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REVIEW ARTICLE

Is screening for prostate cancer with prostate specific antigen an appropriate public health measure?

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Abstract
Screening and treatment for prostate cancer is controversial. In the absence of randomized trials, several prominent medical organizations in the United States and Europe have formulated policies that range from enthusiastic support to significant skepticism concerning the efficacy of screening and subsequent treatment for prostate cancer. Sharp rises in the incidence of prostate cancer have occurred whenever PSA testing has been introduced on a wide scale. Unfortunately, it is unclear whether declines in prostate cancer mortality can be attributed to PSA testing. Other explanations include the early use of anti-androgen therapy or changes in environmental factors such as diet. Repeated testing for serum PSA has produced significant shifts in the types of cases being identified and has raised the possibility of significant over-diagnosis of this disease. The European screening trial and the PLCO trial in the US will hopefully provide some insights into the value of population-based testing.

Introduction

Researchers and clinicians have advocated the use of prostate specific antigen (PSA) testing for over a decade [1,2]. Despite this long history of using PSA as a screening tool for prostate cancer, the practice remains one of the more controversial issues in healthcare. Many prominent organizations within the United States have developed policies for the use of prostate specific antigen (PSA) as a screening tool (Table I). Unfortunately, these recommendations support the entire spectrum of beliefs from strong advocacy to complete repudiation. The debate about whether to perform PSA screening has important implications for both the individual and society at large. On one hand, screening may reduce the morbidity and mortality associated with prostate cancer. On the other hand, screening may subject large numbers of men who were never destined to die from prostate cancer to unnecessary diagnostic and treatment regimens with their associated morbidity.

Which approach is correct? The same evidence is available to clinicians and researchers on both sides of the Atlantic, yet practices differ greatly between the USA and Europe. During the past decade the public health perspective has held greater sway in the UK and in Scandinavia possibly because medical decision-making is more centralized. In the USA a more entrepreneurial medical care environment allied with patient advocates and commercially motivated lobbying has led to a much more aggressive approach to prostate cancer screening and treatment.

The purpose of this article is to review the current evidence supporting PSA testing as an appropriate public health measure to reduce prostate cancer mortality. While some men have undoubtedly benefited from the early detection of prostate cancer by PSA testing, the debate centers on the question of whether a sufficient number of men will have substantial benefit if PSA testing is adopted as public policy. Said another way, how many men must undergo PSA testing, prostate biopsy and treatment to prevent one prostate cancer death?

The article is structured around the criteria recently published by the UK National Screening Committee to evaluate the viability, effectiveness, and appropriateness of a screening program [3]. These criteria focus on four critical areas: the disease, the test, the treatment, and the screening program. The article will review each of these factors as they relate to prostate cancer.

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Table I. Screening policies in the United States of America.

Organization	Policy
American Academy of Family Medicine	Physicians should counsel men between the ages of 50 and 65 regarding the known risks and uncertain benefits of screening so they may make an informed choice, rather than routinely screening men's PSA levels
American Cancer Society	Both the PSA test and the digital rectal exam should be offered annually, beginning at age 50, to men who have a 10-year life expectancy and to younger men who are at high risk. Information about potential risks and benefits of screening should be shared with patients
American College of Physicians	Physicians should describe the potential benefits and known harms of screening diagnosis, and treatment; listen to the patient's concerns; and then individualize the decision to screen
American Urological Association	Men over 50 should consider testing, as should those at high risk, such as African-Americans and men with a family history of prostate cancer. Men at high risk should begin testing at age 45
Centers for Disease Control and Prevention	Routine screening is not recommended because there is no consensus on whether screening and treatment of early stage prostate cancer reduces mortality. CDC supports a man's right to discuss the pros and cons of screening with his physician
US Preventive Services Task Force	Evidence is insufficient to determine whether the benefits of prostate cancer screening outweigh the harms (e.g. frequent false positives, unnecessary biopsies, and potential treatment complications)

Epidemiology and natural history (the disease)

There is little doubt that prostate cancer is a serious health problem. Each year thousands of men suffer painful complications and die prematurely from this disease. In 2004, estimates suggest that 29 900 American men will die from prostate cancer and 230 110 will be diagnosed with this disease [4]. Advocates of PSA testing frequently remind us that there is no cure for advanced prostate cancer and suggest that the only way to reduce mortality from this disease is to identify prostate cancer while it is still clinically confined to the prostate. For prostate cancer, however, a critical question is: Which cancers are destined to kill?

The lifetime risk of a prostate cancer diagnosis is now approximately 16%, whereas the lifetime risk of death from prostate cancer is only 3.4% [5]. Autopsy studies have confirmed that there is a high incidence of latent prostate cancer. As many as 20–50% of men who have died without prostate cancer symptoms have been found to have prostate cancer at autopsy [6,7]. This is true for even very young men [8]. These figures suggest that many prostate cancers that are diagnosed in the United States are not destined to be fatal.

The recent report by Thompson et al. concerning the high prevalence of prostate cancer among men with a PSA level less than 4.0 ng/ml has further fueled the debate concerning what constitutes clinically significant prostate cancer [9]. As part of a large chemoprevention study comparing finasteride against placebo they performed prostate biopsies on 2950 men whose serum PSA never rose above 4.0 ng/ml during the seven-year study period. They found that the prevalence of prostate cancer was 6.6% among men whose PSA was consistently below 0.5 ng/ml and as high as 26.9% among men whose PSA was between 3.1 and 4.0 ng/ml. The men ranged in age from 62–91 years, but more than half were below age 70 years at the time of biopsy. A majority of the men harbored tumors with a Gleason score of 6 or less, but 67 of the 449 men diagnosed with prostate cancer had tumors with a Gleason score of 7 or greater. It is not clear how many of these men are destined to die from prostate cancer in the absence of treatment, nor is it obvious whether treatment will prevent an adverse outcome for those destined to have clinically significant disease.

What do we know about the natural history of prostate cancer in the era before PSA testing? Several key studies have helped shape our understanding of prostate cancer progression. Between 1989 and 2004, Johansson and colleagues published a series of four articles that documented the natural history of untreated prostate cancer in a population-based cohort of patients diagnosed with prostate cancer in Orebro Medical Center in Sweden [10–13]. No screening for prostate cancer took place during the period when this study population of 648 consecutive cases was assembled. Initially the authors found relatively low 5- and 10-year mortality rates among men with clinically localized disease and challenged the use of aggressive initial treatment for all patients with early-stage prostate cancer. Long-term follow-up of the study cohort has demonstrated a rising cause-specific mortality rate for those men who survive 15–20 years following diagnosis.

During a mean observation period of 21 years, 89 patients (40%) experienced progression of disease, and of these 39 (17% of the entire cohort) developed metastatic disease [13]. A total of 203

patients (91% of the entire cohort) died during follow up, with prostate cancer the probable cause of death in 35 men (16% of the entire cohort). Among patients who were 70 years or younger at diagnosis, 22 (22%) died from prostate cancer during follow up. The proportion was lower among older men. Tumor histology was the strongest predictor of death from disease.

Johannson et al. concluded their study by noting that because of the favorable survival rate among untreated patients with early stage disease, a majority of patients would be treated without survival benefit. Their data also indicate, however, that the probability of developing a lethal progression may increase after one or two decades. Therefore their findings suggest a possible benefit of PSA testing among those men diagnosed with localized disease who are likely to have at least a 15-year survival.

In 1994 Chodak et al. published a report describing the results of conservative management of clinically localized prostate cancer [14]. Unlike the Johannson report, this study consisted of a pooled analysis of 828 case records from six non-randomized studies published during the decade preceding the report. None of the patients included in the report underwent a radical prostatectomy or received radiation therapy. Patients who had symptomatic progression or who developed metastases received hormonal therapy.

Patients with poorly differentiated cancers had a significantly lower cancer-specific survival rate (34%) when compared with men who had well- or moderately differentiated cancers (87%). The rate of progression to metastasis differed significantly among men with the three tumor grades. Men with poorly differentiated tumors were much more likely to develop metastases when compared with men who were diagnosed with well-differentiated disease.

In 1998, we reported long-term outcomes of a competing risk analysis of 767 men diagnosed between 1971 and 1984 who were managed expectantly for clinically localized prostate cancer [15]. The results of our study are presented in Figure 1. Few men (4–7%) with Gleason 2 to 4 tumors identified by prostate biopsy had progression leading to death from prostate cancer within 15 years of diagnosis. A majority of the younger men were still alive, but faced the possibility of death from prostate cancer in the future. In contrast, most of the older men with Gleason 2 to 4 tumors identified by biopsy at diagnosis have died from competing medical hazards rather than prostate cancer.

Compared with men with well-differentiated tumors, men with Gleason 5 and 6 tumors identified by prostate biopsy experienced a somewhat higher risk of death from prostate cancer when managed expectantly (6–11% and 18–30%, respectively). Of the younger men with Gleason 5 and 6 tumors, more than half were still alive after 15 years, whereas a majority of the older men died from competing medical hazards.

Men with Gleason scores 7 and 8–10 tumors identified by prostate biopsy experienced a very high rate of death from prostate cancer regardless of their age at diagnosis (42–70% and 60–87%, respectively). Very few of these men of any age survived more than 15 years. Most died from prostate cancer, except for approximately one-third of the oldest men, who died from competing medical conditions.

In summary, prostate cancer is a serious health hazard as evidenced by the large number of men who die from this disease each year. Unfortunately, there is a much larger population of over 9 million men who appear to harbor microscopic prostate cancer [16]. Relatively few of these men are destined to have clinically significant disease. At the present time the Gleason score is still the best predictor of the probability of progression. Unfortunately current screening and biopsy practices have rendered the Gleason score less useful because most men are now diagnosed with either Gleason 6 (3+3) or Gleason 7 (3+4) tumors. Many pathologists are reluctant to report Gleason 2, 3 or 4 tumors on biopsy because of the high probability that patients will harbor higher-grade disease elsewhere in the prostate [17]. Furthermore, there is confusion concerning what constitutes a clinically significant cancer. Pathologists agree to label prostate biopsies as having cancer if they meet the criteria established by Gleason over 30 years ago. Advocates of screening believe a large number of these tumors will progress to clinically significant disease if the patient lives long enough. Detractors of PSA screening counter that a significant number of these tumors are indolent and are unlikely to progress. Currently, there is no test that can reliably differentiate those cancers that are likely to progress from those that are indolent.

Screening for prostate cancer with PSA (the test)

PSA is a glycoprotein produced almost exclusively by the epithelial component of the prostate gland. Men with prostate diseases may have high serum PSA levels because of enhanced production of PSA or from architectural distortions in the gland that allow PSA greater access to the bloodstream. Several conditions can produce a rise in serum PSA levels. These include benign enlargement, inflammation, and the presence of prostate cancer [18]. When first described in 1979, PSA was promoted as a useful

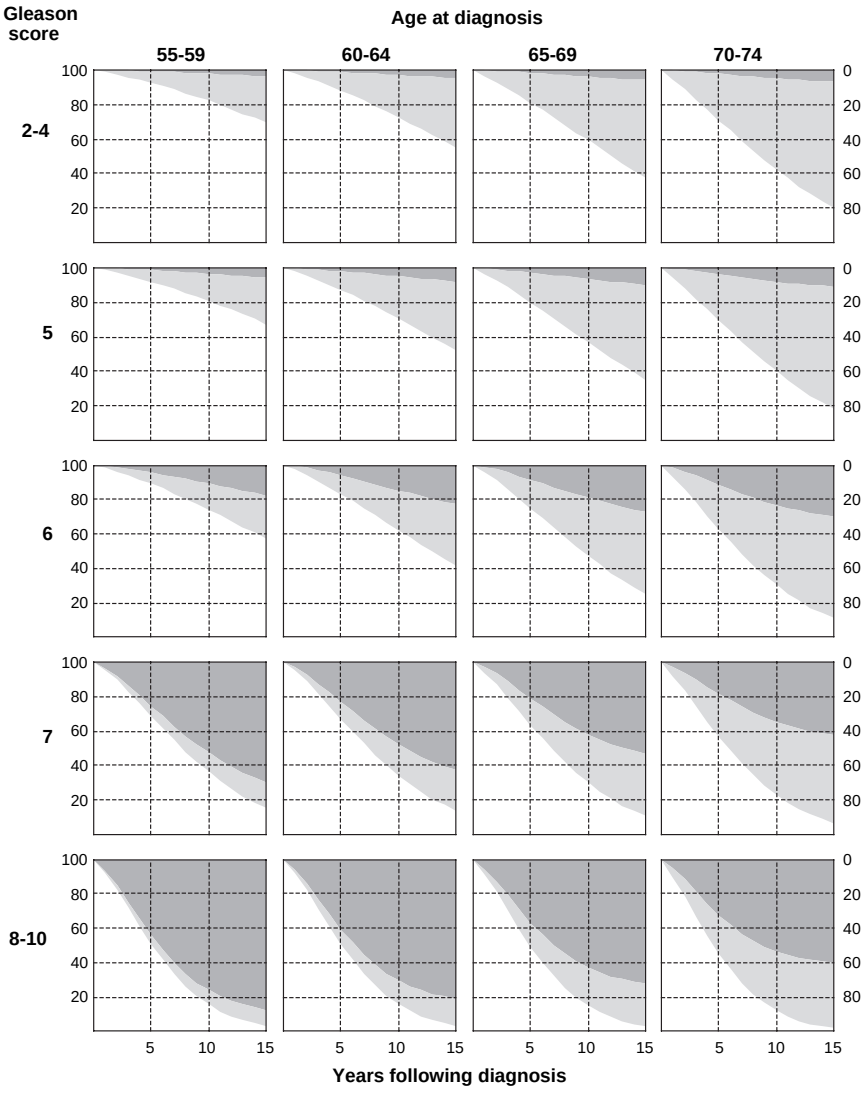

Figure 1. Survival (white lower band) and cumulative mortality from prostate cancer (dark-gray upper band) and other causes (light-gray middle band) up to 15 years after diagnosis stratified by age at diagnosis and Gleason score. The percentage of men alive can be read from the left-hand scale, and the percentage of men who have died from prostate cancer or from other causes during this interval can be read from the right-hand scale. [From Albertsen PC, Hanley JA, Gleason DF, Barry MJ. Competing risk analysis of men aged 55 to 74 years at diagnosis managed conservatively for clinically localized prostate cancer. JAMA 1998;280:975–80, with permission. Copyrighted 1998, American Medical Association].

marker for assessing treatment responses among patients with prostate cancer [19]. Shortly thereafter, research reports explored its usefulness in identifying cancer before it became clinically evident [20,21]. In 1991, Catalona et al. proposed using PSA as a screening test for prostate cancer and suggested 4.0 ng/ml as the appropriate cut-off point to identify men who are at high risk of disease progression [22].

Traditionally the performance of a screening test is assessed by measuring its sensitivity and specificity at various cut-off points. In a series of studies Catalona et al. explored the performance of PSA testing in the range of 4.0 ng/ml or higher [23]. At these levels the sensitivity of PSA testing was reported to be as high as 80% [24]. Unfortunately these studies were based on protocols that only called for a prostate biopsy when the PSA test was above 4.0 ng/ml or when there was an abnormality on digital rectal examination. Since biopsies identify both latent and clinically significant disease, this methodology overestimates the test's sensitivity.

Gann et al. assessed the relationship between PSA levels in baseline serum samples and the subsequent development of clinically significant prostate cancer in a case control analysis of men participating in the Physician's Health Study [25]. They found that at a cut-off point of 4.0 ng/ml, testing for PSA had a sensitivity of 46% to identify prostate cancer that was clinically important within the next 10 years.

The specificity in this population of men over age 63 years was 91%.

Similar findings were noted in a Finnish study that was based on links between a collection of serum samples and cancer registry data [26]. A cut-off point of 4 ng/ml PSA testing had a sensitivity of 44% and a specificity of 94%. However, up to two-thirds of cancers were missed at the 4 ng/ml threshold. In a community-based study of serial screening, 22% of men older than 50 years with PSA concentrations between 2.6 and 4.0 ng/ml had prostate cancer [27]. In the European Randomized Study of Screening for Prostate Cancer (ERSPC), 36.5% of detectable prostate cancers were identified in the 87.5% of men who had PSA concentrations lower than 4 ng/ml. In the Scandinavian trial 15% of enrolled men had PSA values less than 4 ng/ml [28].

The recent publication by Thompson et al. has further confounded the problem of assessing the performance of PSA testing [10]. Their study has demonstrated that there is no level of PSA below which prostate cancers do not occur. Furthermore, the median PSA levels for high-grade and low-grade cancers are roughly comparable for tumors identified in men with a PSA level under the traditional cut-off point of 4.0 ng/ml. As a consequence, PSA testing becomes an increasingly poor discriminator of men with high-grade prostate cancer as the cut-off points that trigger a biopsy are lowered. Furthermore this study has highlighted the very large pool of latent prostate cancers that exist in the general population.

Several other issues confound the efficacy of PSA testing. PSA values may fluctuate for physiological reasons including a recent ejaculation [29]. Because of this Eastham et al. have encouraged patients to repeat minimally elevated PSA values before considering prostate ultrasound and biopsy. As many as 21% of PSA values over 4.0 ng/ml will return to normal during a four year follow-up [30]. During the past decade biopsy protocols have changed such that current clinical practice usually calls for 10 to 12 cores. Increased sampling of the prostate leads to a higher yield of prostate cancer [31]. How many of these additional cancers are clinically significant is difficult to assess.

At this point it is virtually impossible to determine the positive and negative predictive value of PSA testing. A decade ago Catalona et al. estimated that PSA testing using a cut-off point of 4.0 ng/ml yielded a positive predictive value of 28–35% [22,24]. This relatively poor performance is driven in part by the high number of false-positive results. In order to improve the test performance several authors have suggested modified reference ranges that are based on age and race [32,33]. Cut-off points as low as 2.5 ng/ml have been suggested for men in their 40s, while cut-off points as high as 6.5 ng/ml have been suggested for men in their 70s. Others have suggested adjustments that account for the volume or density of the prostate or the transition zone, which is usually the site of benign prostate hyperplasia.

Researchers have explored various forms of PSA that can be detected in the circulation. PSA exists both free and in complexes with macromolecules. For reasons that are uncertain, men with prostate cancer have a lower percentage of circulating free PSA than men with benign prostate hypertrophy [34]. Unfortunately, these tests are also unable to discriminate between men with indolent versus clinically significant prostate cancer.

In summary, an elevated PSA serum level can identify men with advanced prostate cancer and those who have disease recurrence following definitive treatment. Unfortunately an elevated PSA serum level in an otherwise healthy man is much more difficult to interpret. Historically, criticism of the test focused extensively on its high sensitivity. Researchers have attempted to develop additional tests and reference ranges that would lower the high number of false positives without sacrificing its ability to identify prostate cancer. The recent report by Thompson et al. has identified the problem of poor specificity in PSA ranges that historically were considered normal. Furthermore, the extremely high prevalence of prostate cancer in the low PSA ranges has raised questions concerning how best to identify prostate cancers that are likely to progress.

Surgery and radiation for prostate cancer (the treatment)

Over the past several decades surgery and radiation have evolved as the primary methods of treating localized prostate cancer. Both of these approaches have their strong advocates but there are minimal data from randomized trials that document the efficacy of these treatments to cure prostate cancer. During the 1980s Holmberg et al. randomized 695 patients to undergo either radical prostatectomy or expectant management [28]. After eight years of follow up they have seen a relative difference in cancer-specific mortality between the two arms of approximately 50%, but the absolute difference has been modest. Prostate-cancer-specific mortality rates were 14% in the expectant management arm and 7% in the radical prostatectomy arm. Of note, however, is that after eight years of follow-up overall survival between the two treatment arms remains the same. Furthermore this population of patients was not identified by PSA testing. Therefore, researchers

would need to adjust for lead time and disease prevalence associated with PSA testing in order to generalize these findings to contemporary practice within the United States. Any significant differences in survival between aggressively and conservatively managed patients would be unlikely to appear within 10 years of diagnosis.

Even less information from randomized trials is available for patients considering radiation therapy or brachytherapy. In their treatment algorithm Jani and Helman offer guidance in the choices between hormone therapy, neoadjuvant hormone therapy, external beam radiotherapy, interstitial brachytherapy, and radical prostatectomy, but the evidence guiding treatment for early localized disease is tentative [35]. To date, published evidence comes primarily from clinical case series. Therefore, it is no surprise that specialists generally recommend the treatment that they offer. In the USA and the UK, urologists offer radical prostatectomy, whereas radiation therapists offer radiation [36–38].

The benefits of any screening test must be balanced against the potential harms that result from testing or treatment. In the case of PSA testing, the risks of performing the assay itself are trivial; it is the downstream consequences that deserve closer scrutiny. Because of the relatively low specificity of PSA testing, a large number of men will be advised to undergo trans-rectal ultrasound and prostate biopsy who do not have evidence of prostate cancer. The test itself is uncomfortable, but it has become much more tolerable with the application of local anesthetic [39]. The primary risks of the procedure are infection and bleeding, which fortunately occur in only 1–4% of cases [40]. The more important issues concern the potential morbidity associated with treatment. For those men who are not destined to experience any progression of their prostate cancer, any morbidity associated with treatment results in a loss of quality of life.

During the past decade we have worked with five other Surveillance Epidemiology and End Results (SEER) sites in the USA to develop the Prostate Cancer Outcomes Study. This is a large, prospective population based study that has followed men from the date of their diagnosis in 1994–1995 to the present. Each of the men enrolled in the study completed several surveys shortly after diagnosis and again at 12, 24, and 60 months. These surveys were designed to measure the impact of treatment on bowel, bladder, and sexual function along with overall health-related quality of life over time. Results demonstrated significant impacts on bowel, bladder, or sexual function following either radiation or surgery.

For the 1291 men who underwent radical prostatectomy, 8.4% were incontinent and 59.9% were impotent 18 or more months following their surgery [41]. Men who underwent a nerve-sparing prostatectomy had impotence rates of 56%. When asked whether sexual performance was a moderate to large problem, a total of 41.9% responded affirmatively. Men undergoing radiation therapy did not fare much better. Of the 497 patients who received external beam radiation, 28.9% reported a decline in sexual function and 5.4% reported a decline in bowel function 24 months following the completion of treatment [42]. Of the men who were potent prior to treatment, 43% became impotent within two years.

Steineck et al. evaluated quality-of-life outcomes following radical prostatectomy as part of the Swedish randomized trial comparing radical prostatectomy with observation [43]. They found that 80% of men undergoing surgery had erectile dysfunction and 49% had urinary leakage. For men undergoing observation 45% were impotent and 21% had urinary leakage after several years of follow-up. Comparisons of several other quality-of-life indicators demonstrated no differences between the two study arms.

In summary, surgery and radiation remain the primary treatments of localized prostate cancer. Few randomized trials have been conducted that document the relative efficacy of these procedures to cure disease. The one trial published to date documenting the impact of radical prostatectomy has failed to show a survival difference between surgery and expectant management after eight years of follow-up. Although men with high-grade disease clearly have the most to gain from intervention, outcomes analyses following treatment intervention suggest that surgery and radiation carry a significant risk of impotence. Surgery also carries a risk of urinary incontinence and radiation risks bowel dysfunction. Surgeons and radiation therapists continue to improve their skills to minimize the impact of therapy. Unfortunately, risks remain.

Ability of PSA testing to improve cancer outcomes (the screening program)

The value of PSA testing as a public health measure depends on its ability to identify prostate cancer at a time during the course of the disease when treatment can alter the long-term outcome. The lack of understanding of the natural history of prostate cancer identified by PSA testing confounds this simple concept. Furthermore, the relative impact of surgery, radiation, and hormonal therapy remains to be elucidated by randomized trials. Because of this, epidemiologists frequently look to mortality

rates to measure the success of PSA testing to lower morbidity from this disease.

Recent evidence suggests that prostate cancer mortality rates are falling. During the past decade there has been a 16% decline in prostate cancer mortality in the United States [4]. Interestingly, similar but less dramatic trends have been observed in England and Wales where the intensity of PSA testing is much lower and the incidence of prostate cancer has increased minimally when compared with the United States [44]. One explanation could be that the use of PSA testing has resulted in the early use of androgen withdrawal therapy, which delays the progression of prostate cancer sufficiently to yield a positive impact on survival. Evidence to support this theory comes from clinical trials involving patients with advanced localized disease [45,46].

Advocates of PSA testing attribute the decline in prostate cancer mortality to early detection of clinically localized disease and the subsequent intervention with either surgery or radiation. Unfortunately, evidence to support this hypothesis is much more tenuous. Advocates also often cite the ability of PSA testing to identify men with localized prostate cancer as proof that screening is effective. Recent trends in prostate cancer incidence rates have shown a dramatic shift towards early-stage disease [4]. Unfortunately a stage shift is a necessary but insufficient indicator of the success of a screening program. Similar stage shifts were identified following the introduction of screening programs for lung cancer and neuroblastoma [47,48]. Unfortunately early intervention in these diseases did not yield a corresponding decline in mortality rates.

Improvements in 5- and 10-year survival rates following the diagnosis of prostate cancer are also often cited as proof that PSA testing is effective. Unfortunately, the increased lead time associated with PSA testing is the primary reason for improved survival rates. In 2000, Welch and Black published an elegant manuscript exploring the impact of lead time on cancer mortality rates [49]. They noted that the prevalence of any cancer and the consequences of any treatments depend on the level of screening. During the period 1950–1996 five-year survival rates for prostate cancer in the USA increased by 50%. During this same period the incidence of prostate cancer increased by 200%, while prostate cancer mortality rates increased by approximately 10%. Therefore improvements in 5- and 10-year survival results do not necessarily translate into improvements in mortality rates.

The advent of testing for PSA has dramatically changed our understanding of the natural history of prostate cancer. PSA provides a tool for assessing the presence of prostate cancer and the progression of disease following treatment. Testing for serum PSA has resulted in an earlier diagnosis for many men with prostate cancer, when compared with the era preceding PSA testing. This, however, has also resulted in the undesirable effect of increasing our ability to detect subclinical disease that is never destined to cause morbidity.

Based on data collected by the Rotterdam section of the European Randomized Study of Screening for Prostate Cancer (ERSPC), Draisma et al. have developed models that estimate the impact of PSA testing on both lead time and over-detection [50]. Mean lead times and rates of over detection depend upon a man's age at screening. For a single screening test at age 55 years, the estimated lead time was 12.3 years (range 11.6–14.1 years) and the over-detection rate was 27% (range 24–37%). At age 75 years the estimated lead time was only 6.0 years (range 5.8–6.3 years), but the over-detection rate had increased to 56% (range 53–61%). They estimated that annual screening from age 55 to age 67 would result in an over-detection rate of 50% and would increase a person's lifetime risk of developing prostate cancer by 80%. By extending annual or quadrennial screening to the age of 75 years would result in at least two cases of over-detection for every one clinically relevant prostate cancer detected.

It is difficult to adjust for lead-time bias. Simply adding or subtracting several years to/from survival estimates assumes that cases identified as a result of an elevated serum PSA progress at the same rate as those that eventually present clinically. This assumption may or may not be true and can result in length-time bias. The rate of disease progression is usually inversely proportional to the length of the preclinical phase in which testing can identify disease. Slow-growing tumors are preferentially identified when screening tests are applied repeatedly. During the past decade, many men in the United States have received multiple PSA tests. As a consequence, cancers identified during the late 1990s and early 2000s are much more likely to be relatively slow growing when compared with cancers identified during the early 1990s. Length bias increases in magnitude as the detection threshold of a screening test is reduced. Additionally, the spectrum of detected disease is widened to include cases that are unlikely to progress during a patient's lifetime. Therefore the recent effort to lower the cut-off point threshold to 2.5 ng/ml has most likely increased the incidence of indolent prostate cancers [51].

The recently published chemoprevention trial comparing finasteride versus placebo confirms that PSA testing has introduced a length-time bias. Biopsies performed at the end of the study identified

prostate cancer in 18% of the men taking finasteride and 24% of the patients on placebo. This compares with the expected rate of 6% estimated at the start of the study [52]. By lowering the PSA threshold for performing trans-rectal ultrasound and prostate biopsy, clinicians are identifying many cases of prostate cancer that are unlikely to progress to clinically significant disease during a patient's lifetime.

The increased lead time and length time bias introduced by PSA testing has altered out historical understanding of the natural history of prostate cancer and its response to intervention. Compared with earlier series, modern studies examining the treatment and diagnosis of prostate cancer suggest a more favorable outcome with intervention. Many of these studies, however, fail to adjust for the lead time and length time bias [53]. It is not known whether early stage prostate cancer detected as a result of an elevated PSA progresses at the same rate as the clinical prostate cancers seen during the era preceding PSA testing. However, studies from the pre PSA era have clearly demonstrated the minimal impact of well differentiated and moderately differentiated disease on overall patient survival. When lead time and length biases are considered, the probability that older men diagnosed in the PSA era will die of prostate cancer is further reduced. This is especially true for men with well and moderately differentiated disease and those men with significant competing medical hazards.

The distortion introduced by lead time bias also applies to treatments that are implemented as a result of a lower threshold for diagnosis. When disease is diagnosed earlier in its course, treatments will appear to be more effective because survival from the point of diagnosis has increased. Unfortunately, the patient may not have experienced a longer life time. As a result, new therapies often appear promising and may even replace older, safer, and more effective therapies. This cycle of increasing intervention as a result of misconceptions of disease prevalence and therapeutic effectiveness clearly pertains to prostate cancer. It is tempting to attribute improved survival rates and declining mortality rates to the increased use of interventions such as surgery, radiation, or seed implantations, but lead time and length time bias could just as easily account for these findings.

In summary, early detection of prostate cancer may improve clinical outcomes, but the data are tenuous. The strongest case for clinical improvement that has resulted from PSA testing can be made for early intervention with androgen withdrawal therapy as compared with the previous practice of intervening only when metastases developed. Whether PSA testing has caused a decline in prostate cancer mortality because of its ability to identify localized disease is much more debatable. Lead- time and length-time biases suggest that a very large number of men are being identified with prostate cancer who are never destined to die from their disease. These men do not benefit from intervention. The actual impact of treatments to alter clinical outcomes remains to be demonstrated by randomized clinical trials.

Conclusions

Does PSA testing of asymptomatic patients improve their overall health and well-being? The US Preventive Services Task Force recently re-evaluated the evidence supporting the efficacy of PSA testing and again concluded that the evidence was insufficient to determine whether the benefits of prostate cancer screening outweigh the harms (e.g. frequent false positives, unnecessary biopsies, and potential treatment complications) [54]. For this reason, clinical trials in Europe and the United States continue and are expected to yield results by 2009.

Proponents of PSA screening believe that the benefits have already been demonstrated, especially when one considers the dramatic stage shift in prostate cancer towards localized disease and the falling prostate cancer mortality rates. For them, withholding PSA screening while men die of prostate cancer is unethical. Critics of screening worry that PSA testing identifies too many cases of subclinical disease that would never threaten patients' lives. The associated morbidity and cost of a public health policy favoring widespread screening are unacceptable. Until better data become available, the true balance of benefits and risks remains a matter of opinion.

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