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Multicenter Evaluation of the Prostate Health Index to Detect Aggressive Prostate Cancer in Biopsy Naïve Men

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Abstract

Purpose—We evaluated the ability of PHI to discriminate aggressive prostate cancer from indolent or no cancer in a biopsy naïve population.

Materials and Methods—Two independent prospective cohorts of 561 and 395 subjects, respectively, with no prior prostate biopsy who were enrolled at different clinical sites were used to validate the results. We compared the diagnostic specificity of PHI to prebiopsy total and percent free prostate specific antigen using prostate biopsy results. We also determined the optimal PHI threshold to discriminate aggressive prostate cancer (Gleason score 7 or greater) from indolent or no prostate cancer (Gleason score 6 or less).

Results—In the primary cohort higher PHI values were significantly associated with Gleason score 7 or greater. The AUC to detect aggressive prostate cancer was 0.815. At 95% sensitivity PHI specificity was 36.0% vs 17.2% and 19.4% for total and percent free prostate specific antigen, respectively. At 95% sensitivity for detecting aggressive prostate cancer the optimal PHI cutoff was 24, which would help avoid 41% of unnecessary biopsies. A cutoff of 24 led to 36% biopsies avoided with few aggressive cancers missed. These results were confirmed in the validation cohort.

Conclusions—The PHI detected aggressive prostate cancer with better specificity than total and percent free prostate specific antigen in a biopsy naïve population. It could be a useful tool to decrease unnecessary prostate biopsies.

Keywords

prostate; prostatic neoplasms; biopsy; prostate-specific antigen; nomograms

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Since the approval of PSA testing by the FDA (Food and Drug Administration) for PCa detection in 1994, PSA with DRE has allowed for earlier diagnosis and decreased presentation with metastatic disease while prostate adenocarcinoma has become one of the most commonly diagnosed cancers in American men.^{1–3} However, PSA is a poorly specific test. PSA can be within normal range in up to 15% of patients with PCa⁴ or increased due to other common conditions such as benign prostatic hyperplasia and inflammation. The slowly growing nature of this cancer raises concern for unnecessary invasive diagnostic testing and treatment.

While most complications of prostate biopsy are mild and self-limiting, such as rectal bleeding, the incidence of hospitalization due to infection can be as high as 6.3%.⁵ This further underlines the need for a more specific screening modality. In addition, an initial prostate biopsy revealing low risk disease that might never become clinically significant can be anxiety provoking for the patient whether he elects active treatment or an active surveillance program, making the decision to perform initial biopsy even harder for the physician and the patient.⁶

PHI is a mathematical formula recently developed at Beckman Coulter (Brea, California) comprising PSA, p2PSA and fPSA in the equation, $(p2PSA/fPSA) \times (PSA)$.⁷ In contrast to PSA, which measures total PSA in serum, fPSA represents the unbound free form, which increases PCa detection specificity when expressed as a percent of total PSA.⁸ fPSA includes different isoforms such as p2PSA, the isoform most closely related to PCa of all PSA isoforms, which also increases detection specificity.⁹

PHI showed improved performance over total PSA or percent fPSA in several multicenter studies^{7,10–15} and it is FDA approved. However, in most of those studies the mixed setting of initial as well as repeat prostate biopsies was evaluated. Therefore, PHI specificity was not tested for the initial biopsy. Moreover, the only prior study of a multicenter cohort that described PHI performance in men undergoing initial biopsy did not mention PHI ability to discriminate aggressive PCa (Gleason score 7 or greater) from indolent PCa independent of total PSA.¹⁵

We hypothesized that PHI would have better ability than PSA and percent fPSA to avoid initial biopsy and, thus, decrease the number of unnecessary biopsies. For this purpose we tested the ability of PHI to detect aggressive PCa (Gleason score 7 or greater) in a primary cohort and determined the PHI cutoff that provided the greatest specificity. We then validated the assay in a separate multicenter cohort.

MATERIALS AND METHODS

Subjects

Primary cohort participants were enrolled in urology clinics at Beth Israel Deaconess Hospital, Harvard Medical School from 2005 to 2013 as part of the prospective EDRN Clinical Validation Center cohort. Eligible subjects were identified sequentially among patients scheduled to undergo initial prostate biopsy. All provided informed consent for PCa biomarker detection research. Biopsies were performed under transrectal ultrasound

guidance using a standard template and pathologists at each clinical site interpreted the specimens. Men with a history of PCa or a previous positive prostate biopsy were excluded from analysis. Only those who ultimately completed prostate biopsy and blood collection were eligible. The final eligible accrual was 561 men.

Validation cohort participants were enrolled from Weill Cornell Medical College and University of Michigan from 2005 to 2013 with the same process of enrollment and eligibility criteria, also as part of the prospective EDRN Clinical Validation Center cohort. The final eligible accrual was 395 men.

Biochemical Testing

Samples were tested at the EDRN Biomarker Reference Laboratory at Johns Hopkins University. Serum was stored at -80°C until testing. Prebiopsy total PSA, fPSA and p2PSA were determined with the Access® 2 automated immunoassay analyzer.¹⁶ Technologists who performed the assays were blinded to prostate biopsy results. PHI was calculated using the equation, $(\text{p2PSA/fPSA}) \times (\text{PSA})$.

Statistical Analysis

The primary goal of the study was to assess whether PHI had better diagnostic specificity than prebiopsy total PSA and percent fPSA¹⁷ at fixed sensitivity at the initial biopsy. Through repetitive random sampling of the study population 1,000 bootstrap data sets were generated.^{17–19} These data sets provided the difference in specificity of PHI and total PSA at 95% sensitivity for all replicates, allowing calculation of the SE of the difference after adjusting for the correlation between these tests. The estimated SE was then used to test whether the difference in specificity was greater than 0. We applied a 1-sided statistical test assuming normal distribution. The same process was repeated for the PHI specificity comparison at a sensitivity of 90% and 80%, and with percent fPSA at the same sensitivities.⁷

The secondary goal was to test the optimal cutoff points for PHI determined in the primary cohort to discriminate Gleason score 7 or greater PCa from Gleason score 6 or less PCa in the validation cohort. Using ROC analysis of PHI, total PSA and percent fPSA we determined the optimal cutoff point at a fixed sensitivity of 95%, 90% and 80%.²⁰ Bootstrap based replicates were used to estimate a reliable estimate of the 95% CI around the cutoffs.²¹ Because the validation data set was derived from 2 sites, the validity of combining the data was tested by fitting a logistic model with the independent variables PHI and site along with an interaction term for PHI and site.

The 2 cohorts were finally combined for PHI cutoff comparison. Similar bootstrap analysis was done to identify the PHI cutoff and check for improved specificity at fixed sensitivities.

Study population subgroups were compared with the generalized chi-square test for categorical variables and the Wilcoxon rank sum test for continuous variables. Statistical significance was considered at $p < 0.05$. Statistical analysis was done with SAS®, version 9.3 and R, version 3.1.0 (<http://www.r-project.org/>).

RESULTS

In the primary cohort of 561 subjects 114 (20.3%) had Gleason score 7 or greater PCa. In the validation cohort of 395 subjects 122 (30.9%) had Gleason score 7 or greater PCa (table 1). In the primary and validation cohorts more aggressive cancer was associated with increased abnormal DRE ($p < 0.001$ and 0.011 , respectively) and older age (each $p < 0.001$, table 1). Similarly higher prebiopsy total PSA, p2PSA and PHI and lower percent fPSA were associated with a significantly increased presence of Gleason score 7 or greater PCa compared to indolent or no cancer (each biomarker in each cohort $p < 0.001$, table 1).

In the primary cohort higher PHI was associated with more aggressive cancer. Mean $\pm$ SD PHI was 74.6 ± 68.2 in the Gleason score 7 or greater group vs 32.2 ± 18.9 in the Gleason score 6 or less group (table 1). In fact, a rightward skew of the PHI distribution was observed in this group (fig. 1). On ROC analysis to assess PHI ability to detect aggressive PCa in patients with no prior prostate biopsy the AUC was 0.815 (95% CI $0.771-0.858$).

PHI was used at increasing diagnostic sensitivities of 80%, 90% and 95% to detect Gleason score 7 or greater PCa (table 2). PHI values at these sensitivities were 34.3, 27.5 and 24.4 with 64.8%, 45.2% and 36.0% specificity, respectively. As individual biomarkers total PSA and percent fPSA showed significantly lower specificity (17.2% and 19.4%, respectively) at 95% sensitivity while PHI had 36% specificity at that sensitivity (table 2). A threshold of 24 (risk limit 23.4 to 25.4) was chosen as a PHI cutoff to maintain sensitivity as close to 95% as possible (table 2 and fig. 2).

We then performed separate analysis in the validation cohort, which comprised an entirely different population of subjects. In this cohort higher PHI was also associated with more aggressive cancer. Mean PHI was 59.8 ± 50.5 in the Gleason score 7 or greater group vs 31.6 ± 13.8 in the Gleason score less than 6 group (table 1). A similar PHI distribution was observed with an AUC of 0.783 (CI 95% $0.734-0.832$, fig. 1). Biopsy results in the validation cohort were then assessed according to the predetermined PHI threshold of 24, yielding 92% sensitivity and 30% specificity (table 3 and fig. 2). Likewise at a prebiopsy total PSA cutoff of 2.60 ng/ml sensitivity was 98% and specificity was 18%, and with a percent fPSA cutoff of 27% sensitivity was 95% and specificity was 15% (table 3).

When the 2 cohorts were combined to form a single data set, PHI at 95% sensitivity was 22.9, corresponding to 30% specificity. At the same sensitivity the total PSA cutoff was 2.9 with 20% specificity and the percent fPSA cutoff was 26.9 with 18% specificity. In comparison a PHI of 24 showed 36% specificity in the primary cohort alone and a PHI of 21.8 showed 24.8% specificity in the validation cohort alone (table 2).

The next step was to test PHI performance at a cutoff of 24 or higher as the only criterion for proceeding to prostate biopsy (table 3). In the primary cohort limiting biopsy to men with a PHI score of greater than 24 would have avoided 136 biopsies. This corresponded to avoiding unnecessary biopsy in 41% of men without cancer (136 negative findings of a total of 328 cancer-free biopsies) and avoiding cancer over detection in 17% of men with indolent cancer (69 negative findings of a total of 119 Gleason score 6 biopsies). In the validation cohort limiting biopsy to subjects with a PHI score of greater than 24 would have avoided

69 biopsies. This corresponded to avoiding unnecessary biopsy in 36% of men without cancer (69 negative findings of a total of 190 cancer-free biopsies) and avoiding cancer over detection in 24% with indolent cancer (20 negative findings of a total of 83 Gleason score 6 biopsies).

In the primary and validation cohorts few patients with Gleason score 7 or greater PCa were missed at a PHI threshold of 24. In the primary cohort there were false-negative findings in only 5 men. However, in 4 of the 5 patients DRE was abnormal and, therefore, further diagnostic modalities would have been performed regardless of the PHI result. In the remaining subject total PSA was 4.6 ng/ml and the Gleason score was $4 + 3 = 7$. In the validation cohort 10 patients would have been missed, of whom 3 had abnormal DRE. Of the remaining 7 men with normal DRE and PHI less than 24 the Gleason score was $3 + 4 = 7$ in 6 and $4 + 4 = 8$ in 1. Total PSA was not greater than 10 ng/ml in any of the 10 men.

DISCUSSION

The lack of specificity of total PSA to detect clinically significant PCa is at the root of much of the PCa screening controversy.^{4,22,23} To improve screening tools a great deal of research has been directed toward finding new biomarkers.^{8–10,24} The PHI formula uses the specific association of p2PSA with cancerous prostatic tissue, thereby increasing the power of less specific total PSA and percent fPSA.^{7,9–15,25,26} Our results, which were derived from 2 entirely different large cohorts, reveal that PHI has significantly higher specificity than total PSA and percent fPSA at 95%, 90% and 80% sensitivity. At 95% sensitivity in the primary cohort PHI specificity was 36.0% vs only 17.2% and 19.4% for total PSA and percent fPSA, respectively. These findings indicate that PHI may be especially useful in a biopsy naïve population.

Most studies comparing PHI to PSA and percent fPSA did not focus on a biopsy naïve population.^{7,9–14,26} For example, Catalona et al studied men with nonsuspicious DRE and increased PSA, thereby focusing on cancer aggressiveness.⁷ With similar subject selection others found that PHI correlated with the Gleason score, allowing for risk stratification to predict higher grade disease and disease progression.²⁷ However, the decision to perform initial biopsy is distinctly different than the decision to select men for repeat biopsy. In fact, including men with a history of prostate biopsy in the pool of study subjects can add selection bias. That is, men in whom PCa was detected at initial biopsy were removed from such a preselected population.

In contrast, the current cohorts strictly included men with no prior prostate biopsy. In this setting PHI showed better specificity than total PSA and percent fPSA, and the improvement was greater than previously reported in mixed repeat and initial biopsy cohorts.^{7,9–13,26} For example, the AUC of PHI predicting aggressive PCa in our 2 cohorts was 0.815 and 0.783. In contrast, Catalona et al reported an AUC of 0.70.⁷ Thus, our results suggest that PHI could be particularly helpful as a screening tool in prostate biopsy naïve populations.

Our results also translate to a larger number of avoided biopsies as well as more undiagnosed, clinically insignificant cancer. The number of prostate biopsies performed in

the United States increases every year but only a small fraction results in the diagnosis of clinically significant PCa,⁶ meaning that increasingly unnecessary prostate biopsies are performed. In parallel, awareness and concern are growing for the potential side effects of biopsy and repeat biopsy, ranging from infection and bleeding to urinary incontinence and erectile dysfunction.⁵ This in part explains efforts to find new screening tools for PCa that would avoid unwarranted invasive, expensive diagnostic testing.

In our primary cohort a PHI score threshold of 24 as the tipping point for prostate biopsy provided the best combination of sensitivity and specificity. In our 2 cohorts around 40% of biopsies would have been avoided at a 24 PHI cutoff. Invasive treatment for 21% of clinically insignificant cancers would have been avoided, translating to decreased lead time bias and validating previous findings.^{15,25}

In our 2 cohorts few patients with Gleason score 7 or greater disease were missed at a PHI threshold of 24. This suggests that PHI could be applicable in a clinical setting with predetermined cutoffs used for diagnostic test decision making. Although the false-negative rate in the validation cohort was slightly higher, the PHI threshold was determined in the primary cohort, which was an entirely separate cohort. The validation cohort comprised data pooled from multiple sites, thus, inducing more variability in the cohort. Furthermore, the combination of PHI with DRE and the individual parameters of PHI significantly decreased the number of false-negative findings. However, for diagnostic planning in the clinical setting physicians can integrate all clinical information provided by physical examination and biochemical tests.

Although our study cohorts were large and allowed for robust statistical analysis, a limitation of our study is that subjects were enrolled at urology outpatient clinics and as such did not represent a primary screening population. In addition, randomized, controlled trials with PHI as a true decision tool for prostate biopsy are still needed to formally test PHI as a screening modality for PCa.

CONCLUSIONS

In 2 large, independent cohorts we validated that PHI detects aggressive PCa with better specificity than total PSA and percent fPSA. By focusing on a biopsy naïve population this study demonstrates that PHI is a potential tool to screen patients for PCa and aid in the difficult decision to move forward with the first prostate biopsy as well as avoid unnecessary biopsy.

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Abbreviations and Acronyms

DRE	digital rectal examination
EDRN	Early Detection Research Network
fPSA	free PSA
p2PSA	[–2]proPSA serum isoform
PCa	prostate cancer
PHI	Prostate Health Index
PSA	prostate specific antigen

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Figure 1.

PHI results in patients with indolent (Gleason score less than 7) or no PCa and aggressive (Gleason score 7 or greater) PCa in primary (A) and validation (B) cohorts.

Figure 2.

Optimal PHI score cutoffs by Gleason score 7 or greater in primary (A) and validation (B) cohorts. Solid curve represents sensitivity. Dashed curve represents specificity. Plus signs at bottom indicate data density. Vertical gray lines indicate PHI score at 95%, 90% and 80% sensitivity.

Table 1

Subject characteristics in primary and validation cohorts by PCa aggressiveness

	Primary Cohort			Validation Cohort		
	No PCa + Gleason Score 6 or Less	Gleason Score 7 or Greater	Overall	No PCa + Gleason Score 6 or Less	Gleason Score 7 or Greater	Overall
No. pts (%) *	328 (79.7) [‡]	114 (20.3)	561	190 (69.1) [‡]	122 (30.9)	395
Mean ± SD age (range)	61.2 ± 8 (38–87)	65.4 ± 8.5 (47–86)	62.1 ± 8.3	61.7 ± 8.9 (38–87)	64.9 ± 9.6 (43–85)	62.8 ± 8.6 (33–85)
No. race/ethnicity (%):						
White	378 (84.6)	100 (87.7)	478	246 (90.1)	101 (82.8)	347 (87.8)
Black/African American	46 (10.3)	11 (9.7)	57	16 (5.9)	17 (13.9)	33 (8.4)
Other	23 (5.2)	3 (2.6)	26	11 (4.3)	4 (3.3)	15 (3.8)
Hispanic	12 (2.9)	3 (2.6)	15	17 (6.2)	6 (4.9)	23 (5.8)
No. history (%):						
Smoking	197 (44.1)	61 (53.5)	258	122 (44.7)	60 (49.2)	182 (46.1)
Family PCa	112 (25.1)	29 (25.4)	141	79 (28.9)	33 (27.1)	112 (28.4)
No. DRE results (%):						
Abnormal	81 (18.1)	52 (45.6) [‡]	133	21 (7.7)	21 (17.2) [‡]	42 (10.6)
Enlarged	103 (23.0)	20 (17.5)	123	193 (70.7)	70 (57.4)	263 (66.6)
Normal	255 (57.1)	41 (35.9)	296	59 (21.6)	30 (24.6)	89 (22.5)
Mean ± SD International Prostate Symptom Score (range)	8.9 ± 6.8 (0–35)	8.25 ± 8.9 (0–35)	8.8 ± 7.1	7.7 ± 6.9 (0–35)	7.2 ± 5.6 (0–22)	7.6 ± 6.5 (0–31)
Mean ± SD ng/ml total PSA (range)	4.8 ± 3.0 (0.3–24.6)	12.8 ± 25.5 (0.9–232.8) [‡]	6.5 ± 12.2 (0.3–232.8)	4.8 ± 2.9 (0.29–25.6)	8.5 ± 19.1 (1.8–208.8) [‡]	5.9 ± 10.9 (0.3–208.8)
Mean ± SD % fPSA (range)	20.4 ± 9.8 (3.9–65.1)	14.3 ± 7.2 (3.1–43.6) [‡]	19.1 ± 9.6 (3.1–65.1)	19.9 ± 9.4 (4.5–81.6)	14.1 ± 6.4 (2.8–34.7) [‡]	18.1 ± 9 (2.8–81.6)
Mean ± SD pg/ml (–2)proPSA (range)	12.6 ± 8.9 (1.9–69)	52.3 ± 188 (3.9–1,891.6) [‡]	20.7 ± 86.3 (1.3–1,891.6)	17.5 ± 83.5 (1.3–1,385.6)	22.8 ± 27.9 (2.1–189.3) [‡]	19.1 ± 71.2 (1.3–1,385.6)
Mean ± SD PHI (range)	32.2 ± 18.9 (2.5–250.7)	74.6 ± 68.2 (17.6–374.1) [‡]	40.8 ± 38.9 (2.5–374.1)	31.6 ± 13.8 (6.6–90.5)	59.8 ± 50.5 (17.1–327.9) [‡]	40.3 ± 32.8 (6.6–327.9)

* In primary and validation cohorts 9 and 1 men had no DRE data, median number of biopsy cores was 12 (range 6 to 43) and 12 (range 5 to 43), and PCa in 27 and 15 men with Gleason score 6 or less, respectively, was upgraded on prostatectomy pathology.

[‡] Gleason score 6 in 119 and 83 men in primary and validation cohorts, respectively.

Significantly different vs Gleason score less than 7 on generalized chi-square and nonparametric Wilcoxon rank sum tests.

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Table 2

PHI improved Gleason score 7 or greater specificity for PCa detection in primary cohort

	% Predetermined Sensitivity*		
	80	90	95
PHI:			
Cutoff	34.3	27.5	24.4
Specificity	64.8	45.2	36.0
Total PSA:			
Cutoff	4.21	3.29	2.60
Specificity	45.5	26.4	17.2
% fPSA:			
Cutoff	20.5	23.9	27.2
Specificity	41.1	28.5	19.4

* In bootstrap based replicates greater than 0 differences in total PSA and % fPSA specificity were significant vs corresponding PHI specificity.

Table 3

Impact of 24.0 PHI threshold on prostate biopsy

Cohort	% Sensitivity	% Specificity	Predictive Value		Results			
			Pos	Neg	Neg	Pos	False-Neg	False-Pos
Primary:								
PHI 24 or greater*	95.6	34.9	27.3	96.9	156	109	5	291
PSA 2.6 ng/ml or greater	95.6	16.8	22.7	93.8	75	109	5	372
% fPSA 27 or less	94.7	20.1	23.2	93.8	90	108	6	357
Validation:								
PHI 24 or greater*	91.8	30.0	37.0	89.1	82	112	10	191
PSA 2.6 ng/ml or greater	97.5	18.3	34.8	94.3	50	119	3	223
% fPSA 27 or less	95.1	15.0	33.3	87.2	41	116	6	232

* In 400 of 561 subjects in primary cohort and 303 of 395 in validation cohort.