

## Screening for Prostate Cancer in 2006: PSA in the 21st Century

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Few issues in urologic oncology seem so intrinsically correct, but empirically unproven as the utility of screening for prostate cancer. For a predominantly asymptomatic disease until an incurable stage, preemptive diagnosis at a time when intervention might be curative seems intuitively beneficial. As treating physicians, we have patients with clear elements of biologically aggressive disease found through screening and cured with local therapy, who otherwise should have succumbed to the disease. We attribute this “cure” to the screening process, and this serves as anecdote for future patients facing the decision of whether to screen or not. We also have patients with low-volume, low-grade cancers detected through screening and experiencing chronic mental or physical debilitation as a result of their cancer diagnosis or treatment, which may serve as anecdote as well, especially considering the potential that the disease may have followed a benign course.

Critics of screening typically cite concerns related to overdiagnosis and the attendant overtreatment, diagnosis at a time when cure is not possible, economic issues, and the morbidity of screening. Autopsy studies demonstrate that about 35% of men in their fifties have prostate cancer, yet only 15% of men are diagnosed and 3-4% die from it.<sup>1</sup> This contributes to the idea that “men die *with* prostate cancer, not *from* it.” Others worry that prostate cancer screening could potentially misuse important resources with initial estimates of about \$25 billion per year for screening men between ages 50 and 70. Critics also raise the issue of patient morbidity with the anxiety and discomfort associated with the biopsy, the complications of treatment, and the

potential for disease recurrence. Additionally, the heterogeneous behavior of prostate cancer allows a relatively narrow window for screening to be effective in the men most likely to benefit from it. The diagnosis and treatment of incurable, but asymptomatic disease is debatable for some when diagnosis and treatment upon symptomatic progression might have avoided emotional morbidity. One might argue that prostate-specific antigen (PSA) screening is more efficient at identifying the less important, slow-growing tumors and, therefore, contributes to overdiagnosis. These seemingly potent arguments cast doubt on the overall utility of screening and leave the internist or general practitioner wondering what to do since the burden of complaints among patients with low-volume, low-grade cancers primarily falls on them.

While an issue of reasonable contention, overdiagnosis tends to not burden men that typically proceed to surgical therapy. In analyses of radical prostatectomy series, less than 10% of tumors removed are considered “insignificant” as generally judged by pathologic stage, grade, and size.<sup>2</sup> Over-diagnosis has

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not been overlooked by oncology care providers, and most men diagnosed with prostate cancer will have a care plan considering comorbidities, the benefits/side effects of treatment, and the likelihood of disease progression.

While broad screening could potentially incur high costs, as a matter of resource allocation, the cost of prostate cancer screening would be between \$9,000 and \$145,000 (best and worst case scenarios, respectively) per quality-adjusted life year (QALY) saved.<sup>3</sup> This is on par

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with using hydrochlorothiazide or captopril for treating hypertension and much less expensive than mammography screening (\$232,000/QALY gained). There are other ways to make screening more cost effective. Early data from the Prostate, Lung, Colorectal, and Ovarian (PLCO) trial suggests that men with PSA values between 1 and 2 ng/mL might only require screening every two years, while men with PSA levels less than 1 ng/mL might be screened every five years.<sup>4</sup> This alone would still detect 99% of men eventually progressing to a PSA greater than 4 ng/mL and would result in savings up to \$1 billion per year. Morbidity reduction and management are well-developed areas of prostate cancer treatment. Prostate biopsies are much more tolerable with local anesthesia, and pathology results are typically available within a week. The competition of local therapies has enticed providers to pursue and achieve real decreases in rates of side effects. Also, our understanding of what constitutes aggressive cancer has advanced, allowing for active surveillance trials in patients with low-risk disease. While screening might not benefit certain individuals, taken as a whole, screening appears to decrease morbidity and mortality.

Most of the data supporting screening has been inferential by analyzing trends in morbidity and mortality before and after the addition of the PSA blood test. Analysis of the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database has demonstrated a 20% reduction in prostate cancer mortality between 1991 and 1999.<sup>5</sup> Over a similar time period, men in Mexico have experienced a small increase in mortality presumably due to the lack of screening available.<sup>6</sup> These inferences are complicated by the fact that improvements in treatments, including the massive expansion of androgen-deprivation therapies, may have affected prostate cancer survival and the development of metastasis. In Tyrol, Austria, men over 50 years old were offered screening while men in other regions were not. Tyrol men have experienced greater than a 40% decrease in mortality from prostate cancer, which has not been experienced in other regions in Austria.<sup>7</sup> Numerous large randomized trials are currently underway regarding prostate cancer screening, including the PLCO Cancer Screening and the European Randomized Screening for Prostate Cancer (ERSPC) trials that have collectively accrued over 230,000 men. Results from these trials will not be available for several years and are eagerly awaited. Currently, most expert organizations recommend some form of cancer screening using PSA and/or digital rectal exam beginning at the age of 50 in men with a life expectancy of more than ten years with informed decision making. The United States Preventive Services Task Force does not recommend prostate cancer screening with the absence of supportive Level 1 evidence.

## Informed Consent and Ethical Concerns

Along with this lack of Level 1 evidence and the need for informed consent are numerous ethical concerns. Unfortunately, most PSA screening performed today does not involve a thorough consent process. The "required" discussion is an impediment to PSA screening, as internists might forego the discussion and, thus, the test, focusing instead on other prudent medical issues. Given time constraints in today's practice environment, this lengthy discussion cannot happen in a practical manner without some sort of supplemental material in the form of videos or pamphlets that would ideally be reviewed prior to the office visit. Many institutions have constructed these sorts of materials (see Table 1). Even with results of randomized trials, some level of informed consent would still be beneficial prior to including PSA in a general lab panel. Maybe prostate cancer screening is not for "everyone." Patients may forgo diagnostic procedures based on individual utilities of sexual and urinary function. Our philosophical approach is that "knowledge is power," and patients may make educated decisions about treatment choice (including active surveillance) after diagnosis.

Several years ago, enthusiasm was building for the next round of PSA-related markers, such as free, complexed, and pro-PSA. The use of these markers has been examined, but has not realized wide acceptance. While their use results in increases in sensitivity and specificity of diagnostic testing, the benefits are incrementally small, and the complexity of interpreting results is often an intellectual endeavor. Newer diagnostic tests using advanced laboratory techniques are also in development. The addition of these tests also creates a logistic and systemic problem. Some combination of tests may be optimal, but how can this be prospectively studied in a randomized fashion when these types of trials are time-consuming and potentially obsolete when results are available? At this point, PSA velocities have proven more clinically valuable. Recent studies have demonstrated a link between prostate cancer mortality and pre-treatment PSA velocity. Generally, an increase of PSA greater than 0.75 ng/mL in a year would support prostate biopsy, while an increase of greater than 2 ng/mL in a year carries a worse prognosis.<sup>8,9</sup> The threshold for PSA screening has also decreased, with some authorities recommending biopsies in patients with age-specific

**Table 1.**  
**Informational Resources for Prostate Cancer Screening**

**Resources for Prostate Cancer Screening**

Prostate Cancer Screening: A Decision Guide  
[www.cdc.gov/cancer/prostate/decisionguide/index.htm](http://www.cdc.gov/cancer/prostate/decisionguide/index.htm)

Screening for Prostate Cancer: Sharing the Decision  
[www.cdc.gov/cancer/prostate/screening/index.htm](http://www.cdc.gov/cancer/prostate/screening/index.htm)

Leaflet from the Centre for Reviews and Dissemination  
[www.york.ac.uk/inst/crd/em22b.htm](http://www.york.ac.uk/inst/crd/em22b.htm)

Link from UpToDate® Patient Information  
<http://patients.uptodate.com/topic.asp?file=cancer/6435>

Patient Guide from the American Urologic Association  
[www.auanet.org/trimssnet/products/guidelines/patient\\_guides/prostate\\_awareness.pdf](http://www.auanet.org/trimssnet/products/guidelines/patient_guides/prostate_awareness.pdf)

PSA values as low as 2.0 ng/mL. This approach can diagnose a number of potentially aggressive cancers at a more curable stage.

Screening techniques for other malignancies, such as cervical, breast, and colon cancer, tend to be much more invasive than a blood test or digital rectal exam (DRE). Yields of these exams vary widely based on risk group, age, etc., but tend to be less than 10% for the detection of a malignancy (pre-malignant lesions not included). By logical extension, a prostate biopsy could almost be considered as a screening device as the degree of invasiveness is on par with other screening exams, and the yields are universally greater than 10% in men over the age of 62 regardless of age or rectal exam.<sup>10</sup> Improvements in ultrasound probes, biopsy devices (smaller, spring-loaded needles), and local anesthetic techniques have made a diagnostic prostate biopsy fast and tolerable for most men. This approach is not accepted, considered, or even being examined with large trials in regard to prostate cancer screening. Clearly, the approach to prostate cancer is different largely due to estimates of over-diagnosis of up to 50%. The above diseases are universally more fatal in a shorter period of time. Additionally, the social consequences of local prostate therapy tend to be more personally destructive. As a requirement of expanding the indication of prostate biopsy to a screening instrument, we would need to have a better understanding of morbidity and lethality after diagnosis, more accurate staging tools, and embrace an active surveillance approach, initiating treatment at a time prior to the development of advanced disease. Ongoing active surveillance trials and the use of molecular markers hold much promise in this area.

One of the problems with screening trials is the approach to treatment after diagnosis. While treatment of other malignancies tends to follow a step-wise course based on evidence, in the prostate cancer literature, there is only one randomized trial that demonstrates that local treatment of prostate cancer will extend life (prostatectomy versus no treatment) and one other comparison trial with only 100 patients.<sup>11,12</sup> Numerous impediments limit academic production in this area and accruals in head-to-head treatment trials have historically been dismal, resulting in early abandonment. Most sources accept that treatment choice probably does not substantially affect mortality in a seven-to-ten-year window, but time periods beyond this, parenthetically the most important, are subject to speculation and debate. Hopefully, retrospective analysis of treatment choice in the larger screening studies will contain homogenous groups of the different treatment modalities, but these results could be decades away. Unfortunately, questions in this area may never be fully answered

through randomized trials without an acceptable short-term endpoint that is a surrogate for death from prostate cancer.

## Conclusion

On speculation, the future for prostate cancer screening will likely consist of: (1) occasional PSA (or other unspecified blood or urine molecular marker) checks at long intervals based on risk group in the fifth decade, (2) PSA/molecular marker checks based on level after the sixth decade, and (3) 12-core prostate biopsy with local anesthesia and digital rectal exam at intervals based on risk group after the sixth decade. Screening will probably be discontinued when a patient has a negative prostate biopsy and a functional index score that would predict an eight-to-ten year life expectancy. Using this hypothetical algorithm for experiment generation, simultaneous advances would need to occur for more sensitive screening instruments, individual risk assessment (including genetic susceptibility testing pre/post-diagnosis), and screening interval modification.

As physicians who treat prostate cancer, we have an enormous problem with expectation management related to imperfect predictive modeling and unique nuances increasing the complexity of patient discussion. Our patients reasonably expect that we will recommend care that will extend the quality and the quantity of their lives. Clearly, not all prostate cancer behaves the same; however, the connotations of a cancer diagnosis from a patient's perspective are usually different from the clinical reality. Actuarial estimates of average gain from prostate cancer treatment are between zero and three years of additional "quality-adjusted life years" per patient.<sup>13</sup> True or perceived effects of treatment on urinary and sexual function appropriately guide many men's choice of treatment, but results of treatment (e.g., potency after prostatectomy) are not universally reproducible. The empathetic physician thoroughly reviews these and other issues and generally receives reward in conscience only. The wise physician recommends directed patient research and deliberate decision making, while the unwise recommends urgent and narrow treatment options. Walking hand-in-hand with better knowledge about PSA screening will be improvements in treatment, morbidity reduction, and other technological advances in detection. In theory, a negative PSA screening study may not be valid considering this dynamic process. The face of prostate cancer screening might change substantially in the future and may no longer even involve PSA blood testing. **NCMedJ**

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