Published in final edited form as:

Arch Intern Med. 2012 June 11; 172(11): 835–836. doi:10.1001/archinternmed.2012.1226.

The Dilemma of Prostate-Specific Antigen Testing

Robin Leach, PhD and Ian M. Thompson, MD

Department of Urology, University of Texas Health Science Center at San Antonio.

For a man with prostate cancer, treatment decision making is daunting. If the tumor is high grade, decision making may be straightforward because disease-specific mortality is high despite the toxicity of combined therapies that are proved to reduce mortality (eg, radiation and hormonal therapy).¹ For a man with an aggressive tumor, while decision making requires considerable thought, information, and support by the treating physician, the possibility of adverse effects often dims when there is an opportunity to improve survival.

It is these high-grade tumors that we cannot simply ignore as we discuss the public health implications of prostate-specific antigen (PSA) testing. A patient of mine is emblematic of the opportunity to potentially help a patient with PSA testing. He was in his 50s in December 2001 and, with elevated PSA levels during routine testing, a prostate biopsy revealed a Gleason grade 5 + 5 (the most aggressive) adenocarcinoma. Staging studies showed no evidence of cancer spread. The patient opted for a radical prostatectomy and thereafter enrolled in a National Cancer Institute clinical trial (SWOG 9921). He was randomized to receive 2 years of adjuvant androgen deprivation. During a recent clinic visit, he and I reflected that it had now been 10 years since his cancer diagnosis and that his PSA levels had remained undetectable. He continues his athletic coaching career and has watched as his children and grandchildren have grown up. In this particular case, given what we know about the natural history of these very aggressive prostate cancers, it is highly likely that a PSA test and treatment had a profound effect on his length of life and his ability to enjoy his career and family.

For the man with a low-risk tumor, determining the best treatment is also not a straightforward decision and *must be* individualized. While disease-specific mortality in the intermediate term may not be great without active treatment, the option of active surveillance is associated with substantial burdens (financial, emotional, and medical). Surveillance involves regular PSA tests, digital rectal examinations (DREs), and periodic prostate biopsies. In an ongoing multi-institutional surveillance study, biopsy is performed every 2 years.² The burden of this strategy can be substantial: repeated visits for phlebotomy; regular clinic visits; invasive procedures on a repeated basis, with a 2% infection rate from the biopsy; cost; and long-term uncertainty.³ With a low risk of prostate cancer mortality in such patients after 10 to 15 years, active surveillance may be the “best choice” from a public health and cost standpoint. For an individual man, however, the

Correspondence: Dr Thompson, Department of Urology, University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Dr, San Antonio, TX 78229 (thompsoni@uthscsa.edu).

Financial Disclosure: None reported.

burdens of surveillance (PSA tests every 3–6 months, DREs every 6 months, and biopsies every 2 years) may be greater than the morbidity of treatment. With a decrease in complication rates and an improvement in outcomes (eg, improved radiation dosing and surgery almost on an outpatient basis) for all treatments of prostate cancer, a well-informed man may opt for treatment to avoid the long-term burdens and uncertainties of surveillance.

One such case involves a 76-year-old man whom I first saw several years ago. His PSA levels had fluctuated, exceeding 4.0 ng/mL (to convert to micrograms per liter, multiply by 1.0) on several occasions. Ultimately, he underwent a prostate biopsy, which demonstrated a small focus of Gleason grade 3 + 3 (low-grade) adenocarcinoma. Radiation therapy or surgery was initially recommended, but, when the patient learned of the potential adverse sexual effects, he opted instead for active surveillance. The findings of his subsequent prostate biopsies have been negative for cancer, indicating that the original tumor was likely small and has not progressed. He remains sexually active and is very pleased with his decision.

It should be clear that our primary problem is that in our quest for the detection of potentially lethal disease for which we know that treatment can affect mortality,^{1,4} we frequently stumble on low-risk disease. It is the detection of low-risk disease that is problematic; oftentimes, we would be far better off if we did not perform biopsies on men with this cancer phenotype. This problem is being addressed prospectively in several programs.

The Prostate Active Surveillance Study is enrolling low- and intermediate-risk men with prostate cancer who have opted for surveillance in a prospective trial that is designed to identify markers that correlate with disease outcome.² The goal of the study is to develop a predictive tool that incorporates biomarkers (serum, eg, PSA levels, [–2]proPSA; urine, eg, prostate cancer antigen 3; and tissue, eg, gene expression arrays) to identify ultra-low-risk prostate cancers that are likely to be indolent. If a man can be told that his risk of disease progression is less than 5% over the subsequent decade and can be given an appointment 10 years later (when clinical care will likely be utterly different), part of the burden of surveillance will be lifted.

A second critical set of studies involve the collective efforts of the Early Detection Research Network (EDRN) to identify biomarkers not of prostate cancer but of high-grade disease. Ideally, what we want is not to perform a biopsy on a man who is most likely to have low-grade disease but instead to perform a biopsy on a man who potentially has lethal, high-grade disease. Currently, we have 1 method to improve biopsy selection using risk assessment tools. One such tool was developed from the Prostate Cancer Prevention Trial by the Southwest Oncology Group and the National Cancer Institute's EDRN, which uses age, race/ethnicity, PSA levels, DREs, family history, and biopsy history to predict the risk of both low- and high-grade disease.⁵ As an example, patient 1, who has a PSA level of 3.9 ng/mL, is 55 years old and white, with no family history of prostate cancer, normal DRE results, and no history of biopsy, has a 28.8% risk of low-grade disease and a 5.7% risk of high-grade cancer. Patient 2, who has the same PSA level, is 70 years old and African American, has a father who had prostate cancer, and has abnormal DRE results, has a 23.0%

risk of low-grade disease and a 40.6% risk of high-grade cancer. For patient 1, there is a 5-fold greater likelihood of finding indolent disease (potential net harm) than lethal disease (potential net benefit). For patient 2, there is almost a 2-fold greater likelihood of finding lethal disease (net benefit) than indolent disease (potential net harm).

The EDNRN seeks to improve on this method. In an initial validation study, body mass index and prostate volume additively improved prediction of aggressive prostate cancer.⁶ Currently, the EDNRN is analyzing results of a prospective trial to determine whether urinary *PCA3* and/or *TMPRSS2:ERG* fusion transcript can further select men who are most likely to benefit from biopsy, while avoiding biopsy in men who are at low risk of cancer or who are more likely to have indolent disease.

In 2011, it was estimated that 33 720 men would lose their lives to prostate cancer.⁷ This number is unacceptable. We have the tools today to do a far better job in detecting lethal disease early and in initiating therapy in those most likely to benefit, while avoiding detection and treatment of those who will not benefit. The future will be even better as we combine biomarker science with clinical trials to detect and cure men who are otherwise destined to die of their disease.

Acknowledgments

Funding/Support: This work was supported in part by a Cancer Center Support Grant from the National Cancer Institute (P30 CA054174) and by a grant from the EDNRN, National Cancer Institute (U01 CA86402).

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