0152

IFCC-WorldLab EuroMedLab Berlin 2011
Berlin 2011 • 15-19 May

The Beckman Coulter Prostate Health Index (*phi*) increases the specificity of detection of prostate cancer and may reduce the number of negative biopsies

Sébastien Vincendeau [1], Carsten Stephan [2], Alain Houlgatte [3], and Axel Semjonow [4]

[1] Department of Urology, Hospital Pontchaillou, Rennes, France
[2] Department of Urology, Charité-Universitätsmedizin Berlin, Germany
[3] Department of Urology, HIA du Val de Grace, Paris, France
[4] Prostate Center, Department of Urology, University Hospital Münster, Germany

Objectives

Previous studies have shown that [-2]proPSA, an isoform of PSA, could improve the detection of prostate cancer (PCa) compared to tPSA and free PSA (fPSA) (1,2,3). Beckman Coulter offers a commercial automated assay called p2PSA for the quatitation of [-2]proPSA, and has developed the Prostate Health Index (*phi*) which combines the results of total PSA, free PSA and p2PSA (3). The superior clinical performance of the *phi* index were confirmed in a multicenter study. The data were also analyzed to determine the improvement in specificity for the detection of PCa at high sensitivity in comparison to tPSA and %fPSA. The relationship between the *phi* results and the percentage of positive biopsy was investigated. In addition, the reduction in the number of negative biopsies, as a direct consequence of the improved specificity of the *phi* test , was estimated.

Material and Methods

A total of 902 patients with tPSA values between 1.6 – 8.0 ng/mL (WHO-calibrated), 446 with, 456 without PCa, underwent ≥10 core biopsies in four different sites were enrolled in the study. A tPSA range of 1.6 – 8.0 ng/mL with a WHO-calibrated tPSA Access assay corresponds to a range of 2 – 10 ng/mL with a Hybritech- calibrated tPSA Access assay. Similarly, the classical decision point of 4.0ng/mL in Hybritech-calibrated assay corresponds to 3.1ng/mL with a WHO-calibrated assay. Serum samples were prepared from blood drawn prior to DRE. Serum samples from the enrolled patients were prepared within 3 hours of the blood draw then stored frozen at -20°C or -80C° [4]. The serum concentrations of tPSA, fPSA and [-2]proPSA were measured with Beckman Coulter Access immunoassays on an Access2 or Unicel DxI 800 instrument. The Prostate Health Index was calculated using the following formula: (p2PSA/fPSA)*√tPSA [3]. ROC curves were plotted to compare the clinical performances of tPSA, %fPSA and *phi* for the detection of PCa.

Results

- **The Prostate Health Index significantly improves the detection of PCa**

Significant higher median values for tPSA, p2PSA and *phi* are observed for the patients with PCa compared with patients without PCa. The median value of %fPSA was significantly lower in PCa patients compared with with patients without PCa. The ROC curve analysis showed that *phi* (AUC=0.72, 95% CI: 0.66 – 0.79) provided significantly ($p < 0.0001$) better clinical performance to detect PCa compared to tPSA (AUC=0.53, 95% CI: 0.46 – 0.61) and %fPSA (AUC=0.58, 95% CI: 0.51 – 0.65). The difference between the ROC AUC of %fPSA and tPSA did not reach statistical significance ($p=0.3063$). Interestingly, similar results were observed when the analysis was performed in men with tPSA < 3.1ng/mL (data not shown).

- **The Prostate Health Index correlates with the probability of a positive prostate biopsy**

The relationship of *phi* with the probability of positive biopsy was investigated. The percentage of positive biopsies per various ranges of *phi* was plotted. High level of *phi* corresponds to a high probability of positive prostate biopsy (up to 91% at *phi* > 81). At the opposite In the group of patients with phi below 20 (n=78), only 26% had a positive biopsy.

- **The Prostate Health Index improves specificity for the detection of PCa**

As initially observed with the ROC analysis, the phi index seems to increase the specificity at high level of sensitivity. An improvement in specificity at 90% sensitivity was shown for the *phi* (cut off 29; specificity 33%) as compared for tPSA (cut off 3.02; specificity 13%) and %fPSA (cut off 22.8; Specificity 17%). While detecting the same number of PCa cases (sensitivity set at 90%) the *phi* index could improve the detection of true negative cases (specificity) by at least a factor 2 compare to tPSA or %fPSA and therefore detect more true negative patients and less false positive than tPSA or %fPSA.

- **The Prostate Health Index reduces the number of negative biopsies.**

The reduction in the number of negative biopsies due to the improved specificity was investigated for a sensitivity set as 90% (90% of PCa detected). At 90% sensitivity, 149 patients would be identified as true negative with phi (cutoff: 29.26). At the same sensitivity only 73 or 76 patients would have been identified as true negative with tPSA (cutoff: 2.64) or %fPSA (cutoff: 22.78) respectively. Therefore, while detecting the same number of PCa (Sensitivity 90% ie 402 true positive), the use of *phi* would have reduced the number of negative biopsy by 76 in comparison with tPSA or by 73 in comparison with %fPSA. Taking into account a total number of unnecessary biopsies (False positive) of 383 to 380, it is possible to calculate that the use of *phi* would avoid between 18 to 19% of unnecessary biopsies.

Results.

- **Detection of PCa for patients with tPSA > 1.6 and < 8.0 ng/mL**

Patients (n)	902
Diagnosis (n)	
No PCa	456
PCa	446

Test	Area ROC	95% CI	Significance* (p)
tPSA (ng/mL)	0.53	0.46 to 0.61	-
%fPSA	0.58	0.51 to 0.65	0.3063*
phi	**0.72**	0.66 to 0.79	**<0.0001****

* %fPSA vs tPSA
** %fPSA vs phi

- ***phi* reduces the number of negative biopsies**

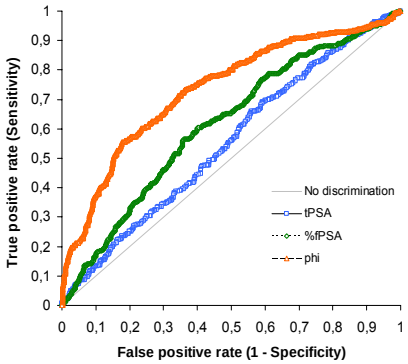
➢ **At 90% Sensitivity**

tPSA (Positive test > cutoff)	True positive	True negative	False positive	False negative
2.64	**402**	**73**	**383**	**44**
%fPSA (Positive test < cutoff)	**True positive**	**True negative**	**False positive**	**False negative**
22.78	**402**	**76**	**380**	**44**
***phi* (Positive test > cutoff)**	**True positive**	**True negative**	**False positive**	**False negative**
29.26	**402**	**149**	**307**	**44**

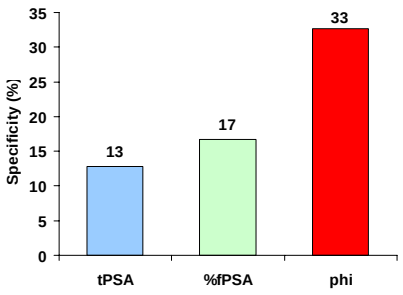
➢ **Unnecessary* biopsy avoided with *phi* at 90% Sensitivity**

	Number of Unnecessary Biopsy	Number of Unnecessary biopsy avoided with *phi*	% of Unnecessary biopsy avoided with *phi*
tPSA	**383**	**76**	**18%**
%fPSA	**380**	**73**	**19%**

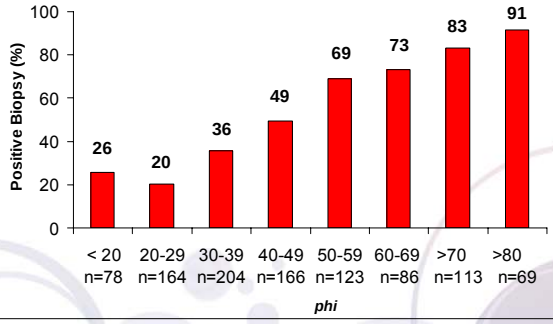
*** Unnecessary Biopsy = False Positive**



- ***phi* improves clinical specificity at 90% Sensitivity**



- **Proportion of positive biopsy according to the *phi* score**



Conclusions.

Using this preliminary data set, interim analysis of this two-center study confirmed the superior clinical performance of the *phi* index for the detection of PCa in men with tPSA between 1.6 and 8.0 ng/mL (WHO calibration). We demonstrated a strong relationship between the *phi* and the probability of a positive biopsy. The improved performance of *phi* for the detection of PCa translates into an improved specificity at high sensitivity by at least a factor 2. This specificity improvement leads to a possible reduction of negative biopsies by 18 to 19% at high sensitivity. These results indicate that *phi* could improve detection of PCa while reducing the cost of care. Further studies are required to evaluate in detail the cost-effectiveness of introducing the *phi* test into routine practice.

References.

1 Sokoll et al. [-2]Proenzyme Prostate Specific Antigen for Prostate Cancer Detection: A National Cancer Institute Early Detection Research Network Validation Study. **Journal of Urology** 2008;180:539-43
2 Mikolajczyk et al. Proenzyme Forms of Prostate-Specific Antigen in Serum Improve the Detection of Prostate Cancer. **Clinical Chemistry** 2004; 50:1017-25
3 Jansen et al. Prostate-Specific Antigen (PSA) Isoform p2PSA in Combination with Total PSA and Free PSA Improves Diagnostic Accuracy in Prostate Cancer Detection. **European Urology** 2010; 57:921-27
4 Semjonow et al. Pre-analytical in-vitro stability of [-2]proPSA in blood and serum. **Clinical Biochemistry** 2010; 43: 926–928