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Trends in Prostate Cancer in the United States

Otis W. Brawley

Correspondence to: Otis W. Brawley, MD, FACP, Chief Medical and Scientific Officer, American Cancer Society, Atlanta, GA (e-mail: Otis.Brawley@cancer.org).

In the United States, prostate cancer is the most commonly diagnosed non–skin cancer and the second leading cause of cancer death. The American Cancer Society estimates that 241 740 American men will be diagnosed with the disease and 28 170 men will die of it in 2012. Prostate cancer demographics have changed dramatically over the past 30 years. The prostate cancer age-adjusted incidence rate increased through the 1980s and peaked in the early to mid-1990s. The incidence rate has declined since. American mortality rates rose through the 1980s and peaked in 1991. Today, the American incidence rates are below 1975 levels. Both the incidence rate and the 5-year survival rates are heavily influenced by the introduction of serum prostate-specific antigen test and the widespread use of it in cancer screening. The effect of screening on prostate cancer mortality is less certain. Screening has caused a dramatic increase in the number and proportion of men diagnosed with localized disease. Outcomes studies among men treated with radical prostatectomy show that greater than 30% serum prostate-specific antigen relapse rates are common. This suggests that many men who are diagnosed with "localized early stage disease" actually have "apparently localized early stage disease," which is really low-volume metastatic disease.

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In the United States, prostate cancer is the most commonly diagnosed non–skin cancer and the second leading cause of cancer death. It is estimated that 241 740 men will be diagnosed with the disease in 2012 and 28 170 will die of it (1). Among men alive today, it is estimated that 1 in 6 (16.2%) will be diagnosed with the disease and approximately 1 in 33 (3%) will die of it. In 1975, lifetime risk of diagnosis was about 1 in 12 (8%), and lifetime risk of death was 3%. It is estimated that 2.28 million Americans were alive after a diagnosis of prostate cancer in 2007 (1).

Prostate Cancer Incidence and Mortality

Trends in US incidence and mortality rates for black and white Americans from 1975 to 2008 are shown in Figure 1 (2). Approximately 10% of the American population is black or African American. The overall American male prostate cancer incidence and mortality rates closely follow that of white men.

The incidence rate rose approximately 2% per year from 1975 into the late 1980s. This trend was caused by incidentally detected disease associated with the increased use of transurethral resection of prostate (TURP) for treatment of benign prostatic hyperplasia (2). TURP-detected cancers were half of all detected cancers in the mid-1980s, but the proportion of TURP-detected tumors fell off as the use of the procedure declined (3).

Widespread prostate specific antigen (PSA)–based screening began in the United States in 1991 and 1992 after publication of studies showing that screening found cancer (4). As is common with the introduction of any new screening test, this caused a dramatic rise in incidence. There was true early detection, meaning some finding of cases that would have been diagnosed in later years. There was also some detection of cancers that would never have been diagnosed or treated. The decline in incidence in the late 1990s represents a clearing out of the prevalent cases, meaning early detection of some cancers that would have been diagnosed in the future.

The prostate cancer mortality rate rose from 1975 until 1991, when it began dropping. The mortality rate has declined by 39% from 1991 to 2008. The 2006–2008 annual mortality rates are slightly below the 1975 rate. The reason for the rise in mortality from 1975 to 1991 is unknown. Some have suggested that changes in the World Health Organization definitions of cause of death increased attribution of cause of death to prostate cancer. The drop in mortality since 1991 may be due to 1) a positive effect of screening and treatment, 2) more changes in attribution of cause of death, 3) hormonal therapy causing some men with metastatic disease to have a true increase in time from diagnosis to death, or 4) possibly increased risk of death from cardiovascular disease among some prostate cancer patients treated with hormonal therapies for early disease (5). All four causes are plausible and could account for the drop in mortality.

Even when accounting for racial differences, incidence rates vary considerably by state (8). Using data gathered from 2003 to 2007, age-adjusted rates for whites vary from a low of 123 per 100 000 in Arizona to a high of 183 per 100 000 in Minnesota (1). This difference reflects variance in intensity of screening practices rather than variance in inherent population risk. After accounting for racial differences in the population, there is much less state-by-state variation in mortality. Some of the most convincing data to suggest that screening is not very effective are ecologic studies showing that a higher prevalence of screening is correlated with a higher prostate cancer incidence rate but is not correlated with a difference in prostate cancer mortality rate (6).

Race and Prostate Cancer

The US government began publishing black and white cancer incidence and mortality data in the 1970s and data for Native

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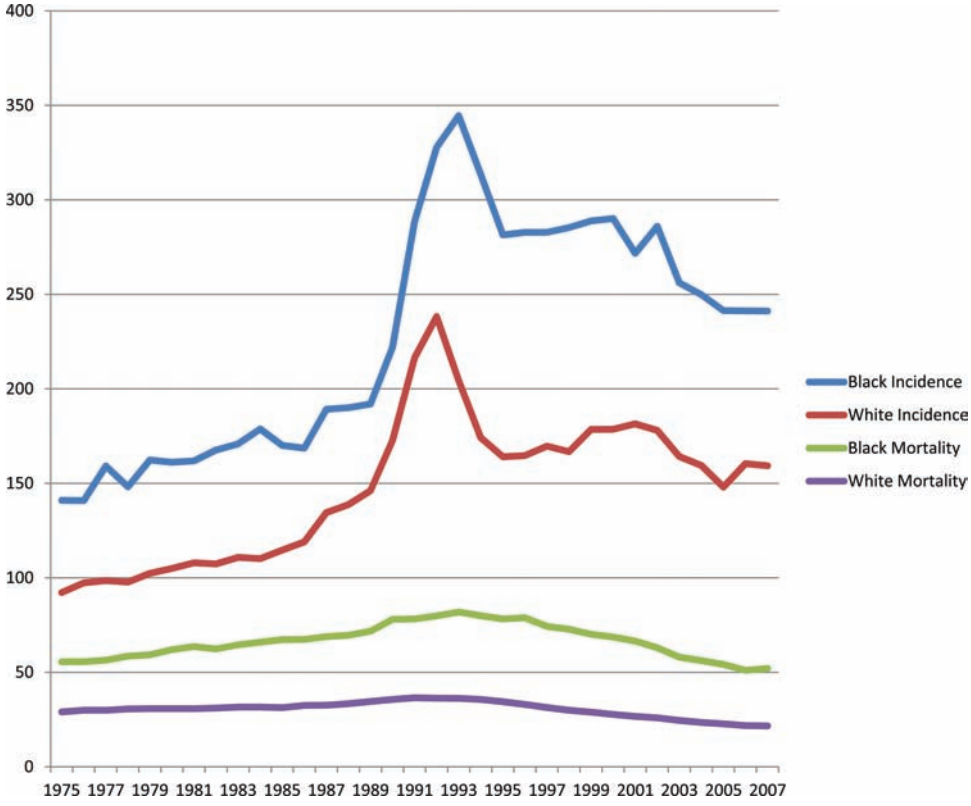

Figure 1. Prostate cancer incidence and mortality (1975–2007). Age-adjusted prostate cancer incidence and mortality rates per 100 000 for black and white Americans as measured in the National Cancer Institute Surveillance Epidemiology and End Results program. Overall US male rates are very similar to US white rates. Data is age-adjusted to the year 2000 population standard.

Table 1. Incidence and mortality rate per 100 000 by race 2003–2007*

Race/ethnicity	Incidence	Mortality
All Races	156.0	24.7
White	149.5	22.8
Black	233.8	54.2
Asian/Pacific Islander	88.3	10.6
American Indian/Alaskan native	75.3	20.0
Hispanic	107.4	18.8

* Age-adjusted prostate cancer incidence and mortality rates annualizing 2003–2007 rates for the five races and ethnicities captured by the National Cancer Institute (NCI) Surveillance, Epidemiology, and End Results (SEER) program (7). Data are per 100 000 and age-adjusted to the year 2000 population standard.

Americans, Asian Americans, and Americans of Hispanic ethnicity in the early 1990s. Annualized incidence and mortality rates by race/ethnicity for the period 2005–2008 are in Table 1 (7). These racial/ethnic categories are defined by the US Office of Management and Budget (OMB) (8). The OMB is clear that these are sociopolitical categories, not based in biology. This distinction is important as incidence, mortality, and survival statistics are likely affected by differences in education and other socioeconomic/environmental factors.

Race is both a prostate cancer risk factor and a prognostic factor. Currently, African American men have a risk of diagnosis that is 1.7 times above that of whites and risk of death that is 2.3 times greater. African American men and Jamaican men of African descent have the highest prostate cancer incidence and mortality rates in the world. Presumably, because of the popularity of screening in the United States, white American men also have one of the highest incidence rates in the world (9). The disease is more common in Caucasians living in North America and northwestern Europe, compared with people from Asia and South America. Men of Asian descent living in the United States have a lower prostate cancer risk compared with white Americans, but their risk is higher than that of men of similar backgrounds living in Asia (10).

Stage at Diagnosis

Screening has dramatically changed the distribution of stage at diagnosis over the past 30 years. The proportion of men diagnosed with distant disease has gone down largely because the denominator has been filled with men diagnosed with local and regional disease. The incidence rate of localized disease has dramatically increased, but of note, the incidence rate of combined regional and distant disease has not decreased. One possible explanation is that screening may be increasing the burden of low-risk cancers without significantly reducing the burden of more aggressively growing cancers (11).

The National Cancer Institute's Surveillance Epidemiology and End Results (SEER) database, which provides so much of the prostate cancer demographic data, does not collect information by American Joint Committee on Cancer (AJCC) stage, but it groups cancers into local, regional, and distant stages (7). Local stage corresponds to AJCC stages I and II. Regional stage describes disease that has spread to areas near the prostate. It includes AJCC stage III and stage IV cancers that have not spread to distant parts of the body. Regional stage includes T4 tumors

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that have spread to nearby lymph nodes (N1). Distant stage describes all cancers that have spread to distant lymph nodes, bone, or other organs (M1).

Screening has clearly led to an increasing number of men diagnosed with localized disease. Among men diagnosed during the period 1999–2006, 80% had localized disease, 12% had regional disease, and only 4% had distant disease. Three percent of men in the SEER database were not staged at diagnosis.

It might be more appropriate to call local disease at diagnosis, "apparently" localized disease. One-third to 40% of men diagnosed with "apparently" localized disease and treated with radical prostatectomy eventually relapse by serum PSA (12,13).

Grade at Diagnosis

Over time, there has been migration of grade at diagnosis. It is primarily a shift from well-differentiated to moderately differentiated disease; this may weaken grade-based prognostic categorizations in studies over time (14). This grade migration was independent of patient age. It is likely due to changes in pathologic interpretation rather than to changes in disease characteristics. Recent SEER data show that nearly half of all prostate cancers diagnosed in recent years are of low grade, Gleason score 2–6, and there is very little black–white difference grade at diagnosis as shown in Table 2.

Survival Rates

With the shift toward a greater proportion of men diagnosed with localized disease, the proportion living more than 5 years after diagnosis has increased (7). Among men diagnosed in the mid-1970s, 69% lived 5 years. In the mid-1980s, it was 76%. Today, 5-year relative survival rates for men with local and regional disease are 100%. The 10-year relative survival for the cohort diagnosed with local and regional disease in 1998 is 95%, and 15-year survival is 82%. Less than one-third of men diagnosed with metastatic disease survive 5 years (7). Today, there is minimal racial difference in stage distribution at diagnosis and in 5-year survival statistics.

Overdiagnosis

Overdiagnosis is the phenomenon of finding tumors that fulfill the histological criteria for malignancy but have little potential for spread and causing death. Cancer screening by its very nature is prone to overdiagnosis and lead-time bias. Lead-time bias is increasing survival by finding disease earlier. It has been estimated that 50%–60% of screen-detected cancers are tumors that are not significant to the specific patient's health (15,16). Stage at diagnosis and 5-year survival statistics are, of course, heavily influenced by overdiagnosis.

Welch and Albertsen compared incidence and mortality trends over the period 1986–2005, to estimate that 1.3 million Americans received unnecessary treatment for prostate cancer (17).

Prostate Cancer Risk Factors

The only well-established risk factors for prostate cancer are age, race/ethnicity, and family history of the disease. In the United States, history of screening has become a risk factor for diagnosis.

Table 2. Prostate cancer grade of disease at diagnosis*

Gleason Score	All, %	Whites, %	Blacks, %
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

* Distribution of prostate cancer by Gleason Score and race. Abstracted from National Cancer Institute (NCI) Surveillance, Epidemiology, and End Results (SEER) data (7).

Age

Prostate cancer is primarily a disease of older men. Over the last 30 years, there has been a trend toward a larger number of younger men being diagnosed. Prior to the PSA screening era, the median age at diagnosis was 70 years. The median age at diagnosis over the past decade was 67 years. The incidence rate in 2005 relative to 1986 was 0.56 in men aged 80 years and older, 1.09 in men aged 70–79 years, 1.91 in men aged 60–69 years, 3.64 in men aged 50–59 years, and 7.23 in men younger than age 50 years (7).

In 2005, less then 10% of men diagnosed in the United States were less than 55 years old. Approximately one-third were aged 55–64 years, another third were aged 65–74, and nearly one-fourth of all men diagnosed were aged 75 years or older.

The age distribution of men diagnosed during the period 2003–2008 is shown in Table 2. Age-specific incidence and mortality rates for black and white Americans (2003–2008) are shown in Figure 2. Risk of diagnosis goes down dramatically after age 80, but risk of prostate cancer death increases throughout adult life.

Other than screening history, age is by far the strongest risk factor for prostate cancer incidence and death. Age is also a prognostic factor. Contrary to popular thought, young age in and of itself is not associated with worse outcomes after prostate treatment (18).

Race/Ethnicity

It is frequently mentioned that blacks have a higher incidence and mortality rate than whites. Interestingly, few have studied why whites have higher incidence and mortality compared with Asians, Hispanics, or Native Americans. There are studies suggesting that the prostate cancer risk for Asians, Hispanics, and Native Americans increases as members of these groups acculturate into US white society (19).

Grade, percent of tumor in the biopsy specimen, stage of disease, and overall health are very crude predictors of outcome. Better prognostic tools are needed. It is of note that when these factors are normalized, race does not appear to be a factor in outcome.

Differences in treatment patterns by race have been documented for nearly 20 years (20–23). The consistent pattern is that African Americans get less aggressive therapy at every stage of disease. When done rigorously, equal treatment yields equal outcome among equal patients. As there are questions concerning the efficacy of most prostate cancer treatments, one cannot say with absolute certainty what effect differences in treatment patterns have contributed to the higher mortality rate and risk of death of African Americans.

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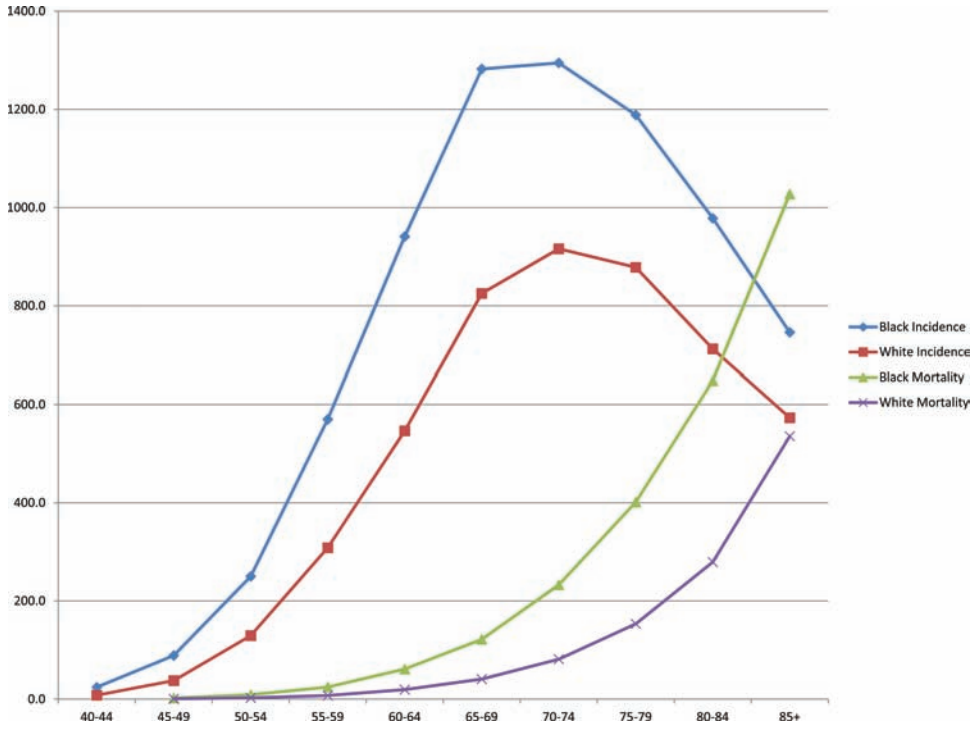

Figure 2. Age-specific incidence and mortality rates (per 100 000) for black and white American men as measured in the National Cancer Institute Surveillance Epidemiology and End Results program for diagnosis or death between 2003 and 2007.

Race may actually be a surrogate for socioeconomic factors. Literacy has also been correlated with stage at presentation (24). Education is also a prognostic factor for prostate cancer death. African Americans who have less than 12 years of education have a relative risk of prostate cancer death that is 1.51 times (95% confidence interval [CI] 1.03–2.22) greater than that of African Americans with a college education. Whites have a comparable relative risk of 1.48 (95% CI 1.25–1.75). Similarly, lack of health insurance is associated with disease severity at diagnosis (25,26).

Family History

Family history of prostate cancer does increase risk of diagnosis and, to a lesser extent, death from prostate cancer. Having a father or brother with prostate cancer more than doubles a man's risk of diagnosis (27). Risk is higher for men with an affected brother than for those with an affected father. The risk is much higher for men with several affected relatives, particularly if their relatives were young at the time the cancer was found. In some cases, there may be an inherited or genetic factor; however, one cannot exclude common environmental factors within a family. Some familial risk may simply be the fact that a man is more likely to seek screening if a close relative is diagnosed. Trends in prostate cancer incidence have in some ways affected family history of the disease.

Genetic studies suggest that strong familial predisposition may be responsible for between 5% and 10% of prostate cancers. Some genes and common gene variations are correlated with increased risk of prostate cancer. One of these is called Hereditary Prostate Cancer Gene 1 (*HPCG*). Mutations in *BRCA1* or *BRCA2* genes have been linked to increased risk of breast and ovarian cancer in women and may also increase prostate cancer risk in some men. If truly causal for prostate cancer, these mutations account for a very small percentage of prostate cancers.

Screening

Those who get screened clearly increase their risk of disease diagnosis. By most estimates, a man choosing annual screening increases lifetime risk of diagnosis from 8% to perhaps as high as 20% (28).

The Prostate Cancer Prevention Trial demonstrated that screening is a significant risk factor for diagnosis of prostate cancer (29,30). In this trial, men with a serum PSA less than 3.0 ng/ml and no history of prostate cancer were randomized to the drug finasteride or placebo and followed for 7 years. The control arm was median age 62 at their start of the study and 69 at the time of the trial's end. They were rigorously screened every year for 7 years, and all men with eight normal screens over 7 years were asked to submit to a prostate biopsy.

Approximately 14% of men were diagnosed with a prostate cancer through annual screening, and an additional 14% were diagnosed with prostate cancer by a biopsy done after eight normal screening tests (26,27). It is fair to say that PSA screening diagnosed 14% of these men with prostate cancer and missed as much prostate cancer as it finds. It is estimated that 3% of men aged 60 will ultimately die of prostate cancer and 28% can be diagnosed. This is evidence of overdiagnosis.

Conclusion

The demographic of diagnosed prostate cancer has changed dramatically over the past 30 years. Widespread use of PSA screening has lowered the median age at diagnosis and increased the number of men diagnosed with localized disease. There now exists a large population of survivors. Some of those with localized disease have indolent tumors that will never become symptomatic or cause death. Because of overdiagnosis, the true efficacy of prostate cancer

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treatment is uncertain. Prostate cancer–specific mortality rates are declining. It is however certain that we are curing some men who do not need to be cured. The question remains, "Are we curing men who need to be cured?" An unanswered, unsettled question is, "Are we doing more harm than good in diagnosing this disease?"

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Affiliations of author: American Cancer Society, Atlanta, GA; Departments of Hematology, Medical Oncology, Medicine and Epidemiology, Emory University, Atlanta, GA.

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