New Developments to Overcome the Pitfalls of Current Prostate Cancer Screening

A White Paper for Urologists

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Prostate cancer is the most common nonskin cancer diagnosed in men, with an estimated 220,800 new cases diagnosed in 2015, and accounting for an estimated 27,560 deaths in 2015.[1] It is the second leading cause of cancer deaths in men after lung cancer.[1] Prostate cancer is a heterogeneous disease in severity, ranging from slow-growing indolent tumors to rapidly progressing, highly aggressive carcinomas associated with significant morbidity and mortality.[2]

Typically, prostate cancer develops slowly, with a long asymptomatic phase such that most men with prostate cancer die of other causes before their disease becomes symptomatic.[3] Following diagnosis, the probability of survival in the next 5 years is near 100% for patients with localized or regional disease, and increases with incremental prior years of survival (Figure 1).[4] The lifetime risk of dying of prostate cancer is less than 3%,[5] with about 2% of all prostate cancer deaths occurring before age 55 years, 29% occurring between age 55 and 74 years, and 69% at age 75 years and older.[4]

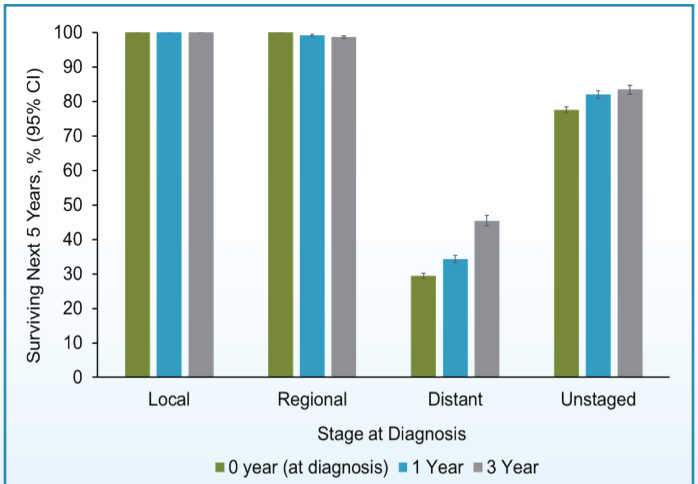

Figure 1.— Probability of surviving the next 5 years given survival 0, 1, or 3 years after prostate cancer diagnosis by stage at diagnosis.[4]

Prostate Cancer Screening — Controversy and Shortcomings

In the United States, early detection of prostate cancer is driven by prostate-specific antigen (PSA)–based screening, followed by prostate biopsy for diagnostic confirmation.[6] Approximately 19 million men undergo PSA screening annually, resulting in approximately 4.7 million abnormal findings on tests (based on a PSA > 4.0 ng/mL), leading to approximately 1.3 million biopsy procedures performed.[7] Deaths in the United States from prostate cancer have decreased approximately 4% per year since 1992 (5 years after the introduction of PSA testing)[8]; however, there are conflicting data that fail to convincingly demonstrate a significant decrease in prostate cancer–specific mortality attributable directly to PSA screening.[9-12]

The vast majority of men with prostate cancer have clinically localized disease at a potentially more curable stage, which is attributable to widespread use of PSA screening.[2,13] However, widespread use of PSA screening has led to an increase in the rate of negative results on biopsies, as well as a high rate of overdetection or overdiagnosis of prostate cancer (Figure 2).[14]

PSA screening has resulted in substantial overtreatment (with attendant adverse effects) of potentially indolent tumors that would have remained asymptomatic and not required treatment for the remainder of a man's life.[2,13] Overdiagnosis is generally defined in this context as detection

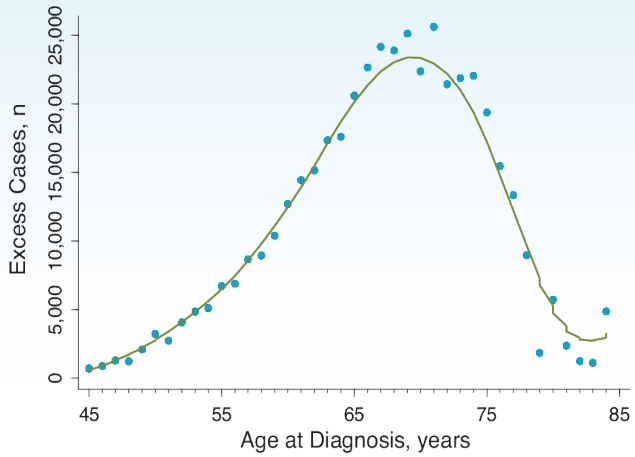

Figure 2.— Number of excess prostate cancer cases by age at diagnosis 1987 to 1995.[14] The 95% confidence interval is extremely narrow and is not shown here. ©Vickers et al.; licensee BioMed Central Ltd.

of a prostate cancer that would have remained asymptomatic and undetected during an individual's lifetime in the absence of screening.[2,6] Although it is difficult to determine the exact magnitude of overdiagnosis associated with any screening and treatment program, estimates from the 2 largest prostate cancer screening trials suggest overdiagnosis rates, based on PSA screening, of 17% to 50%.[2] The rate of overdiagnosis and subsequent overtreatment secondary to PSA-based prostate cancer screening appears to be greater than that for other cancers for which routine screening currently occurs (eg, breast, colorectal, or cervical cancers).[15] According to a national registry of men diagnosed with prostate cancer in community-based urology practices in the United States, surgery rates for low-, intermediate-, and high-risk cancer were approximately 50%, 70%, and 50%, respectively between 2010 and 2013.[16] Rate of radiation therapy among those same groups was approximately 10%, 20%, and 20%, respectively, and androgen deprivation therapy use was approximately 0%, 5%, and 25%, respectively.[16]

PSA screening is also associated with a high degree of false-positive results, which vary to some extent based on the chosen cutoff threshold for biopsy. The common PSA threshold for biopsy of greater than 4.0 ng/mL is associated with a positive predictive value of about 30% in men aged 50 years or older, and a negative predictive value of about 85% in men with a median age of 69 years at biopsy.[17] At 9 years of follow-up from the large European Randomized Study of Screening for Prostate Cancer (ERSPC) in 182,000 men, 75.9% of men who underwent biopsy after elevated results on PSA (cutoff varied by country between 3.0 and 4.0 ng/mL) had a false-positive result.[15]

PSA-driven false-positive results, overdiagnosis, and overtreatment of prostate cancer are associated with a number of potentially harmful sequelae that appear to greatly outweigh the modest, at best, benefits of PSA screening (Table 1).[18] Based on an interpretation of the 2 major trials of PSA screening (the US Prostate, Lung, Colorectal, and Ovarian [PLCO] Cancer Screening Trial and the ERSPC), the US Preventive Services Task Force (USPSTF) determined that the benefit of PSA screening and early treatment ranges from 0 to 1 cancer deaths avoided per 1000 men screened.[2] The most frequently reported direct harms associated with prostate cancer screening relate to anxiety.[19] Two well-designed surveys indicate that men with false-positive PSA results have greater short-term and long-term prostate cancer anxiety than do men with true-negative results, and that men with false-positive results have more subsequent tests/visits compared with men who have true-negative results.[20,21]

The 2 primary risks associated with prostate biopsy are bleeding and infection.[19] Estimated incidence of hematuria is approximately 6% to 13%, but the risk of serious bleeding requiring transfusion is low. The estimated rate of urinary tract infection is 0.3% to

Harmful Outcomes Associated With PSA Screening and Subsequent Overdiagnosis and Treatment

Harmful Outcome	Approximate Risk	References
Harms of Screening		
Patient anxiety about developing prostate cancer, for up to 1 year after screening (men with negative prostate biopsy after suspicious PSA screening test)	26%	Fowler et al, 2006[20]
Additional PSA test, biopsy, and/or urologist visit over the next year (vs patients with initial negative PSA result [< 2.5 ng/mL])	73% vs 42%; 15% vs 1%; 71% vs 13%, respectively	Fowler et al, 2006[20]
Lead time*	5.4 to 6.9 years	Draisma et al, 2009[36]
Harms of Biopsy		
Moderate or major bothersome symptoms, including pain; fever; blood in urine, semen, or stool; infection; and temporary urinary difficulties	Up to 32%	Rosario et al, 2012[23]
Hospitalization	1% to 6.9%	Moyer et al, 2012[2] Loeb et al, 2011[22]
Complications of Treatment		
Serious CV event due to treatment	2 in 1000 men	Moyer et al, 2012[2]
DVT or PE due to treatment	1 in 1000 men	Moyer et al, 2012[2]
Erectile dysfunction due to treatment	29 in 1000 men; up to 19% to 27%	Moyer et al, 2012[2] Wolf et al, 2010[19]
Urinary incontinence due to treatment	18 in 1000 men; up to 12% to 16% long term	Moyer et al, 2012[2] Wolf et al, 2010[19]
Death due to treatment	< 1 in 1000 men; 0.1% to 0.2% within 30 days	Moyer et al, 2012[2] Wolf et al, 2010[19]

CV, cardiovascular; DVT, deep vein thrombosis; PE, pulmonary embolism.
*Average time by which screening advances diagnosis of prostate cancer among patients who would have been diagnosed with prostate cancer during their lifetimes in the absense of screening.

4%, and that of serious infection is < 2%.[19] Prostate biopsy is also associated with a 2.65-fold increased risk (95% confidence interval [CI], 2.47-2.84; *P* < .0001) of hospitalization within 30-days of the procedure owing to infectious or noninfectious complications compared with a control population, based on analysis of a Medicare database (6.9% vs 2.7%).[22] Interim results of an ongoing, randomized, controlled trial reported that 32% of men experienced 1 or more adverse events after prostate biopsy that required clinician follow-up and were classified as moderate/major problems; these adverse events include: pain; fever; blood in urine, semen, or stool; infection; transient urinary difficulties; or other issues.[23]

Patients who are treated for potentially asymptomatic prostate cancer are at risk for the adverse events associated with such treatment. Radical prostatectomy is associated with a 20% increased absolute risk for urinary incontinence and a 30% increased absolute risk for erectile dysfunction compared with watchful waiting after 1 to 10 years; and perioperative deaths or cardiovascular events occur in approximately 0.5% or 0.6% to 3% of patients, respectively.[2] Radiation therapy is associated with a 17% absolute increased risk for erectile dysfunction and an increased risk for bowel dysfunction compared with watchful waiting after 1 to 10 years.[2]

Attendant with the increased overdiagnosis and overtreatment associated with PSA screening are the associated costs. Approximately $1.86 billion is spent annually on PSA tests alone,[7] and the estimated national expenditure for care of men with prostate cancer in 2014 in the United States was $13.4 billion, according to the National Cancer Institute.[24]

Prostate Cancer Screening — Guidelines

In 2012, the USPSTF published guidelines recommending against PSA-based screening for prostate cancer in the general population, citing convincing evidence that PSA-based screening results in overdiagnosis of asymptomatic cancer that would likely have remained asymptomatic for the man's lifetime, resulting in increased biopsies and treatment with little to no demonstrated reduction in prostate cancer mortality.[2]

Clinical practice guidelines of major medical societies regarding screening with PSA conflict with those of the USPSTF, with most recommending shared decision-making between physician and patient, consideration of risk factors, and recommendations regarding screening intervals.[17] For example, the American Urological Association (AUA) recommends consideration of screening, with shared decision-making, for men aged 55 to 69 years, or for men aged 70 years or older who have a greater than 10- to 15-year life expectancy. The AUA also recommends consideration of a 2 year or longer interval for screening instead of annual screening to reduce exposure to potential harms.[6] The American Cancer Society (ACS) recommends screening in men over 50 years of age at average risk with greater than 10 years' life expectancy, using shared decision-making. The ACS recommends screening at 45 years of age for men at higher risk (ie, those who are black, or those who have had a first-degree relative diagnosed with prostate cancer before 65 years of age) and at age 40 for those at appreciably higher risk (multiple family members diagnosed with prostate cancer before 65 years of age).[19] ACS guidelines further recommend a PSA level of ≥ 4.0 ng/mL as the cutoff for referral to a urologist for further evaluation or biopsy for men at average risk for prostate cancer, and a PSA level of 2.5 ng/mL to 4.0 ng/mL as the range in which to consider an individualized risk assessment incorporating other risk factors that may be used to recommend a biopsy.[19]

Despite conflicting guidelines, PSA screening is routinely used as a primary screening tool by primary care practitioners, which is then repeated by a urologist on patient referral because of the elevated PSA levels identified by the primary care practitioner at the outset. Continued use of PSA screening may be due to a clinician's fear of missing a serious, potentially lethal cancer or for potential liability concerns, or screening may be performed at a patient's request.[25-28] Mainly, urologists lack a suitable biomarker alternative.

New Developments in Screening and Diagnosis of Prostate Cancer

The focus of early detection has shifted from efforts to diagnose any and all prostate cancers to an effort to diagnose clinically significant prostate cancers at an early stage.[29] This is reflected in a trend toward a decreased number of initial biopsies performed (from 24% to 16%), increased use of repeat PSA testing (from 72% to 82%), and increased use of prostate cancer antigen-3 (PCA3) testing (from 11% to 27%) by urologists for those patients referred to their offices from primary care practices because of previous elevated PSA screening results.[26]

Few additional options are currently available to guide urologists in determining whether a biopsy is warranted in the first place or even if an additional biopsy procedure should be performed at all. Fear of occult prostate cancer leads to additional procedures; therefore, many men undergo second, third, and fourth repeat biopsy procedures to rule out the presence of cancer.[30] These shortcomings

have led many researchers to investigate ways to optimize the use of PSA and develop novel serum and tissue biomarkers to address the need for more accurate, dependable screening tools. The goal is to identify patients more likely to benefit from biopsy, and potentially from treatment for early prostate cancer, while reducing inaccurate readings, unnecessary invasive testing in healthy men, and attendant excess healthcare costs. Laboratory tests account for only approximately $.023 of every dollar spent on healthcare, but test results affect between 70% and 80% of clinical decisions made, accentuating the need for more accurate diagnostic laboratory tests to help identify those patients most likely to benefit from biopsy and spare those who are not.[31]

Apifiny® is the only cancer specific, nongenomic, non-PSA–based blood test designed to aid clinicians in the assessment of risk for the presence of prostate cancer. Apifiny has been developed using breakthrough technology that involves the use of autoantibodies as biomarkers against peptides derived from prostate cancer tissue.[32] Apifiny measures 8 signature autoantibodies in the blood stream that are released by the immune system in response to the presence of prostate cancer.[33] The scores from the developed algorithm can be used to indicate a relative high or low risk of the presence of autoantibodies known to be associated with an immune response to prostate cancer, particularly for patients with intermediate (4.0 to 10 ng/mL) PSA levels that are associated with a high rate of false-positive results due to a lack of sensitivity and specificity in this range.[33] Measurement of these cancer-specific biological markers may be used in men with an elevated PSA (> 2.5 ng/mL) to help provide additional insight to support a more informed clinical decision about performing a biopsy. Potential benefits of Apifiny to aid in diagnostic decisions may include earlier detection of cancer and, therefore, improved survival rates, as well as a reduction of unnecessary biopsies, with a consequent reduction in associated morbidity and healthcare costs related to overdiagnosis and overtreatment.

Several other serum, urine, or biopsy tissue–derived biomarkers are available to aid in prostate cancer diagnosis, but most, unlike Apifiny, are based on PSA testing. Prostate Health Index (PHI) is a multi-analyte immunoassay that measures PSA, free PSA, and p2PSA in serum.[13] The 4Kscore® Test is also a multi-analyte immunoassay that measures total PSA, free PSA, intact PSA, and human kallikrein–related peptide 2 (hk2) in blood and utilizes an algorithm to calculate the risk for high-grade prostate cancer.[13] PCA3 is a urine assay for detection of prostate cancer, based on the overproduction of PCA3 by neoplastic prostate tissue.[34] It requires prostatic massage before collecting the specimen, and is currently FDA-approved only to facilitate biopsy decision making among men with previous negative prostate biopsy results.[34] ConfirmMDx is an assay that uses multiplex methylation-specific polymerase chain reaction to measure the epigenetic status of prostate cancer–associated gene biomarkers. However, ConfirmMDx requires residual prostate biopsy core tissue samples and is limited by a poor positive predictive value when the assay is positive.[35]

Conclusions

The degree of potential overdiagnosis and associated overtreatment of prostate cancer appears to be greater than that for any other cancer for which routine screening currently occurs and is associated with serious adverse effects. PSA-based screening for prostate cancer, including its limitations, has been well understood by clinicians and reimbursement authorities for over 3 decades. There is a need to move beyond PSA testing with new biological markers that are cancer specific to improve early detection of cancer. Such markers will more accurately identify patients who are most likely to benefit from biopsy and, potentially, treatment for early prostate cancer while reducing inaccurate readings, unnecessary invasive testing in healthy men, and associated morbidity and healthcare costs.

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Dr Hafron is a partner and director of research at the Michigan Institute of Urology, PC (MIU), in St Clair Shores, where he is the principal investigator for multiple clinical research trials. He has published numerous peer-reviewed journal articles on topics related to his expertise and has presented his work at many national and international scientific meetings. He is the recipient of many clinical research awards. Dr Hafron is on the editorial board of the journals *International Urology and Nephrology* and *Advances in Urology*. He is on the board of directors of the United Physicians organization. Dr Hafron is a paid scientific advisor and speaker for Armune BioScience.

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