PSA testing: When it's useful, when it's not

Routine PSA testing leads to more diagnoses of prostate cancer, but does not save lives. At least one group of men, however, may reap a small benefit.

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PRACTICE CHANGER

Do not routinely screen all men over the age of 50 for prostate cancer with the prostate-specific antigen (PSA) test. Consider screening men younger than 75 with no cardiovascular or cancer risk factors—the only patient population for whom PSA testing appears to provide even a small benefit.[1,2]

STRENGTH OF RECOMMENDATION

B: Based on a meta-analysis of 6 randomized controlled trials (RCTs) with methodological limitations, and a post hoc analysis of a large RCT.

Djulbegovic M, Beyth RJ, Neuberger MM, et al. Screening for prostate cancer: systematic review and meta-analysis of randomized controlled trials. *BMJ.* 2010;341:c4543.

Crawford ED, Grubb R 3rd, Black A, et al. Comorbidity and mortality results from a randomized prostate cancer screening trial. *J Clin Oncol.* 2011;29:355-361.

ILLUSTRATIVE CASES

▶ A 65-year-old obese man with high blood pressure comes in for a complete physical and asks if he should have the "blood test for cancer." He had a normal prostate specific antigen (PSA) the last time he was tested, but that was 10 years ago. What should you tell him?

▶ A 55-year-old man schedules a routine check-up and requests a PSA test. His last test, at age 50, was normal. The patient has no known medical problems and no family history of prostate cancer, and he exercises regularly and doesn't smoke. How should you respond to his request for a PSA test?

Prostate cancer is the second leading cause of cancer deaths among men in the United States, after lung cancer. One in 6 American men will be diagnosed with prostate cancer; for about 3% of them, the cancer will be fatal.[3,4]

Widespread testing without evidence of efficacy

The PSA test was approved by the US Food and Drug Administration (FDA) in 1986.[5] Its potential to detect early prostate cancer in the hope of decreasing morbidity and mortality led to widespread PSA screening in the 1990s, before data on the efficacy of routine screening existed.

By 2002, only one low-quality RCT that compared screening with no screening had been published. The investigators concluded that screening resulted in lower mortality rates, but a subsequent (and superior) intention-to -treat analysis showed no mortality benefit.[6] Two large RCTs, both published in 2009, reported conflicting results.[7,8]

The European Randomized Study of Screening for Prostate Cancer (ERSPC) enrolled 182,000 men ages 50 to 74 years and randomized them to either PSA screening every 4 years or no screening. Prostate cancer-specific mortality was 20% lower for those in the screening group compared with the no-screening group; however, the absolute risk reduction was only 0.71 deaths per 1000 men.[7]

CONTINUED

The US Prostate, Lung, Colorectal, Ovarian Cancer (PLCO) Screening Trial randomized 77,000 men ages 55 to 74 years to either annual PSA and digital rectal examination (DRE) screening or usual care. After 7 years of follow-up, no significant difference was found in prostate cancer deaths or all-cause mortality in the screening group vs the control group. It is important to note, however, that 52% of the men in the control group had ≥1 PSA screening during the study period, which decreased the researchers' ability to fully assess the benefits of screening.[8]

PSA's limitations and potential harmful effects

The PSA test's significant limitations and potentially harmful effects counter the potential benefits of screening. About 75% of positive tests are false positives, which are associated with psychological harm in some men for up to a year after the test.[6] In addition, diagnostic testing and treatment for what may be non-life-threatening prostate cancer can cause harm, including erectile dysfunction (ED), urinary incontinence, bowel dysfunction, and death. Rates of ED and incontinence 18 months after radical prostatectomy are an estimated 59.9% and 8.4%, respectively.[9]

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Do the benefits of PSA testing outweigh the harms—and for which men? The meta-analysis and post hoc analysis detailed in this PURL help clear up the controversy.

STUDY SUMMARY

Widespread screening doesn't save lives

Djulbegovic et al examined 6 RCTs, including the ERSPC and PLCO studies described earlier, that compared screening for prostate cancer (PSA with or without DRE) with no screening or usual care.[1] Together, the studies included nearly 390,000 men ages 45 to 80 years, and had 4 to 15 years of follow-up. The results showed that routine screening for prostate cancer had no statistically significant effect on all-cause mortality (relative risk [RR]=0.99; 95% confidence interval [CI], 0.97-1.01), death from prostate cancer (RR=0.88; 95% CI, 0.71-1.09), or diagnosis of stage III or IV prostate cancer (RR=0.94; 95% CI, 0.85-1.04). Routine screening did, however, increase the probability of being diagnosed with prostate cancer at any stage, especially at stage I. For every 1000 men screened, on average, 20 more cases of prostate cancer were diagnosed.

Healthy men may benefit from screening

Crawford et al conducted a post hoc analysis of the PLCO trial, which had found no benefit to annual PSA testing and serial DRE compared with usual care for the general population.[2] Their analysis compared the mortality benefits (both prostate cancer–specific and overall) of annual PSA screening for healthy men with no or minimal comorbidities vs the mortality benefits for men with any risk factor for the 2 leading causes of death: cancer and cardiovascular disease.

Annual PSA testing yielded more diagnoses of prostate cancer in both healthy and at-risk men. Deaths from prostate cancer were infrequent in both groups, occurring in 0.22% (164/73,378) of all participants.

Men with ≥1 risk factor had similar prostate cancer–specific deaths with both yearly screening and usual care (62 vs 42 deaths, adjusted hazard ratio [AHR]=1.43; 95% CI, 0.96-2.11); their prostate cancer–specific mortality rate was 0.27% (95% CI, 0.21-0.34) and 0.19% (95% CI, 0.14-0.25), respectively.

However, healthy men younger than 75 years had fewer prostate cancer–specific deaths with annual PSA screenings (22 vs 38; AHR=0.56; 95% CI, 0.33-0.95; *P*=.03). Specifically, the prostate cancer mortality rate was 0.17% (95% CI, 0.11-0.25) in the group that received screening vs 0.31% (95% CI, 0.22-0.42) in the usual care group. Thus, the absolute risk reduction for prostate cancer-specific mortality in men without comorbidities who received yearly screening instead of usual care was 0.14% (0.31% vs 0.17%, *P*=.03), with a number needed to screen of 723 to prevent one death from prostate cancer. There was a non-significant reduction in all-cause mortality in the intervention group vs the control group (AHR=0.93; 95% CI, 0.86-1.02; *P*=.11).

WHAT'S NEW

At best, screening has a small benefit

These trials indicate that only a small group of

men will potentially benefit from PSA screening. Prior to this meta-analysis, a Cochrane review published in 2006 had concluded that there was insufficient evidence to support or refute the routine use of mass screening for prostate cancer.[10] The meta-analysis by Djulbegovic et al, which included 4 additional trials, 2 of them large, found no benefit of PSA screening in reducing mortality from prostate cancer for the general population.[1]

Annual screening does appear to provide a small reduction in prostate cancer deaths but no significant reduction in all-cause mortality in men younger than age 75 who have no risk factors for cancer or cardiovascular disease.

CAVEATS

Study limitations, some unknowns

These studies did not address whether certain groups at higher risk of developing prostate cancer, such as African American men and those with a family history of prostate cancer, would benefit from PSA screening. In addition, both of the studies detailed in this PURL had substantive weaknesses.

Methodological limitations of the studies in the meta-analysis included the lack of intention-to-treat analysis and allocation concealment, which favors finding a benefit for the screening arm, and PSA screening in the nonscreening arm, which biases the results toward *not* finding a screening benefit that might exist. Despite these weaknesses, this meta-analysis brings together the best available evidence of the value of screening for prostate cancer.

In addition, there was no quantitative assessment of complication rates included in the meta-analysis. None of the 6 trials collected data on the effect of screening or treatment on participants' quality of life.

In the post hoc study showing a benefit for screening healthy men, the decrease in prostate cancer deaths was small in magnitude, did not have an impact on all-cause mortality, and was of marginal statistical significance. Although the data came from the largest multicenter study to date of prostate cancer screening, the results of a post hoc analysis of a single trial should be interpreted with caution. The study was initially designed to test the effect of screening on a general population. Whenever a study deviates from the original hypothesis to evaluate a subset of the study population, the investigators increase the risk of finding a difference where none exists. Thus, it is possible that the findings of benefit for healthy men may not truly be present.

What's more, the risk factors identified by the authors could be interpreted as arbitrary. They included diverticulosis, which is not known to increase the likelihood of cancer or heart disease, as a risk factor. By the same token, smoking—a known risk factor for both cancer and cardiovascular disease—was not addressed. Finally, potential harms associated with false-positive tests and prostate cancer treatment were not addressed in these studies.

CHALLENGES TO IMPLEMENTATION

Old habits die hard

Clinicians have recommended PSA screening for men >50 years, and men have requested such screening, for more than 2 decades. Physicians often opt to order a PSA test rather than to take the time to explain potential harms and benefits and listen to the patient's thoughts and feelings about the value of screening. In addition, physicians who believe the lack of benefit from screening does not apply to their patients will continue to order the PSA test. (See "The perils of PSA screening" [editorial] on page 319.)

Patients may opt to continue to be screened although they have developed a risk factor for cardiovascular disease. Also, a decision *not* to screen directly contradicts the recommendation of the American Urological Association, which calls for *annual* PSA testing for asymptomatic men with a life expectancy >10 years starting at 40 years of age.[11]

Shared decision-making

The US Preventive Services Task Force (USPSTF) provides a basis for shared decision-making between physicians and patients concerning prostate cancer screening. The USPSTF states that there is insufficient evidence to recommend for or against pros-

Routine screening has no significant effect on all-cause mortality, but does increase the probability of being diagnosed with prostate cancer.

tate cancer screening for the general male population younger than age 75 and recommends against screening men age 75 and older or those with a life expectancy of less than 10 years.[12]

Decisions regarding PSA screening should be shared and documented for all men between the ages of 50 and 75 years. Advise patients with risk factors that the evidence shows little value and possible harm from screening. Tell healthier men that PSA testing appears to offer a small benefit, at best. JFP

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