**ABSTRACT**

Prostate cancer has become the most common cancer in men over the age of 50 over the past 20 years, since the introduction of the prostate specific antigen blood test; Which is recognized as a specific organ marker: with low specificity and sensitivity in the discrimination between prostate cancer and benign prostatic hypertrophy.

ProPSA and PSA precursor have been studied as a new marker for accurately detecting prostate cancer.

Our thesis is a systematic review discussing the available literature on the clinical validity of the Prostate Health Index. A systematic search of the electronic databases was carried out, taking into account the period from 2000 to January 2017.

These studies have suggested that p2PSA is the most specific form of PSA, being preferentially expressed in cancerous tissue and being significantly elevated in the serum of men with cancer.

It is now evident that the measurements of p2PSA, % p2PSA and PHI improve the specificity of the available old tests (PSA and derivatives) in the detection of prostate cancer.

In addition, the increase in PHI values appears to correlate with more aggressive forms of cancer.

Some studies have compared p2PSA and its derivatives with other new biomarkers: they found that p2PSA was significantly more accurate. Indeed, the implementation of these tests in clinical practice has the potential to increase the physician's ability to detect PCa and avoid unnecessary biopsies, while having an effective impact on the cost-effectiveness ratio.

**Keywords**

PHI, Prostate Health Index, Prostate cancer, History of validation.

**Introduction**

PSA is widely known as the serum marker of early detection of prostate cancer (PCa). Its introduction into clinical practice in the early 1990s has changed the epidemiological profile of this cancer resulting in increased localized forms, reduced metastatic forms and decreased cancer-related mortality. But the PSA also allowed increasing the number of biopsies of negative prostates (reference has created).

This led to the search for new isoforms (free PSA, PSA density, and PSA velocity) to more accurately predict the presence of prostate cancer. Recently, subforms of free PSA (fPSA) have been discovered, such as precursor forms of PSA (proPSA).

Theoretically, seven isoforms of proPSA should exist, although only [-1], [-2], [-4], [-5] and [-7] proPSA have been validated. However, all forms of proPSA are enzymatically inactive. It is possible to detect three truncated forms of proPSA in the serum ([−2], [−4] and [−5/−7] proPSA), of which the [−2] proPSA (P2PSA) is the most stable form biologically.

Beckman Coulter developed an index called PHI (Prostate Health Index), which combines in a mathematical formula (−2) proPSA, free PSA and total PSA (logistic regression model, (−2) proPSA / free PSA) × √(Total PSA)).

The purpose of our article, in the light of literature data, is to
evaluate the role of PHI in the subdivision of patients in the famous gray area "PSA = 4 to 10 ng / ml" into 5 subgroups:

- Patients at whom it is necessary to avoid a biopsy.
- Patients in whom the cancer is really indolent, eligible for active surveillance.
- Patients with good prognosis or intermediate prognosis for whom radical prostatectomy is necessary.
- Patients in whom the cancer is high risk, aggressive requiring multimodal treatment from the outset.
- Patients in whom the cancer is indolent, but conducive to progression (dynamism in the phenotype and the genotype).

**Research Strategy**

A systematic search of the PubMed, Scopus, Science Direct and MedScape electronic databases was conducted in accordance with the PRISMA statement (http://www.prisma-statement.org).

Lists of titles, excerpts or keywords were searched from January 2000 to January 2017 for combinations of the following free search terms: "pro prostate specific antigen", "proenzyme PSA", "proPSA", "[-2] proPSA" P2PSA ""," Prostate Health Index "and" PHI ".

The search was conducted for each term alone or in combination with "prostate cancer" and "prostate biopsy".

**Eligibility Criteria**

The titles and summaries of each available study were reviewed, with emphasis on the diagnostic and predictive characteristics of P2PSA, % P2PSA, and PHI compared to PSA and other available CaP biomarkers.

Only scientific articles in English reporting original data were included: priority was given to the most complete studies when the same population was reported and similar results were shown. Studies that did not report a specific and detailed result or that did not add novelty were excluded.

**Discussion**

The first Dutch, French and American tests, between 2005 and 2010, revealed the predictive relevance of proPSA compared to other derivatives. Mr. Stamey has the brilliant idea via Beckman Coulter to develop the PHI, a combined index used in the same equation, the values of (-2) proPSA, PSAL and PSAT: ((-2) proPSA / PSAL) \times √ (tPSA).

The levels of P2PSA and phi differed significantly between men with and without PCa. The highest PCa predictive value in both cohorts was obtained by PHI with AUC values of 0.780 and 0.709, a significant increase over tPSA (AUC: 0.585 and 0.534) and % fPSA (AUC: 0.675 and 0.576).

In addition, % P2PSA (P2PSA / fPSA) had significantly higher AUCs compared to tPSA and % fPSA (AUC: 0.716 and 0.695, respectively). At 95% and 90% sensitivity, phi specificities were 23% and 31% compared to 10% and 8% for tPSA, respectively.

In both cohorts, multivariate analysis showed a significant increase in the predictive value of PCa after the addition of P2PSA to a model consisting of tPSA and fPSA (AUC increase from 0.675 to 0.785 and from 0.581 to 0.697, respectively), and specificity at a sensitivity of 95% increased from 8% to 24% and from 7% to 23%, respectively.

In addition, % P2PSA, phi and the model consisting of tPSA and fPSA with or without the addition of P2PSA missed the smallest number of tumors with biopsy or pathological Gleason score ≥ 7 at 95% and 90% sensitivity.

Catalona et al. [3] conducted a double-blind, multicentre, case-control study to validate PHI in the PSA range between 2.0 and 10.0 ng / ml. 13,720 men were enrolled in eight medical centers from October 2009 to June 2015, 8920 patients met the eligibility criteria: age ≥ 50 years, normal result DRE and PSA from 2.5 to 10 ng / ml.

They found that PHI had the highest predictive accuracy of PCa (AUC=0.783) compared to P2PSA (AUC=0.648), fPSA (AUC=0.615), fPSA (AUC=0.557), and total PSA (AUC=0.525).

In addition, men with a PHI > 55 had a 62% probability of being diagnosed with PCa at the biopsy, compared to 16% of men with a PHI < 25.

In particular, compared to a PHI <25, the relative risk of detection...
of PCa was 1.6; 3.0 and 4.7 times higher at PHI values of 25.0-34.9; 35-54.9 and ≥ 55, respectively:

- At a threshold of PHI = 20, Gleason Score (GS) was > 7 in 9% of missed cancers.
- The same group recently published a prospective, multicentre study [4] involving 8920 men undergoing prostate biopsy. AUC for PHI (0.784) was significantly higher than for % fPSA (AUC=0.649; p = 0.005) and total PSA (AUC=0.527; p<0.001) in men with PSA≥2.5 ng/ml. The authors concluded that PHI has comparable performance characteristics using Hybritech performs.

In 2015, Guazzoni et al. [5] conducted a prospective observational study of 2680 men with PSA between 2 and 10 ng/ml and a normal digital rectal examination and who underwent a prostate biopsy. In this cohort, PHI and % P2PSA were the strongest predictors of positive prostate biopsy results. PHI and % P2PSA improved the accuracy of a baseline multivariate model (including tPSA, fPSA, prostate volume, and age) by 37% and 10%, respectively (p <0.001). Similarly, in patients with a total PSA of 4 to 10 ng/ml, the inclusion of PHI and % P2PSA significantly increased the accuracy from 62% to 83% (+11%) in both models (p < 0.001).

A multi-institutional study (Baltimore, Houston, San Francisco, Minnesota and Vancouver) [6] revealed the following: in multivariate logistic regression models. Logistic regression is one of the most commonly used multivariate analysis models in epidemiology. It makes it possible to measure the association between the occurrence of an event (qualitative explained variable) and the factors likely to influence it (explanatory variables).

The % P2PSA and PHI obtained independent predictive status and significantly increased the accuracy of the multivariate models from 8% to 31% (p≤0.034). At a cut-off of 28.8 PHI, 116 biopsies (52.25%) could have been avoided and PCa would have been neglected in 6% of patients, but none with a GS≥7, demonstrating real clinical utility.

The ERASMUS study of the European association of Urology (EAU) [7] between 2005 and 2015 involved 619 patients from seven European urology centers with a tPSA of 2 to 10 ng/ml who underwent an initial prostate biopsy for suspicion of PCa. P2PSA, % P2PSA and PHI significantly increased the accuracy of the multivariate model. For a sensitivity of 90%, the PHI = 27.6 could avoid 290 biopsies (48.5%), 26 cancers (9.8%) being neglected (with GS = 6).

Another multicentric European study was published by Stephan et al. [8]. This study involved 1,362 patients with tPSA between 2.6 and 8.0 ng/ml (668 PCa, 694 non-cancerous). Serum concentrations of tPSA and fPSA were both calibrated against a WHO reference material. The % P2PSA and PHI were significantly higher in all PCa subgroups (positive results of initial or repeat biopsy or negative RDE results) compared to patients without PCa (p <0.0001). PHI had the largest (AUC=0.75) and provided a significantly better clinical performance for predicting PCa compared to the % P2PSA (AUC=0.72; p=0.018), P2PSA (AUC=0.63; p=0.0001), % fPSA (AUC=0.61) or total PSA (AUC=0.56).

There was a significant increase in PHI in patients with GS≥7 (PHI> 60) compared to GS <7 (PHI< 43, p = 0.0018). The proportion of aggressive PCa (GS≥7) increased with PHI. These same syntheses are found in the latest American Urological Association (AUA) report of 2016.

Two recent studies in Asia (Japan and Taiwan) confirm previous findings in another ethnic group of the world. Lee et al. [9] reported data on 2390 consecutive men with total PSA between 2.0 and 10.0 ng/ml who underwent prostate biopsy. When PHI was used as a biopsy indicator and the sensitivity was set at 95%, the “Unnecessary biopsies” were avoided in 38% of men.

Scardino et al. [10] retrospectively analyzed Asian serum samples archived from 2300 patients over than 50 years who underwent their first prostate biopsy with a PSA of 4 to 10 ng/mL and a negative result of digital rectal exam (DRE). PHI was found to be the best predictor of prostate biopsy results, with a sensitivity of 90%. The use of PHI could have avoided unnecessary biopsies in 1040 patients (45.2%).

Finally, the Canadian Karakweiz et al. [11] developed and validated, in more than 729 patients, a PHI nomogram to predict PCa during prolonged prostate biopsy. Inclusion of PHI in a multivariate logistic regression model based on patient age, prostate volume, DRE and biopsy history significantly increased the predictive accuracy of 7% from 0.73 to 0.80 (p<0.001). The analysis of the decision curve showed that the use of the IPS index generated the highest net benefit. This nomogram has also been validated externally in a recent European multicentric study [12].

Conclusion
Since the successive discovery of PSA, PCA3, PHI, spectroscopy, nanoparticles and others, the diagnostic has become the trend of the third millennium between urologists and molecular biologists.

The challenge is to refine, amend and make pragmatic our diagnostic thinking and our daily therapeutic attitudes. Indeed, this old scheme has given way to a heterogeneous myriad of low risk, intermediate risk or high risk cancers: all three categories are dynamic mosaics and their evolution is often unpredictable, non-identical and non-uniform.

In the future, PHI and fusion genes will certainly be additional variables, in a mathematical reasoning algorithm, which can only be beneficial for the reflection of urologists and the pre-diagnostic and pre-therapeutic discussions between therapists, doctors, patients and their families.

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