Critical Thinking for Early Diagnosis of Prostate Cancer

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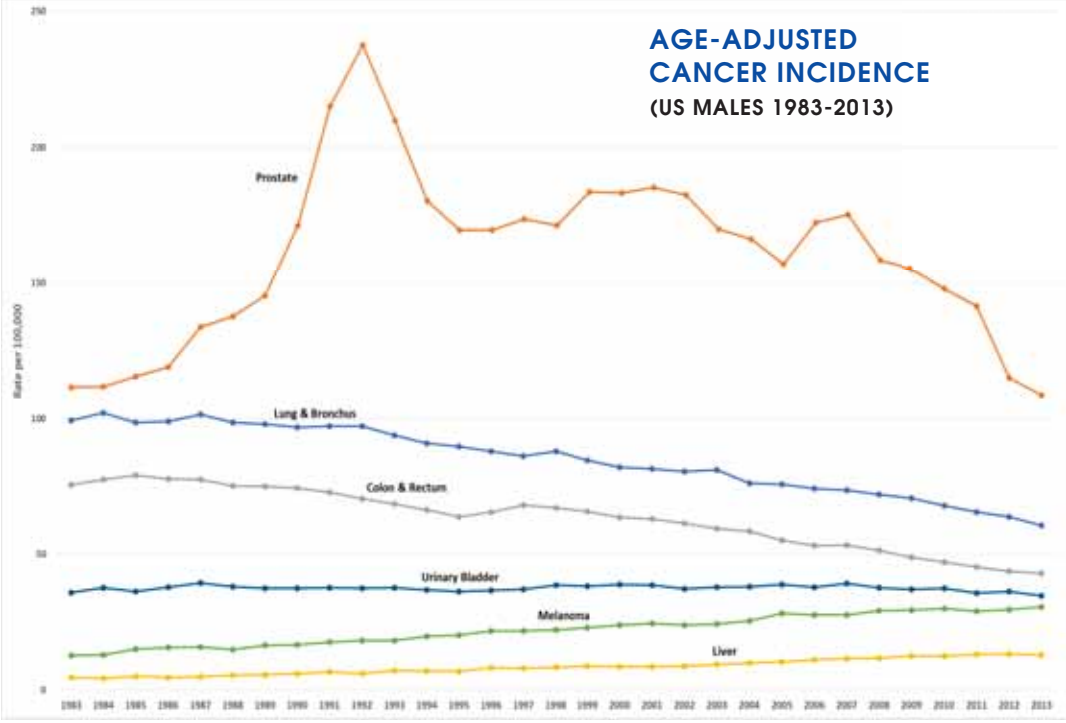
The best outcomes in cancer treatment can be achieved with early diagnosis. Prostate-specific antigen (PSA) is unique in that it is the only tissue-specific biomarker that can aid in the early diagnosis of cancer, in addition to its use for post-treatment monitoring. PSA is only expressed in prostate tissue and, in combination with a digital rectal examination (DRE), is an effective screening tool for the diagnosis and early detection of prostate cancer.

Although controversy continues to surround the use of PSA testing as a screening aid, much of that actually relates to misconceptions about how to implement PSA and how best to follow-up on a suspicious test result. The dramatic spike in prostate cancer detection and decline in mortality due to prostate cancer that accompanied the introduction of PSA screening in the early 1990s, and the results of more recent long-term studies in large patient populations are evidence of the value of PSA testing when properly understood and applied.

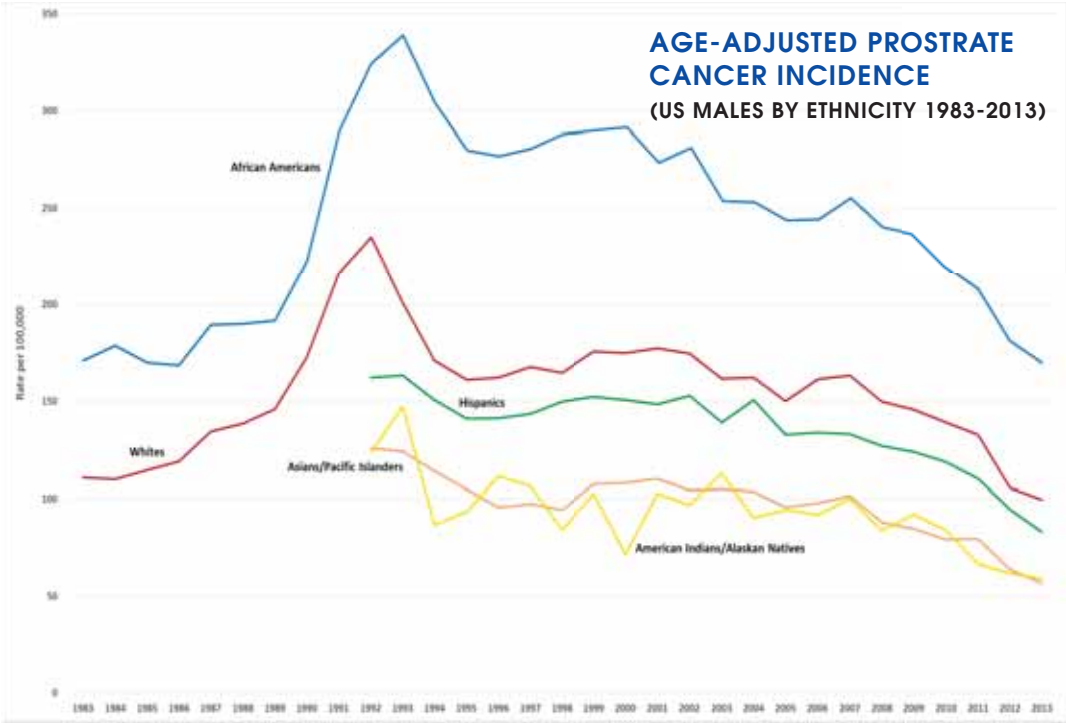
Prostate cancer represents 27% of all cancers in men and is the second deadliest form of cancer in this population. In 2016, an estimated 26,000 men died of prostate cancer. The disease is especially prevalent among African-American men and men who have first-degree relatives with prostate cancer. More aggressive prostate cancer tends to occur more often in younger men.

A sharp decline in the age-adjusted incidence of prostate cancer in the early 1990s coincided with the introduction of PSA testing and the approval by the U.S. FDA in 1994 of PSA diagnostics together with DRE for screening asymptomatic men.



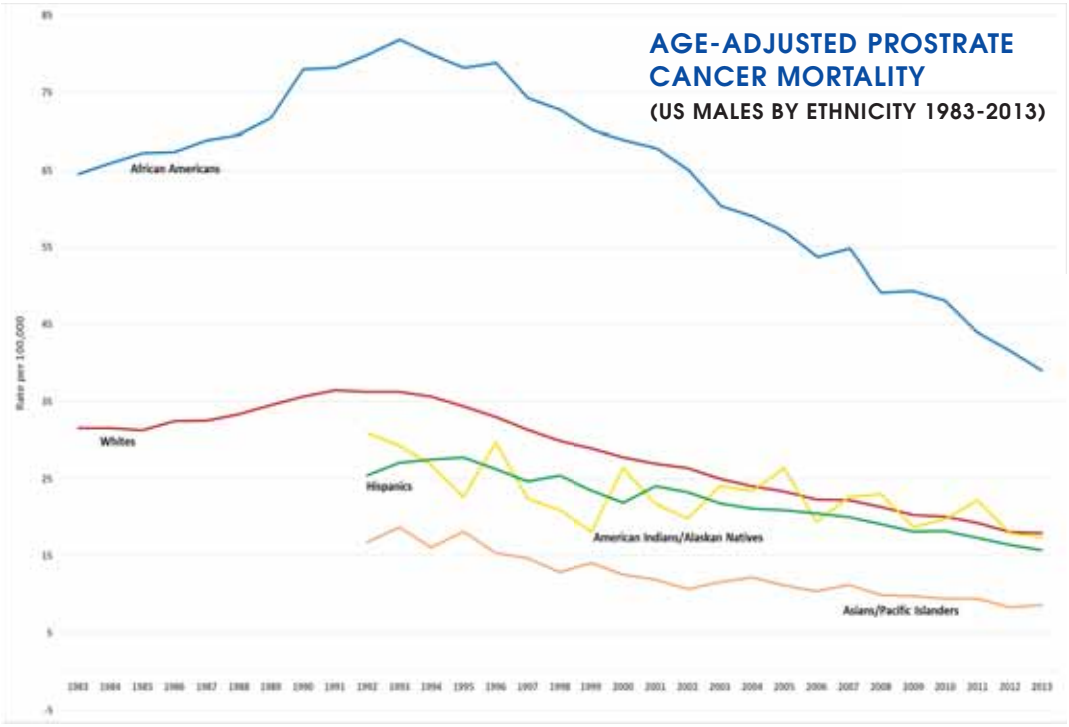
Source: SEER Program, National Cancer Institute, Bethesda, MD

The incidence continued to decline gradually over the subsequent years. The peak and decline in prostate cancer incidence seen during the early 1990s was particularly notable among African-American men, who are at increased risk for the disease.



Source: SEER Program, National Cancer Institute, Bethesda, MD

This sub-population has also showed a substantial drop in prostate cancer mortality throughout the years following 1994 and the approval of PSA screening.



Source: SEER Program, National Cancer Institute, Bethesda, MD

Understanding Early Prostate Cancer Diagnosis and Treatment

An elevated PSA test result does not necessarily imply the need for immediate treatment or even a follow-up biopsy procedure. When immediate treatment is ruled out, depending on the PSA level and findings on DRE, together with other factors such as patient age and comorbidities, one of two paths is recommended:

PASSIVE SURVEILLANCE

- Suspect localized, low-risk (indolent) tumor
- Limited to men with a short life expectancy
- Initiate symptomatic treatment only with disease progression
- Decision made to forego definitive treatment

ACTIVE SURVEILLANCE

- Suspect localized, low-risk tumor, Gleason <6 (indolent)
- Postponing immediate treatment
- Transrectal ultrasonography (TRUS)-guided biopsy to detect stage and grade migration
- Monitoring via PSA and DRE
- Definitive treatment if evidence of progression

In general, about two-thirds of prostate tumors will be slow growing, while one-third will be more aggressive and present a greater short-term risk.

The Prostate Cancer Screening Conundrum

Prostate cancer, like many other types of tumors, is often asymptomatic until it has progressed and sometimes even become invasive and metastatic. This highlights the value of being able to screen for PSA, an organ/tissue-specific biomarker for cancer risk, to improve early detection of prostate tumors. PSA is an enzyme that liquefies semen and is secreted exclusively by prostatic epithelial cells.

Screening for prostate cancer has two components: DRE and age-specific PSA testing. The DRE assesses several features of the prostate that can be indicative of cancer: nodularity; size; symmetry; and texture/firmness/bogginess. DRE adds critical information to the screening process, and particularly in light of the fact that poorly differentiated tumors may not raise PSA levels.

Best practices for screening should include baseline PSA testing for men beginning at age 40. Screening should assess age-specific PSA levels, as PSA tends to rise as men age and the prostate increases in size. Overall, as the age-specific level of PSA rises, so does the relative risk for prostate cancer, with a substantial increase in risk at PSA levels of 4.0 ng/mL and higher.

PSA LEVELS AND THE RISK OF PROSTRATE CANCER

THE RISK OF PROSTRATE CANCER DETECTION IF A BIOPSY IS PERFORMED AT VARIOUS LEVELS OF PSA

PSA (ng/mL)	Relative Risk for Prostrate Cancer (%)
≤ 1.0	8.8[1]
1.1 - 2.0	17.0[1]
2.1 - 3.0	23.9[1]
3.1 - 4.0	26.9[1]
> 4.0	45.5[2]

1. Thompson IM, Pauler DK, Goodman PJ, et al. Prevalence of prostate cancer among men with a prostate-specific antigen level ≤4.0 ng/mL. *N Engl J Med.* 2004;350(22):2239–2246

2. Presti JC Jr, O'Dowd GJ, Miller MC, Mattu R, Veltri RW. Extended peripheral zone biopsy schemes increase cancer detection rates and minimize variance in prostate-specific antigen and age-related cancer rates: results of a community multi-practice study. *J Urol.* 2003;169(1):125–129;

To supplement the level of total PSA, measures of free (unbound to proteins) PSA provide additional information to support a decision of whether or not to consider TRUS-guided biopsy. As a general rule, in comparing the percentage of free versus total PSA:

- <25% free PSA is suspicious for prostate cancer
- >25% free PSA may be indicative of benign prostate hyperplasia (BPH) or other noncancerous conditions

Another factor to consider as part of PSA screening is the PSA density, defined as the PSA value in relation to prostate size. Most important is the PSA velocity, or trending information, which indicates the rate of change in the PSA level over time.

The confusion and controversy surrounding the use of PSA testing—when to screen and when not to—continues because prostate tumors may be very slow growing and require only monitoring; however, early on, too many unnecessary biopsies had cost and policy ramifications that influenced PSA screening recommendations by groups including the US Preventive Services Task Force, American Cancer Society, and American Urological Association. These guidelines either recommended against screening or set the age for baseline screening at >50 or 55 years of age if men had no particular risk factors.

It is important to understand that the controversy around PSA screening is not about the PSA test, but rather about when/whether to treat based on the test result. The age-adjusted mortality rates for prostate cancer in the U.S. have declined 50% since FDA approval of the PSA test. Since 1994, mortality due to prostate cancer has declined more than mortality for any other type of cancer. The value of PSA screening in terms of early detection of prostate cancer and reducing related morbidity, mortality, and cost is well established, when implemented with the passive versus active surveillance approach describe previously.

Conclusions

Recent studies in very large patient populations have shown PSA testing to be of great value and associated with significant reductions in prostate cancer mortality. The longer the study follow-up the better the results tend to be. My personal best practices for PSA screening are shown below.

PSA Screening Personal Best Practices

Screen all men over the age of 40 with a life expectancy greater than 10 years

- Follow the trend or velocity
- Perform biopsy if PSA >2.5 ng/ml at age 50 with a small prostrate

Screen at-risk men at age of 40 (those with positive family history, African-Americans)

- Perform biopsy if PSA increases >0.5 ng/ml/year

Patients appreciate the convenience and reduced anxiety of in-office testing

- Receive PSA results in 15 minutes
- Leave my office knowing their test results

Critical Thinking for Early Diagnosis of Prostate Cancer

There is no question that early detection is important in controlling disease, and especially a progressive, potentially invasive disease such as cancer. Prostate cancer screening may reduce the incidence of advanced disease and mortality. PSA testing empowers patients and their physicians to make informed treatment decisions.

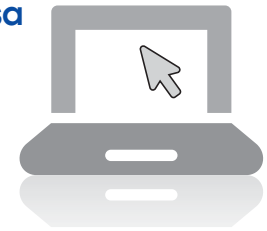
New USPSTF Draft Recommendations on PSA Screening

On April 11, 2017, the U.S. Preventive Services Task Force issued updated draft recommendations on PSA screening for prostate cancer. The revisions are based in part on new evidence that increases confidence in the benefits of screening, and make the guidelines closer to recommendations by the American Urological Association and the American Cancer Society.

- For men ages 55-69, African American men, and men with a family history of prostate cancer, the Task Force supports an individualized approach to PSA screening, based on clinician-patient discussions about the potential harms and benefits.
- The USPSTF did not change its recommendation against PSA-based screening for prostate cancer for men ages 70 and older.

For additional information, go to: https://screeningforprostatecancer.org

To learn more about PSA testing in your office visit us at http://go.sekisui-dx.com/psa



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