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Focus on...

Prostate Health Index (PHI)

Proven To Outperform Traditional PSA Screening In Predicting Clinically Significant Prostate Cancer

Prostate Cancer in Ireland & Worldwide

In Ireland, prostate cancer is the most commonly diagnosed invasive cancer in men.*

Over 3,300 men are diagnosed with prostate cancer each year in Ireland.**

In 2012, incidence of prostate cancer in Ireland was 4th highest of 27 European countries.**

Prostate cancer comprises almost one third of all invasive cancers in Irish men (30.3%).*

The cancer incidence rate in Irish males was 10% higher than the EU average, partly due to increased diagnosis of prostate cancer in Ireland (52% higher).*

* Source: Cancer in Ireland 1994-2014: Annual Report of the National Cancer Registry.
** Source: Cancer in Ireland 2013: Annual Report of the National Cancer Registry

Introduction

Traditional markers for Prostate cancer (Pca), such as prostate-specific antigen (PSA) and free prostate-specific antigen (fPSA) lack diagnostic specificity. Thus, definitive diagnosis is still based on invasive prostate biopsies which are associated with patient discomfort, anxiety, and financial costs. Add to this complications which occur frequently and there is a real need for a more specific Pca marker to reduce unnecessary biopsies.

PHI (Prostate Health Index)

The Prostate Health Index (PHI) is a mathematical formula that combines total PSA, free PSA and a new serum marker known as [-2] proPSA (p2PSA) into a single score that can be used to aid in clinical decision-making, and is estimated to be 3 times more specific in detecting prostate cancer in patients than PSA screening alone.[1] p2PSA is strongly expressed in the peripheral zone of cancerous tissues of the prostate and is rarely expressed in the transition zone, which is the main site of most benign prostatic hyperplasia. It is therefore a more specific marker for prostate cancer than PSA.

PHI Proven to Outperform Traditional PSA Screening in Predicting Clinically Significant Prostate Cancer

In 2011, Catalona et al published the results of a large multicentre trial of PHI for prostate cancer detection in 892 men with total PSA levels from 2 to 10ng/ml and normal digital rectal examination (DRE) who were undergoing prostate biopsy. The mean PHI scores were 34 and 49 for men with negative and positive biopsies, respectively. Setting the sensitivity at 80-95%, the results of the study showed:

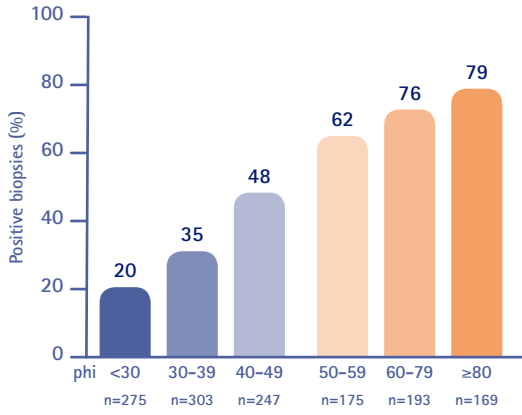
- PHI had greater specificity for distinguishing PCa on biopsy compared with PSA or percentage free PSA (%fPSA).
- On receiver operating characteristic analysis, PHI had an area under the curve (AUC) of 0.70, compared with 0.65 for %fPSA and 0.53 for PSA.
- An increasing PHI was associated with a 4.7-fold increased risk of prostate cancer and a 1.61-fold increased risk of Gleason score greater than or equal to 4+3=7 disease on biopsy.[1]

Several large international studies have also reported on PHI, including the PRO-PSA Multicentric European Study. Lazzeri and colleagues showed that using p2PSA or PHI significantly improved the prediction of biopsy outcome over total and free PSA. The use of %p2PSA or PHI would reduce the number of unnecessary biopsies by ≥ 15% at 90% sensitivity and PHI would miss the fewest high grade tumours.[3]

Clinical Utility

1. PHI improves the detection of prostate cancer & reduces the occurrence of unnecessary biopsies

The higher the PHI, the greater the risk of having prostate cancer.



Stephan et al, Clinical Chem Acta, 2013

The PHI is of particular interest within two clinical scenarios:

- **Total PSA values of <4ng/mL in patients with a negative digital rectal examination result: The PHI can be the only raised marker and is raised several months before the diagnosis of prostate cancer is made.**

- **Intermediate values of between 4 and 10ng/mL, found during the course of a benign pathology** falsely positive PSA results can also benefit from the PHI. It can help to decide whether to take a prostate biopsy or not and leads to a significant decrease in unnecessary invasive procedures.

2. Correlation Between PHI & Gleason Score

A significant correlation has also been noted between PHI and Gleason Score. Sanda et al 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.[4]

In 658 men with PSA levels of 4 to 10 ng/mL the multicentre study population 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 ≥4+3=7.

3. Cost Effectiveness of p2PSA and PHI

Owing to its high accuracy in predicting PCa, PHI could result in the avoidance of a considerable number of negative prostate biopsies, thus reducing direct costs.

Studies such as Nichol et al evaluated the cost-effectiveness of PHI in a hypothetical health plan with 100.000 male members aged 50 to 75 years old.

Using PHI in addition to PSA cut-off values of ≥2ng/mL for recommending a prostate biopsy was estimated to save $356,647 over a 12 month period.[5]

4. PHI and PCA3

The significance of PHI, PCA3 and their combination is currently the subject of numerous studies. Certain studies suggest that PHI has a better performance with regards to making the decision to take an initial biopsy, and PCA3 for subsequent biopsies. One must be rigorous with the use of these study results, which have been obtained in well-defined populations (clinical, initial biopsy or subsequent biopsies, total PSA, family history of the disease etc.), and sometimes with multi-parameter analyses.

5. p2PSA and PHI in active surveillance programmes

Studies have shown that baseline p2PSA and derivative values can help identify those men at risk of future unfavourable reclassification during AS programmes.[6,7]

A study conducted by Makarov et al showed the ratio of PHI was significantly greater (37.23 ±15.76 vs 30.60 ±12.28; P=.03) in men who ultimately had unfavourable biopsy findings.[6]

References

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Key information

[-2]proPSA

- New serum marker
- Almost exclusively expressed by cancerous prostate cells (unlike total PSA)
- Can be measured from a simple blood sample (unlike PCA3)

PHI (Prostate Health Index)

- An index calculated from the serum concentration of [-2]proPSA, combined with total PSA and free PSA
- Increase the performance of [-2]proPSA in detecting prostate cancer
- PHI has a greater specificity for detecting PCa compared with PSA or %fPSA

Clinical interest of PHI

In patients with a serum level of total PSA between 2 and 10 ng/mL (Hybritech Standard)

- To non-invasively identify patients who are highly likely to present with a positive prostate biopsy result
- To detect potentially aggressive cancers (significant correlation between PHI/Gleason)
- Potential use in monitoring of patients.
- Result in avoidance of negative prostate biopsies, thus saving time and reducing direct costs.

In practice

[-2]proPSA and PHI calculation

Sample

- 1 mL of frozen serum
- Important: the serum sample must be separated from cells within 3 hours from sample collection.
- The sample must be collected no sooner than 72 hours after prostate manipulation such as the digital rectal examination, prostate massage or a transrectal ultrasound.

Interpretation

In patients with a serum level of total PSA between 2 and 10 ng/mL (Hybritech Standard).

PHI* index values (Hybritech calibration)	Probability of cancer (at 95% specificity)
0 – 21	8,4% (1,9 – 16,1 %)
2 1 – 40	21,0% (17,3 – 24,6 %)
> 40	44,0% (36,0 – 52,9 %)

* Calculation includes the simultaneous assaying of [-2] proPSA, free PSA and total PSA (Technique HYBRITECH Beckman Coulter). Total or free PSA results generated by other methods or at other times cannot be used in the calculation.

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