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PROSTATE CANCER (D PAREKH, SECTION EDITOR)

Risk-Based Prostate Cancer Screening: *Who* and *How*?

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Abstract The purpose of this review is to identify clinical risk factors for prostate cancer and to assess the utility and limitations of our current tools for prostate cancer screening. Prostate-specific antigen is the single most important factor for identifying men at increased risk of prostate cancer but is best assessed in the context of other clinical factors; increasing age, race, and family history are well-established risk factors for the diagnosis of prostate cancer. In addition to clinical risk calculators, novel tools such as multiparametric imaging, serum or urinary biomarkers, and genetic profiling show promise in improving prostate cancer diagnosis and characterization. Optimal use of existing and future tools will help alleviate the problems of overdiagnosis and overtreatment of low-risk prostate cancer without reversing the substantial mortality declines that have been achieved in the screening era.

Keywords Prostate cancer · Screening tools · Prostate-specific antigen · Risk-based · Clinical risk

Background

In the United States, prostate adenocarcinoma is the most common incident cancer, with 238,590 estimated cases expected to be diagnosed in 2013 [1]. Since the early 1990s, there has been a >40 % decrease in prostate cancer mortality in the U.S., although with 29,720 deaths expected this year, it remains the second leading cause of cancer death among men [1, 2]. Together with advancements in treatment, there is strong evidence that prostate specific antigen (PSA) screening itself has played a substantial role in reducing prostate cancer mortality over the last 30 years [3, 4••]. However, widespread use of PSA screening has also contributed to a well-described stage migration and to the detection and subsequent overtreatment of low-risk, indolent disease [5].

Conflicting interpretations of recent U.S. [6•] and European-based [7, 8] studies investigating the impact of PSA screening on intermediate-term mortality has fueled controversy surrounding the use of PSA. A separate report from the Göteborg randomized screening trial [9••] reported greater follow-up time (median 14 years) and a near 50 % reduction in prostate-cancer-specific mortality. Additionally, European investigators reported significant reductions in incidence of metastatic prostate cancer in those men who underwent regular PSA screening [10]. The U.S. trial, widely misinterpreted as providing evidence against the benefit of screening, did demonstrate that more frequent PSA testing does not necessarily offer benefit over ad hoc, opportunistic screening [6•, 11•].

Truth exists on both sides of the debate: PSA screening saves thousands of lives but does so at the cost of high rates of overtreatment of indolent tumors. The question—and the solution to the controversy—ought to be not whether to screen, but how to use screening more judiciously and intelligently. PSA-based screening is often performed at an inappropriate frequency or in men who may not benefit from early detection, such as those who are older with multiple comorbidities and/or <10 years life expectancy [12]. What is needed is to identify those with clinically significant disease—disease for which treatment will truly reduce mortality—and who will benefit from screening, using what tools. Disease risk prediction tools and nomograms incorporate multiple clinical parameters, such as PSA, age, and race, in order to provide a comprehensive assessment of significant prostate cancer risk. The purpose

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of this review article is to critically assess the utility and limitations of our current tools for screening, as well as identify the population of at-risk men.

Who Is At Risk?

Increasing age is the best-established risk factor for diagnosis of prostate cancer. In the U.S. and Europe, guidelines recommend that clinicians begin offering PSA screening to men between 40 and 50 years of age [13–16]. Data from the ERSPC demonstrated a clear mortality benefit of PSA screening in men 55–59 years of age [7], as well as those 60–64 years of age [9••]. Some have argued that the benefits of screening decline after age 70—especially for men who have been screened previously—but in fact, these men are being screened at fairly high rates [8]. Risk-adjusted PSA screening should reduce testing in elderly men or those with comorbidities who would be less likely to benefit from early detection. Similarly, consideration of the health status of men who are older may argue in favor of screening benefits. An analysis from the Cancer of the Prostate Strategic Urologic Research Endeavor registry [17•] found that while likelihood of high-risk disease increased with increasing age (26 % of men ≥75 years), cancer-specific survival differences for age categories were greatly influenced by treatment decisions, which are themselves driven by age [18, 19] to a greater extent than disease risk. Both initial and subsequent screening decisions should not reflect chronological age alone but, rather, the combination of age, life expectancy, and comorbidities [20].

Ethnicity is another important determinant of screening decisions. African American men have the highest rates of prostate cancer in the U.S., with an estimated incidence of 228.7 per 100,000 expected in 2013, as compared with white (141.0 cases), Hispanic (124.9 cases), American Indian (98.8 cases), or Asian (77.2 cases) populations [1]. Furthermore, African Americans are also more likely to present at a younger age, with higher grade or stage of disease [21], and are at greater risk for prostate cancer death [21–24]. Additionally, several studies have observed lesser downward stage migration within non-Caucasian, lower socioeconomic populations [25•, 26, 27]; thus, the benefits of screening may be much greater in these populations. Genetics and environmental exposures, including diet and access to health care, are all thought to contribute to these observed trends [28–30].

The impact of family history as a risk factor for development of prostate cancer varies with the degree of relatedness and number of relatives affected. A recent, large study of familial prostate cancer confirmed that risk is directly related to number of relatives and patient's age, since the investigators found that the highest relative risk was in men <65 years of age with three affected brothers (hazards ratio [HR]=23) and lowest in men 65–74 years of age with an affected father only (HR=1.8) [31].

Medical comorbidities have also been investigated for potential associations with prostate cancer. Cardiovascular diseases and associated conditions, including obesity, diabetes, and metabolic syndrome, may play a role in prostate cancer progression and death [32–36]. Emerging evidence suggests that modifiable lifestyle factors directly impact disease diagnosis and progression. Men who perform moderate amounts of exercise weekly have been shown to have lower risk of prostate cancer diagnosis, as well as risk of high-grade disease [37]. Additionally, tobacco smoking at the time of prostate cancer diagnosis is associated with increased prostate-cancer-specific mortality, as well as biochemical recurrence, after adjusting for stage, grade, and PSA screening history [38]. Men with male factor infertility have been found to have increased risk of prostate cancer [39]. However, as was noted above, men with a greater number of significant comorbidities, as indicated by higher Charlson comorbidities indices, may *not* benefit from PSA screening, because of direct impact on all-cause mortality, as opposed to prostate cancer mortality [40•, 41•].

Current Tools

PSA

To date, PSA remains the single most important factor for identifying men at increased risk of prostate cancer [42, 43]. PSA testing gained FDA approval for screening in 1994, with initial recommendations to perform biopsy for a PSA of ≥4.0, since this threshold was found to be clinically useful in the detection of disease [44], but investigators later found that about a fifth of cancers are present with PSA values of <4.0 ng/mL [45]. Furthermore, data from the Prostate Cancer Prevention Trial (PCPT) that assessed PSA cutoffs ranging from 1.1 to 4.1 ng/mL showed no single threshold that provided both high sensitivity and specificity, demonstrating, rather, a continuum of prostate cancer risk at all PSA values [46].

It is increasingly clear that many men—particularly the majority of those screened who are found to have low baseline PSAs—do not require repeated screening on an annual basis. Initial PSA and risk of clinically significant disease have been investigated, since several studies have identified absolute threshold values to predict risk of subsequent diagnosis [47–50]. Investigators from the Malmö Preventive Project, within a case–control nested analysis, found that PSA levels at age 60 predicted lifetime risk of

clinically significant prostate cancer, since men whose initial PSA was below the median (1.06 ng/mL) had 0.5 % risk of metastasis by age 85 and 0.2 % risk of death from prostate cancer, suggesting little benefit to regular screening every 1 or 2 years in these men [51••]. Additionally, investigators from the ERSPC trial reviewed clinical data for men with very low initial PSA (<1.0 ng/mL) and their risk of developing significant disease. The authors reported that widening the screening interval to 8 years, instead of 4 years, would result in only minimal risk of missing aggressive disease [52].

Other PSA kinetics, such as PSA velocity (PSAV), have been proposed as a marker of disease presence [53], as well as a useful variable for identifying those with clinically significant or life-threatening disease [54, 55]. But since PSAV and PSA are highly collinear, it has been purported that PSAV does not add to clinical utility beyond that of an isolated PSA test [56, 57], and the utility of PSA kinetics in the screening setting remains controversial.

Digital Rectal Exam

North American and European urology guidelines recommend incorporation of a digital rectal exam (DRE) with PSA screening [13–15]. In a large multicenter prospective trial, PSA when used in combination with DRE improved cancer detection rate, as compared with either test used alone. Furthermore, men with newly diagnosed cancer found initially by DRE were also more likely to harbor disease with aggressive features [58].

Imaging

Conventional diagnostic imaging is obtained via transrectal ultrasound (TRUS). About 70 %–75 % of cancers originate in the posterior portion of the gland and, in up to two thirds of cases, appear as hypoechoic areas on TRUS [59]. TRUS allows for structural assessment of the gland; thus, locally advanced disease may appear as a bulging prostatic capsule. Due to the limited sensitivity and specificity of diagnostic ultrasound (both about 50 %), other techniques such as color Doppler, contrast-enhanced technique, and elastosonography may improve the diagnostic accuracy of this exam [59].

Pelvic computed tomography as a diagnostic and/or local staging test is limited in accuracy and, thus, infrequently used in workup. This is largely because the density of cancerous tissue does not significantly differ from normal and lesions <2 cm are often undetected [59]. Bone scans are also uncommonly used in diagnosis and traditionally reserved for patients with suspected metastatic disease (i.e., PSA>20 ng/mL). Recently, there have been significant efforts made toward investigating advanced magnetic resonance imaging (MRI) techniques to improve the detection, characterization, and staging of prostate cancer, which are further described in the Future Directions section.

Integrated Prediction of Prostate Cancer Risk

The rationale for using multivariable clinical risk prediction tools is to improve accuracy beyond use of a single clinical variable, such as PSA. In addition to PSA, other factors, such as PSAV, PSA density, DRE, use of finasteride, age, race, family history, and history of negative biopsy, are considered as prostate cancer risk prediction tools. Clinical risk calculators are developed by analyzing large populations of data in order to understand the impact of specific clinical factors on disease risk and identify those who would benefit from prostate biopsy. Typically, these models aim for a total predictive accuracy of >70 %–80 % to be valid [60]. One method of describing accuracy includes area under the curve (AUC) of the receiver operating characteristics (ROC). The AUC measures the area under ROC curves to create a single number to define accuracy, since the "ideal" ROC would have an AUC of 1, while a random ROC would yield an AUC of .5.

The PCPT risk calculator was developed from men in the placebo arm of the PCPT, a phase III randomized, double-blind, placebo-controlled trial comparing rates of cancer in men taking finasteride versus placebo for 7 years [21, 61]. Investigators analyzed age, race, DRE, PSA, PSAV (within 3 years of biopsy), biopsy history, and family history of prostate cancer, and an end-of-study biopsy was performed—regardless of PSA level—which provided a unique source of data on prostate cancer detection at low PSA levels. The PCPT calculator (available online at http://tinyurl.com/caprisk) was developed to predict risk of cancer diagnosis, as well as distinguish between low- and high-grade disease [21], and has been externally validated to be a superior method to PSA testing alone [62–64, 65•].

Investigators from the ERSPC trial analyzed men between the ages of 55 and 74 who were randomized to the screening arm of this trial and analyzed variables including the American Urologic Association Symptom Score, PSA, TRUS, and DRE to develop the ERSPC risk calculator. This is an Internet-based tool (www.prostatecancer-riskcalculator.com) that considers PSA, prostate volume assessed by TRUS, and prior biopsy result [66]. The ERSPC has been externally validated in Swedish and Finnish cohorts, in which this tool discriminated between those with and without cancer but overestimated risk of positive biopsy [67]. When the ERSPC calculator was compared with the PCPT method, it was found to outperform the latter model when used for both European and North American cohorts [68–70].

The Sunnybrook risk calculator was developed using clinical data from 3,108 Canadian men and utilize PSA, percent free

PSA, age, family history, race, International Prostate Symptom Score, and DRE [71]. This tool assesses risk for any cancer and high-grade (Gleason score ≥7) disease and has reportedly fairly high accuracy for predicting either event (AUC 0.74 and AUC 0.77, respectively) [71]. The original investigators later performed a prospective, multiinstitutional evaluation and found the Sunnybrook calculator to outperform the PCPT in terms of predicting any disease (AUC 0.67 vs. 0.61), as well as aggressive disease (AUC 0.72 vs. 0.67) [65•].

Future Directions

In the last decade, there has been tremendous effort put forth investigating other serum or urinary biomarkers to improve prostate cancer risk assessment. Prostate cancer antigen 3 (PCA 3) is a prostate-specific noncoding mRNA, significantly overexpressed in prostate cancer tissue and highly specific in predicting prostate cancer risk and aggressiveness [72]. This marker holds promise in the detection and characterization of prostate cancer and has, in fact, been successfully incorporated into the PCPT risk calculator [73]. Another RNA-based marker, TMPRESS2-ERG fusion gene, which is expressed in over half of the cases of clinically localized prostate cancer [74], has also shown recent promise as an prognostic factor. Several studies show associations with histological grade [75, 76] and tumor stage [77, 78]. Investigators reviewed tissue samples of 226 men who were treated with radical prostatectomy and found that in those for positive TMPRSS2-ERG fusion gene expression (N=114, 50.4 %), PSA, Gleason sum, and margin status were independently associated with biochemical and progression-free survival [79].

The prostate-specific antigen isoform [-2]proPSA has been associated with prostate cancer and, in a recent prospective multicenter study, was shown to improve a multivariate prediction model that incorporated PSA and percent free PSA and correlated with risk of aggressive disease [80]. Vickers and colleagues used four serum kallikrein markers, including total PSA, free PSA, intact PSA, and kallikrein-related peptidase 2 to develop a statistical model to predict prostate biopsy results [81]. This model was successful in predicting the biopsy results in men with elevated PSA, suggesting that biopsy rates could be significantly reduced, while a relatively few men with elevated PSA levels and cancer would be advised not to undergo biopsy, most of whom would have low-grade disease [82].

There has been significant investigation of specific genetic allele mutations associated with prostate cancer, with more than 30 single-nucleotide polymorphisms implicated in prostate carcinogenesis [83]. A recent investigation that used linkage analysis found that mutations in HOXB13 G84E and other variants were associated with early onset and hereditary prostate cancer [84]. The authors further noted that these mutations are uncommon, and at this point, it is unclear how to incorporate these findings into large-scale screening practices. It is likely genetics will play a larger role in diagnosis and management of prostate cancer in the near future.

Multiparametric MRI combines anatomic T2-weight imaging with MR spectroscopic (MRS) imaging, diffusion-weighted imaging (DWI), and/or dynamic contrast-enhanced MRI to allow for anatomic, biologic, and metabolic analysis. There has been increasing interest in the use of these specialized techniques as either diagnostic or prognostic tools. DWI technology evaluates proton diffusion properties within water. As compared with healthy gland tissue, prostate cancer has a higher cellular content and limits water molecule movement. DWI has been shown to be the most effective single parameter for prostate cancer detection [85]. MRS assesses physical and chemical properties of surrounding tissue, as well as concentrations of certain metabolites such as citrate, creatinine, and choline. Recent studies have found MRS to be particularly useful for differentiating tissue by Gleason grade [86], and this method was found to be a more sensitive tool for higher grade (4+3) disease [87]. Multiparametric MRI techniques may also improve transition zone cancer detection [88, 89].

Multiparametric MRI techniques can allow for targeted biopsies, as well as potential characterization of tumor aggressiveness. While useful for evaluating patients with rising PSA who have had a history of negative biopsy, MRI has not, at this point, been shown sufficiently accurate to obviate the need for a TRUS and systematic, mapped biopsy. Perhaps the greatest potential for multiparametric MRI is helping guide treatment decisions in terms of choosing surveillance as opposed to radical intervention.

Conclusion

While certain clinical factors, such as increasing age, race, and family history, are well-established risk factors for the diagnosis of prostate cancer—and of more aggressive disease—optimized utilization of screening tools is necessary to ensure appropriate follow-up testing and treatment decisions. Men with high comorbidity and limited life expectancy should not be screened, and those with low PSAs can certainly be rescreened less often than annually. Conversely, those with multiple risk factors should be screened early and closely. The diagnostic

and predictive accuracy of traditionally used screening tools, such as PSA and DRE, may be improved with the addition of specialized imaging techniques and serum and urinary biomarkers. Genetic profiling has also shown promise in identifying hereditary disease, as well as potential for identifying those at risk for more aggressive disease.

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Dr. Matthew R. Cooperberg reported no conflicts of interest relevant to this article.

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