



Faith Krucina. *Upbeat*. Acrylic on canvas, 36" × 24". Courtesy of Artistic Images by Faith, Dunedin, Fla.

The decline in both prostate cancer mortality and metastatic disease may be in part a result of PSA-based screening.

Prostate Cancer: Screening and Early Detection

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Background: *Despite more than a decade of prostate-specific antigen (PSA)-based screening, the proven impact of screening on mortality due to prostate cancer continues to be controversial.*

Methods: *A literature review of issues pertaining to the epidemiology, screening, early detection, and mortality as they relate to prostate cancer was conducted. Included in the review are PSA refinements, controversies of screening, and organization guidelines. Finally, recent reports of mortality rates in the post-PSA era are presented for discussion.*

Results: *Prostate cancer mortality rates have begun to decline for the first time since statistics have been recorded. The recent decline in age-adjusted mortality rates from prostate cancer is significant, and this decline appears to be earlier than would have been predicted. This finding, coupled with the dramatic decline in metastatic disease, implies that PSA-based screening may be responsible for a significant portion of this improvement in mortality.*

Conclusions: *The cost of prostate cancer screening appears to be acceptable. Randomized studies of PSA-based screening are currently ongoing, although the results may not be available for a decade. Currently, the best evidence is derived from population-based studies that appear to show a benefit to prostate cancer screening.*

Introduction

Prostate cancer screening remains a source of major controversy in the United States.¹ The potential benefits and harms continue to be debated among health professionals despite more than a decade of prostate-specific antigen (PSA)-based screening and early detection. Among the concerns are the possibility that screening and early detection will not impact on the deaths related to prostate cancer, the potential for treatment-related morbidity and mortality, and the cost of screening, diagnosis, and treatment to society. This article discusses these concerns and highlights

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the latest developments in prostate cancer screening and early detection.

Diagnosing Prostate Cancer

Epidemiology

Prostate cancer remains the most common cancer in men (excluding skin cancer) with an estimated 180,400 new cases in 2000.² This represents a decline from the original peak estimate of 334,500 cases in January 1997, and it is lower than the reduced projection of 184,500 in July 1997.^{3,4} The rapid increase in prostate cancer incidence in the 1980s and early 1990s and the decline that has recently followed is likely related to the effects of early detection that are largely attributed to PSA testing. Accordingly, the large increase in prostate cancer over the past decade likely reflected the prevalence of the disease rather than the true incidence. Nevertheless, prostate cancer represents approximately 29% of all newly diagnosed cancers, and it is likely to remain a significant health problem in the future.

For the average American man, the odds of being diagnosed with prostate cancer in his lifetime are approximately 1 in 6. There are certain known risk factors that increase the odds that a man will develop prostate cancer in his lifetime. The most commonly implicated factors include age, race, and family history. Prostate cancer is a disease associated with aging, and more than 75% of prostate cancers are diagnosed in men 65 years of age or older.^{5,6} The median age at diagnosis of prostate cancer is 71 years in white men and 69 years in African American men; the median age at death due to prostate cancer is 78 years in white men and 76 years in African American men.

African American men have a substantially higher incidence of prostate cancer compared with age-matched white Americans.^{5,6} Additionally, they tend to present at a more advanced stage and have a worse outcome when compared with whites. The African American mortality rate from prostate cancer is approximately twice that of white Americans. In data collected between 1986 and 1993,³ the 5-year cancer-specific survival rates were 75% and 90% in African American and white men, respectively. Reasons for the increased prostate cancer incidence and mortality among African Americans are poorly understood and continue to be an area of intense research.

In addition to age and race, familial and hereditary factors play an important role in the development of prostate cancer. Members of families with a high inci-

dence of prostate cancer may be at increased risk of cancer because of shared environmental exposure or due to similar genetic make-up. Approximately 25% of men diagnosed with prostate cancer will have a positive family history. A man with one affected first-degree relative is estimated to have a 2- to 3-fold greater risk of being diagnosed with prostate cancer than the general population.⁶ A man with a first-degree and second-degree relative with prostate cancer may have an increased risk by a factor of 6 above the general population.

Hereditary prostate cancer is also thought to be responsible for up to 10% of prostate cancers. This refers to a specific Mendelian inheritance pattern of a susceptibility gene. These men are usually diagnosed prior to 50 years of age and may have as many as three or more affected family members. A major prostate cancer susceptibility locus was recently discovered on chromosome 1(1q24-q25), and studies have shown that men with prostate cancers linked to this gene present at a younger age and have higher grade and stage cancers.⁷ This gene, called HPC1, is believed to be involved in only 33% of hereditary prostate cancers or 3% of total cases. The impact of a familial and hereditary prostate cancer on the natural history of the disease is currently under investigation.

Prostate-Specific Antigen (PSA)

Shortly after its clinical introduction in the late 1980s, PSA dramatically changed the way we diagnose, stage, and follow patients with prostate cancer. While initially approved for the follow-up of patients with prostate cancer following treatment, PSA quickly emerged as an important diagnostic tool used in early detection and prostate cancer screening. Its popularity and widespread use are thought to have been responsible for the dramatic increase in new cases of prostate cancer detected in the 1990s.⁴ Furthermore, PSA-detected tumors were responsible for the development of a new clinical stage of prostate cancer (stage T1c). Stage T1c prostate cancers are defined as PSA-detected, nonpalpable tumors and are the most common clinical presentation of patients over the last 10 years.

PSA is a 33 kD protein primarily manufactured by the prostate epithelium and functions to liquefy the seminal coagulum.⁸ Because PSA is expressed in the serum by both benign and malignant prostate tissue, it is organ specific but not cancer specific. A variety of noncancer conditions may elevate serum PSA including urinary retention, prostatitis, vigorous prostate massage, and ejaculation. Also, instrumentation such as cystoscopy, Foley catheter placement, and prostate biopsy can falsely elevate PSA. Therefore, a serum PSA should not be obtained immediately following such events and

probably should be delayed until approximately 6 weeks later. Finasteride causes an artificial lowering of PSA by an average of 50% after 6 months of therapy, and patients on such medication should have their PSAs doubled for an accurate index value.⁹

PSA and Digital Rectal Examination

The best means of detecting prostate cancer currently involves both a serum PSA and a digital rectal examination (DRE). Neither test alone can detect all tumors, and at least 20% of significant prostate cancers will have a PSA below 4.0 ng/mL.¹⁰ The positive predictive values (PPVs) of DRE alone and PSA alone in the detection of prostate cancer are 31.4% and 42.1%, respectively.¹¹ However, the combination of the two tests increases the PPV to 60.6% in patients who undergo initial screening. Therefore, a blood test alone is insufficient; both tests should be obtained in a patient concerned about his risk for prostate cancer.

Transrectal Ultrasound-Guided Biopsies

Currently, the diagnostic procedure of choice in patients suspected of having prostate cancer is a transrectal ultrasound (TRUS)-guided biopsy of the prostate. Sextant biopsies that obtain tissue via an 18-gauge needle from a spring-loaded gun are obtained bilaterally from the apex, middle, and base of the gland. This is an office procedure usually done under local 2% lidocaine jelly, and major complications are relatively rare.¹² However, there is at least a 25% chance of a false-negative test using the strategy of a single set of sextant biopsies.¹³ This has prompted some investigators to recommend that additional cores be obtained at the initial biopsy session. One such strategy involves obtaining four lateral and three midline biopsies in addition to the sextant technique described above, and this improved the cancer detection rate by 35% in one series.¹⁴ However, identifying clinical parameters in individual patients that would justify the benefit of an increased detection rate vs the cost in terms of both patient discomfort/morbidity and pathology charges remains to be determined. Recently, Presti et al¹⁵ reported a significant improvement in cancer detection over traditional sextant biopsy techniques using an eight-core strategy. In this study, cores were obtained from the apex and mid-lobar mid-gland similar to the sextant strategy, and two additional cores were obtained from the far lateral peripheral zone at the base and mid-gland. These lateral peripheral lobe biopsies increased cancer detection by 14%. This strategy appears to have struck a balance between the need for improvement in cancer detection due to the limitations of sextant biopsy while still preserving patient tolerability and comfort in an outpatient setting.

Refinements in Cancer Detection

In order to improve on the accuracy of PSA as a more specific test in the early detection of prostate cancer, a number of techniques have been utilized. A PSA value of 4.0 ng/mL has traditionally been used as the upper limit of normal in testing. However, as mentioned previously, up to 20% of men with prostate cancer will have a value less than 4 ng/mL. Additionally, only 25% of men with a PSA between 4-10 ng/mL will have a positive biopsy. It is because of these limitations that attempts have been made to improve the accuracy of PSA in cancer detection through adjustments such as age- and race-specific PSA, PSA velocity, and PSA density.

Age- and Race-Specific PSA

The concept of age-specific PSA was based on the desire to improve cancer detection in young men by lowering the normal range of PSA while raising the value in older men in an attempt to increase specificity and ultimately decrease the number of unnecessary biopsies. This idea was based on the assumption that PSA will increase with increasing size of the prostate due primarily to benign prostatic hyperplasia in men as they age, thus accounting for a higher serum PSA. The adjustment as proposed by Oesterling and associates¹⁶ lowered the normal range to 2.5 ng/mL in men between ages 40-49 years, while the value was increased to 6.5 ng/mL in men ages 70-79 years. However, a substantial number of potentially clinically significant tumors would have been missed using these age-adjusted values in older men, particularly those over the age of 70 years.¹⁷ Considering the increasing number of men between the ages of 60 and 79 years, coupled with the increasing life expectancy, this will likely continue to be an area of controversy. Perhaps the most valuable lesson learned from these age-specific reference ranges is the concept that "normal" PSA values are relative, not set in stone; and that these values can be adjusted based on the clinical situation. Currently, the decision to perform (or not to perform) a biopsy should be based on a variety of factors including patient motivation, risk factors, life expectancy, and comorbidities rather than solely on an absolute PSA value.

In addition to age, race-specific PSA values have now been proposed. This recommendation is based on investigations that have demonstrated a higher PSA value at the time of diagnosis among African American men vs white men.^{18,19} One study from the Walter Reed Army Medical Center¹⁸ involving more than 400 African American men with prostate cancer reported that almost 40% of cancers would have been missed using traditional age-adjusted PSA values. The authors further concluded that a PSA value above 2 ng/mL was

associated with a 93% specificity in African American men in their 40s. The exact PSA cut-off value in African Americans remains to be defined; however, it appears prudent to lower the threshold for recommending a biopsy to these high-risk men when PSA values are above 2-2.5 ng/mL.

PSA Velocity

PSA velocity is the rate of rise of PSA over time, and its major strength is that it decreases the day-to-day variability (up to 15%-20%) that has been demonstrated in serial PSA determinations. The rationale for its use is that PSA rises faster in men with prostate cancer than in those with benign enlargement. This was first reported in the Baltimore Longitudinal Study of Aging,²⁰ where it was found that 72% of men with prostate cancer had a PSA rise of 0.75 ng/mL per year compared to only 10% of those without cancer. This study followed men over at least 2 consecutive years, and patients' initial PSA levels were <4 ng/mL. Others have found that PSA velocity lacks sensitivity and specificity, particularly in men with PSA levels of >4 ng/mL. Currently, PSA velocity has limited value, but if done, at least three consecutive PSA values should be measured over a minimum of 18 to 24 months.

PSA Density

The most common cause of an elevated PSA level in the absence of cancer is benign enlargement of the prostate. The concept of PSA density was proposed initially as a means of adjusting for the benign prostate hypertrophy (BPH) component by dividing the serum PSA by the prostate volume (usually estimated by TRUS). Initially, a cut-off ratio of 0.15 was proposed, with a ratio of >0.15 indicative of cancer and <0.15 more likely benign.²¹ However, several practical factors limit the clinical usefulness of PSA density, including the daily biologic variability of PSA and the variability and relative inaccuracy (10%-30%) of TRUS-calculated volume, which can vary by up to 30%. Its use is relatively limited currently but may provide support for avoiding a repeat biopsy in a patient with a palpable normal prostate and a PSA between 4-10 ng/mL.

Percentage of Free PSA

The majority of PSA in the serum is bound to the protein inhibitor alpha-1-antichymotripsin. Usually, less than 5% of PSA is present in the free, noncomplexed form. For unknown reasons, the proportion of PSA that is unbound (percentage of free PSA) is lower in men with prostate cancer than in men with benign prostates. Currently, the percentage of free PSA is used to increase specificity of total PSA when the

serum PSA is between 4 and 10 ng/mL. The largest study reported by Catalona et al²² demonstrated that in such patients using a cut-off of 25% of free PSA yields a sensitivity of 95% and a specificity of 20%. This strategy is reported to avoid 20% of "unnecessary biopsies." However, these results were based on a single set of sextant biopsies with a known false-negative rate of 25%. Therefore, while free PSA may improve biopsy accuracy, its best use currently is in aiding clinicians in the decision making regarding the need for a repeat biopsy in men with a palpably normal DRE and a PSA between 4-10 ng/mL.

Screening Controversies

Few topics in prostate cancer are more controversial than the issue of screening. One of the problems within this area is the balance of economic forces and scientific rationale vs the application of health care policy to an individual patient at risk for developing and perhaps dying of his disease. This battle is waged in the background of a cancer with a prolonged doubling time that may require as long as a decade to elapse before demonstrating what impact (if any) a new treatment may have on the natural history of the disease. Most patients and family members are unwilling to leave their fate to chance. Additionally, it is well known that relying on detection of prostate cancer only after the development of symptoms has historically resulted in the detection of advanced and often incurable cancers.

Certain criteria are thought to be essential for mass screening to be widely accepted by health care policy makers. First, the disease must be common or serious enough to warrant screening. As the most common cancer in men and the second leading cause of cancer deaths, prostate cancer certainly meets this criterion. Second, a test must be available to detect the disease at an early, presymptomatic stage. Studies employing PSA and DRE have again supported this. Third, there must be supporting evidence that treatment of the disease after early detection will result in a reduction in disease morbidity and/or mortality. It is on this final point of contention that the strongest argument against screening exists, and until there is proven benefit to the treatment of these early detection cancers, controversy will continue regarding screening for prostate cancer.

To add support to the argument that screening does not save lives, critics have introduced concerns regarding not only the possibility of overdiagnosis, but also length-time and lead-time bias (Figs 1-2).²³ Lead-time bias suggests that the natural history of the disease is not truly affected by screening. For example, a patient may be diagnosed with prostate cancer at 50 years of age

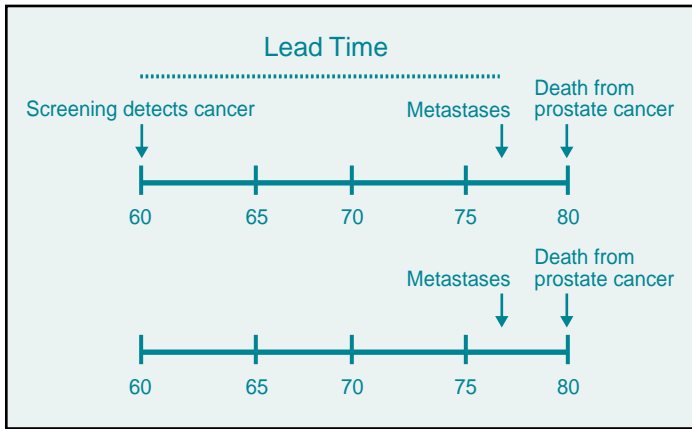


Fig 1. — Lead-time bias suggests that the natural history of the disease is not truly affected by screening. Printed with permission from Medical Education Collaborative, Golden, Colo.

through PSA-based screening. He then undergoes treatment but ultimately progresses and dies at 60 years of age. Accordingly, the same patient without screening develops symptomatic bony metastases at age 58, undergoes treatment with androgen deprivation therapy, and dies at age 60. Thus, in this theoretical scenario, even though he was diagnosed 8 years prior through screening, his death was not affected by screening or early detection. Length-time bias is slightly different but also suggests no benefit to screening. Length-time bias suggests that annual screening is more likely to detect slow-growing tumors, while fast-growing and potentially lethal tumors are less likely to be detected. Thus, it is argued that screening for prostate cancer does not detect the very tumors for which it is intended.

Another concern involves the cost of screening. While a full discussion of the economics of prostate cancer screening is beyond the scope of this article, certain points should be considered. First, cost includes not only the cost of detection but also treatment and treatment-related complications. Furthermore, cost can be measured in terms of number of lives saved, life years saved and quality-adjusted life years (QALY). A 1990 report estimated that the cost of screening could be as high as \$25 billion annually if all men 50 to 70 years of age in the United States participated in screening.²⁴ However, these same authors demonstrated that the cost using values of quality-adjusted life-years (QALY) gained through screening is actually better than the cost-benefit ratios of screening mammography for women under the age of 50 and

better than some forms of medical treatment for hypertension. Therefore, it could be argued that when considering all the costs of screening and particularly QALY gained, prostate cancer screening is justifiable.

Results of Early Detection

There is overwhelming evidence that the widespread use of PSA has resulted in the improvement of detection of prostate cancer at an earlier stage. In published data¹¹ based on results of annual Prostate Cancer Awareness Week, serial screening for prostate cancer significantly improved the rate of early cancer detection. In the SEER database, the rate of distant metas-

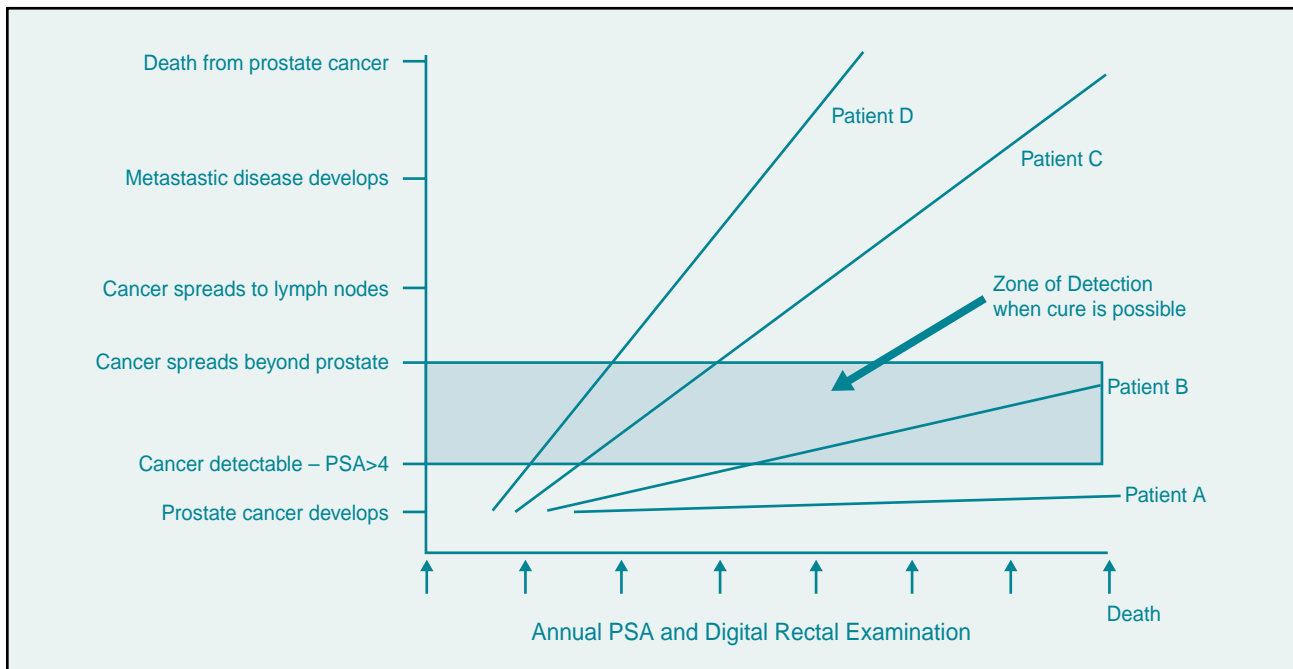


Fig 2. — Length-time bias suggests that annual screening is more likely to detect slow-growing tumors, while fast-growing and potentially lethal tumors are less likely to be detected. Printed with permission from Medical Education Collaborative, Golden, Colo.

tases fell more than 50% between 1990-1994, a finding thought to be largely attributable to PSA use.²⁵ Furthermore, in data comparing radical prostatectomy specimens from the pre-PSA era with those in the last decade, tumors in 70%-80% of men are now being detected while the tumors are still pathologically organ confined compared with less than 30% prior to the use of PSA.²⁶ These findings have raised criticism that many of these PSA-detected tumors are clinically insignificant, but in fact that does not appear to be the case. Recent pathology evidence from men with PSA detected tumors reveal that less than 10%-15% of all prostatectomy specimens contain what might be considered clinically insignificant tumors similar to those found at the time of autopsy.²⁷ However, PSA detection alone may be inadequate if not performed as part of an early detection program, as evidenced by the large number of tumors with microscopic extraprostatic extension (up to 50% in some series) despite lack of tumor palpability.²⁸

Prostate Cancer Mortality Rates

Prostate cancer is the second leading cause of cancer deaths in US men, with 31,900 deaths estimated in 2000 alone.² Overall, prostate cancer deaths represent approximately 11% of all cancer deaths in the United States. It is estimated that the lifetime risk of dying of prostate cancer is approximately 3%. The death rates increased throughout the 1980s with a peak incidence in 1990.²⁹ Since then, there has been a steady decline in the death rate, with an initial decrease of 6.6% reported between 1990 and 1995.²⁵

One of the most important signs of benefit from prostate cancer screening would be a reduction in the mortality rate to levels below those that existed prior to the introduction of PSA-based testing. For the first time, such evidence is now emerging. A recent report³⁰ demonstrated a 16.1% reduction in age-adjusted prostate cancer mortality rates among white men beginning in 1992 and 10.9% among African American men beginning in 1993. The rates continued to drop through 1997 for both races. The authors note that this decrease in mortality has occurred earlier than would have been expected given the relatively slow growth rate of prostate cancer. This likely reflects the impact of screening on the detection of high-grade cancers prior to the development of metastases. In support of this theory, they note a decline in the incidence of distant disease that predated the fall in cancer mortality.

Similar to the decline in US death rates, Canadian death rates have declined since 1991, with the most dramatic decreases seen in the last available years,

1996 and 1997.³¹ The exact causes for the decline are currently unknown. However, since the impact of early detection and screening for prostate cancer might not be observed for up to a decade following its implementation, it is unlikely that these early efforts are solely responsible for the decline. It is likely that the dramatic decline in the death rates from prostate cancer observed in North America is the result of a combination of factors. These include early detection through PSA-based screening, improved diagnostics through ultrasound-guided needle biopsies, and more effective treatment such as radical prostatectomy for localized disease.

If the observed decreases in prostate cancer mortality are due to screening, then the observed benefits should be proven in the follow-up of randomized trials employing PSA testing. One early report from Labrie and associates³² compared death rates from screened and unscreened men from Quebec. Men in the screened arm had a significantly lower risk of dying of prostate cancer than did those whose cancers were detected based on the development of symptoms. However, problems with the study, including a high rate of PSA testing in the control arm, confound the results. While not a randomized study, encouraging data of the benefits of PSA screening on survival have been reported in Austria's Tyrol region.³³ In 1993, PSA screening was aggressively launched in the Austrian State of Tyrol, and by 1998, approximately 66% of men had been tested. Prostate cancer deaths declined 32% in 1997 and 42% in 1998 among men 40 to 79 years of age following enactment of a PSA-based screening program.

Currently, two large randomized trials are ongoing in Europe and North America designed in an attempt to determine if PSA-based screening reduces prostate cancer mortality in a cost-effective manner without reducing quality of life.^{34,35} These trials are already being viewed with skepticism by many because of the possible contamination of the control arm with the widespread use of PSA available to the study participants (controls) outside of the study. Also, there is no consensus on what type of treatment should be offered to patients once diagnosed, and treatment efficacy may vary depending on the resources and local expertise of the geographic region. Given these limitations, the reduction in prostate cancer deaths observed among population-based studies may provide the best source for the effectiveness of PSA-based screening.

Organizational Guidelines

At present, the American Urologic Association, the American College of Radiology, and the American Foun-

dation for Urologic Disease recommend annual screening beginning at age 50 years for the general population and at 40 years for African American men or men with a family history of prostate cancer. The American Cancer Society (ACS), the International Union Against Cancer, the US Preventive Health Services Task Force, and the Canadian Task Force have not endorsed routine screening for prostate cancer.³⁶ According to one source, the position of the National Cancer Institute is that there is too little evidence about mortality reduction from prostate cancer screening and therefore advocates neither for nor against it.³⁷ More recently, the American Academy of Family Physicians and the ACS have modified their positions, encouraging men to be apprised of the pros and cons and decide individually. Thus, universal endorsement of screening for prostate cancer currently does not exist. Most organizations that do not endorse universal screening are awaiting additional evidence, and many plan to revisit and update their guidelines by next year.

Optimal Interval of Screening

While annual screening intervals are generally recommended among those proponents of prostate cancer screening, there is emerging evidence that the intervals may be modified based on patient characteristics. Recently, evidence from longitudinal screening studies has suggested that a man's entry PSA level at the time of first screening may be a strong predictor of his eventual risk of being diagnosed with prostate cancer.³⁸ For example, a man with a serum PSA of <2.5 ng/mL has approximately a 1% chance of being diagnosed with prostate cancer over the next 4 years. This is in comparison to an almost 13% chance for men with a PSA between 2.6 and 4 ng/mL and a 38% chance among men with a PSA between 4.1 and 10 ng/mL.

Similar data³⁹ have been derived from serially screened men who participated in Prostate Cancer Awareness Week, where less than 1% of men with an initial PSA of <2 ng/mL were found to have prostate cancer during interval follow-up. Additionally, information from the Baltimore Longitudinal Study of Aging⁴⁰ demonstrated that men with an initial PSA level of less than 2 ng/mL had a 4% chance of converting to a PSA of 4.1 to 5 ng/mL during a 4-year follow-up. This is compared to men with a PSA level of between 2.1 to 4 ng/mL who had a 27% to 36% of converting to a PSA of 4.1 to 5 ng/mL. Together, these studies imply that among patients with a PSA of less than 2 ng/mL and a normal DRE, prostate cancer screening could be safely performed every other year and perhaps less often. Furthermore, evidence from the Baltimore Longitudinal Study of Aging⁴¹ suggests that prostate cancer screening

could be safely stopped at 65 years of age among men with a PSA equal to or below 1 ng/mL. Decreasing the screening interval and perhaps discontinuing screening after a defined age among low-risk patients as determined by PSA and DRE could substantially improve the cost-benefit ratio of prostate cancer screening in the United States and is an area worthy of future study.

Conclusions

Prostate cancer screening remains a controversial and hotly debated topic among health policy officials. While universal endorsement among many organizations awaits further proof, recently the pendulum appears to be swinging in favor of screening. Prostate cancer mortality rates have begun to decline for the first time since statistics have been tracked, and the reduction in death rates appears to be one of the most persuasive arguments in support of screening and early detection. The decline in death rate, coupled with the continued stage migration, suggests high-grade tumors are being detected before metastases develop. These declines are also likely due to a combination of factors including not only PSA-based screening, but also improved diagnosis and the implementation of more effective therapy than was previously available only 20 years ago.

This decline in death rates is encouraging, but to date only modest reductions in the death rate have been realized. The fact remains that unless there is a major paradigm shift, the actual number of patients dying of prostate cancer each year will continue to rise due to a larger population at risk as baby-boomers continue to age. Further reductions in the death rate from prostate cancer will likely be achieved using a combination of strategies, including chemoprevention and more effective treatment. However, in the near future, it is likely that the most dramatic reduction in prostate cancer deaths will result directly from PSA-based screening and early detection efforts coupled with effective treatment for localized disease. This achievement may ultimately pave the way for universal endorsement of prostate cancer screening.

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