Medicine by the Numbers

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The NNT Group rating system:

Green:	Benefits greater than harms
Yellow:	Unclear benefits
Red:	No benefits
Black:	Harms greater than benefits

➤ PSA Screening for Prostate Cancer

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PSA SCREENING FOR PROSTATE CANCER

NNH = 5 for performance of unneeded biopsy

Benefits	*Harms*
None were helped (preventing death from any cause, preventing death from prostate cancer)	1 in 5 was harmed (undergoing a prostate biopsy for a false-positive test) 1 in 34 was harmed (developed erectile dysfunction) 1 in 56 was harmed (developed urinary incontinence)

Details for This Review

Study Population: Average-risk men screened with prostate-specific antigen (PSA) test for prostate cancer

Efficacy End Points: Detection of prostate cancer, prevention of death or metastasis from prostate cancer, and prevention of death from any cause

Harm End Points: Need for biopsy (when given the risk of a false-positive PSA result)

Narrative: U.S. men have a 16% chance of a prostate cancer diagnosis in their lifetime and a 3% chance of dying from prostate cancer.[1] Autopsy studies have shown that up to two-thirds of older men die with asymptomatic prostate cancer. It appears that most men will develop prostate cancer if they live long enough, although it usually does not affect longevity.[1]

Given the high incidence of prostate cancer, there have been aggressive efforts to screen patients with the hopes of diagnosing local (nonmetastatic) cancer that can be treated before it progresses and leads to death. Elevated serum PSA levels are loosely correlated with prostate cancer. Routine PSA screening was widely adopted on the theory that tracking PSA levels would identify prostate cancer and save lives; therefore, broad screening began in many Western countries without evidence from major randomized trials to support this theory. In the systematic review summarized here, researchers pooled the data from six randomized controlled trials with a total of 387,286 patients (poorly designed trials were excluded).[2] Results from the systematic review follow (only one of the five trials reported adverse events. Other sources list adverse events from biopsy as high as 4.1%[3]):

- Absolute mortality rate in PSA group: 19.8%
- Absolute mortality rate in control group: 20%
- Prostate cancer mortality rate in PSA group: 0.7%
- Prostate cancer mortality rate in control group: 0.8%
- Prostate cancer diagnosis rate in PSA group: 6.4%
- Prostate cancer diagnosis rate in control group: 4.4%
- Adverse medical events (infection, bleeding) due to biopsy in PSA group: 0.7%
- Biopsy for false-positive PSA result in PSA group: 20%

The studies randomized patients to screening with PSA vs. no screening. Predefined outcomes of interest were all-cause mortality and death from prostate cancer, diagnosis of prostate cancer, effect of screening on stage at diagnosis, false-positive and false-negative results, harms of screening, quality of life, and cost-effectiveness. All-cause mortality and prostate cancer mortality were not statistically affected by PSA screening. There were more cancers diagnosed in the PSA-screened groups (6.4% vs. 4.4%), suggesting a 2% difference (and a number needed to treat [NNT] of 50) for diagnosing a cancer in the absence of a mortality benefit. There was a slight increase in diagnosis of stage 1 and 2 prostate cancer, but no increase in the diagnosis of higher or late stage 3 or 4 prostate cancer. Many of the trials did not report complications or quality-of-life measures.[2] The Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial reported a complication rate of 0.7% for prostate biopsy, including infection, bleeding, clot formation, and urinary difficulties.[4,5] The European Randomized Study of Screening for Prostate Cancer (ERSPC) trial reported that 76% of PSA positive results were false positives.[6]

In 2012, updated follow-up data were published from the ERSPC trial (182,160 men in eight European countries).[6] This randomized controlled trial showed no overall mortality benefit to PSA testing, but there was a reduction in prostate cancer mortality of 1.07 deaths per 1,000 men. To prevent one prostate cancer death, 935 men would need to be screened and 37 cancers would

need to be detected. However, to reiterate, overall mortality was unaffected by screening. Moreover, approximately 20% of men screened needlessly underwent biopsy because of a false-positive PSA result (number needed to harm [NNH] = 5).[6,7]

Caveats: The quality of the mortality data in the systematic review was considered moderate by the GRADE approach (a method of grading the quality of data[8]). The quality of the data for diagnosing cancer and effect of screening on stage of cancer was low, and there are no good data to determine whether PSA screening is useful for high-risk populations or persons. This review also did not address quality-of-life factors.[2] Findings from the U.S. Preventive Services Task Force review of these and other PSA data suggest significant increases in anxiety because of false-positive PSA results.[7] With false-positive rates of 75%,[5] it is clear that this is a nonspecific test.

Most prostate biopsies are unnecessary. Although significant complications from biopsy are uncommon, the high rate of screening ultimately means that thousands of men incur complications including bleeding and infection. A recent Canadian study found a steady rise in hospitalization for biopsy-induced infection to as much as 4.1% (six times the combined complication rate reported in the PLCO trial, which included all adverse events from biopsy).[3] In addition, financial costs and short-term pain should not be overlooked, despite being unreported in these data. More concerning is the number of men who undergo unnecessary prostatectomy, a procedure known to be associated with long-term sequelae: erectile dysfunction (36%), urinary incontinence (28%), serious cardiovascular events (3%), vascular events (1% to 2%), and treatment-related mortality (0.5%).[9] Such sequelae were observed in the PSA screening data, demonstrating a clear association with increased rates of erectile dysfunction (NNH = 34) and urinary incontinence (NNH = 56) in men who elect to undergo PSA screening[7]: erectile dysfunction rate in PSA group, 47.9%; erectile dysfunction in control group, 45%; urinary incontinence rate in PSA group, 7.8%; and urinary incontinence rate in control group, 6%.[7]

Why does detection of prostate cancer not lead to increased survival? This is not clear, but the data from this large review strongly argue against routine PSA screening in asymptomatic men.[2] Routinely screening all men with PSA tests leads to interventions that are not saving lives and are clearly causing harm. The USPSTF recommendation has stirred many partisans on both sides of the issue.[10,11] PSA supporters have criticized the USPSTF decision (faulting problems with the PLCO and ERSPC trials), and some have suggested complex modeling to better identify candidates for PSA screening. It seems that the position of the American Urological Association, a long-time staunch supporter of routine PSA testing, is evolving in this direction as well.[12]

Time and further evidence may identify a group of asymptomatic men who benefit from PSA screening; however, currently, such a cohort has not been identified. Clinicians who continue to use the PSA test despite these data should ensure that their patients understand the harm-benefit balance of the test through shared decision making, a position that the American Urological Association also supports.

This series is coordinated by Dean A. Seehusen, MD, MPH, *AFP* Contributing Editor, and Daniel Runde, MD, from the NNT Group.

This review is available from the NNT Group at http://www.thennt.com/nnt/psa-test-to-screen-for-prostate-cancer/.

Author disclosure: No relevant financial affiliations.

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