that the median time from PSA elevation to metastases was 8 years.[51] Several types of treatment options are available for patients whose prostate cancer has recurred or progressed.[52]

Disparities in stage at diagnosis and treatment

- Analyses of data from the National Cancer Database, a national hospital-based registry, found that patients without health insurance or with Medicaid insurance were more likely than those with private insurance to be diagnosed with advanced stage (AJCC Stage III-IV) prostate cancer, compared to early stage (AJCC Stage I-II) prostate cancer.[53-54] Insurance status is associated with access to preventive services and primary care. The 2006 National Health Interview Survey (NHIS) found that 53.6% of uninsured adults had no usual source of health care, compared with 9.9% of privately insured adults.
- A study of factors associated with PSA screening within the past 2 years using 2005 NHIS data found that men without a usual source of health care were significantly less likely to have had a PSA test within the past 2 years. Among men aged 50-79, 51.2% of those with a usual source of care had a recent PSA test, compared to 25.3% without.
- Previous studies have documented that African Americans were more likely than whites to be diagnosed with advanced stage prostate cancer. From 1988-1989 to 2004-2005, however, the incidence (per 100,000) of T3 and T4 prostate cancers among African American patients decreased from 90.9 to 13.3 while the incidence among whites decreased from 52.7 to 7.9.[55] Figure 5 shows trends in incidence rates by stage for African American and white men from 1988 to 2006. These figures suggest that as overall incidence rates for more advanced disease (including localized T3 and T4 tumors as well as regional and distant stage) have declined, disparities in disease severity by race have also been reduced. Table 4 compares disease severity characteristics among African American and white men diagnosed in 2004-2006. Although African American men continue to have higher PSA levels at diagnosis, the distribution of Gleason scores is now quite similar.

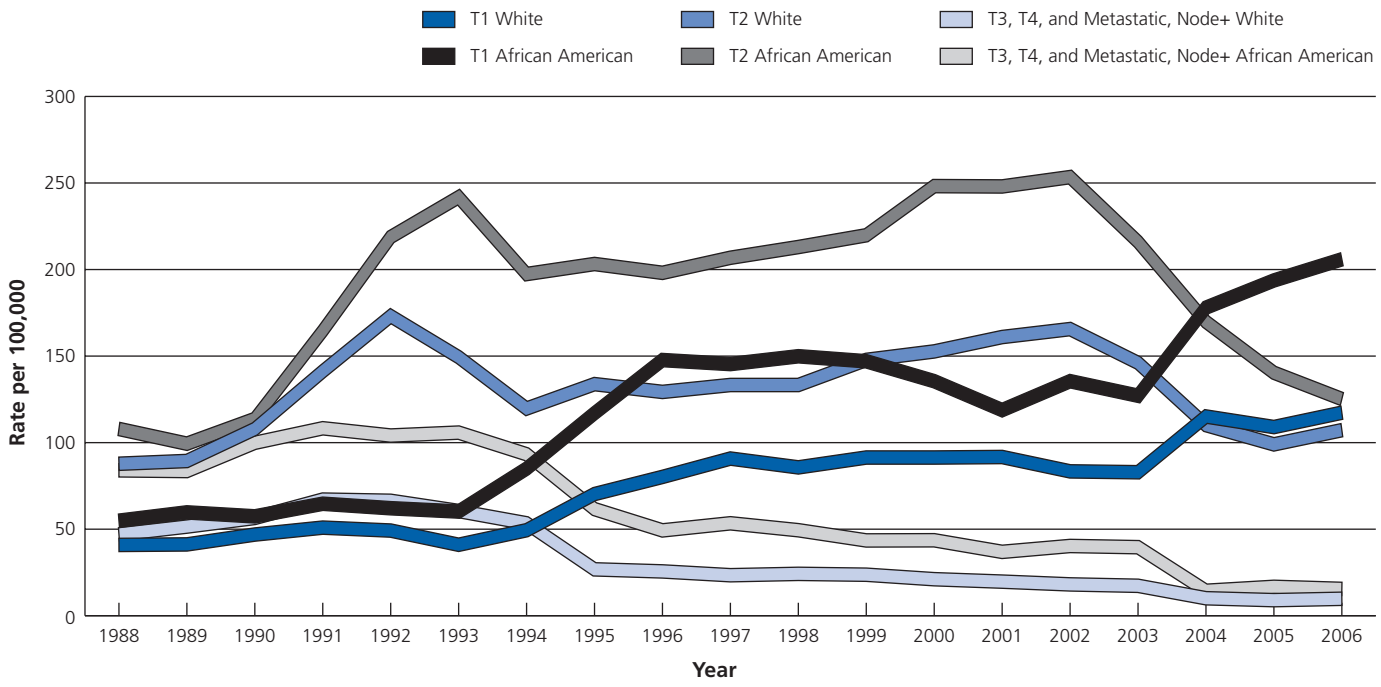
Figure 4. Prostate Cancer Treatment Patterns by Risk Category (Disease Severity) and Age, US, 2004-2006



RP = radical prostatectomy; RT = radiation therapy

Data Source: Surveillance Epidemiology and End Results (SEER) Program, SEER 17 Registries, 2004-2006, Division of Cancer Control and Population Science, National Cancer Institute, 2009.

Figure 5. Trends in Prostate Cancer Incidence by Stage and Race, US, 1988-2006



Data Source: Surveillance, Epidemiology, and End Results (SEER) Program, SEER 9 Registries, 1988-2006, Division of Cancer Control and Population Science, National Cancer Institute, 2009.

- Decreasing disparities in disease severity between African Americans and whites likely result from increased awareness of the higher prostate cancer risk among African Americans among health care providers and the general public and the uptake of PSA screening among African American men. The 2005 NHIS found that non-Hispanic African American men aged 40-49 were more likely to have had a PSA test in the past 2 years than non-Hispanic white men (25.7% and 14.6%, respectively). Men aged 40-49 with a family history of prostate cancer were more likely to have had a PSA test than men with no family history (36.6% and 14.8%, respectively). These data suggest that health care practitioners are implementing recommendations for discussing PSA screening at an earlier age with high-risk men, including African Americans and those with a family history of prostate cancer. The prevalence of recent PSA screening among 50- to 79-year-old men was 49.9% in non-Hispanic African Americans and 48.8% in non-Hispanic whites. An analysis of data from the NHIS 2000 survey found that the majority (73.8%) of African American men who had had at least one PSA test reported that they had physician discussions about the advantages and disadvantages of the test.[56]

Numerous studies have documented differences in treatment between African American and white men with prostate cancer.[57-60] In particular, African American men with localized prostate cancer are less likely to have curative treatment (radical prostatectomy or radiation therapy). Among patients receiving curative treatment, African American men are more likely to receive radiation therapy than radical prostatectomy.[57, 61] Differences in treatment patterns by race persist in the most recent years of data available from the SEER registries (Table 5). Differential treatment patterns by race/ethnicity may result from health system, physician, and patient factors, including communication and understanding of treatment options.[57, 62-65] Several studies have also found higher levels of medical mistrust among African American men with prostate cancer, particularly those who delayed seeking care.[66-67] Disparities in receipt of curative treatment among African American and Hispanic patients may contribute to poorer survival in these groups.[47, 55, 68] Previous studies have reported African American and white patients with various types of cancer have similar survival rates when recommended treatment is administered uniformly and where patients are treated in equal-access facilities.[69-70]

Table 4. Prostate Cancer Age Distribution and Clinical Characteristics (%) by Race, US, 2004-2006

Characteristic	All patients	White	Black
Age			
Mean	67.0	68.0	65.0
18-64	40.0	38.5	49.9
65-74	35.3	35.5	33.6
75+	24.8	26.0	16.5
PSA level, ng/mL			
Median	6.5	6.4	7.2
≤2.5	7.0	7.2	5.7
2.6-4	6.7	6.9	5.6
4.1-6.9	32.5	32.9	30.0
7-10	15.7	15.7	15.5
10.1-20	12.9	12.6	14.9
>20	10.9	10.3	15.0
Unknown	14.3	14.4	13.3
Gleason Score			
2-6	46.3	46.8	42.8
3+4	23.7	23.5	25.1
4+3	9.3	9.2	9.8
8-10	14.2	14.1	14.9
Unknown	6.5	6.4	7.4
Clinical Tumor Stage			
T1	52.2	51.8	55.3
T2	39.5	40.0	36.2
T3	2.3	2.4	2.2
T4	1.0	1.0	1.3
Unknown	5.0	5.0	5.0
Seer Summary Stage			
Localized	80.9	80.9	80.9
Regional	11.7	11.9	10.4
Distant	4.3	4.1	5.7
Unknown	3.1	3.1	3.0

Data Source: Surveillance, Epidemiology, and End Results (SEER) Program, SEER 17 Registries, 2004-2006, Division of Cancer Control and Population Science, National Cancer Institute, 2009.

Survivorship

The National Cancer Institute estimates that approximately 2.2 million men with a history of prostate cancer were alive in January 2006. Nearly half of all male cancer survivors in the US are prostate cancer survivors. The prominence of prostate cancer survivors results in part from the large number of men diagnosed every year (217,730 in 2010) and the very high relative survival rates for this cancer. Prostate cancer survivors face a number of challenges, including the possibility of recurrence, complications of treatment, and functional impairments, which can severely impact quality of life. Many studies are under way to improve treatment for prostate cancer and improve quality of life for survivors. Important areas of research include how to better differentiate between early cancers that need aggressive treatment and those that can be safely left untreated and how to improve existing treatments so that they are less likely to produce unwanted side effects.

The decisions regarding the treatment and management of prostate cancer are often difficult because of the significant side effects of treatment that include sexual dysfunction, incontinence, urinary irritation, and bowel problems, all of which may have a negative impact on quality of life. One of the most common and most distressing side effects of prostate cancer treatment is the impact on sexual function, with upward of 75% of prostate cancer survivors reporting some degree of post-treatment erectile dysfunction.[71-73] Sexual dysfunction and urinary problems are common among prostate cancer survivors receiving radical prostatectomy, external beam radiation, or brachytherapy.[74-75] Recent findings suggest that nerve-sparing surgical procedures may mitigate some of the sexual side effects associated with radical prostatectomy.[76] In addition to functional impairments in sexuality, men whose treatment includes androgen suppression (the suppression or blockage of male hormones through surgery or hormone therapy) may experience a feminization of the body, reduced sexual desire, and diminished intimacy with their spouse.[77]

The physical side effects of prostate cancer treatment can lead to significant emotional and psychological distress, as well as complications in spousal or partnered relationships.[78] In addition, other emotional concerns such as fears about disease progression and recurrence, anxiety, and depression may also have a negative impact on prostate cancer survivors' quality of life. Findings from the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) study, a national disease registry with more than 10,000 prostate cancer patients, indicated that 2 years after completion of treatment, fears about disease recurrence remained high, particularly among those with poorer physical health.[79] Likewise, a study of prostate cancer patients using Medicare data found that elevated PSA scores and secondary androgen ablation therapy were associated with rising fears of recurrence and poorer quality of life.[80] Still other research has begun to investigate prostate cancer survivors' perceptions about the effectiveness of their treatments and satisfaction with their treatment decisions. One study reported that most men felt confident that their cancer was well controlled and were satisfied with their treatment decisions.[81] However, a different set of factors affected each of these issues; perceived cancer control was most affected by adverse medical factors such as high Gleason scores whereas confidence in treatment decisions was highest among men who received radical prostatectomy or brachytherapy. In a large, multi-center study of more than 1,200 prostate cancer patients, satisfaction with treatment outcomes was significantly associated with patients' changes in sexual and urinary function, as well as with the degree of emotional distress among their spouses.[76]

Table 5. Prostate Cancer Treatment (%) by Race and Disease Severity, US, 2004-2006

Risk of progression & recurrence	White			Black		
	No treatment	RP+/-RT	RT alone	No treatment	RP+/-RT	RT alone
Low	17.7	35.7	46.8	20.9	26.7	52.5
Intermediate	18.3	45.2	36.4	21.3	40.3	38.5
High	32.2	28.2	39.6	38.0	22.9	39.1
Total	21.2	38.6	40.4	25.4	32.3	42.3

RP = radical prostatectomy; RT = radiation therapy

Data Source: Surveillance, Epidemiology, and End Results (SEER) Program, SEER 17 Registries, 2004-2006, Division of Cancer Control and Population Science, National Cancer Institute, 2009.

An important issue when considering the side effects of prostate cancer treatment is the degree to which these symptoms occur as part of the normal aging process. Hoffman et al. compared participants in the Prostate Cancer Outcomes Study (PCOS) to age- and ethnicity-matched controls with no history of prostate cancer and found that over a 5-year period, prostate cancer survivors had significantly greater declines in both sexual and urinary function.[82] Patients also reported higher levels of distress associated with these declines, but bowel function and general quality of life scores were not affected by cancer status.[82] In summary, treatment for prostate cancer is associated with complications that may negatively impact patient quality of life. In light of the currently documented modest gains in life expectancy from aggressive treatment when compared to clinical observation (active surveillance or watchful waiting), it is important for patients and their providers to discuss potential side effects as they relate to quality of life during treatment decision-making.

American Cancer Society Research

The American Cancer Society Cancer Prevention Study-II (CPS-II) is part of a large, international consortium that includes more than 16,000 cases of prostate cancer. The mission of this consortium is to identify genetic factors that increase risk for cancer, and further to study how these genetic factors interact with lifestyle and environmental factors. Through the work of this consortium, the first genetic markers ever to be associated with risk of prostate cancer were identified. These markers are currently being used in risk prediction models to help identify men at high risk of prostate cancer.

The American Cancer Society funds individual investigators in medical schools, universities, research institutes, and hospitals throughout the country through its Extramural Grants program. The program is currently funding 97 grants in prostate cancer research, totaling $54,973,800. Ongoing studies include:

- The identification of biologic markers for the early detection of recurrent prostate cancer
- Stress management and exercise during prostate cancer treatment
- The role of inflammation in prostate cancer
- Improving magnetic resonance imaging of prostate cancer
- Racial and ethnic differences in prostate cancer risk and treatment
- Understanding the molecular mechanisms of prostate cancer

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