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Platinum Priority – Brief Correspondence

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A Multicentre Evaluation of the Role of the Prostate Health Index (PHI) in Regions with Differing Prevalence of Prostate Cancer: Adjustment of PHI Reference Ranges is Needed for European and Asian Settings

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Abstract

Asians have a lower incidence of prostate cancer (PC). We compared the performance of the Prostate Health Index (PHI) for 2488 men in different ethnic groups (1688 Asian and 800 European men from 9 sites) with PSA 2–20 ng/ml and PHI test and transrectal ultrasound-guided biopsy results available. Of these, 1652 men had PSA 2–10 ng/ml and a normal digital rectal examination and underwent initial biopsy. The proportions of PC (Gleason ≥6) and higher-grade PC (HGPC, Gleason ≥7) across different PHI ranges were compared. The performance of PSA and PHI was compared using the area under the receiver operating characteristic curve (AUC) and decision curve analyses (DCA). Among Asian men, HGPC would be diagnosed in 1.0%, 1.9%, 13%, and 30% of men using PHI thresholds of <25, 25–35, 35–55, and >55, respectively. At 90% sensitivity for HGPC (PHI >30), 56% of biopsies and 33% of Gleason 6 PC diagnoses could have been avoided. Among European men, HGPC would be diagnosed in 4.1%, 4.3%, 30%, and 34% of men using PHI thresholds of <25, 25–35, 35–55, and >55, respectively. At 90% sensitivity for HGPC (PHI >40), 40% of biopsies and 31% of Gleason 6 PC diagnoses could have been

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avoided. AUC and DCA confirmed the benefit of PHI over PSA. The benefit of PHI was also seen at repeat biopsy ($n = 397$) and for PSA 10–20 ng/ml ($n = 439$). PHI is effective in cancer risk stratification for both European and Asian men. However, population-specific PHI reference ranges should be used.
Patient summary: The Prostate Health Index (PHI) blood test helps to identify individuals at higher risk of prostate cancer among Asian and European men, and could significantly reduce unnecessary biopsies and overdiagnosis of prostate cancer. Different PHI reference ranges should be used for different ethnic groups.

It has been shown that the Prostate Health Index (PHI) outperforms prostate-specific antigen (PSA), free PSA (fPSA), and PSA density in predicting prostate cancer (PC), and could significantly reduce unnecessary prostate biopsies by 30–50% [1–4]. A PHI reference guide with corresponding PC risk (PHI <25: 11%; PHI 25–35: 18%; PHI 35–55: 33%, PHI >55: 52%) commonly quoted in laboratory reports is the one described by Catalona et al. [1], which was established in mainly Caucasian men with PSA 2–10 ng/ml and normal digital rectal examination (DRE). The PC rate found in systematic biopsies for PSA <10 ng/ml varies across different ethnic groups, ranging from 26–47% for Caucasians to only 15–25% for Asian men [5,6]. Therefore, different PHI reference ranges may be needed for different ethnic populations.

We conducted a European and Asian multicentre study that involved nine clinical sites. The European sites included Paris, Rennes (France), Hamburg, and Münster (Germany) and 90–98% of the men were Caucasian in these European cohorts. The Asian sites included Hong Kong, Shanghai (China), Singapore, Tai Chung, and Taipei (Taiwan). Men with PSA 2–20 ng/ml (Hybritech calibration) and 10–12-core transrectal ultrasound-guided systematic prostate biopsies were included. A prebiopsy blood sample was taken, centrifuged within 3 h, immediately stored at −80 °C, and subsequently analyzed for PSA, fPSA, and [−2]proPSA (p2PSA) on an immunoassay system (Beckman Coulter, Fullerton, CA, USA) [7]. PHI was calculated using the formula $p2PSA/fPSA \times \sqrt{PSA}$. Outcomes included PC and higher-grade PC (HGPC, Gleason $\geq 3 + 4$). A total of 2488 men (1688 Asian and 800 European) with PSA 2–20 ng/ml and normal DRE were included for analyses.

The cohort was divided into three different groups for separate analyses: group 1 ($n = 1652$) had PSA 2–10 ng/ml, normal DRE, and initial biopsies; group 2 ($n = 397$) had PSA 2–10 ng/ml, normal DRE, and repeat biopsies; and group 3 ($n = 439$) had PSA 10–20 ng/ml and normal DRE.

Baseline characteristics for the European and Asian cohorts in group 1 are listed in Supplementary Table 1. The European cohorts had a higher percentage of repeat biopsies, higher median PHI, lower PSA, and similar median prostate size in comparison to the Asian cohorts. PC detection rates for European and Asian men (group 1) for different PHI ranges are listed in Table 1. PC and HGPC risks were fourfold higher for European than for Asian men (χ^2 test, $p < 0.001$).

Values for the area under the receiver operating characteristic curve (AUC) for PC prediction are listed in Supplementary Table 2. In predicting PC and Gleason ≥7 PC, PHI had the highest AUC in both European and Asian cohorts, except for Gleason ≥3 + 4 PC for European men, for which PHI and PSA density had similar performance.

For men in group 1, Table 2 lists the sensitivity, specificity, and number of prostate biopsies that could have been avoided for different PHI cutoffs in relation to HGPC. The number of HGPCs missed and Gleason 6 PC

Table 1 – PCs for different PHI cutoffs for men in group 1 (prostate-specific antigen 2–10 ng/ml, normal digital rectal examination, and initial biopsies)

	PHI cutoff				Total	p value [a]
	<25	25–35	35–55	>55		
European cohort ($n = 503$)						
PC	17/49 (35%)	30/116 (26%)	100/178 (56%)	115/160 (72%)	262/503 (52%)	<0.001
Gleason ≥ 3 + 4 PC	2/49 (4.1%)	5/116 (4.3%)	53/178 (30%)	55/160 (34%)	115/503 (23%)	<0.001
Gleason ≥ 4 + 3 PC	0/49 (0%)	2/116 (1.7%)	12/178 (6.7%)	16/160 (10%)	30/503 (6.0%)	<0.001
Asian cohort ($n = 1149$)						
PC	20/397 (5.0%)	31/412 (7.5%)	72/276 (26%)	28/64 (44%)	151/1149 (13%)	<0.001
Gleason ≥ 3 + 4 PC	4/397 (1.0%)	8/412 (1.9%)	35/276 (13%)	19/64 (30%)	66/1149 (5.7%)	<0.001
Gleason ≥ 4 + 3 PC	2/397 (0.5%)	6/412 (1.5%)	11/276 (4.0%)	8/64 (13%)	27/1149 (2.3%)	<0.001

PC = prostate cancer; PHI = Prostate Health Index.
[a] χ^2 test for PC versus the different PHI cutoffs.

Table 2 – Biopsies and Gleason 6 PC diagnoses that could be avoided at different PHI cutoffs (for Gleason ≥7 PC) in European and Asian cohorts

PHI cutoff	HGPC SV	HGPC SP	Bx saved *n* (%) [a]	Gleason ≥7 PC missed *n* (%) [b]	Gleason 6 Dx reduced *n* (%) [c]
European (*n* = 503)					
25	99%	10%	49 (9.7)	2 (1.7)	15 (10)
32	95%	28%	116 (23)	6 (5.2)	29 (20)
35	94%	37%	165 (33)	7 (6.1)	40 (27)
40	90%	48%	199 (40)	12 (10)	45 (31)
45	78%	59%	258 (51)	26 (23)	62 (42)
55	53%	72%	343 (68)	60 (52)	87 (59)
Asian (*n* = 1149)					
25	96%	36%	392 (34)	3 (4.5)	15 (18)
30	89%	59%	646 (56)	7 (11)	28 (33)
35	82%	74%	810 (71)	12 (18)	39 (46)
45	55%	92%	1021 (89)	29 (44)	69 (81)
55	27%	96%	1086 (95)	47 (71)	76 (89)

PC = prostate cancer; HGPC = higher-grade PC; PHI = Prostate Health Index; SV = sensitivity; SP = specificity; Bx = biopsy; Dx = diagnosis.
[a] Biopsies saved if all men with a PHI score below cutoff are not biopsied (% of all biopsies, *n* = 503 for the European and *n* = 1149 for the Asian cohort).
[b] Expressed as a percentage of all Gleason ≥7 cancers (*n* = 115 for the European and *n* = 66 for the Asian cohort).
[c] Expressed as a percentage of all Gleason 6 cancers (*n* = 147 for the European and *n* = 85 for the Asian cohort).

diagnoses avoided is listed for each cutoff. Among European men, at 90% sensitivity for HGPC (PHI 40), 40% of biopsies and 31% of Gleason 6 PC diagnoses could have been avoided. Among Asian men, at 90% sensitivity for HGPC (PHI 30), 56% of biopsies and 33% of Gleason 6 PC diagnoses could have been avoided. In the case of Gleason ≥ 4 + 3 PC, a PHI cutoff of 40 for 90% sensitivity would avoid 40% (201/503) of biopsies and 31% (45/147) of Gleason 6 PC diagnoses among European men. For Asian men, a PHI cutoff of 30 for 90% sensitivity in detecting Gleason ≥ 4 + 3 PC would avoid 53% (605/1149) of biopsies and 26% (22/85) of Gleason 6 PC diagnoses.

Group 2 included 397 men with PSA 2–10 ng/ml, normal DRE, and repeat biopsies; 75% of the men were European. Median PSA was 5.9 ng/ml (interquartile range [IQR] 4.5–7.4). Supplementary Table 3 shows PC diagnosis for different PHI ranges. The AUC for PC detection is 0.78 for PHI, 0.73 for PHI density, 0.58 for PSA density, and 0.44 for PSA. The AUC for HGPC is 0.78 for PHI, 0.74 for PHI density, 0.66 for PSA density, and 0.52 for PSA.

Group 3 included 439 Asian men with PSA 10–20 ng/ml and normal DRE. The small number of European men (*n* = 33, 7%) were not included in the analysis. Median PSA was 13 ng/ml (IQR 11–15). Supplementary Table 3 shows PC diagnosis for different PHI ranges. The AUC for PC detection is 0.76 for PHI, 0.77 for PHI density, 0.67 for PSA density, and 0.47 for PSA. The AUC for HGPC detection is 0.77 for PHI, 0.81 for PHI density, 0.75 for PSA density, and 0.44 for PSA.

DCA curves for different biopsy indication scenarios are shown in Supplementary Figure 1. In all scenarios, the net clinical benefit was higher for PHI than for all other markers, except in the group 1 European cohort (Supplementary Fig. 1D), for which PHI was similar to PSA density in predicting HGPC.

We created forest plots showing the odds ratio for PHI in the different centers for the different outcomes in group 1 (data not shown). The plots showed substantial heterogeneity of the effect of PHI when predicting PC. The grouping factor Asia/Europe was able to explain the observed heterogeneity in part. For the outcomes any PC and Gleason ≥ 4 + 3 there was no significant residual heterogeneity, while there was some residual heterogeneity for Gleason ≥ 3 + 4. After subdividing Europe into the constituent countries, there was no significant residual heterogeneity. Therefore, we presented results grouped by continent across all outcomes.

Men in the European cohort had a fourfold higher risk of PC and HGPC compared to Asian men. Baseline age and PSA were higher among Asians, while prostate size was comparable. All nine cohorts were clinically referred patients and not from any structured PSA screening program. The differences in PC risk are probably related to ethnic differences.

Druskin et al. [8] reported that PHI density (AUC 0.82) had better performance than PHI (AUC 0.79) in predicting clinically significant PC. In the current study, PHI density did not perform better than PHI in most scenarios except for group 3. The larger sample size and multiethnicity in the current study may be more representative concerning the usefulness of PHI density.

Other well-performing tools for PC diagnosis (eg, risk calculators) include PSA density, which requires estimation of prostate volume [9]. Multiparametric magnetic resonance imaging (MRI) improves the diagnosis of clinically significant PC [10], but in general is associated with higher costs and requires radiological expertise. It has been shown that MRI and PHI are complementary to each other, as each modality missed some significant PC [8]. As PHI is a simple blood test, it can be ordered by general practitioners and there is no need for interpretation expertise. As the cost of a blood test will probably decrease with time, the role of PHI as a screening tool is worth investigating.

Our study has a number of strengths, including the largest sample size to date for PHI research and the involvement of different ethnic groups from nine sites. Limitations include the low number of prostate MRI scans performed and potential underdiagnosis, a lack of biopsy information such as the number of positive cores or the percentage of cancer in each core, and no cost-effectiveness analysis, as the costs are different for each site.

In conclusion, our results show that PHI was more effective than PSA density, %fPSA, or PSA in predicting PC in all subgroups including those with PSA 2–10 ng/ml, PSA 10–20 ng/ml, or any history of a prior negative biopsy. By using PHI, more biopsies could have been avoided among Asian men (56% vs 40%) while reducing 30% Gleason 6 diagnoses in both groups. Population-specific PHI reference ranges and cutoff values should be identified.

Author contributions: Peter K.-F. Chiu had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.eururo.2018.10.047.

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