

The Prostate Health Index: a new test for the detection of prostate cancer

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Abstract: A major focus in urologic research is the identification of new biomarkers with improved specificity for clinically-significant prostate cancer. A promising new test based on prostate-specific antigen (PSA) is called the Prostate Health Index (PHI), which has recently been approved in the United States, Europe and Australia. PHI is a mathematical formula that combines total PSA, free PSA and [-2] proPSA. Numerous international studies have consistently shown that PHI outperforms its individual components for the prediction of overall and high-grade prostate cancer on biopsy. PHI also predicts the likelihood of progression during active surveillance, providing another noninvasive modality to potentially select and monitor this patient population. This article reviews the evidence on this new blood test with significant promise for both prostate cancer screening and treatment decision-making.

Keywords: prostate health index, PHI, prostate cancer, PSA, free PSA, screening, prognosis

Introduction

In 2013, there will be an estimated 238,590 new cases of prostate cancer and 29,720 deaths, making it the second leading cause of cancer death in US men [ACS, 2013]. Widespread prostate cancer screening with prostate-specific antigen (PSA) has led to a dramatic reduction in the proportion of men diagnosed with metastatic disease and prostate cancer death rates [Schroder *et al.* 2012]. However, PSA screening continues to be highly controversial due to its limited specificity for clinically significant prostate cancer, resulting in unnecessary biopsies for false positive results as well as detection of some indolent tumors that would not have caused harm during the patient's lifetime.

To preserve the benefits of screening and early detection and to reduce these harms, there has been great progress into alternate ways of using the PSA test with better performance characteristics. In the early 1990s, several studies showed that a greater percentage of PSA circulating in the unbound or form ('free PSA') indicated a greater likelihood that the elevation was from benign conditions rather than prostate cancer [Lilja *et al.* 1991; Stenman *et al.* 1991].

More recently, several PSA isoforms have been identified that can further increase the specificity

for prostate cancer [Mikolajczyk *et al.* 2004]. In particular, the [-2] form of proPSA ('p2PSA') has become commercially available, with improved performance over either total or free PSA for prostate cancer detection on biopsy [Catalona *et al.* 2003; Sokoll *et al.* 2010].

The Prostate Health Index (PHI) is a new formula that combines all three forms (total PSA, free PSA and p2PSA) into a single score that can be used to aid in clinical decision-making [Catalona *et al.* 2011]. PHI is calculated using the following formula: $([-2]proPSA/free\ PSA) \times \sqrt{PSA}$. Intuitively, this formula makes sense, in that men with a higher total PSA and p2PSA with a lower free PSA are more likely to have clinically significant prostate cancer. In this article, we review the evidence on PHI in prostate cancer screening and management.

Results

US studies on PHI in prostate cancer screening

In 2011, Catalona and colleagues published the results of a large multicenter trial of PHI for prostate cancer detection in 892 men with total PSA levels from 2 to 10 ng/ml and normal digital rectal examination (DRE) who were undergoing

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prostate biopsy [Catalona *et al.* 2011]. The mean PHI scores were 34 and 49 for men with negative and positive biopsies, respectively. Setting the sensitivity at 80–95%, PHI had greater specificity for distinguishing prostate cancer on biopsy compared with PSA or percentage free PSA (%fPSA). On receiver operating characteristic analysis, PHI had an area under the curve (AUC) of 0.70, compared with 0.65 for %fPSA and 0.53 for PSA. Although the PHI test has been approved by the US Food and Drug Administration only in the 4–10 ng/ml PSA range, this study showed that PHI performed well in the 2–10 ng/ml PSA range. [Loeb *et al.* 2013].

More recently, Sanda and colleagues showed that not only did PHI outperform free and total PSA for prostate cancer detection, but it also improved the prediction of high-grade and clinically-significant prostate cancer [Sanda *et al.* 2013]. In 658 men with PSA levels of 4 to 10 ng/ml from the multicenter study population, this study showed a significant relationship between PHI and the Gleason score on prostate biopsy. PHI had a higher AUC (0.698) compared with %fPSA (0.654), p2PSA (0.550) and PSA (0.549) for clinically significant prostate cancer based on the Epstein criteria. Furthermore, a quarter of the study population had PHI levels <27, and only a single patient in this PHI range had a biopsy Gleason score $\geq 4+3 = 7$. These combined findings suggest that the use of PHI could significantly reduce unnecessary biopsies and the overdiagnosis of nonlethal disease.

Since the aforementioned results came from a large multicenter trial, it is important to note that PHI has also been examined in a grassroots population with consistent findings. Specifically, Le and colleagues compared PHI with to its individual components in men undergoing a prostate biopsy with PSA levels from 2.5 to 10 ng/ml and negative DRE from a prospective screening population of 2034 men [Le *et al.* 2010]. On ROC analysis, PHI had the highest AUC (0.77) compared with p2PSA (0.76), %fPSA (0.68) and PSA (0.50) for prostate cancer detection.

International studies on PHI in prostate cancer screening

Several large international studies have also reported on PHI, including the PRO-PSA Multicentric European Study. Among 646 European men from five centers undergoing

prostate biopsy for a PSA of 2–10 ng/ml or suspicious DRE, Lazzeri and colleagues showed that using p2PSA or PHI significantly improved the prediction of biopsy outcome over total and free PSA [Lazzeri *et al.* 2013b]. While the use of %p2PSA or PHI would reduce the number of unnecessary biopsies by $\geq 15\%$ at 90% sensitivity, PHI would miss the fewest high-grade tumors.

The same authors also reported a subset of men from this multicenter PROMetheuS trial to specifically evaluate men with a positive family history of prostate cancer [Lazzeri *et al.* 2013a]. They found that proPSA and PHI were significant independent predictors of prostate cancer in this high-risk population. When added to a model containing PSA and prostate volume, p2PSA and PHI led to a 8.7% and 10% increase in accuracy, respectively ($p < 0.0001$). In addition, p2PSA and PHI were associated with Gleason score on biopsy, suggesting their potential utility to reduce unnecessary biopsies in men with a positive family history. Additional study is warranted to further examine the potential utility of PHI in other high-risk populations, including men of African descent.

Several groups have also compared the performance of PHI with other prostate cancer biomarkers leading up to a prostate biopsy. For example, Scattoni and colleagues reported on a comparison between PHI and PCA3 in European men undergoing initial or repeat biopsy. Overall, PHI had a higher AUC (0.70) than either PCA3 (0.59) or %fPSA (0.60) [Scattoni *et al.* 2013]. Another series of 300 patients undergoing first biopsy in Italy had a 36% prostate cancer detection rate [Ferro *et al.* 2013]. They reported an AUC of 0.77 for PHI, which compared favorably with 0.73 for PCA3 and 0.62 for free PSA. On decision curve analysis, PHI had greater net benefit at threshold probabilities $>25\%$. Stephan and colleagues also performed a comparison of PHI with both PCA3 and the urinary TMPRSS2:ERG test in 246 men undergoing either initial or repeat prostate biopsy [Stephan *et al.* 2013]. In the overall population, PHI and PCA3 had a statistically similar AUC for prostate cancer detection on biopsy, and in general, the inclusion of both variables led to significant net benefit compared with standard parameters. However, their comparative performance differed between clinical scenarios, with PCA3 performing best in men undergoing repeat biopsy. Nevertheless, only PHI correlated with Gleason

score among men with prostate cancer, while PCA3 and TMPRSS2:ERG did not.

PHI for risk stratification and treatment outcomes

The recent Melbourne Consensus Statement discusses the importance of dissociating diagnosis from treatment and considering active surveillance as a way to reduce overtreatment for men with low-risk disease [Murphy *et al.* 2013]. There is currently no consensus over the optimal patient selection and follow-up protocol for patients on active surveillance. Some programs use PSA kinetics to help determine the need for intervention, but others have found that changes in total PSA are not always reliable predictors of histological findings, at least in the short term [Ross *et al.* 2010]. The Johns Hopkins active surveillance program includes men with very low-risk prostate cancer (clinical stage T1c, PSA density <0.15, Gleason ≤6 in a maximum of 2 positive cores with ≤50% involvement) and has traditionally used annual repeat prostate biopsies to assess for signs of progression. Increasing recognition of the risks of prostate biopsy highlights the need for other noninvasive modalities that can be used to monitor patients during active surveillance [Loeb *et al.* 2012]. Numerous recent studies have suggested that magnetic resonance imaging (MRI) may be helpful during active surveillance [Morgan *et al.* 2011]. In addition, Tosoian and colleagues showed that both baseline and longitudinal values of PHI predicted which men would have reclassification to higher-risk disease on repeat biopsy during a median follow up of 4.3 years after diagnosis [Tosoian *et al.* 2012]. Baseline and longitudinal measurements of PHI had C-indices of 0.788 and 0.820 for upgrading on repeat surveillance biopsy, respectively. In contrast, an earlier study in the Johns Hopkins active surveillance, PCA3 did not reliably predict short-term biopsy progression during active surveillance [Tosoian *et al.* 2010]. Additional studies are warranted to further examine the use of PHI in different active surveillance populations.

Risk stratification is also important for men undergoing definitive treatment and those with more advanced disease. Although relatively fewer studies have been studied using phi in this clinical context, a recent pilot study of men with biochemical recurrence reported significantly higher p2PSA and phi in men with metastatic progression compared those without clinical metastasis

[Sottile *et al.* 2012]. Future studies are necessary to further evaluate and validate a role for PHI in the management of more advanced disease.

Conclusion

Although no single marker in isolation has perfect performance characteristics, PHI is a simple and inexpensive blood test that should be used as part of a multivariable approach to screening. In multiple prospective international trials, this composite measurement has been shown to outperform conventional PSA and free PSA measurements. Unlike PCA3 and TMPRSS2:ERG, PHI is also consistently associated with Gleason score and upgrading during active surveillance. PHI should be considered as part of the standard urologic armamentarium for biopsy decisions, risk stratification and treatment selection.

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Conflict of interest statement

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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