Prostate-Specific Antigen Testing to Screen for Prostate Cancer

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Prostate cancer is a common cause of cancer-related morbidity and mortality in men. Prostate-specific antigen (PSA) measurement to screen for prostate cancer has been promoted as a way to reduce morbidity and mortality from prostate cancer. This paper examines the usefulness of PSA screening for asymptomatic prostate cancer, focusing on outcomes for all patients screened.

The sensitivity and specificity of PSA testing for prostate cancer are low and have not been studied properly in asymptomatic men being screened for prostate cancer. PSA screening detects localized prostate cancer undetected by digital rectal examination in fewer than 1% of men screened.

The effectiveness of early treatment of prostate cancer, compared with deferral of treatment until symptoms develop, is unproven, and good survival rates have been reported among patients who defer aggressive treatment. Complications of treating prostate cancer with radical prostatectomy or radiation treatment include death, impotence, urethral stricture, incontinence, and rectal injury. At the present time, there is insufficient evidence to support a policy of PSA screening, and its use should be discouraged until randomized controlled trials demonstrate benefit from PSA screening.

Key words. Prostate-specific antigen; prostate neoplasms; mass screening; treatment outcome. (*J Fam Pract 1995; 41:270-278*)

Don was a 65-year-old white postal worker who retired 6 months before presenting to the hospital emergency department with urinary retention and rapidly progressive leg weakness over 18 hours. For 3 months, he had experienced gradually worsening lower thoracic back pain. A magnetic resonance imaging (MRI) scan revealed a tumor compressing the spinal cord. Emergency radiation therapy was instituted. A biopsy revealed prostate cancer metastatic to the spine. He required a second course of radiation treatment and high doses of morphine to control bone pain. Don died 4 months later of prostate cancer.

Mark was 57 years old when he saw his primary care physician for a routine checkup. Despite feeling a normal prostate and eliciting no prostate symptoms, his physician advised prostate-specific antigen (PSA) screening. His PSA was slightly elevated at 9.6 μg/L. Repeat PSA value 2 weeks later was 9.2 μg/L. Transrectal ultrasound was performed, and a hypoechoic region was noted and biopsied. Mark received a diagnosis of prostate cancer, stage A_2. Radical prostatectomy was done. He did well until the age of 63, when he died of a myocardial infarction.

Joe is 65 years old and in excellent health. His parents died at ages 85 and 83, and he has a 79-year-old sister who jogs with him three times each week. He voids twice each night after retiring, and notes his urinary stream is a bit weaker than normal. His prostate is moderately and symmetrically enlarged. He has a friend who recently had a blood test to check for prostate cancer. He asks his family physician if he should have a "cancer test."

These three fictional but representative patients are at the core of the dilemma regarding screening for the early detection of prostate cancer. If only we could have diagnosed and treated Don's disease when it was confined to the prostate, perhaps he would not have suffered pain,

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paralysis, and death from prostate cancer. Mark was treated early and was fortunate not to have impotence or incontinence as a result. However, had his prostate cancer never been diagnosed and treated, his course, including death from myocardial infarction, might have been the same. Without PSA screening, the difference for Mark might have been being spared years of fear and anxiety associated with knowing he was a "cancer victim," and not being subjected to the pain, risk, and expense of major surgery. Joe is a man poised between these two scenarios. Should we advise Joe to undergo PSA testing in the hope of avoiding Don's tragic outcome, or advise against it and avoid the iatrogenic morbidity experienced by Mark, not to mention the potential for iatrogenic mortality experienced by an unfortunate few who undergo surgical treatment for prostate cancer?

Prostate-Specific Antigen

Prostate-specific antigen is a protease produced by both normal and malignant prostatic epithelial cells, but not by any other cell in the body. It is not detectable in females. Immunochemically, it is an organ-specific marker[1] that was approved by the Food and Drug Administration (FDA) on February 26, 1986, for use as an aid in the prognosis and management of patients with prostate cancer. Initially, its use in screening was discouraged because it was shown to be elevated in 55% to 83% of men with benign prostatic hypertrophy.[1] Catalona and co-workers[2] first suggested the usefulness of PSA screening in 1991. This article reviews the use of PSA in screening healthy men for prostate cancer.

Evidence for Cancer Screening

We should screen for cancer when high-quality evidence demonstrates that more patients are helped than harmed by screening.[3] The only evidence that could conclusively demonstrate such a result would be a randomized controlled trial, allocating patients to screening or no screening and demonstrating reduced cause-specific mortality without concomitant increased mortality due to the intervention. Such trials have shown, for example, that mammograms in combination with clinical breast examinations in women over age 50 are beneficial. This type of trial for prostate cancer has been launched by the National Cancer Institute, but no such trials have ever been completed. Without evidence from a randomized controlled trial, we cannot be sure that PSA screening is beneficial. Sackett and colleagues[3] argue that we should screen *only* when randomized trials have demonstrated that the healthy people among whom we promote PSA screening would actually benefit from it.

Table 1. Screening Criteria for Health Maintenance Interventions

1. The condition must have a significant effect on the quality or quantity of life.
2. Acceptable methods of treatment must be available.
3. The condition must have an asymptomatic period during which detection and treatment significantly reduce morbidity and/or mortality.
4. Treatment in the asymptomatic phase must yield a therapeutic result superior to that obtained by delaying treatment until symptoms appear.
5. Tests that are acceptable to patients must be available at reasonable cost for detection of the condition in the asymptomatic period.
6. The incidence of the condition must be sufficient to justify the cost of screening.

Based on Frame PS, Carlson SJ. A critical review of periodic health screening using specific screening criteria. Parts 1–4. J Fam Pract 1975; 2:29–36; 123–29; 189–94; 283–89.

In the absence of randomized trials, six criteria have been proposed by Frame and Carlson[4–7] as prerequisites for screening (Table 1). This paper includes a review of the effects of prostate cancer, followed by a discussion of the accuracy of PSA testing; an examination of the potential benefit of screening for prostate cancer, including the effects of early detection and treatment; a discussion of the potential harm from detection and treatment of prostate cancer; and a consideration of the degree to which the criteria of Frame and Carlson are met as well as the limitations of those criteria for prostate cancer screening.

Effects of Prostate Cancer

Prostate cancer can have a significant effect on the quality and length of life. It is the second leading cause of cancer mortality in men. An estimated 40,400 men will die of prostate cancer in 1995.[8] Approximately 244,000 new cases of prostate cancer will be diagnosed in 1995[8]; 29% to 35% stage C, and 9% to 24% stage D at presentation.[9–11] Prostate cancer is the cause of about 3% of male deaths in the United States, and about 13% of all cancer deaths.[12] On the other hand, asymptomatic prostate cancer, which is common, may have no effect on the quality or quantity of life. For a 50-year-old man with a life expectancy of 25 years, the lifetime risk of microscopic prostate cancer (identified at autopsy) has been estimated at 42%, compared with risks of clinical or fatal prostate cancer of 9.5% and 2.9%, respectively.[13] The effect of asymptomatic prostate cancer on the quality or quantity of life, therefore, is unpredictable.

Accuracy of PSA Test in Screening for Prostate Cancer

The perfect screening test would have 100% sensitivity and 100% specificity. It would identify all people with a given disease and rule out disease in all people free of that disease. When assessing a screening test, we need to know the sensitivity and specificity in the population to be screened to avoid spectrum bias.[14,15] This is impossible in the case of PSA and prostate cancer screening. In all published studies of PSA screening for prostate cancer, an appropriate reference standard was applied only to men with positive screening tests.[16–20] Consequently, each of these studies is compromised by "verification bias" or "workup bias."[21,22] Since we do not know how many men with normal PSA or digital rectal examination (DRE) screening tests had prostate cancer, we cannot determine the sensitivity or specificity of these tests in this population. It would probably be unethical to perform a biopsy on all men in such a study, but follow-up of men with normal screening tests for an appropriate length of time to determine how many manifested prostate cancer would provide an appropriate reference standard. No such follow-up has been reported. A positive predictive value can be calculated from these studies, but it will vary as the prevalence of the disease varies.

Catalona and associates[2] reported results of PSA testing in a group of 235 men referred for prostate biopsy because of abnormal DRE, ultrasound findings, or other signs or symptoms of prostate disease. Because of the likelihood of spectrum bias, this is not an ideal sample. All men, however, underwent a reference standard test: prostate biopsy. The sensitivity of a PSA >4.0 μg/L for prostate cancer was 78.7% (48/61), and the specificity was 66.7% (116/174). The prevalence of prostate cancer in this group of men was 26%.

Another way of looking at the accuracy of PSA testing is to examine how the test has performed in a population undergoing screening. Catalona et al[16] recruited 6630 men from the community at large for a study of the usefulness of PSA testing to detect prostate cancer. This population of men presented for screening, *not* for evaluation of symptoms of possible prostate cancer. Prostate biopsy was recommended to all men with either a PSA above 4.0 μg/mL or an abnormal DRE. Positive results for DRE or PSA testing, or both, were found in 1710 men (26% of the sample). Thirty-two percent (543) of the men with a positive screening test did not have biopsies. A total of 264 cases of prostate cancer were detected, of which 146 were detected by DRE alone and 118 more were found when PSA tests were added to DRE. In previous studies of PSA for prostate cancer screening, biopsy was done only if results of PSA testing *and* either DRE or transrectal ultrasound of the prostate were positive. Likewise only men with positive DRE results *and* either positive PSA or positive transrectal ultrasound findings underwent confirmatory biopsy.

Since it is generally agreed that curative therapy does not currently exist for prostate cancer that has spread beyond the confines of the prostate gland, it is critical to know how many localized (stage A or B) cancers were detected. A total of 114 organ-confined cancers were confirmed with pathologic staging. Of these, 64 were detected by DRE and 50 by PSA alone. For each case of organ-confined prostate cancer detected only with PSA, 133 men were screened, 34 had a positive screening test, 3 were found to have cancer detected that had spread beyond the prostate gland, and 1 had localized cancer detected by DRE. Of men with positive screening tests, 2.9% of those with a positive PSA alone had documented organ-confined cancer. This represents 0.75% of the men screened.

Data taken from this study were the basis for the recent FDA approval of a new indication for the PSA assay. The FDA has approved this assay for the measurement of serum PSA in conjunction with DRE as an aid in the detection of prostate cancer. No recommendation for or against PSA screening for prostate cancer was made by the FDA.

Potential Benefit of Screening for Prostate Cancer

Survival of men in whom prostate cancer has been diagnosed is related to the extent of tumor. When the cancer is confined to the prostate gland, median survival is greater than 5 years. Organ-confined disease is frequently curable. Patients with stages A_1 through B_2 have tumors that can progress and cause death.[23] Patients with locally advanced disease usually cannot be cured. Some will die of prostate cancer, although median survival may be as long as 5 years. Less optimistic prognoses have been reported. In one report,[24] lymph node metastases occurred in 50% of stage C patients, at which time they would be reclassified as stage D_1. Survival rates among untreated patients were 42% to 54% at 1 year, 22% at 3 years, and 10% at 5 years. Currently available therapies will not cure prostate cancer that has spread to other organs. Median survival for these patients, the majority of whom will die of prostatic cancer, is 1 to 3 years. The theoretical benefit of PSA screening is that identification of organ-confined prostate cancer will allow curative therapy to be accomplished before the cancer has progressed to an incurable stage.

Table 2. Complications of Treatments for Prostate Cancer

Complication	% of Patients in Wasson Study*			% of Patients in Catalona Study†		
	Radical Surgery	External Beam Radiation	Interstitial Radiation	Radical Surgery	External Beam Radiation	Interstitial Radiation
Mortality	1.1	0.2	0.6	0.1–2	<0.1	Not reported
Incontinence, any	26.6	6.1	Not reported	5–15	<1	Not reported
Incontinence, complete	6.8	1.2	5.4	Not reported separately	Not reported separately	Not reported
Urethral stricture	12.4 requiring long-term treatment	4.5 requiring long-term treatment	9.8 requiring long-term treatment	0.6–25	4	Not reported
Impotence	84.6 (31.5 for nerve-sparing procedure)	41.4	12.4	30–60	40–60	Not reported
Rectal injury	2.7 (1.3 needing long-term treatment or colostomy)	11.4 (2.3 needing long-term treatment or colostomy)	14.4 (3.2 needing long-term treatment or colostomy)	0.1–7	30–50 (acute proctitis) 2–5 (chronic proctitis or enteritis)	3 (rectal discomfort)

Modified from Wasson JH, Cushman CC, Bruskewitz RC, et al. A structured literature review of treatment for localized prostate cancer. Arch Fam Med 1993; 2:487–93. Copyright 1993, American Medical Association.

†Adapted from Catalona WJ. Treatment of prostate cancer. N Engl J Med 1994; 331:996–1004. Copyright 1994, Massachusetts Medical Society. All rights reserved.

Effects of Early Detection and Treatment

To meet the criteria proposed by Frame and Carlson,[4–7] prostate cancer must have an asymptomatic period during which detection and treatment significantly reduces morbidity or mortality or both. Furthermore, treatment in the asymptomatic phase must yield a therapeutic result superior to that obtained by delaying treatment until symptoms appear (Table 1).

Prostate cancer does have an asymptomatic phase during which detection is possible. Serum PSA measurement can increase the detection rate of prostate cancer and increase the rate of detection of organ-confined prostate cancer (stage A or B).[16,20] To further meet the Frame and Carlson criteria, the key questions are: does treatment in the asymptomatic period significantly reduce morbidity, mortality, or both? and does treatment in the asymptomatic phase yield a therapeutic result superior to that obtained by waiting to treat until symptoms appear?

There is no definitive proof that treatment of stage A or B prostate cancer improves outcome. A randomized controlled trial with sufficient power to detect a meaningful difference in outcome would be required, and no such trial has been done. The sole randomized controlled trial comparing radical prostatectomy (RP) with expectant primary treatment showed no reduction in mortality in the surgically treated group.[25] Only 95 patients were enrolled in the trial, however, a number too small to reliably exclude improved outcome following prostatectomy. In the absence of a randomized controlled trial, less reliable evidence must be used to assess treatment efficacy.

Wasson and co-workers[26] carried out a structured literature review of treatment for localized prostate cancer. The methodological inadequacies of the 144 articles reviewed made it impossible to determine treatment effectiveness; ie, evidence demonstrating the superiority of any treatment over the "watchful waiting" approach could not be found. Wasson's review documented substantial rates of complications (Table 2).

Fleming et al[27] performed a decision analysis comparing deferred treatment, RP, and external beam radiation (EBR). Without adjusting for quality of life, small increases in life expectancy were predicted for men aged 70 or younger undergoing RP. With adjustments for quality of life, "watchful waiting" patients fared as well as or better than patients who had RP or EBR, except under the most optimistic assumptions favoring RP or EBR. The investigators concluded that the choice of watchful waiting is a reasonable alternative to invasive treatment for many men with localized prostatic carcinoma.

Johansson and colleagues[28] examined the course of 223 consecutive patients with early-stage prostate cancer who were initially untreated. Only 8.5% died of prostate cancer during a mean follow-up of 123 months. The 10-year, disease-specific survival was 86.8% and was equally high (87.9%) in a subgroup of 58 patients who met current indications for RP. The disease-specific survival rate in their population-based study was equivalent to disease-specific survival rates reported in uncontrolled treatment trials. The authors concluded that the radical treatment of early-stage prostate cancer should be considered experimental.

Chodak and associates[29] performed a pooled analysis of 828 case records of men who were treated conservatively with observation and delayed hormone therapy but no radical surgery or irradiation for clinically localized prostate cancer. They divided the patients into three

groups: those with well-differentiated tumors, those with moderately differentiated tumors, and those with poorly differentiated tumors. Ten years after diagnosis, disease-specific survival was 87% for men with well or moderately differentiated tumors and 34% for those with poorly differentiated tumors. Survival of men with untreated well or moderately differentiated prostate cancer was equal to the normal life expectancy of the population, adjusted for age. Watchful waiting was considered a reasonable option for men with clinically localized well or moderately differentiated prostate cancer. In men with poorly differentiated tumors, the prognosis is poorer, yet treatment has an uncertain impact. Chodak and colleagues[29] called for new management strategies for men with these cancers, because compared with conservative treatment, neither radical surgery nor radiation therapy substantially lowers the high rates of metastasis and mortality.

Adolfsson et al[30] reviewed published series of prostate cancer patients treated with RP, deferred treatment, or EBR. The calculated weighted mean number of distant failures for those managed with deferred treatment was 25.1 per 1000 person-years at risk. The calculated mean number of deaths due to prostate cancer was 16.8 per 1000 person-years at risk, and the calculated mean number of deaths due to intercurrent disease was 48.8 per 1000 person-years at risk. The respective calculated weighted means for patients treated with RP were 12.6, 7.0, and 9.9 per 1000 person-years at risk. For patients treated with EBR, the respective values were 29.0, 38.2, and 36.3 per 1000 person-years at risk. A weighted mean disease-specific survival was calculated for each of the three groups. The calculated disease-specific survival was 83% for the deferred treatment patients, 93% for those treated with RP, and 74% for those treated with EBR. None of these were randomized or even comparative trials. As demonstrated by the difference in deaths due to intercurrent diseases, the groups were not directly comparable, and selection bias is a possible explanation for the difference in treatment results. The quality of life with respect to the morbidity of both the disease and the treatment was not examined.

Sackett[31] has identified levels of evidence that are useful in determining the reliability of research papers (Table 3). Use of these levels of evidence has proven simple and useful.[32] None of the published work describing the efficacy of different treatments for prostate cancer is of level I quality. One level II study demonstrated equivalent outcomes for patients treated with RP and those given deferred treatment when symptoms developed.[25] Level IV studies[26–30] indicate that the watchful waiting or deferred treatment option is a reasonable choice, with acceptable long-term survival, and may be equivalent or preferable to RP or EBR. At this time, we do not know whether the third and fourth criteria proposed by Frame and Carlson are met by PSA screening. We do know that there is no evidence documenting that these criteria have been met. It has not been demonstrated that treatment of asymptomatic prostate cancer significantly reduces morbidity or mortality or yields a therapeutic result superior to that obtained by delaying treatment until symptoms appear.

Table 3. Levels of Evidence Useful in Determining the Reliability of Research Papers

Level I	Randomized trials of high power with low false-positive (alpha or type I) and low false-negative (beta or type II) errors
Level II	Randomized trials with high false-positive (alpha or type I) and/or high false-negative (beta or type II) errors (low power)
Level III	Non-randomized concurrent cohort comparison between contemporaneous patients who did and did not receive the treatment in question
Level IV	Non-randomized historical cohort comparisons between current patients who did receive the treatment in question and former patients (from the same institution or from the literature) who did not
Level V	Case series without control subjects

Reprinted with permission from Sackett DL. Rules of evidence and clinical recommendations on the use of antithrombotic agents. Chest 1986; 89(suppl):2S–3S.

Potential Harm from Screening

All treatments for prostate cancer, including RP, involve risk, even if only for transient harm, such as pain, hospitalization, and temporary disability. Lu-Yao and co-workers[33] have reported complication rates in a population-based study of radical prostatectomy in Medicare patients. Among patients between 65 and 70 years of age, a group that is eligible for Medicare and for whom some recommend screening, the 30-day mortality was 1.05%. Cardiopulmonary complications, eg, heart failure, myocardial infarction, pulmonary embolism and infarction, and respiratory failure, occurred in 4.05%. Vascular complications, eg, arterial embolism, phlebitis, and thrombophlebitis, occurred in 0.27%. Surgical repairs were done in 0.67%. Some morbidity was experienced by nearly 5%. Treatment of prostate cancer can result in serious long-term complications or death[34] (Table 2).

It is unnecessary to risk harm if it is known that the active treatment does not improve the outcome. For instance, an individual is found through screening to have prostate cancer, but that cancer is among the 75% of prostate cancers detectable at autopsy that would never have caused morbidity or mortality.[13] For this patient,

treatment may have side effects (harm) with no possibility of benefit.

Screening for prostate cancer is considered harmful when disease is detected early but the outcome is not improved. One reason is that men receiving this diagnosis are given more time with the knowledge of their disease, rather than less.[35] For example, assume that Joe, the third hypothetical patient in the introduction, decides to undergo PSA testing. The test is positive and he is told that he has prostate cancer—2 years before it would have become apparent without screening. He dies 5 years later of prostate cancer. As a result of screening, he suffered from knowing he was a cancer victim for 5 years instead of 3 years; ie, he was given 2 additional years of disease.

In another example, Joe receives a diagnosis of localized prostate cancer and is treated 2 years before it would have been detected without screening. Three years after receiving this diagnosis, he dies of a myocardial infarction. Without screening, Joe would have known about having prostate cancer for only 1 year rather than 3 years before dying of an unrelated cause. Again, his outcome is unchanged by screening.

In both cases, Joe had to live with the knowledge of his cancer for 2 additional years. Detecting his cancer in an asymptomatic phase did not improve his health. In truth, he was harmed by the extra years of knowing he had the disease. Detecting disease earlier is not the critical issue. Improving the health of the person screened is the issue. An additional burden of early diagnosis occurs when treatment does not change the outcome but does result in significant complications. In this circumstance, the patient not only has additional time perceiving himself as a victim of prostate cancer but also has additional time suffering from the complications of his treatment.

There are three reasons why early diagnosis without improved outcome may be particularly problematic in the case of prostate cancer. First, there is a substantial amount of subclinical prostate cancer; ie, prostate cancer often exists in the absence of symptoms.[13] Second, lead-time bias (the apparent increase in survival time seen when a disease is diagnosed early, when such an increase is due *only* to the time gained by the early diagnosis) is particularly likely in the case of prostate cancer, which is known to develop slowly in many men.[3] Third, this capability for slow growth also increases the likelihood of length-time bias, the apparent increase in survival time seen when slower growing tumors are diagnosed. Slow-growing tumors are more likely to be diagnosed on screening but less likely to cause morbidity or mortality.[3]

Harm might also befall men with false-positive screening tests who experience complications as a result of the workup of their positive tests, such as infectious complications of transrectal biopsy. These include urinary tract infection,[36] which can result in pyelonephritis.[37] Biopsy of the prostate also can induce bacteremia[38] and prostatic infection, including abscess formation.[39] At least one infectious fatality following transrectal prostatic biopsy has been reported.[40] It is inevitable that some men undergoing evaluation of positive PSA screening test results will experience morbidity and possibly mortality as a result of such complications and the "cascade effect."[41] These complications can befall the 78% of men with positive PSA test results who are subsequently found not to have prostate cancer.[16]

Using limited resources for medical care of minimal or no benefit drains resources that, if used elsewhere, would provide greater benefit to the total population.[42,43] Thus, one potential drawback of PSA screening may be that it reduces the resources available for more beneficial treatments, with a negative effect on the overall health of the total population. Until we are certain that PSA screening is beneficial, we should at least be cognizant that in offering this test to detect prostate cancer, we are using resources to carry out an unproven intervention. A recent decision analysis reported that when quality of life is included in the analysis, screening for prostate cancer by any means could not be considered economically attractive.[44]

Discussion

Screening for prostate cancer is intuitively appealing. Family physicians, internists, urologists, and oncologists have cared for men, like Don, who have suffered greatly and died from prostate cancer. Because curative treatment for advanced prostate cancer is not available, we like to intervene early when effective treatment might prevent suffering and death from prostate cancer. Screening modestly increases detection of prostate cancer, including localized prostate cancer. Common sense tells us that screening for prostate cancer must be beneficial. Unfortunately, using common sense or intuition to decide that screening is beneficial can lead to medically unsound judgments.[35]

When we offer screening to healthy people, we are implying that their long-term health will be improved if we detect disease and initiate treatment. We cannot hope to improve their current health. By definition, screening is for people without symptoms. For this reason, screening should be considered only when there is evidence that the implied promise of a better long-term outcome will be fulfilled. Meeting the criteria proposed by Frame and Carlson would suggest that such an outcome is achievable. Prostate cancer, however, has not been shown to meet all the proposed criteria. In fact, it is possible that treatment in an early, asymptomatic phase is no better,

and possibly worse, than no treatment. The validity of this hypothesis, however, is uncertain because it is based on low-quality evidence from several case series and on one low-power, randomized clinical trial too small to be reliable. Likewise, we cannot be sure that delayed treatment provides improved or equal outcomes. What we can be certain of is that measures taken to diagnose prostate cancer early and treat it aggressively will harm some men.

PSA screening has three possible outcomes. In the best-case scenario, screening results in greater benefit than harm. It also may have a neutral effect, proving neither beneficial nor harmful. The third possibility is that the potential benefit of PSA screening may be outweighed by the harm associated with subsequent treatment. We do not have data to decide reliably which of these three possibilities is the actual result of screening. If the only two possible results of screening were the same or an improved outcome, a strong case could be made for a policy of screening all men until it is established that screening does not improve outcomes. We cannot reliably rule out the possibility that worse outcomes will occur, however, nor can we conclude that PSA screening meets Frame and Carlson's criteria for a screening test. We know that PSA screening will harm some men, though it might help others. If the first priority is to avoid harm (*primum non nocere*), it is premature to offer PSA screening to patients. When patients inquire about PSA screening, they should, at a minimum, be counseled regarding the uncertainties of PSA screening, to ensure that they make an informed decision about PSA screening.[45,46] It is not inappropriate to discourage screening. However, since there is currently no clear scientific evidence that PSA screening lacks benefit or produces more harm than benefit, the final decision should be left to the patient.

The criteria proposed by Frame and Carlson[4–7] may not go far enough as a standard on which to base a decision about screening. The six criteria do not require that the health of the entire population screened be taken into consideration. If good evidence existed that criteria 3 and 4 were met, but screening led to unexpected harm in the screened population, one could mistakenly conclude that screening was beneficial. For example, an unexpected but consistent outcome of drug therapy for hypercholesterolemia to prevent coronary heart disease has been an increased rate of noncoronary heart disease deaths in the actively treated groups. This increased noncoronary heart disease mortality has balanced out the decreased coronary heart disease mortality and called into question the benefit of cholesterol screening.[47–49]

In addition, Frame and Carson's criteria do not ensure that screening produces *better* outcomes because they do not address the problems of lead-time and length-time bias. If we do not require that screening be proven effective by well-done randomized controlled trials, we risk subjecting healthy people to reduced levels of health, despite our best intentions to benefit them.

To fulfill our implied promise of better health to those to whom we would offer screening, we must be guided by high-quality evidence. Level I and level II evidence is suggested as the minimum necessary to guide decisions about screening. Such is the approach of both the US Preventive Services Task Force and the Canadian Task Force on the Periodic Health Examination. These task forces do not recommend PSA screening.[23,50] The organizations that advocate PSA screening, for example, the American Cancer Society and the American Urological Association, do not rely on level I or II evidence, but rather level IV and V evidence and opinion to support their recommendations. Physicians who have the opportunity should actively support entry of their patients into the randomized controlled trial of prostate cancer screening sponsored by the National Cancer Institute. Physicians without such an opportunity would be wise to avoid a policy of PSA screening until such studies are completed and have demonstrated benefit from PSA screening.

Conclusions

Prostate cancer is a common form of cancer that can cause significant morbidity and mortality. PSA screening has been proposed as a method of reducing the burden of illness caused by prostate cancer. However, the accuracy of the PSA test is less than optimal and has not been fully characterized in a screened population. When added to DRE as a means of screening for prostate cancer, the PSA test identifies localized prostate cancer in fewer than 1% of men screened. Treatment of localized prostate cancer has not been proven to be of more benefit than deferral of treatment until symptoms appear. Deferring treatment in men who have localized prostate cancer has a reasonably good prognosis. Treatment of prostate cancer sometimes results in harm and occasionally death. Length-time and lead-time bias are likely to make PSA screening appear beneficial even if it is not. Criteria proposed by Frame and Carlson to determine when screening tests should be done have not been met in the case of PSA screening for prostate cancer. Support from high-quality, level I or level II evidence from randomized controlled trials of PSA screening is lacking. At the present time, there is insufficient evidence to support a policy of PSA screening, and its use outside of clinical trials should be discouraged until randomized controlled trials demonstrate benefit from PSA screening. Patients choosing PSA screening should be fully informed of the uncertainties surrounding PSA screening before undergoing screening.

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