Prostate Health Index Density

By Kalli Spencer

For some time researchers have been searching for alternative prostate cancer blood tests. Prostate-specific antigen (PSA) is still the best test that is available. Even though it only detects changes in the prostate it is also affected by factors other than prostate cancer (PCa) such as infections and an enlarged prostate (benign prostate hyperplasia). This results in several unnecessary prostate biopsies in those with rising PSAs. A PSA isoform (Protein similar to PSA) called [−2]proPSA (p2PSA) has been shown to be more specific than PSA for PCa diagnosis. Prostate Health Index (phi) was derived from a formula incorporating p2PSA, total PSA (tPSA) and free PSA (fPSA). It was approved by the United States Food and Drug Administration (FDA) in 2012 for men aged 50 or above with PSA values of 4–10 ng/ml and a normal digital rectal examination (DRE) finding. Prostate health index density includes the prostate volume measured on ultrasound. Phi has been demonstrated to be superior compared to PSA, fPSA, and PSA density in predicting PCa. In patients with a negative systematic prostate biopsy, there is still a 15–30% risk of PCa diagnosed on repeated biopsy. For this reason, continued surveillance with a PSA and DRE is important in patients with initial negative biopsies. Patient selection for a repeat biopsy is also important in order to maximize cancer detection, while avoiding unnecessary biopsy related complications.

A study by Liu et al in 2021 investigated the relationships between initial phi and phi density level and the detection of PCa and high grade PCa (HGPCa) over time with a long follow-up period in patients with initial negative prostate biopsies[1]. They found that patients with an initially negative prostate biopsy, a higher baseline phi level predicted an increase in PSA as well as PCa and a HGPCa diagnosis over a median follow-up period of more than 6 years. It was also observed that a higher baseline phi was associated with a higher risk of PI-RADS 4 or 5 lesions detected on subsequent MRI of the prostate. PIRADS is a classification system to grade the severity of prostate cancer on MRI (PIRADS 4 and 5 indicates high grade cancer). In men with phi < 25, 28 out of 163 men had MRI prostate at follow-up and only 1 PI-RADS 4 and no PI-RADS 5 lesion was reported. In men with phi ≥ 35, 38 out of 103 had an MRI of the prostate done, with 2 PI-RADS 4 and 7 PI-RADS 5 lesions reported. A higher phi density was significantly associated with higher risk of both PCa and HGPCa diagnosis, with phi density of ≥1.2 having a 21% risk of HGPCa compared with 0% in phi density of <0.4. 86.5% of the cohort had phi density <1.2, and among them 94.5% did not have PCa and 97.7% did not have HGPCa diagnosis on follow-up. It appears that phi density has better ability to predict men with very high and very low risks of HGPCa in the long run, and phi density cutoffs of 0.4 and 1.2 may be better than phi cutoffs for guiding the subsequent need for investigations. Phi density has been reported to be associated with clinically significant PCa on biopsy and radical prostatectomy specimens in other studies. Using phi or phi density can effectively stratify the risk of PCa and HGPCa diagnosis over 6 years. For men with lower initial phi or phi density with one negative prostate biopsy, the next follow-up PSA testing can be performed at least a few years later. On the other hand, for men with higher phi (≥35) or phi density (≥1.2), more aggressive follow-up investigation including more frequent PSA blood taking, MRI and/or repeated biopsy should be performed to avoid delayed diagnosis of HGPCa. Therefore, phi and phi density could guide follow-up plans of patients with a prior negative biopsy. Men with phi density ≥1.2 predicted an increasing PSA trend of +0.95 ng/ mL/year, while those with phi density <1.2 had a relatively static course. Therefore, men with one negative biopsy and a baseline phi density of ≥1.2 will likely have a higher risk of rapid rise in PSA.

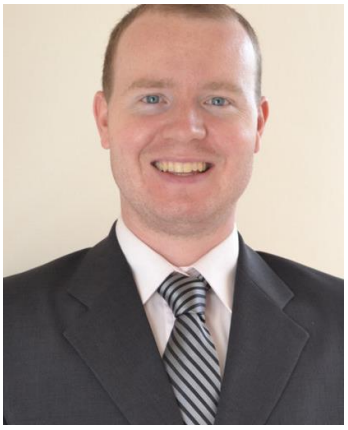
This is the first study of its kind to investigate the role of baseline phi and phi density in predicting future PCa risk. Self reported limitations of the study include its retrospective nature. Not all men received a pre biopsy MRI so all biopsies at baseline were systematic TRUS biopsies which can lead to underdiagnosis of cancers in a proportion of men at initial biopsy. Not every man had a follow-up biopsy or MRI prostate, and undiagnosed cancers might exist in the cohort. The authors observed that

men without a re-biopsy were mainly men in the lower baseline phi groups with static PSA over almost 6.5 years, and the risk of significant cancer in this cohort (with previous negative biopsy and a static PSA over a long time period) would be exceedingly low.

PHI is already a part of the European Association of Urology cancer guidelines and PHI density may have broader clinical utility in the near future. In summary men with a prior negative prostate biopsy, a higher phi (≥35) or phi density (≥1.2) will need closer follow-up and repeated investigation, while men with lower phi (<25) or phi density (<0.4) with minimal HGPCa risk could have less frequent follow-up.

Reference

1. Liu AQ, Remmers S, Lau S et al. Initial Prostate Health Index (phi) and phi density predicts future risk of clinically significant prostate cancer in men with initial negative prostate biopsy: a 6-year follow-up study. Nature: Prostate Cancer and Prostatic Diseases 2021.



About the Author

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Kalli is an internationally renowned Urological Surgeon, specialising in oncology and robotic surgery. He trained and worked in South Africa, before relocating to Australia where he has worked at Macquarie University Hospital and Westmead Hospital. His passion for what he does extends beyond the operating room, through publichealth advocacy, education and community awareness of men's health, cancer and sexuality.

Kalli has been involved with the Prostate Cancer Foundation of Australia for many years, advocating for improved cancer care and facilitating community prostate cancer support groups.