Published in final edited form as:

Urol Clin North Am. 2016 February ; 43(1): 1–6. doi:10.1016/j.ucl.2015.08.001.

The Prostate Health Index: Its Utility In Prostate Cancer Detection

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Summary

The prostate health index (phi) is a FDA-approved blood test combining total, free and –2proPSA with greater specificity than free and total PSA for clinically-significant prostate cancer. This article reviews the evidence on the performance of phi to predict prostate biopsy outcome, its incorporation into multivariable risk-assessment tools, and its ability to predict prognosis after conservative management or prostate cancer treatment.

Keywords

prostate health index; phi; prostate cancer; screening; detection

Introduction

Prostate cancer is the second most common cause of cancer death in U.S. men. In 2015, an estimated 220,800 men will be diagnosed with prostate cancer, and there will be 27,540 prostate cancer-related deaths. The prevalence of prostate cancer increases with age. Of all new prostate cancer cases, only 0.6% are diagnosed among men younger than 44 years of age, with the majority of cases being diagnosed at ages 65 to 74.¹ Prostate cancer is generally asymptomatic until it has reached an advanced stage, a strong incentive to the widespread use of prostate-specific antigen (PSA)-based screening for early detection within the window of curability.

The goal of PSA screening is to test asymptomatic men and improve health outcomes by diagnosing the cancer at an early stage. A benefit of screening is a reduction in the proportion of advanced-stage cases at the time of diagnosis and a decrease in the prostate

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cancer-specific mortality rate. However, PSA screening has been controversial due to numerous limitations. Although higher PSA levels are a strong predictor of prostate cancer risk, the total PSA measurement is not specific for prostate cancer and is influenced by other factors such as benign prostatic hyperplasia, prostatitis and other benign conditions.² Consequently, many men undergo unnecessary biopsies leading to the over detection of some indolent tumors.³

The Prostate Health Index (phi), approved by the US Food and Drug Administration in June 2012, addresses many of the drawbacks associated with PSA screening. Its specificity is greater because phi is a combination of three different isoforms of PSA: total PSA, free PSA, and [-2]proPSA,⁴ combined in the mathematical formula: $\text{phi} = ([-2]\text{proPSA}/\text{fPSA}) \times \text{PSA}$. Phi is a simple blood test, but it outperforms any of its individual components for the identification of clinically-significant prostate cancer.^{5,6} The objective of this article is to review the major studies on phi in prostate cancer detection and risk stratification.

Phi as a predictor of biopsy outcome

A large prospective multicenter study of phi was initiated in the US from 2003 to 2009, and ultimately enrolled 892 men with total PSA levels of 2-10 ng/ml and findings that were not suspicious for cancer on digital rectal examination.⁷ Participants underwent at least 10-core prostate biopsy, which was the initial biopsy in 79%, repeat biopsy in 18% and unknown in 3%. The primary objective of the study was compare the specificity of phi versus percent free PSA (%fPSA) at 95% sensitivity for prostate cancer detection. The results showed that phi had significantly greater specificity at 95% sensitivity compared to %fPSA (16.0% vs. 8.4%, $p=0.015$). It was also more specific than total PSA. Similar patterns were observed at the 90%, 85%, and 80% sensitivity thresholds. On receiver operating characteristic (ROC) analysis, phi outperformed both %fPSA (area under the curve, AUC 0.703 vs 0.648, $p=0.004$) and total PSA (AUC 0.525). There was also a significant association between phi with the Gleason score on biopsy. Compared to the lowest phi category (scores of 0-24.9), men with the highest phi scores (>55) had a significantly higher risk of detecting any prostate cancer (RR 4.7, 95% CI 3.0-8.3), and Gleason ≥ 7 disease on biopsy (RR 1.61, 95% CI 0.95-2.75).

A later study in this population examined the relationship of phi with clinically-significant disease in greater detail.⁶ Specifically, among 658 men from the prospective trial undergoing initial or repeat prostate biopsy for a PSA level of 4-10, phi was a more accurate predictor of clinically-significant prostate cancer on biopsy using a variety of different criteria for criteria for significant disease. On ROC analysis, phi had a higher AUC for Gleason ≥ 7 (0.707) and Epstein significant disease (0.698) compared to its components PSA (AUC's 0.551 and 0.549), %fPSA (AUC's 0.661 and 0.654) and p2PSA (AUC's 0.661 and 0.654), respectively.

The specificity of phi for clinically-significant prostate cancer also was evaluated in biopsy-naïve men from the National Cancer Institute's Early Detection Research Network (EDRN) Clinical Validation Center cohort.⁵ Using Gleason ≥ 7 disease on biopsy as the primary endpoint, de la Calle et al. compared phi to its component parts. The first cohort included

561 men from Harvard with a mean PSA of 6.5 ng/ml and abnormal DRE in 23.7%. Of these men, 20.3% were found to have Gleason 7 disease on biopsy, and phi had an AUC of 0.82 for high-grade disease. Using a cutoff of 24 as the criterion for biopsy would have avoided 41% of unnecessary biopsies among men without prostate cancer and 17% of overdiagnosed cases. These results were compared to a validation population including 395 men from two other US institutions (Weill Cornell Medical College and University of Michigan), with a mean PSA of 5.9 ng/ml and abnormal DRE in 10.6%. In this cohort, 30.9% had Gleason 7 disease on biopsy, and the AUC for phi was 0.78. Using a phi cutoff of 24 as the criterion for biopsy would have avoided 36% of unnecessary biopsies among men without prostate cancer, and 24% of overdiagnosed indolent cancers in the validation population.

Phi also has been evaluated prospectively in several European populations. Guazzoni et al. reported on 268 men with PSA levels of 2-10 ng/ml and negative DRE who were scheduled for extended prostate biopsy (18-22 cores) at a large academic center in Italy.⁸ The primary objective of the study was to compare phi with commonly used reference tests, including total PSA, %fPSA and PSA density. Overall, 39.9% of the population was diagnosed with prostate cancer, and these men had a significantly higher phi (median 44.3 versus 33.1, $p<0.001$). At 90% specificity, phi had greater sensitivity (42.9%) than %fPSA (20.0%) or PSA density (26.5%). Predictive accuracy was higher for phi (AUC 0.76) than for PSA density (61%), %fPSA (58%), and total PSA (53%). At 90% specificity, phi had greater sensitivity (42.9%) than %fPSA (20.0%) and PSA density (26.5%). The addition of phi to a multivariable model with age, prostate volume, total and free PSA led to a significant gain in predictive accuracy (0.83 from 0.72, $p<0.001$). Phi was also a significant independent predictor of high-grade disease.

Lazzeri et al. subsequently reported on a large prospective evaluation of phi in 646 men age >45 years from 5 European countries.⁹ All of the men in this study were undergoing initial prostate biopsy with at least 12 cores for a PSA level from 2-10 ng/ml with or without an abnormal DRE. The primary objective of the study was to compare the performance characteristics of phi to total and free PSA for prostate cancer detection; a secondary endpoint was to examine the relationship to Gleason score on biopsy. The 264 (40.1%) men diagnosed with prostate cancer had a significantly higher median phi compared to those with negative biopsy (48 vs 32, $p<0.001$). On multivariable analysis including total, free, and %fPSA, the addition of phi led to a significant 6.4% and 7.5% gain in predictive accuracy for overall and Gleason 7 prostate cancer on biopsy, respectively. At 90% sensitivity, use of phi would have avoided 100 unnecessary biopsies (15.5%) while missing only 1.1% of aggressive cancers (compared to 7.5% missed using %fPSA).

Phi as a component of multivariable risk stratification

There has been a paradigm shift in prostate cancer decision-making from a one-size-fits-all approach using total PSA, as was done in the early 1990's, toward multivariable risk assessment taking into account individual patient characteristics. Such an approach is recommended by numerous contemporary clinical practice guidelines, such as the Melbourne Consensus statement.¹⁰

Given the substantial international evidence showing the superiority of phi over PSA, several tools have been created that combine phi with other clinical risk factors to aid in prostate biopsy decisions. Lughezzani et al. reported a study including 729 men from a major tertiary referral center in Italy undergoing extended prostate biopsy (66.5% initial, 33.5% repeat).¹¹ These men had total PSA levels ranging from 0.5-20 ng/ml, and 17.7% had a suspicious DRE. Similar to the previous studies, phi had superior predictive accuracy for biopsy outcome (AUC 0.80) compared to %fPSA (AUC 0.62) or total PSA (AUC 0.51). The addition of phi to a multivariable model with age, prostate volume, DRE and prostate biopsy history led to a statistically significant 7% gain in predictive accuracy. The authors created a nomogram combining these 5 variables, which had an AUC of 0.80. The nomogram was well calibrated for men at low to intermediate risk. Of note, using PSA or %fPSA in the nomogram instead of phi resulted in significantly inferior predictive accuracy (AUC 0.73 and AUC 0.75, respectively).

This nomogram was subsequently externally validated in an independent population of men undergoing initial or repeat 12-core prostate biopsy at 5 European centers from the PRO-PSA Multicentric European Study Group (PROMETtheuS) described above.¹² This study included 883 patients with total PSA levels of 0.5 to 20 ng/ml, of whom 17% had positive DRE. As in the previous study, phi on its own had a higher AUC (0.68) for prostate cancer detection than total or free PSA. The phi-based nomogram had an AUC of 0.75, was well-calibrated in men at low to intermediate risk, and showed the greatest net benefit on decision curve analysis.

Researchers from Ireland also created a multivariable phi-based nomogram to aid in prostate biopsy decisions.¹³ From 2012 to 2014, 250 men aged >40 years were referred to the Irish Rapid Access Clinic for prostate biopsy for an elevated age-specific PSA level or abnormal DRE. All of the men underwent at least 12-core prostate biopsy, and 112 (45%) had prostate cancer detected. Similar to other studies, phi as a stand-alone test had greater predictive accuracy for overall (AUC 0.71) and particularly high-grade prostate cancer detection (AUC 0.78) compared to total and free PSA. A multivariable model was then constructed including age, family history, DRE, previous negative biopsy and either PSA or phi. The model using phi had an AUC of 0.77 for overall prostate cancer and 0.79 for high-grade disease, and significantly outperformed PSA-based model as well as the predictions of the online Prostate Cancer Prevention Trial (PCPT) risk calculator. In a subset of men undergoing repeat prostate biopsy, the phi-based multivariable model had an AUC of 0.85 for any prostate cancer, and 0.88 for Gleason 7 disease. These studies confirm that phi is a useful addition to multivariable nomograms for initial or repeat biopsy to improve the accuracy of risk stratification. Phi has also been integrated into the Rotterdam risk calculator app, a multivariable prediction tool available on smartphones and tablets for easier use at the point of care.¹⁴

Phi as a predictor of treatment outcome

Numerous studies have demonstrated a significant relationship between phi and adverse tumor features at radical prostatectomy, including pathologic stage, grade, tumor volume, and composite outcomes of clinically significant prostate cancer.¹⁵⁻¹⁸ These studies include

both single-institution and prospective multicenter studies, and they corroborate the previously discussed evidence regarding the association of phi with more aggressive disease on biopsy among men with a full pathologic assessment.

More recently, Lughezzani took the next step by examining whether phi also predicts the risk of biochemical recurrence (BCR) in 313 men undergoing robotic-assisted radical prostatectomy from 2010 to 2011.¹⁹ The mean patient age was 64 years, and the median preoperative phi was 46. At a median follow-up of 28 months, 34 (10.9%) men had biochemical recurrence. The 2-year BCR-free survival rate was 97.7% for men with a phi <82, versus 69.7% with phi levels ≥ 82 ($p<0.001$). Even among the 228 (72.8%) men with organ-confined disease, phi was able to significantly stratify the 2-year BCR-free survival (98.0% at phi <82 vs. 83.3% at phi ≥ 82, $p=0.005$). On multivariable analysis with age, prostate volume, clinical stage, and biopsy Gleason score, phi remained a significant independent predictor of BCR. Although the follow-up was relatively short, this study suggests that phi may be useful to help predict prognosis after radical prostatectomy.

Meanwhile, phi has been examined for a role in patient selection and monitoring during active surveillance, as was recently reviewed.²⁰ Hironaka et al. studied phi in a small group of men from a prospective active surveillance cohort in Japan.²¹ Inclusion criteria for the protocol were age 50-80, stage T1cN0M0, PSA ≤ 20 ng/ml, Gleason ≤ 6 in ≥ 2 cores with a maximum of 50% involvement. Among 67 men who underwent surveillance biopsy at one year, baseline phi was significantly higher among those who experienced reclassification (median 60.3 vs. 47.8, $p=0.01$). On multivariable analysis with age, prostate volume, percentage of positive biopsy cores and maximum core involvement, phi was the only significant independent predictor of biopsy reclassification (OR 3.7, 95% CI 1.4-9.5, $p=0.008$). Despite the limited sample size, this study suggests that the baseline phi score can help to further improve candidate selection for active surveillance.

Among US men in the Johns Hopkins active surveillance program, Tosoian et al. examined both baseline and longitudinal values of phi as a predictor of biopsy reclassification, defined as an increase in grade or volume of cancer on surveillance biopsy.²² In this program, men underwent PSA and DRE every 6 months with yearly surveillance biopsies. At a median follow-up of 4.3 years, 37.7% of men had biopsy reclassification, of which 16.7% were reclassified specifically by Gleason upgrading. In a multivariable Cox model adjusting for age, date and PSA density, phi measurements at baseline predicted a significantly greater risk of biopsy reclassification. Similar results were reported in a separate model using longitudinal values of phi. Changes in phi over time were significantly greater among men with Gleason upgrading, and longitudinal measurements of phi had a concordance index of 0.82 for grade reclassification.

Comparison of phi to other prostate cancer tests

Several other marker tests are commercially available for prostate biopsy decisions. One of these is the 4 kallikrein panel (4KScore), which is conceptually similar to phi by using a combination of PSA-based markers and has also been validated in US and European populations to improve specificity.²³ Both are presented as options in the 2015 National

Comprehensive Cancer Network Guidelines.²⁴ Unlike phi which is FDA approved, the 4KScore is a CLIA-certified test and is currently more expensive in the U.S. In a comparative study including 531 Swedish men, phi and the 4KScore had similar discrimination for overall prostate cancer detection (AUC 0.704 vs 0.690) and high-grade disease (AUC 0.711 vs. 0.718).²⁵ Both markers provided significant incremental value compared to a model with PSA and age alone. A key difference between the tests in clinical practice is that the 4KScore uses a proprietary algorithm which also incorporates the patient's age, DRE and prior biopsy status along with the 4 kallikrein markers to estimate the number of men it is necessary to biopsy to find one high-grade prostate cancer. Although either test can be used for decisions about initial or repeat biopsy, the 4KScore does not yet have a validated algorithm for active surveillance.

The other major commercially available marker is urinary PCA3, which is FDA approved as an aid for repeat prostate biopsy decisions. Seisen et al recently evaluated 138 patients aged >50 years undergoing initial prostate biopsy at an academic medical center in France for either a suspicious DRE and/or PSA level from 4-20 ng/ml.²⁶ Overall, 44.9% of the cohort was found to have prostate cancer on biopsy. Men with prostate cancer had significantly higher median PCA3 and phi scores compared to those with negative biopsies and were significantly more likely to have a PCA3 >35 (p=0.01) and a phi >40 (p=0.01). On receiver operating characteristic analysis, PCA3 had better discrimination than phi for any prostate cancer (AUC 0.71 vs. 0.65, p=0.03). However, the authors also compared the performance of these tests for identifying clinically-significant prostate cancer (Gleason score ≥ 7 , more than 3 positive cores or >50% cancerous involvement of any core). They found that phi outperformed PCA3 for detection of clinically-significant prostate cancer (AUC 0.80 vs. 0.55, p=0.03). As a result, they concluded that phi should be used rather than PCA3 for decisions about initial biopsy to reduce overdiagnosis of insignificant disease.

Similarly, Cantiello et al. compared the performance of phi and PCA3 to predict adverse pathologic features at radical prostatectomy.¹⁶ This study included 156 men undergoing radical prostatectomy at 2 institutions. In a multivariable model with age, BMI, PSA, free PSA, prostate volume, biopsy Gleason score, percent of positive cores and clinical stage, both phi and PCA3 led to a significant improvement in predictive accuracy for the endpoint of extracapsular tumor extension. However, only phi provided significant incremental predictive accuracy for the prediction of tumor volume >0.5cc, prostatectomy Gleason score ≥ 7 , seminal vesicle invasion, and composite endpoint of clinically-significant prostate cancer.

In a separate study, Cantiello et al. specifically reported on 188 men who met the Prostate Cancer Research International Active Surveillance (PRIAS) criteria and were given the option of active surveillance but chose radical prostatectomy instead, of which 96 men also met the more restrictive Epstein criteria for active surveillance. They found that while both phi and PCA3 provided incremental predictive information regarding the presence of insignificant prostate cancer, phi was superior to PCA3.¹⁷

Finally, the use of magnetic resonance imaging (MRI) continues to increase for prostate cancer detection, treatment planning and prognostication. Furthermore, recent studies have

shown that MRI-ultrasound fusion biopsy can increase the detection of clinically-significant prostate cancer.²⁷ Although high-quality multiparametric-based diagnostics are not yet universally available, within an imaging-based paradigm, phi can be used to guide the need for further assessment with MRI, since MRI is much more expensive and time-consuming than a simple blood test. It is likely that a combination of phi and MRI could further reduce the chances of finding low-grade insignificant tumors on biopsy. Together, these tests are promising noninvasive modalities that could be used in active surveillance protocols.

Summary

Numerous large, prospective studies from geographically diverse regions have consistently demonstrated that phi is more specific for prostate cancer detection than existing standard reference tests of total and free PSA. It is a simple blood test that is approved by the US FDA and many other countries worldwide. Increasing phi scores predict a greater risk of clinically-significant disease on biopsy and adverse prostatectomy outcomes. Phi outperforms PCA3 for identifying significant prostate cancer, and also predicts the risk of biopsy reclassification during active surveillance.

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Key Points

- 1) The prostate health index is a mathematical formula that combines total, free and proPSA.
- 2) Phi is more specific for the detection of clinically-significant prostate cancer than free and/or total PSA.
- 3) Phi was approved by the US FDA in 2012 and is included in the National Comprehensive Cancer Network Guidelines for early prostate cancer detection.
- 4) Increasing phi scores predict a greater risk of high-risk pathology and biochemical recurrence after radical prostatectomy.
- 5) Phi performed at the initiation and during the course of active surveillance predicts subsequent biopsy reclassification.