Optimising the Diagnosis of Prostate Cancer in Asia

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Optimising the Diagnosis of Prostate Cancer in Asia

Het optimaliseren van de prostaatkankerdiagnostiek in Azië

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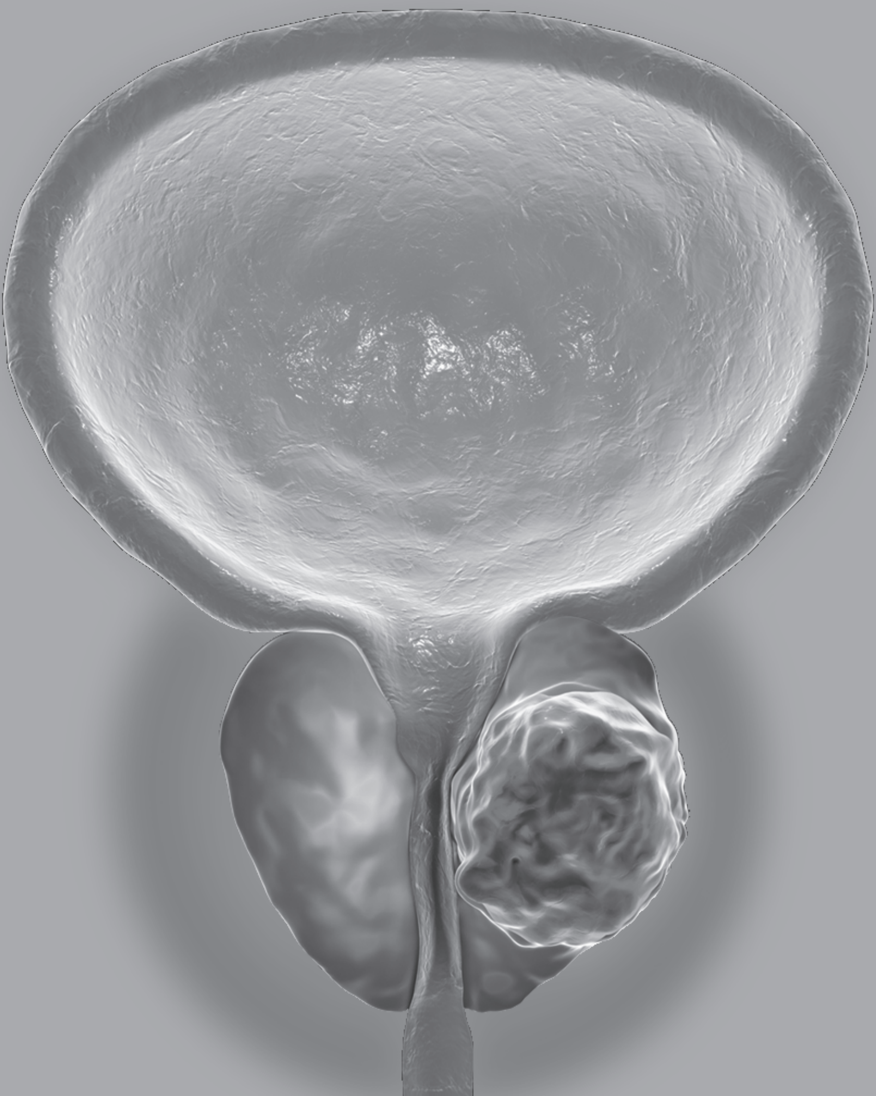

CHAPTER 1

General Introduction

PROSTATE CANCER DETECTION BY PROSTATE SPECIFIC ANTIGEN (PSA)

Prostate specific antigen (PSA) is a protein produced by the prostate luminal epithelial cells, and is detected in both seminal fluid and serum. It is a serine protease and its function is to help liquefy semen after ejaculation. [1, 2] PSA is also known as human kallikrein peptidase (hK3) and is a member of the human kallikrein family with 15 members to date. These proteases are produced from chromosome 19 and they have similar amino sequences. [3]

PSA was discovered in the 1970s but it was until 1980s when it was being applied for prostate cancer detection. [4-9] Being present at a level x10^6 times higher in semen (in the range of 0.5-5.0 mg/mL), PSA (ng/mL) is released into the blood stream due to a disruption of cellular architecture in the prostate gland. This can occur in prostate cancer or benign conditions like prostatitis, benign prostatic hyperplasia, or prostatic manipulation like digital rectal examination or instrumentation. [8, 10]

It is highly organ specific but not cancer specific as the values of PSA overlap extensively benign prostatic conditions (predominantly benign prostatic hyperplasia or prostatitis) or prostate cancer. [9, 11, 12]

Despite the poor sensitivity and specificity of PSA in predicting prostate cancer, especially at a mildly elevated range of 4-10 ng/mL, it has been and still is extensively utilized in early prostate cancer detection. This has led to earlier diagnoses and, in combination with adequate treatment lead to a reduction in prostate cancer mortality, but also to harms including over-investigation (unnecessary prostate biopsies), over-diagnosis (detection of indolent cancers), and related over-treatment.

PROSTATE CANCER SCREENING – PROS AND CONS AND THE WAY FORWARD

Since Prostate Specific Antigen (PSA) has been put into clinical use for prostate cancer screening in the early 1990s, an overall reduction of prostate cancer mortality is seen in the United States. [13] Whether a screening intervention can however result in an improvement of cancer specific survival would need evidence from randomized controlled trials (RCT). The 2 largest RCTs, namely the European Randomized Study of Screening for Prostate Cancer (ERSPC)[14] in Europe and the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer screening trial in United States [15], were initiated in 1993 and randomized thousands of men to repeated PSA screening or control groups.

The ERSPC showed that PSA screening (with or without digital rectal exam) every 4 years in 162,243 men in the core age group of 55-69 resulted in a 20% reduction in prostate cancer mortality and 41% reduction in metastatic disease at 9 years of follow-up. [14] However, 1410 men need to be screened and 48 men need to be treated in order to prevent one death from prostate cancer. The number needed to screen (NNS) and number needed to treat (NNT) to reduce one cancer death progressively reduced to 570 and 18 at 16 years follow-up, respectively. [16] In the Swedish section of ERSPC with 2-yearly screening, the prostate cancer mortality reduction was 42% at 18 years, and the NNS and NNT was only 139 and 13. [17] In the Rotterdam section of ERSPC, the prostate cancer mortality reduction increased from 32% to 51% at 13 years after correction of non-attendance and contamination. [18]

The PLCO trial offered yearly PSA screening for 6 years and digital rectal exam (DRE) for years in 76,693 men at 55-74 years old. [15] At a median of 17 years of follow-up, there was no difference in prostate cancer mortality between screened and control groups. [19]

Pooling together the results of these 2 trials resulted in an insignificant prostate cancer mortality reduction(RR 0.96, 95% CI 0.70-1.30). [20] However, the contamination rates in the control group of these trials, i.e. PSA or DRE screening in the control group, needs to be taken into consideration. The ERSPC study had 20% contamination in control group. [14] On the other hand, the contamination rate in PLCO study was up to 52% at the 6th year of study. [15] A follow-up survey published in 2016 showed that the contamination rate should be up to 85% during and after the initial 6-year screening period. [21] Therefore, there was almost no difference in screening rates in the 2 groups in PLCO study, and its result should be interpreted with caution. Extended analyses actually showed that, with good compliance and no contamination, the PLCO trial actually reduced prostate cancer mortality as well. [22, 23]

The benefit of cancer mortality reduction was counter-balanced by the harms of over-investigation and over-diagnosis of indolent prostate cancers. Prostate cancer investigation with transrectal ultrasound (TRUS) biopsy could result in a number of complications including life-threatening sepsis (1-3%), bleeding, and pain. [24] Therefor, unnecessary biopsies in men without prostate cancer results in harm. In addition it leads to unnecessary costs

The large RCT's and reports from daily clinical practice, where PSA testing is widely embraced have shown clearly that a significant proportion of prostate cancers is in fact indolent, i.e. low-volume, low grade cancers. Actively treating these cancers will only result in over-treatment and associated treatment complications. [25] Therefore, screening the right men with the right tools is crucial to improve the harm-benefit ratio of prostate cancer screening.

The data above show that PSA testing and early detection is undoubtedly beneficial for some individuals. However, a one size fits all approach on the basis of the result of one single blood test is not the way to go. Including other relevant information to better assess the individual risk of having a potentially life threatening prostate cancer is the way to go. [26] This has been the goal of decades of prostate cancer research and has resulted in the discovery of many other biomarkers and prediction models where biomarker information is combined with clinical data. This all have led to the development of so-called risk-adapted screening algorithms. [27, 28]

DIFFERENCES IN THE EPIDEMIOLOGY OF PROSTATE CANCER AND THE PERFORMANCE OF PSA IN ASIAN POPULATION

The age-standardised cancer incidence of prostate cancer in Asian men was about 10 per 100,000, far less than the reported 64-75 per 100,000 in Caucasian according to epidemiology studies. [29] Nevertheless, the incidence of prostate cancer in Asian has been increasing in recent years with the increasing use of PSA for early detection.

The percentage of prostate cancer being diagnosed in PSA grey-zone of 4-10 ng/mL is also significantly lower in Asian. The positive biopsy rates in systematic biopsies for PSA 4-10 ng/ml varies across different ethnic groups, ranging from 26-47% in Caucasian to only 15-25% in Asian. [30, 31]

Therefore, both incidence and performance of PSA vary widely in different ethnic groups. This implies that research on performance characteristics of biomarkers and other risk stratification models and tools, predominantly developed in Caucasian men, need to be assessed and adjusted if necessary to an Asian setting.

PROSTATE HEALTH INDEX (PHI)

Prostate specific antigen (PSA) originated from preproPSA, which contains a 17-amino acid leader sequence. [32] Cleavage of the preproPSA results in a proenzyme called proPSA or [-7] proPSA with 244 amino acids. [33, 34] Subsequent cleavage of the 7-amino acid leader sequence of proPSA by human kallikrein peptidase 2 (hK2) produces the active form of PSA with 237 amino acids. [35] When incomplete removal of the 7-amino acid leader sequence occurs, proPSAs with 2, 4 or 5 leader amino-acids would be created ([-2] proPSA, [-4] proPSA, and [-5] proPSA). [35] These proPSAs exist as part of the free PSA in serum.

Mikolajczyk et al reported significantly elevated forms of proPSA, in particular [-2] proPSA, in prostate cancer tissue. [36, 37] The [-2] proPSA, or more recently called p2PSA, has been shown to be a promising biomarker for prostate cancer. Multiple clinical studies have since proved the utility of [-2] proPSA in men with elevated PSA 2-10 ng/mL before initial or repeated biopsies. [38-41]

Besides predicting prostate cancer, it also predicts Gleason score 7 or above prostate cancers. [-2] proPSA was combined with free PSA and total PSA in a formula that calculates the Prostate Health Index (PHI) (Figure 1). [39, 40, 42] The PHI blood test was approved by the Food and Drug Administration (FDA) in the United States in 2012 for men aged 50 or above with PSA 4-10 ng/mL and a normal digital rectal examination (DRE) to reduce unnecessary biopsies. [43]

$$\text{Prostate Health Index (PHI)} = \frac{\text{p2PSA}}{\text{Free PSA}} \times \sqrt{\text{PSA}}$$

Figure 1. Prostate Health Index (PHI) formula.

OBJECTIVES OF THIS THESIS

The first objective of the thesis is to assess the performance of currently available methods to reduce the harms of prostate cancer screening and whether and how these tools can be applied to Asian populations. The second objective of the thesis is to investigate in more detail the role of the serum biomarker Prostate Health Index (PHI) in prostate cancer diagnosis in Asian populations.

OUTLINE OF RESEARCH QUESTIONS ADDRESSED IN THIS THESIS

The first part of this thesis focuses on risk stratification tools in prostate cancer detection and its application in Asian populations, and is described in 4 chapters addressing the following research questions:

1. Can we screen for prostate cancer and reduce the coinciding overdiagnosis? (Chapter 2)
2. Can we use PSA density to risk stratify Asian men? (Chapter 3)
3. Can we use Rotterdam prostate cancer Risk calculator in Asian men and is adjustment to an Asian setting indicated? (Chapter 4)
4. Can risk prediction models also be of aid in reducing complications of prostate biopsy? (Chapter 5)

The second part of the thesis focuses on the use of Prostate Health Index in prostate cancer diagnosis in Asian populations, and is described in 6 chapters addressing the following research questions:

1. What are the performance characteristics of PHI in the Asian setting and do we need a different PHI reference range for Asian and Caucasian? (Chapters 6-9)
2. Has PHI added value in PSA based risk prediction models? (Chapter 10)
3. To what extent can PHI reduce the number of unnecessary biopsies in a contemporary Asian clinical setting? (Chapter 11)

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CHAPTER 2

Can we screen and still reduce overdiagnosis?

Peter Ka-Fung Chiu, Monique J. Roobol

Active surveillance for localized prostate cancer. 2nd edition. Chapter 2. 2018.

ABSTRACT

Screening for cancer aims to find cancers as early as possible when the chance of cure is highest and as such involves healthy people who don't have any symptoms at that point in time. Overdiagnosis is the diagnosis of a latent disease that would not have been diagnosed during a person's lifetime (and would not have affected the person at all) without screening. Whether the diagnosis of a cancer in a particular patient can be considered as overdiagnosis is an interaction of how latent the disease is and how long the patient will live. A relatively rapid growing cancer might not necessarily harm the patient or be the cause of death if the patient had a short remaining lifetime. On the other hand, a slow growing cancer might harm the patient if he or she lives long enough. Prostate cancer is particularly amenable to overdiagnosis as there is a considerable reservoir of so-called latent disease which can be detected by a relatively simple procedure, the systematic prostate biopsy. Although obvious as it may seem, prostate cancer screening is frequently mixed up with PSA based screening. While systematic large scale screening for prostate cancer by a PSA-only approach may not be appropriate, it does not mean that there should no prostate cancer screening at all. The issue is not that black and white. Better tools for detection of (potentially aggressive) prostate cancer have emerged since the PSA era, which include multivariate approaches, i.e. combining relevant information from multiple sources like e.g. clinical data, blood, urine markers, genetic tools, and novel imaging techniques. Such an approach may help to reduce unnecessary testing (e.g. biopsy) and over-diagnosis of non-lethal cancers, while, and this is crucial, not missing the diagnosis of a potentially lethal prostate cancer.

In this chapter, we aim to summarize the harms and benefits of prostate cancer screening, and assess the possibilities on who, when and how to screen prostate cancer aiming to keep the benefit and avoid the harm.

Autopsy studies of subclinical prostate cancer

To be able to fully grasp the potential problem of overdiagnosis it is important to understand the natural history of prostate cancer. In a very nice overview of van der Kwast et al the different types of prostate cancer in relation to their clinical presentation and symptoms is given (Figure 1).[1]

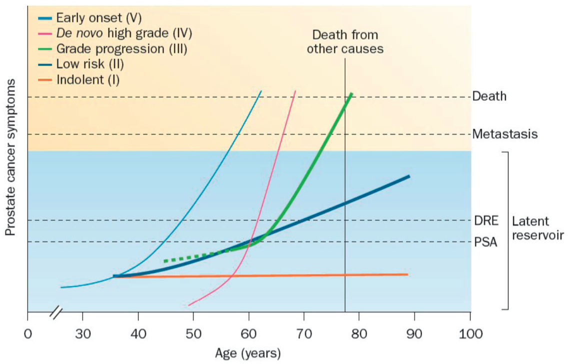

Figure 1. Scheme depicting the age-related natural history of five hypothetical forms of prostate cancer (presented by the curved lines I–V) in relationship to their clinical signs and symptoms, visualizing their sojourn time in the latent reservoir (grey coloured zone). The X-axis represents patient age. Signs and symptoms of prostate cancer are represented by the horizontal lines. Indolent (curve I) and low risk (curve II) cancers are thought to remain in the latent reservoir, although low-risk prostate cancer can grow in size and become PSA-detectable and DRE-detectable over time. When grade progression occurs in initially low-risk prostate cancers (curve III), these tumours can escape from the latent reservoir and become clinically detectable. It is thought that a small fraction of *de novo* poorly differentiated late-onset prostate cancers (curve IV) develop rapidly with a short sojourn time in the latent reservoir, precluding their timely detection by PSA screening. The size of the curved lines indicates their frequency in a population. A very small fraction of early-onset prostate cancers (curve V) with growth kinetics comparable to those of late-onset prostate cancers with grade progression (curve III) represents a biologically distinct subset of prostate cancers. Abbreviation: DRE, digital rectal examination.[1]

To be able to address the problem of overdiagnosis, first the proportion of indolent cancers needs to be identified. Autopsy studies of non-prostate cancer related deaths and observational natural history studies might provide some insight into this problem. A Greek autopsy study showed that subclinical cancers were found in 13.8% (60-69 years), 30.5% (70-79 years), and 40% (80-89 years) men.[2] More recent autopsy studies showed that in 1,056 white and black men in the United States, the proportion of latent prostate cancer was as high as 44-46% (50-59 years), 68-72% (60-69 years), and 69-77% (70-79 years), with the vast majority having potentially indolent Gleason score 6 or less cancers (84-93%).[3] These men obviously would not benefit from a diagnosis of prostate cancer in their lifetime.

Natural history of untreated low-risk prostate cancer

Johanssen et al followed up 223 Swedish men with localized prostate cancer who were diagnosed in the pre-PSA era (1977-1984) without initial active treatment.[4] In 2004, it was reported that most observed men had an indolent course in the first 15 years, but progression and death from prostate cancer increased sharply from 15-20 years in those men still alive. In 2013, an updated analysis of the series was reported after 30 years of follow-up.[5] After the death of 99% of men in the cohort, it was found that only 17% of men died of prostate cancer (which means 83% died of competing causes), and prostate cancer deaths occurred mostly between 15 and 25 years from diagnosis.[5]

Albertsen et al described another cohort of 767 men (age 55-74) diagnosed with localized prostate cancer around 1971-1984 and observed for more than 20 years.[6] At 20 years, the prostate cancer mortality rate was 30 per 1000 person-years in Gleason 6 cancer, 65 per 1000 person-years in Gleason 7 cancer, and 121 per 1000 person-years in Gleason 8-10 cancers. More than 70% of men died of other causes for Gleason 6 men at 20 years.[6] It should be noted that both cohorts represented an era without PSA testing, and it is expected that most of these patients were diagnosed at a later stage as compared with prostate cancer detected nowadays. Therefore, the early localized prostate cancers that were diagnosed in more recent years might have a more indolent course than those in the natural history studies.

The control arms of the 2 randomized trials of surgery versus observation also provided insights in the natural history of localized prostate cancer; the Scandinavian Prostate Cancer Group 4 (SPCG4)[7] in pre-PSA era and Prostate cancer Intervention Versus Observation Trial (PIVOT)[8] in the early PSA era. SPCG4 randomized 699 men with prostate cancer (cT1-T2) in 1989-1999 to radical prostatectomy or watchful waiting.[7] Only 5% patients were cT1c, and 75% had palpable disease (cT2) at time of diagnosis. The prostate cancer

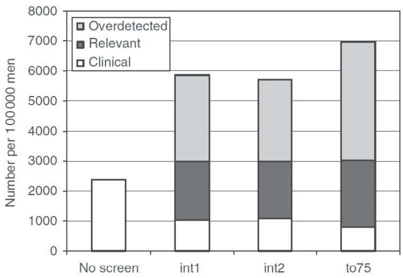

Figure 2. Number of cancers detected per 100 000 men in 25 years for three screening scenarios (1-year interval ages 55–70: int1, 2-year interval ages 55–70: int2, 4-year interval ages 55–75: to75) for clinically detected cancers (interval cancers), relevant cancers (screen-detected cancers that would have given rise to clinical symptoms later in life) and overdetected cancers (screen-detected cancers that would never give rise to clinical symptoms and would not lead to death caused by prostate cancer).

mortality in the observation group was about 20% at 15 years, and in the low risk subgroup, the cancer mortality was only 10% at 15 years.

PIVOT randomized 731 men with prostate cancer (cT1-T2) in 1994-2002 to radical prostatectomy or observation.[8] About half of the patients were cT1c and 90% was Gleason score 6-7. Prostate cancer mortalities of both arms were less than 20% at 15 years, and in the low risk subgroup the cancer mortality was less than 5% at 15 years.

In summary, localized prostate cancer shows an excellent 15-year cancer-specific survival without initial curative-intent treatment, and only younger (<65 years old) patients might benefit from detection and radical treatment.

Estimation of the extent of overdiagnosis

Overdiagnosis on a population level can be estimated by either epidemiological or clinical criteria. Epidemiological studies can estimate overdiagnosis using 2 approaches, the so-called lead-time approach or calculating excess incidence created by active screening.[9] In clinical studies, overdiagnosis is often expressed as the number or percentage of low-risk prostate cancers that are being detected. The different approaches have a widely variable estimation of overdiagnosis and are in addition, difficult to translate to an individual.[9-11]

The ERSPC study first reported 20% reduction of prostate cancer mortality by PSA-based screening in 2009 at a median follow-up time of 9 years.[12] A 30% reduction in metastatic prostate cancer was also shown.[13] However, the excess incidence of predominantly low risk prostate cancer cases was significant. This was expressed in the so-called numbers needed to screen and numbers needed to diagnose (in excess to a clinical situation) in order to prevent one death from prostate cancer being 1410 and 48 men respectively. With additional follow-up these numbers reduced to 781 men and 27 men.[14] Mathematical simulation models on the basis of the Rotterdam section of ERSPC data showed that compared to a situation without screening, applying a 4- year interval PSA based screening algorithm from 55 until age 70 would lead to 40% of prostate cancers detected to be over diagnosed.[15] Three alternative screening strategies (1) screening from age 55 to 70 with 1-year intervals (2) screening from age 55 to 70 with 2-year intervals and (3) screening from age 55 to 75 with 4-year interval showed percentages of potentially over diagnosed prostate cancers of 49%,48% and 57% respectively.[15]

The higher rate of overdiagnosis when screening men at higher age is confirmed by other modeling studies. Gulati et al using a contemporary cohort of US men modelled the effects of 35 screening strategies that vary by start and stop ages, screening intervals, and thresholds for biopsy referral concluded that less intensive screening in older men (higher PSA threshold for biopsy referral) reduces the risk for overdiagnosis.[16]

This is confirmed by a recent cost-effectiveness analysis of the MIcrostimulation SCreening ANalysis (MISCAN) model, based on ERSPC data. There it was shown that a screening algorithm with two year intervals between the ages 55-59 (3 screenings) had the best incremental cost-effectiveness ratio.[17] However, if a better quality-of-life for the post treatment period could be achieved (i.e applying active surveillance for low-risk prostate cancer), men at older age up to 72 could also be included in a screening program.[17]

Next to detecting prostate cancers that are very likely to have an indolent course based on their clinical characteristics at time of diagnosis there is obviously another factor that is closely related to over diagnosis; i.e life expectancy. As is shown above a low risk prostate cancer at time of diagnosis can become potentially life threatening if its host lives long enough.

Finding the balance between two difficult to predict individual-level outcomes is needed. This balance is graphically displayed in Figure 3 where it is obvious that we need to be able to predict both course of disease and life expectancy to be able to screen for prostate cancer with keeping the proven benefits and avoiding the harms.

The next sections of this chapter hence focus on who and how to screen for prostate cancer.

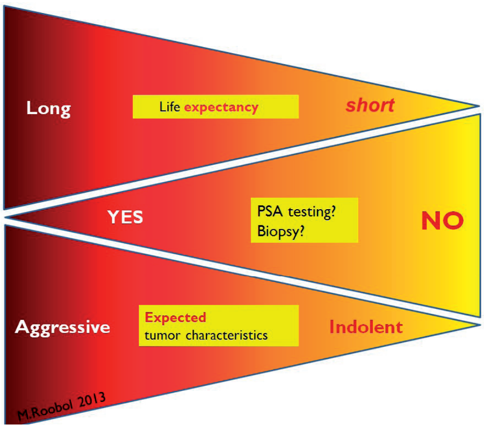

Figure 3. Prostate cancer screening in association with life expectancy and disease course.

Who to screen?

There are certain patient groups that have been associated with higher risks of potentially aggressive prostate cancer in population studies, and they included those with positive family history, ethnically black men, and those with genetic predisposition to prostate cancer.

Family history of prostate cancer

Meta-analyses on family history and prostate cancer risk demonstrated a relative risk (RR) of 2.5 in having a life-time risk of prostate cancer in men with positive family history of prostate, and up to RR of 3.5-4.4 with two affected first-degree relatives.[18] Those with brother having prostate cancer had an even higher risk of prostate cancer than those with father having prostate cancer (RR 3.1 Vs 2.4).[19] The effect of family history was also associated with earlier disease onset (before 65 years old) (RR 2.9 Vs 1.9).[20] In the Swiss arm of the ERSPC, men with positive family history of prostate cancer had a 60% higher chance of diagnosing prostate cancer, but most of them were low grade cancers.[21]

Racial differences on prostate cancer

The lifetime risk of a prostate cancer diagnosis varies in different ethnic groups. In a study in United Kingdom (UK), the risk ranged from 13.3% in Caucasian, 29.3% in Black, to 7.9% in Asian men. The risk of dying from prostate cancer also varied from 4.2% in Caucasian, 8.7% in Black, to 2.3% in Asian men.[22] Therefore, different races had a similar diagnosis-to-death ratio of around 3:1, and Black men did not have a higher risk of dying from prostate cancer once diagnosed.[22] An earlier meta-analysis, however, showed that Black men diagnosed with prostate cancer had a 13% higher risk of prostate cancer death, which was not fully explained by comorbidity, PSA screening, or access to health care.[23]

Genetic mutations associating with higher risk of prostate cancer

Twin studies suggested that the inherited component of prostate cancer risk is more than 40%.[24] Genomewide association studies (GWAS) evaluated the entire genome for commonly inherited variants (>1-5% population frequency), and more than 40 prostate cancer susceptibility loci explaining approximately 25% risk were found.[25] A more recent meta-analysis of 43,303 prostate cancer and 43,737 controls from European, African, Japanese, and Latino men have identified 23 new susceptibility loci for prostate cancer, explaining 33% of familial risks.[26] In terms of screening or early detection, it is not cost-effective to screen for all susceptible loci, and whether this would provide a better harm-to-benefit ratio.

Is the presence of a risk factor a license to screen?

A study using estimates from the literature reported that screening men with a PSA level at the highest 10^{th} percentile at 45 years old provided a better harm-to-benefit ratio comparing with those with positive family history and black race. A higher PSA at 45 years accounted for 44% of prostate cancer deaths, while family history and black race only accounted for 14% and 28% cancer deaths, respectively.[27] Hence, it is important to weigh both harm and benefit as equally important, in a high risk population there might be a larger benefit, but with applying a screening approach that is not selective for potentially lethal disease the harm may be equally increased.[28]

When to screen?

When to screen for prostate cancer is another controversial topic. It includes the starting and ending age for screening, including the so-called baseline PSA measurement at relatively young age and the screening interval

Starting screening, baseline PSA at younger age

A large case-control study in the Swedish population showed that a higher baseline PSA at younger age groups of 45-49 and 51-55 years was associated with higher risk of metastasis and prostate cancer deaths after a follow-up of 25 year. More than 40% of metastasis and deaths from prostate cancer occurred in men with PSA with the highest 10^{th} percentile (> 1.6 ng/ml at age 45-49 and > 2.4 ng/ml at age 51-55).[27]

In a study investigating the PSA level of again Swedish men at the age of 60, a PSA level of <1 ng/mL was associated with only 0.5% risk of metastasis and 0.2% risk of prostate cancer death at the age of 85.[29] In a Danish study, men with a PSA concentration of 4-10 ug/L had a 7-fold risk of prostate cancer death compared with men with PSA < 1 ug/L.[30] These data were confirmed in analyses based on the ERSPC where it is repeatedly shown that men aged 55-69 with baseline PSA levels below 1.0 ng/ml have a very low risk of prostate cancer detection, let alone dying from the disease.[31, 32]

In a comparison of prostate cancer incidence and mortality between the Dutch, Swedish and Finnish parts of ERSPC and a cohort without PSA screening (Northern Ireland) results showed that that the yield of prostate cancer screening increased with the increasing baseline serum PSA level at study entry. The benefits of early detection may be small for men with a baseline serum PSA of 0-3.9 ng/mL at study entry. The number needed to investigate (NNI) to save one prostate cancer death was 24,642 in men with initial PSA <2 ng/mL, compared to NNI of 133 in men with PSA 10-20 ng/mL.[33]

However, starting PSA testing at mid age might also result in yet more testing, biopsies and subsequent over diagnosis. The retrospective analyses presented above, recommending e.g. retesting intervals up to 10 year if the baseline PSA is considered low, cannot assess the effect in contemporary daily clinical practice. In an editorial by Carter et al. this lack of knowledge is clearly described. The authors question whether it is realistic to assume that a clinician will advise not to return for a PSA test within the next 10 years when the data actually show that more than half of the prostate cancer deaths in men aged 45-49 occur in men with a PSA of less than 1.6 ng/ml (90% of the population).[34] So while the concept of a baseline PSA test at midlife definitely sounds appealing in retrospective analyses, the question remains whether this advice will be followed in contemporary practice.

Screening interval

As mentioned above, in the Rotterdam section of ERSPC, men of age 55 to 65 years with a baseline PSA of less than 1 ng/mL was associated with very low cancer detection after 8 years. Only 3.3% men had PSA >3ng/mL and 0.49% cancer detection rate. As a result, an 8-yearly interval for screening in men with baseline PSA less than 1 ng/mL was recommended.[32]

A similar conclusion was drawn on the basis of a multiethnic study in United States. Gelfond et al reported a 10-year prostate cancer risk of 3.4% for men (median age 58) with PSA <1 ng/mL, and among the diagnosed cancers 90% were of low risk cancers. In contrast, those with PSA 3.1-10 ng/mL had a 39.0% 10-year risk of prostate cancer diagnosis. A recommendation of screening interval of 10 years or more was suggested for men with baseline PSA <1 ng/mL.[35]

In comparing 2-yearly (Goteborg section) and 4-yearly (Rotterdam section) PSA-based screening in the ERSPC trial in men with age 55-64, a 2-year screening interval reduced the incidence of advanced prostate cancer by 43% but increased the detection of low-risk prostate cancer by 46%.[36] This direct relationship between benefit and the intensity of a PSA based screening algorithm was recently confirmed by another ERSPC analyses by Auvinen et al., where it was shown that the extent of overdiagnosis and the mortality reduction was closely associated.[37] Efforts to maximize the mortality effect applying a PSA based screening algorithm in all men are bound to increase overdiagnosis. The authors correctly note that this harm-to-benefit ratio might be improved by focusing on men considered to be at high risk but how we actually can achieve that remains unclear.[37]

Ending age of screening

In a simulation study by Ross et al, the number needed to treat (NNT) in order to prevent one cancer death increased with age. Comparing with screening until age 65 (NNT 7.7), NNT of screening to 75 (NNT 12.5) and 80 (NNT 17.5) years was 2-3 times higher.[38] Zhang et al described the optimal stopping age of PSA testing from both patients' and societal perspectives from a decision process model. Patients' perspective was to maximize expected QALYs, while societal perspective was to maximize cost effectiveness for QALYs. From the patients' perspective, the optimal policy was stopping PSA testing and biopsy at 76, while the estimated age was 71 from societal perspective.[39]

With increasing age, the benefits of early detection reduces when deaths from other causes increases. The optimal age to stop screening is difficult to be determined. As mentioned before in the natural history studies and in the RCTs comparing surgery and watchful waiting (SPCG4[7] and PIVOT[8]), men with life expectancy less than 10-15 years are not recommended to have any prostate cancer screening in the American and European Urological association guidelines.[40, 41]

However, due to the continuous increase in life expectancy of men, the difficulty in estimating the remaining lifetime of older men, and the availability of better treatment with fewer complications, we are now facing a changing scenario. Therefore, it would be difficult to set a rigid age to stop screening. An individual assessment with proper counselling and shared decision making should be offered instead.

How to screen?

Nowadays, there are better tools than PSA in screening for prostate cancer which might improve the harm-to-benefit ratio in screening. As the newer tools have better sensitivity or specificity in detecting prostate cancer, a proportion of unnecessary biopsies based solely on elevated PSA might be avoided. This could reduce both unnecessary biopsies and over diagnosis. The most obvious way to move forward, while the 100% sensitivity and specificity lethal prostate cancer test is lacking, is to combine relevant information into prediction tools. In addition, novel imaging techniques can certainly be of aid in identifying those men that can benefit from early detection and treatment.

PSA-based prostate cancer risk calculators

There are many risk calculators available, all having their advantages (widely externally validated, easy to use) and disadvantages (only suitable in particular settings, requiring complicated data and calculations). A meta-analysis of 6 risk calculators (out of 127 unique prediction models) included Prostataclass, Finne, Karakiewcz, Prostate Cancer Prevention Trial (PCPT), Chun, and the European Randomized Study of Screening for Prostate Cancer Risk Calculator 3 (ERSPC RC3).[42]

It showed that PCPT risk calculator did not differ from PSA testing in terms of AUC (0.66), while Prostataclass and ERSPC RC3 had the highest AUC of 0.79. The latter models doubled the sensitivity of PSA testing (44% Vs 21%) while maintaining the same specificity.[42]

Calibration of the models, which is important in assessing the actual predicted risk, was however poorly reported. In assessing the performance of prediction models, it was reported that both discrimination (AUC) and calibration are important.[42] Decision-analytic measures (decision curve analysis) should be reported if a model relates to clinical decisions.[43]

Novel biomarkers for prostate cancer prediction

Urine PCA3

The Prostate Cancer Antigen 3 (PCA3) is a non-coding messenger RNA found to be elevated in urine of most men with prostate cancer. A post-prostatic massage urine sample is needed for analysis. A higher PCA3 score was associated with a greater risk of prostate cancer. The discriminative ability of PCA3 was significantly better than PSA (AUC 0.76 Vs 0.58).[44, 45] However, when combined to an existing risk calculator (ERSPC RC3) there was hardly any additional predictive capability.[46] PCA3 is currently approved by United States Food and Drug Administration (FDA) in 2012 as a prostate cancer diagnostic test in men with previous negative prostate biopsy.

Urine TMPRSS2-ERG

The gene fusion TMPRSS2-ERG between transmembrane protease serine 2 (TMPRSS2) gene and the v-ets erythroblastosis virus E26 oncogene homolog (ERG) gene exist in up to 80% of prostate cancers. Urine levels of TMPRSS2-ERG correlate with clinically significant prostate cancer.[47] Adding post-DRE urine PCA3 to urine TMPRSS2-ERG further improved the prediction of prostate cancer and clinically significant prostate cancer on repeated prostate biopsies. The AUC for prostate cancer detection was 0.72, 0.65, 0.77, and 0.88 for PSA, PCA3, TMPRSS2-ERG, and combination of PCA3 and TMPRSS2-ERG, respectively.[48] This is confirmed by a larger prospective multicentre study (n=443), in which TMPRSS2-ERG had independent additional predictive values to PCA3 and ERSPC risk calculator in predicting prostate cancer.[49]

Prostate health index (PHI)

PSA isoform [-2]proPSA (p2PSA) was shown to be more accurate than PSA or %free PSA in predicting prostate cancer.[50] Prostate Health Index (PHI) was created by combining PSA, free PSA, and p2PSA in the formula (p2PSA/free PSA) × √total PSA. PHI and p2PSA had specificity 3 times of that of PSA, with best performance in the range of PSA 2-10. This could reduce unnecessary biopsies while maintain a high cancer detection rate.[51] In 2012, the FDA has approved the use of PHI and p2PSA in men older than 50 years old with a total PSA 4-10 ng/mL and normal DRE to reduce unnecessary prostate biopsies. PHI was also associated with more aggressive or clinically significant prostate cancers.[52, 53] Using a simulation model, PHI was shown to be more cost effective than PSA-only screening.[54]

Four-kallikrein panel (4K)

The 4-kallikrein panel consisting of PSA, free PSA, intact PSA, and human kallikrein 2 (hK2) was shown to differentiate pathologically indolent and aggressive disease. It was shown that more than 50% of biopsies could be reduced by applying the 4K panel, while missing 12% high grade cancer and avoiding overdiagnosis of one-third of low grade cancers.[55-57]

These findings were confirmed in a large cohort of 6129 men in the Prostate Testing for Cancer and Treatment (ProtecaT) study, with better AUC compared with PSA (0.82 Vs 0.74). Using 6% risk of high grade cancer as cutoff, more than 40% biopsies could be reduced while delaying diagnosis of only 10% of high grade cancers.[58]

A 4Kscore was created by combining the 4-kallikrein panel with age, DRE findings, and history of prior prostate biopsy, and was validated to accurately identify men with high-grade prostate cancer.[59] Using the 4Kscore can reduce 30-58% biopsies while delaying diagnosis in less than 5% high grade cancers. However, when combined in a multivariate prediction model the added value is limited.[46]

STHLM3

The population based Stockholm 3 (STHLM3) study reported that the so-called STHLM3 model, which included plasma protein biomarkers (PSA, free PSA, intact PSA, hK2, MSMB, MIC1), genetic polymorphisms (232 single nucleotide polymorphisms), and clinical variables (age, family history, previous prostate biopsy, DRE), predicted Gleason 7 or above prostate cancer in a large development (n=11130) and validation (n=47688) cohort in

Sweden. The STHLM3 model performed significantly better than PSA (AUC 0.74 Vs 0.56) for Gleason 7 or above prostate cancers, and could reduce 32% biopsies.[60] The issue of overdiagnosis was however not fully addressed as most prostate cancers diagnosed were still low grade cancers, and the cost effectiveness of such an extensive model is questionable.[61]

Which novel biomarker for prostate cancer diagnosis should we choose?

All of the aforementioned novel biomarkers and imaging techniques like MRI have proved to be more specific and more discriminative (in terms of AUC) than PSA, and could potentially reduce a significant proportion (up to 50%) biopsies while delaying diagnosis in only a handful of clinically aggressive prostate cancers. However, there are very few head-to-head comparisons of different novel tools in terms of performance and cost-effectiveness, and the ever increasing cost of novel tests would make screening for prostate cancer unaffordable. This creates a difficult scenario for both physicians and patients in choosing the optimal test before biopsy decisions.[62] One conclusion can be drawn from these data: combining relevant pre-biopsy information as compared to decision making on the basis of a single PSA measurement will always help to reduce unnecessary testing and overdiagnosis.

Prostate imaging - Multiparametric MRI of the Prostate

Conventional TRUS prostate has a poor sensitivity and specificity in identification of prostate cancers, and therefore the main use of it is to guide prostate biopsy but not for diagnosis.[63] Recently the multi parametric MRI entered the urological diagnostic practice and is considered a promising imaging modality for the detection of prostate cancer.[64] A systematic review showed that targeted biopsy (with MRI information) had a higher detection rate of significant prostate cancer (sensitivity 0.91 Vs 0.76) and a lower detection rate of insignificant cancer (sensitivity 0.44 Vs 0.83).[65]

CONCLUSIONS

On the basis of natural history and screening studies we can conclude that the risk of overdiagnosis of prostate cancer is present and considerable when applying systematic PSA based screening in combination with random TRUS based prostate biopsy. This should however not prevent us from screening for prostate cancer at all, as none of us want to return to the era when many prostate cancers presented at an advanced or metastatic stage. We should aim to screen the right men (at particular high risk of aggressive prostate cancer and/or with a long life expectancy), at the right time, with the right tools. With all available knowledge we are able to reduce the current rate of unnecessary biopsies and overdiagnosis of low grade/risk prostate cancer. However, adapting our way of working by adopting recommendations and guidelines is still difficult but should be the way forward.

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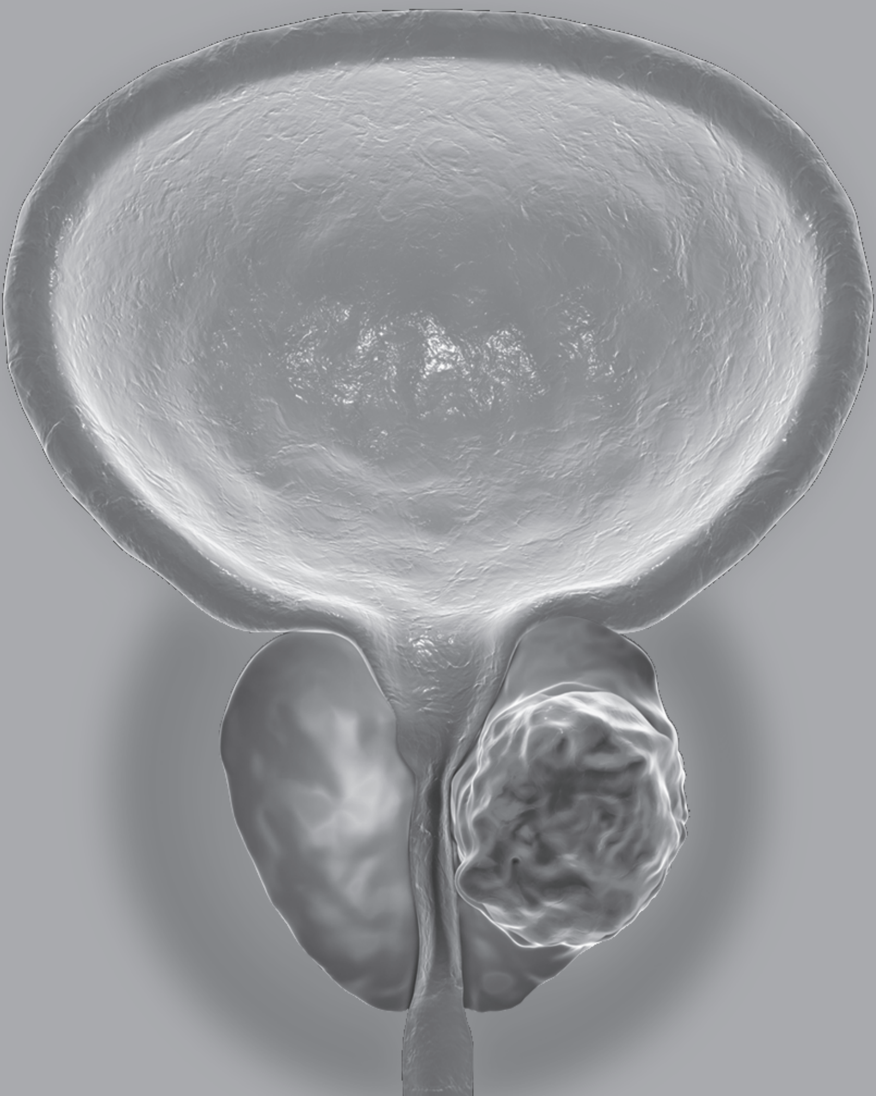

CHAPTER 3

Role of PSA density in diagnosis of prostate cancer in obese men

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ABSTRACT

Purpose
To compare the performance of PSA density in the diagnosis of prostate cancer in obese and non-obese Chinese men.

Methods
The results of transrectal ultrasound-guided(TRUS) prostate biopsies of Chinese men with PSA<20ng/mL were reviewed. Parameters including age, body mass index(BMI), TRUS prostate volume, and TRUS biopsy results were recorded. The diagnostic yields of PSA density(>0.15ng/mL/mL as positive) in obese and non-obese men with PSA<20ng/mL were compared. Obesity was defined as BMI≥27kg/m^2 according to WHO recommendation for Hong Kong Chinese.

Results
TRUS biopsy, BMI, and PSA density data were available for 854 men(mean age 65.9+/-7.3). The mean PSA values for the obese and non-obese patients were 7.9+/-3.7ng/mL and 8.2+/-4.1ng/mL, respectively(p=0.416). TRUS volumes in obese and non-obese men were 63.2ml and 51.6ml, respectively(t-test, p<0.001), and PSA density was significantly lower in obese men(0.145 vs. 0.188, p<0.001). For obese men, positive PSA density was associated with four times(41.1% vs. 9.5%, p<0.001) the risk of prostate cancer, compared to only twice the risk(18.8% vs. 9.7%, p=0.001) in non-obese men. The specificity and area under the curve of PSA density were 74.2% and 0.731, respectively, for obese men, and 51.4% and 0.653, respectively, for non-obese men. Among patients with a diagnosis of prostate cancer, the obese patient group had a significantly higher proportion of patients with Gleason 7-10 prostate cancer than the non-obese patient group(48.9% vs. 32.7%, chi-square test, p=0.035), and a trend towards a higher proportion of bilateral lobe involvement.

Conclusion
PSA density had better performance in obese men. Positive PSA density in obese men was associated with four times the risk of prostate cancer.

INTRODUCTION

Obesity is becoming increasingly common in both Caucasian and Asian populations [1-2]. Although many diseases are known to be closely related to obesity, there is increasing evidence of a complex relationship between obesity and prostate cancer [3]. Studies have suggested that obese patients tend to have larger prostates [4-5]. Obese patients or patients with higher body mass indices (BMI) have been shown to have lower prostate-specific antigen (PSA) levels in both Caucasian and Asian populations [6-8]. Furthermore, some evidence suggests that obesity is associated with higher Gleason scores in prostatectomy specimens and an increased risk of biochemical failure after treatment [9-10]. The poorer treatment outcomes might be related to the delay in diagnosis of prostate cancer due to the relatively lower PSA levels in obese patients, the increased difficulty of physical examinations, and the increased chance of missing the diagnosis in a biopsy due to larger prostate size [3].

Currently, there are many PSA derivatives that improve the performance of serum PSA in the diagnosis of prostate cancer. Among them, PSA density is a relatively simple approach for clinical use [11-13]. A PSA density cutoff of 0.15 is associated with better diagnostic accuracy for prostate cancer than total PSA alone [14].

As obese patients tend to have lower PSA levels and larger prostates, the performance of PSA density might be affected. Therefore, we assessed the performance of PSA density in obese and non-obese patients in a Chinese population.

METHODOLOGY

The cases of Chinese men with PSAs of less than 20 ng/mL who had undergone transrectal ultrasound-guided (TRUS) prostate biopsies during the 2009-2012 period were reviewed. The TRUS biopsies were performed in two regional hospitals in our area, using 10 or 12 core needle biopsies.

Parameters including age, body mass index, TRUS prostate volume, and TRUS biopsy results were recorded. The prostate volume was measured with transrectal ultrasound using the ellipse formula. PSA density was calculated by dividing total PSA by prostate volume, and a PSA density >0.15 ng/mL/mL was considered positive. Following the recommendation of the WHO, obesity for Hong Kong Chinese was defined as a body mass index (BMI) $\geq 27 kg/m^2$ [2]. Cancer grades were classified using the Gleason score (GS): low grade (GS≤6) or high grade (GS≥7).

Statistical analyses were performed using IBM SPSS v.19.0 software (IBM Corp., Armonk, NY, USA). A two-sided p value <0.05 was considered significant. Continuous and categorical variables were compared using t-tests and Chi-square tests respectively, and a 2-sided p-value of <0.05 was considered significant. The diagnostic yields of PSA density in obese and non-obese men were compared using sensitivity, specificity, and receiver operating characteristic (ROC) curves. The relationship between PSA density and the proportion of high Gleason grades was analyzed with a Chi-square test. The association between obesity and Gleason score and between obesity and prostate cancer's bilateral lobe involvement were also analyzed.

RESULTS

During the study period, BMI and PSA density data were available for 854 men (mean age 65.9 +/- 7.3 years) with PSA <20 ng/mL. TRUS biopsies were performed in the two centers, and 133 (15.6%) men were diagnosed with prostate cancer. The prevalence of prostate cancer for different PSA ranges is listed in Table 1. There was no significant difference between the proportion of prostate cancers in the 10-core and 12-core biopsies. The Gleason scores of the diagnosed prostate cancers were ≤6 in 68.5% of the cases and ≥7 in 31.5% of the cases.

Table 1. Comparing prevalence of prostate cancer of different PSA ranges between 10 and 12 core biopsies.

PSA (ng/mL)	All	Hospital 1 (10 cores)	Hospital 2 (12 cores)	p-value[a]
<4	8.3% (7/84)	11.5% (3/26)	6.9% (4/58)	0.477
4-9.9	14.2% (77/544)	16.6% (30/181)	12.9% (47/363)	0.253
10-19.9	21.7% (49/226)	18.5% (17/92)	23.9% (32/134)	0.333

[a] Chi-square or Fisher's exact test

One hundred and sixty-one patients (18.9%) were obese (BMI ≥27). The mean PSAs for obese (BMI ≥27) and non-obese (BMI <27) patients were 7.9 +/- 3.7 ng/mL and 8.2 +/- 4.1 ng/mL, respectively (t-test, p=0.416). The TRUS prostate volumes for obese and non-obese patients were 63.2 ml and 51.6 ml, respectively (t-test, p<0.001), and PSA density was significantly lower in obese men (0.145 vs. 0.188, p<0.001). The overall sensitivity and specificity for PSA density (i.e., > 0.15) was 67.7% and 55.5%, respectively, and the area under the ROC curve (AUC) was 0.662.

Comparing the use of PSA density for the diagnosis of prostate cancer in obese and non-obese patients with PSA<20 ng/mL, the proportion of prostate cancers diagnosed in PSA density-positive patients in obese and non-obese patients were 41.1% (23/56) and 18.8% (67/356), respectively (Chi-square test, p<0.001). In patients with PSA<20 ng/mL, obese PSA density-positive patients had four times the risk of prostate cancer (41.1% vs. 9.5%, Chi-square test, p<0.001), whereas non-obese patients had two times the risk of prostate cancer (18.8% vs. 9.7%, Chi-square test, p=0.001) (Table 2). For patients with PSA <10 ng/mL, the proportion of prostate cancers diagnosed in PSA density-positive patients was 43.8% (14/32) of obese patients and 18.8% (39/208) of non-obese patients (Chi-square test, p=0.002).

The sensitivities, specificities, and ROC AUC of the total PSA and PSA densities are listed in Table 3. For PSAs less than 20 or 10 ng/mL, PSA density had significantly better specificity and AUC than total PSA in obese patients only.

Table 2: Performance of PSA density for obese and non-obese men

	No Prostate cancer	Prostate cancer	Chi-square p-value
Obese and PSA <20			
PSA density negative	95	10 (9.5%)	
PSA density positive	33	23 (41.1%)	p<0.001
Non-obese and PSA <20			
PSA density negative	306	33 (9.7%)	
PSA density positive	289	67 (18.8%)	p=0.001
Obese and PSA <10			
PSA density negative	81	10 (11.0%)	
PSA density positive	18	14 (43.8%)	p<0.001
Non-obese and PSA <10			
PSA density negative	283	25 (8.1%)	
PSA density positive	169	39 (18.8%)	p<0.001

Table 3. Comparing sensitivity, specificity and ROC AUC of total PSA and PSA density in obese and non-obese men

	PSA 4	PSA density 0.15	p-value
Obese and PSA <20			
Sensitivity	93.8%	70.0%	
Specificity	8.1%	74.2%	
ROC AUC	0.507	0.731	p=0.004
Non-obese and PSA <20			
Sensitivity	96.0%	67.0%	
Specificity	8.9%	51.4%	
ROC AUC	0.623	0.653	p=0.5
Obese and PSA <10			
Sensitivity	91.4%	58.3%	
Specificity	10.4%	81.8%	
ROC AUC	0.452	0.692	p=0.008
Non-obese and PSA < 10			
Sensitivity	94.0%	60.9%	
Specificity	11.8%	62.6%	
ROC AUC	0.637	0.668	p=0.58

The proportion of patients with a Gleason score ≥7 in PSA density-positive patients and in PSA density-negative patients were 36.0% and 22.8%, respectively (Chi-square test, p=0.076). Obese patients with positive PSA densities were associated with higher Gleason grades. The proportions of patients with a Gleason score ≥7 in the obese and non-obese groups were 48.9% and 32.7%, respectively (Chi-square test, p=0.035).

Moreover, there was a trend suggesting that obese patients had a higher chance of bilateral disease. For PSA <10 ng/mL, the proportions of patients with bilateral disease in the obese and non-obese groups were 48.4% and 29.8%, respectively (Chi-square test, p=0.046). For PSA <20 ng/mL, the proportions of patients with bilateral disease in obese and non-obese groups were 46.8% and 34.1%, respectively (Chi-square test, p=0.099).

DISCUSSION

Our results suggest that PSA density has significantly better performance for the diagnosis of prostate cancer in obese patients. Using PSA density 0.15 as a cutoff, obese patients with PSA <20 ng/mL had a four times (41.1% vs. 9.5%) greater risk of being diagnosing with prostate cancer if their PSA density was positive, whereas the increase in risk was only two fold (18.8% vs. 9.7%) in non-obese patients. This relationship was consistent in patients with PSA <10 ng/mL. This is the first time the performance of PSA density in prostate cancer diagnosis has been found to be related to body size. Therefore PSA density should be included in counseling of obese patients with elevated PSA.

Obese men with prostate cancer suffer from higher rates of biochemical recurrences and mortality [9-10,16]. It has been postulated that the combination of lower PSA and larger prostate sizes (and more difficulties in digital rectal examinations) might lead to delay of diagnosis in obese men, subsequently leading to more advanced disease upon diagnosis and poorer treatment outcomes. To date, there has been no good solution to this situation.

We postulate that as obese men have significantly higher prostate volumes (TRUS volumes in obese and non-obese men were 63.2 ml and 51.6 ml respectively, t-test, p<0.001), but only slightly lower total PSA [8], the PSA density in obese men is likely to be lower than in non-obese men with the same risk of prostate cancer. Therefore, a high PSA density is more useful in predicting the risk of prostate cancer in obese men. The overall ROC curve AUC of PSA density in our study (0.662) was similar to published results by Djavan (0.628) and Catalona (0.680) [13,15].

Consistent with previous studies [9], our results showed that obesity is associated with higher Gleason grades in men diagnosed with prostate cancer. A higher rate of bilateral core involvement was also observed in this study. Therefore, obesity is associated with more advanced disease at diagnosis.

The drawbacks of this study are its retrospective nature and the lack of comparison with other markers such as free-to-total PSA, p2PSA, and PCA3 [17-18]. However, as PSA density does not require additional laboratory testing and the prostate size measurement can be performed during consultations, it would be a simple method for improving PSA performance as a predictor of cancer, particularly in obese patients.

CONCLUSION

PSA density has better specificity and AUC in obese men, and those with positive PSA density (>0.15) have four times the risk of prostate cancer. TRUS prostate volumes and PSA density should be obtained for better counseling of this group of patients.

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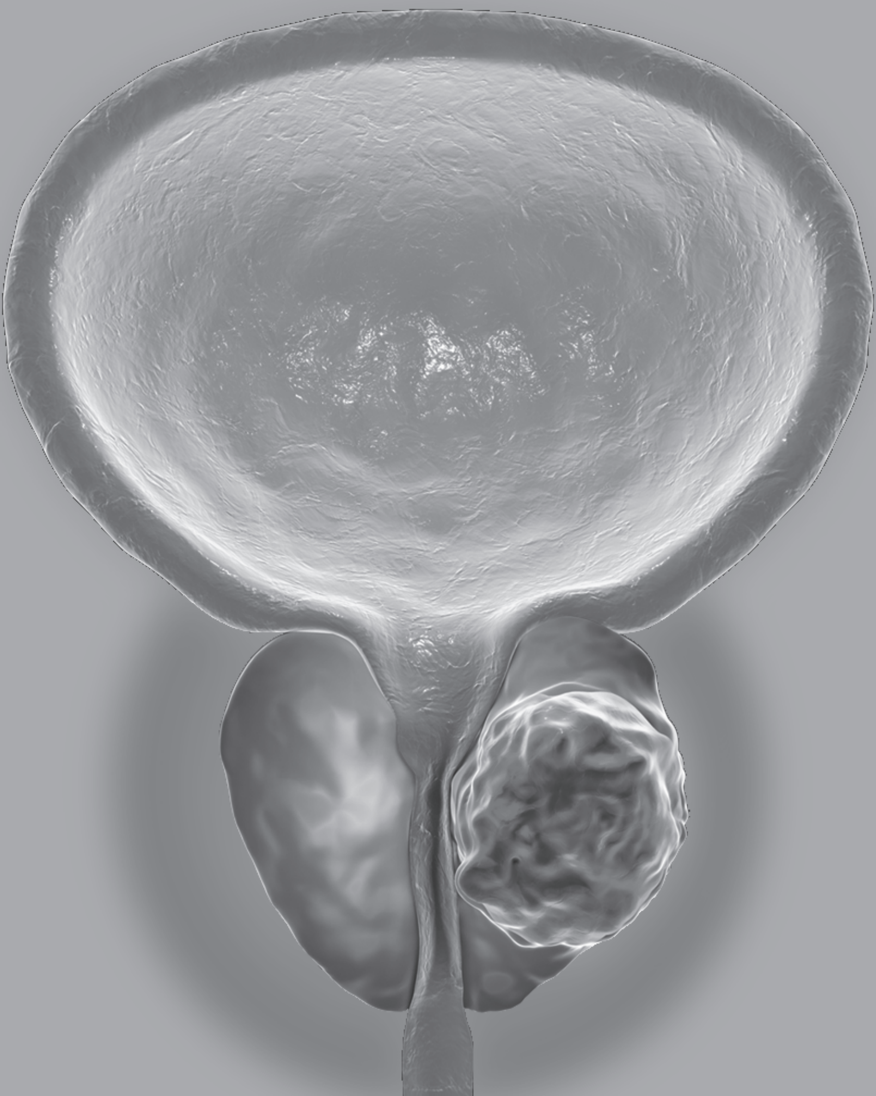

CHAPTER 4

Adaptation and external validation of the European Randomized Study of Screening for Prostate Cancer (ERSPC) risk calculator for the Chinese population

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ABSTRACT

Background

To adapt the well performing ERSPC risk calculator to the Chinese setting and perform an external validation.

Methods

The original ERSPC risk calculator 3(RC3) for Prostate cancer(PCa) and high grade PCa(HGPCa) was applied to a development cohort of 3006 previously unscreened Hong Kong Chinese men with initial transrectal biopsies performed from 1997-2015, Age 50-80, PSA 0.4-50ng/mL, and Prostate volume 10-150ml. A simple adaptation to RC3 was performed and externally validated in a cohort of 2214 Chinese men from another Hong Kong hospital. The performance of the models were presented in calibration plots, area-under-curve(AUC) of Receiver operating characteristics(ROC), and decision curve analyses.

Results

PCa and HGPCa was diagnosed in 16.7%(503/3006) and 7.8%(234/3006) men in the development cohort, and 20.2%(447/2204) and 9.7%(214/2204) men in the validation cohort, respectively. The AUCs using the original RC3 model in the development cohort were 0.75 and 0.84 for PCa and HGPCa respectively, but the calibration plots showed considerable over-estimation. In the external validation of the recalibrated RC3 model, excellent calibration was observed, and discrimination was good with AUCs of 0.76 and 0.85 for PCa and HGPCa, respectively. Decision curve analyses in the validation cohort showed net clinical benefit of the recalibrated RC3 model over PSA.

Conclusions

A recalibrated ERSPC risk calculator for the Chinese population was developed, and it showed excellent discrimination, calibration, and net clinical benefit in an external validation cohort.

INTRODUCTION

Prostate-specific antigen (PSA) has been widely used as a screening tool for prostate cancer diagnosis. The European Randomized Study of Screening for Prostate Cancer (ERSPC) has shown a 21% reduction in prostate cancer mortality at 13 year follow-up, but it was also associated with unnecessary biopsies, overdiagnosis and overtreatment of potentially indolent cancers. [1] Therefore, using PSA as the only tool to stratify risk of patients is not appropriate.

Risk calculators have been created in different populations to better predict prostate cancer with the aim of reducing unnecessary biopsies. Commonly used risk calculators included the ERSPC risk calculator [2-3], the Prostate Cancer Prevention Trial (PCPT) risk calculator [4], and the Sunnybrook risk calculator [5]. Most risk calculators incorporated prostate volume as it greatly improved the predictive performances. [6]

Validation studies for the different risk calculators have mainly been done in Caucasians, and within this particular setting already showed variable performance of the different risk calculators, mainly related to calibration. [7-13]

A well validated risk calculator for prostate cancer in Chinese is lacking. In this study, we aim to apply the original ERSPC risk calculator 3 (RC3) [2] for initial biopsies which overall shows excellent discrimination in different settings, in a cohort of Chinese men. After recalibration to the Chinese setting, an external validation of the newly adapted ERSPC RC was performed.

MATERIALS AND METHODS

From August 1997 to December 2015, 5165 Chinese patients in a prospectively maintained database with transrectal ultrasound (TRUS) guided prostate biopsy performed in a tertiary referral centre (Hospital 1) in Hong Kong were included (Development cohort). Out of 5165 patients, 3006 consecutive patients having initial biopsies with Age 50-80 years, PSA 0.4-50ng/mL(WHO calibration), and TRUS prostate volume (TRUS-PV) 10-150ml were included for validation of the original ERSPC risk calculator 3(RC3) (www.prostate-riskcalculator.com). [2] The variables in the original RC3 included TRUS-PV, TRUS finding (normal or abnormal), DRE (normal or abnormal), and PSA. PSA was taken in a clinical setting in both hospitals, in men with different degrees of urinary tract symptoms.

TRUS-PV was calculated by the ellipsoid formula. All biopsies were evaluated by genitourinary pathologists blinded to blood results. The primary outcomes were prostate cancer (PCa) and high grade prostate cancer (PCa), the latter being defined as Gleason 7 or above PCa. This study conformed to the provisions of the Declaration of Helsinki, and was approved by the ethics committee of both hospitals.

We applied the ERSPC RC3 to the development cohort (Hospital 1) and recalibrated the model for the Chinese population. This recalibrated formula was externally validated in a validation cohort of 2214 Hong Kong Chinese men from another tertiary referral centre (Hospital 2). The TRUS biopsies in this clinical cohort were performed from September 1999 to December 2013, and 2214 consecutive men with the same inclusion criteria as the development cohort were included.

The baseline characteristics of the cancer and non-cancer patients were compared using Mann-Whitney U test for continuous data and the chi-square test for categorical data. The discriminative ability of the RC3 was analyzed using receiver operating characteristics (ROC) and area under the curves (AUC). Calibration plots were created with observed and predicted risk of prostate cancer. Decision curve analyses (DCA) [14] were performed to show any net benefit of the recalibrated model over PSA in the validation cohort. Statistical analyses were performed in IBM SPSS Statistics for Windows version 22(IBM Corp., Armonk, NY, USA). Calibration plots and DCA curves were created with R version 3.1.1 (The R Foundation for statistical computing, Vienna, Austria). A 2-sided p-value of <0.05 was considered significant.

RESULTS

Baseline characteristics of the development and validation cohorts were listed in Table 1. All 5220 men from the development and validation cohorts had TRUS biopsy performed. In the development cohort (Hospital 1), 16.7%(503/3006) and 7.8%(234/3006) men were diagnosed with PCa and HGPCa, respectively. In the validation cohort (Hospital 2), 20.2%(447/2214) and 9.7%(214/2214) men were diagnosed with PCa and HGPCa, respectively. Table 2 listed the baseline characteristics of cancer and non-cancer patients. Patients with prostate cancer had significantly higher age and PSA values, higher proportion of abnormal DRE, and smaller prostates.

The ERSPC RC3 for PCa and HGPCa was applied to the development cohort (n=3006), and the calibration plots are shown in Figure 1A and 1B. The AUCs were 0.75 (95% CI: 0.73-0.78) and 0.84 (95% CI: 0.81-0.87) for PCa and HGPCa respectively, but the calibration was poor with over-estimation of 10-40% for PCa and 10-30% for HGPCa across the whole range of predicted probabilities.

Adaptations of the formulas (by setting-specific adjustments to the intercept constant) were performed separately for PCa and HGPCa, and the recalibrated models were applied to the validation cohort (n=2214). The external validation showed excellent calibration (Figure 1C-1D) across the whole range of predicted probability with calibration slopes of 0.91 and 0.92, and intercepts of 0.17 and 0.03, for PCa and HGPCa respectively. The AUCs of the recalibrated model for PCa and HGPCa were 0.76 (95% CI 0.73-0.79) and 0.85

Table 1. Baseline characteristics of the development and validation cohorts

Median IQR[1]	All n=5220	Development cohort Hospital 1 n=3006	Validation cohort Hospital 2 n=2214
Age (years)	68 62 - 73	67 62 - 72	68 62 - 73
PSA (ng/mL)	7.3 5.2 – 11.2	7.3 5.3 – 11.5	7.2 5.2 – 11.0
TRUS-PV[2] (ml)	43.0 31.0 – 59.7	46.4 33.0 – 63.2	39.5 29.5 – 54.9
Abnormal TRUS findings		254 (8.4%)	N/A[3]
Abnormal DRE	825 (15.8%)	437 (14.5%)	388 (17.5%)
TRUS biopsy cores			
6-8 cores	1193 (22.9%)	1071 (35.6%)	122 (5.5%)
9-10 cores	3513 (67.3%)	1908 (63.5%)	1605 (72.5%)
>10 cores	495 (9.5%)	14 (0.5%)	481 (21.7%)
Missing	19 (0.4%)	13 (0.4%)	6 (0.3%)
Any grade prostate cancer	950 (18.2%)	503 (16.7%)	447 (20.2%)
High grade prostate cancer	448 (8.6%)	234 (7.8%)	214 (9.7%)

[1]IQR = Inter-quartile range, [2]TRUS-PV = Transrectal ultrasound prostate volume, [3]N/A = not available

Table 2. Baseline characteristics of the cancer and non-cancer patients from pooled data of both hospitals.

Median IQR[1]	All n=5220	Cancer patients n=950	Non-cancer patients n=4270	p-values[3]
Age (years)	68 62 - 73	71 66 - 75	67 62 - 72	<0.001
PSA (ng/mL)	7.3 5.2 – 11.2	10.0 6.2 – 18.9	7.0 5.1 – 10.1	<0.001
TRUS-PV[2] (ml)	43.0 31.0 – 59.7	34.3 25.1 – 46.6	45.5 32.9 – 61.7	<0.001
Abnormal TRUS[4]		83/503 (16.5%)	171/2503 (6.8%)	<0.001
Abnormal DRE	825 (15.8%)	319 (33.6%)	506 (11.9%)	<0.001
Gleason sum				
<6		24 (2.5%)		
6		468 (49.3%)		
7		181 (19.1%)		
8-10		267 (28.1%)		
Missing		10 (1.1%)		

[1]IQR = Inter-quartile range, [2]TRUS-PV = Transrectal ultrasound prostate volume. [3]analyses between cancer and non-cancer patients. [4]TRUS abnormality data available in development cohort only (n=3006)

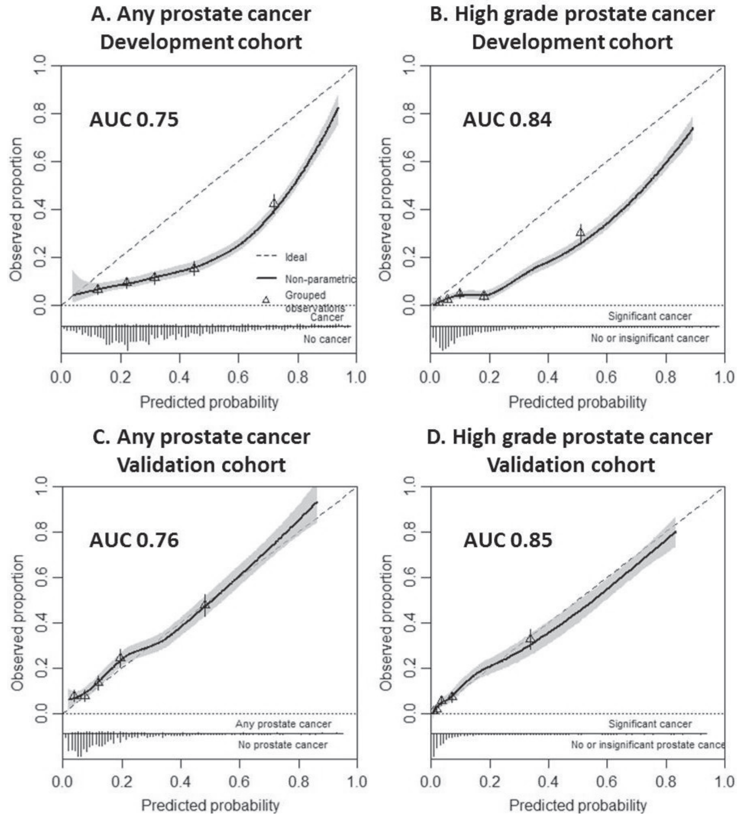

Figure 1. Calibration plots for A. Any prostate cancer in the development cohort using the original ERSPC RC3 formula, B. High grade prostate cancer in the development cohort using the original ERSPC RC3 formula, C. Any prostate cancer in the validation cohort using the Recalibrated ERSPC RC3 formula, D. High grade prostate cancer in the validation cohort using the Recalibrated ERSPC RC3 formula

(95% CI 0.82-0.87) respectively. The AUCs of PSA only for PCa and HGPCa in the same cohort were 0.68 (95% CI 0.68-0.71) and 0.76 (95%CI 0.72-0.80) respectively.

The performance of the adapted formula was found to be similar in different time periods (1999-2004, 2005-2009, and 2010-2013) and in different number of biopsy cores (≤8, 9-11, and ≥12 biopsy cores) in the validation cohort.

Decision curves were plotted in both development and validation cohorts for assessment of clinical utility. (Figure 2) The black line and grey line represent the strategies of performing biopsies in all and none of the patients, respectively. For the portion of the coloured curves with net benefit above both black and grey lines, the area between them represents its clinical applicability. Figure 2A compares the original and the recalibrated ERSPC RC3

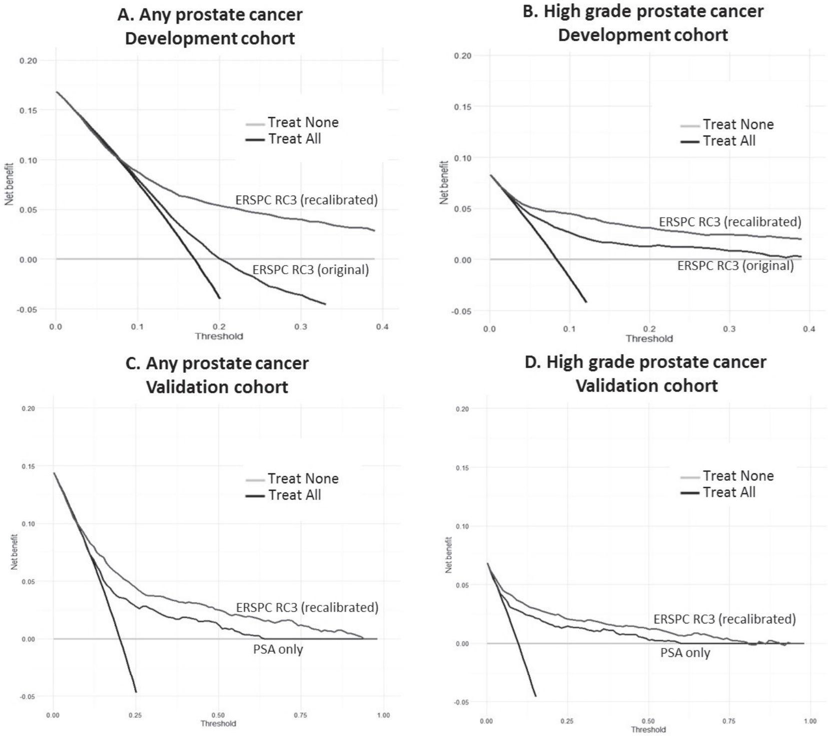

Figure 2. Decision curve analyses for A. Any prostate cancer in the development cohort comparing original and recalibrated ERSPC RC3 formula, B. High grade prostate cancer in the development cohort comparing original and recalibrated ERSPC RC3 formula, C. Any prostate cancer in the validation cohort comparing PSA and recalibrated ERSPC RC3 formula, D. High grade prostate cancer in the validation cohort comparing PSA and recalibrated ERSPC RC3 formula.

in PCa prediction in the development cohort, and the recalibrated RC3 curve demonstrates higher net clinical benefit than the original RC3 curve. The same phenomenon is observed in HGPCa (Figure 2B). In the validation cohort, the recalibrated RC3 demonstrates net clinical benefit over PSA only for both PCa (Figure 2C) and HGPCa (Figure 2D) across the whole range of risk thresholds.

The number of biopsies that can be avoided and the number of cancers missed at different predicted probability from the new model in the validation cohort are listed in Table 3. At 5% and 10% risk threshold for PCa, 12.0% and 41.8% of all biopsies could have been saved respectively. At 5% and 10% risk threshold for HGPCa, 57.9% and 76.9% of all biopsies could have been saved respectively.

The nomograms for any grade PCa and HGPCa were shown in Figure 3A and Figure 3B, respectively.

Table 3. Number of biopsies that can be reduced compared to all-biopsy strategy using the recalibrated ERSPC RC3 in the validation cohort (n=2214).

Risk threshold	**No. men biopsied***	**No. biopsies saved (% of total*)**	**No. PCa detected#**	**No. PCa missed (% of total #)**	**No. HG PCa missed (% of total #)**
PCa	2214	0	447	0	0
5%	1948	266 (12.0%)	432	15 (3.4%)	3 (0.7%)
10%	1288	926 (41.8%)	375	72 (16.1%)	12 (2.7%)
15%	905	1309 (59.1%)	320	127 (28.4%)	35 (7.8%)
20%	656	1558 (70.4%)	269	178 (39.8%)	52 (11.6%)
Risk threshold	No. men biopsied**	No. biopsies saved (% of total**)	No. HGPCa detected##	No. of HGPCa missed (% of total##)	
HGPCa	2214	0	214	0	
2.5%	1412	802 (36.2%)	198	16 (7.5%)	
5%	933	1281 (57.9%)	173	41 (19.2%)	
10%	511	1703 (76.9%)	144	70 (32.7%)	
15%	354	1860 (84.0%)	127	87 (40.7%)	
20%	269	1945 (87.9%)	116	98 (45.8%)	

DISCUSSION

In this study, it has been shown that the original ERSPC risk calculator 3 (RC3) for initial biopsies showed good discrimination but overestimated the positive biopsy rates of PCa and HGPCa in a total of 3006 Hong Kong Chinese men. After a simple recalibration of the ERSPC RC3 for Chinese patients, the external validation in another Hong Kong Chinese cohort of 2214 men demonstrated excellent discrimination and calibration. The decision curves show net clinical benefit over the whole range of thresholds in both PCa and HGPCa. Significant proportions of prostate biopsies could have been saved at different risk thresholds using the risk calculator.

The ERSPC RC was shown to perform well in another Dutch clinical cohort, despite that it was, contrary to the development cohort, a contemporary clinical setting, showing excellent calibration in addition to an AUC of 0.77. [7] When the ERSPC RC was applied to Finnish and Swedish men, again good AUCs of 0.76 and 0.78 respectively were shown, however calibration showed a 10-15% overestimation of the probability of being diagnosed with prostate cancer. [8] In a clinical cohort of Swiss men, comparing the performance of the ERSPC RCs and the PCPT RC 2.0, the ERSPC RC showed poor calibration and both had fair AUCs of 0.65 and 0.66 for any PCa and AUCs of 0.73 and 0.70 for significant

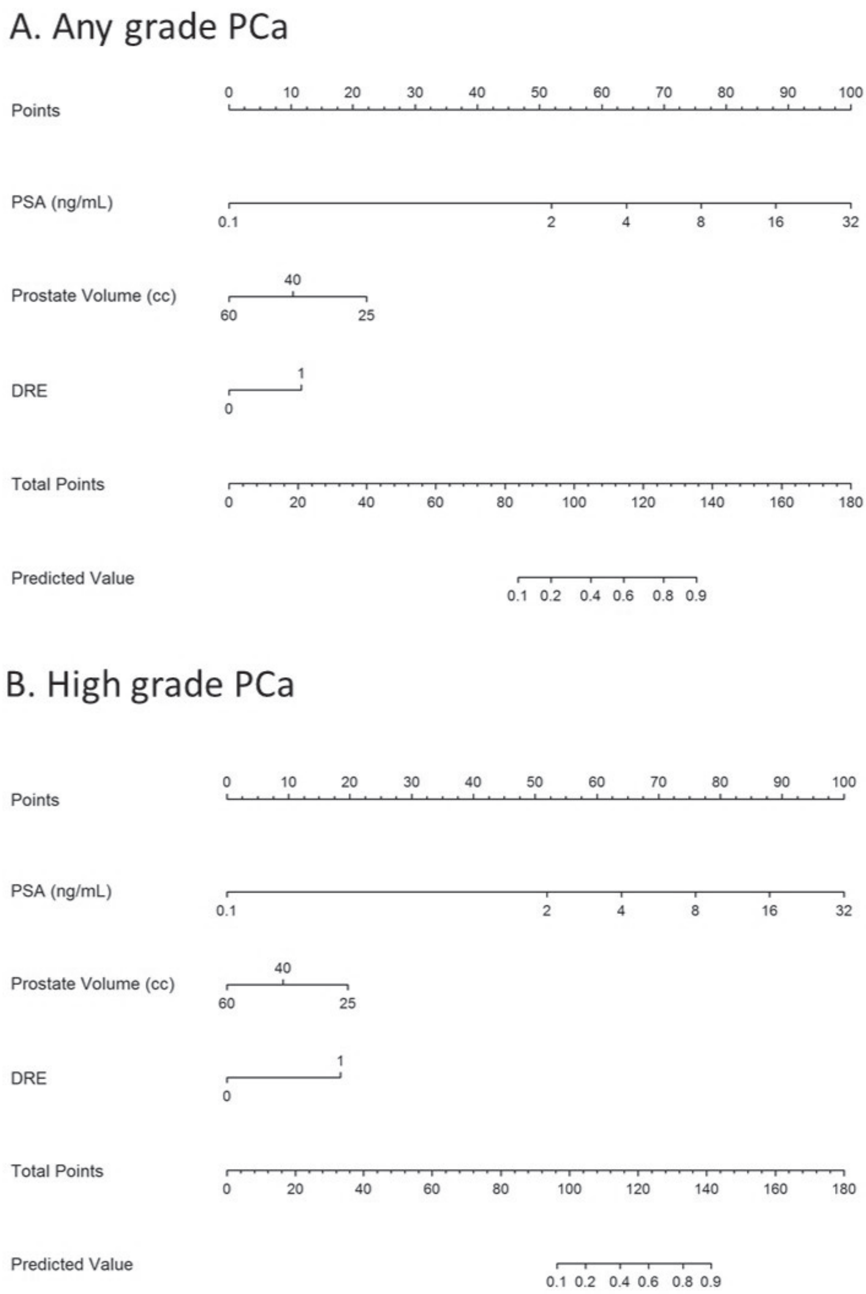

Figure 3. Nomograms for A. Prediction of Any grade prostate cancer, and B. Prediction of High grade prostate cancer.

PCa respectively. Decision curve analyses revealed a comparable net benefit for any prostate cancer and a slightly greater net benefit for significant prostate cancer using the ERSPC-RC. [11] In an Irish population with a wide range of PSA and 58% positive biopsy rate, the ERSPC RCs was shown to perform better than PCPT RC 2.0 (AUC 0.71 Vs 0.64), but both RCs under-estimated the rates of PCa and HGPCa. [12] A study in Canadian men also showed the superior performance of ERSPC RCs over PCPT RCs (AUC 0.71 Vs 0.63).[10] The PCPT-RC was better calibrated in the higher prediction range (40-100%), whereas the ERSPC-RC had better calibration and avoided more biopsies in the lower risk range (0-30%). [10] A study of PCPT RC on 10 different European and North American cohorts showed that the AUC of predicting HGPCa varied from 0.64 to 0.88. [13]

In summary, the performance of both RC's is variable in different Caucasian population due to differences in setting and prevalence. Over-estimation or under-estimation of PCa risks and poor calibrations were observed. This implies that external validation is crucial even within a comparable setting.

As a result of PCa epidemiological differences in different regions of the world, a specific risk calculator is needed to allow accurate PCa risk prediction. This can be done with creating yet another model or by recalibration of an existing RC with proven good discriminatory capability, based on high quality data of sufficient sample size, followed by a proper external validation. Regular adjustments to existing models might also be required in the face of changing epidemiology. [15]

To our knowledge a validated well performing risk calculator or nomogram suitable for the Chinese population is currently not available. In the current study, the ERSPC RC3 was recalibrated in a clinical Chinese cohort and that was externally validated in another Chinese population. Excellent calibration was observed in the external validation cohort. This new model, although originally based on European data can be of value in the Chinese setting and will be incorporated in a mobile phone app (Rotterdam prostate cancer risk calculator) and website (www.prostatecancer-riskcalculator.com) in English and Chinese language specifically for prediction of PCa and HGPCa risks in Chinese men.

In recent years, prostate health index (PHI) has been shown to perform better than PSA in predicting PCa and HGPCa in both Caucasians and Asians. [16-17] Nomograms incorporating PHI have been shown to further improve the performance of PHI in external validation studies, [18] but the additional value of PHI to existing ERSPC RCs was small. [19] Addition of PCA3 and a 4-K panel to the original ERSPC risk calculator in prescreened men improved the AUC of the model by 3% and 1% respectively. [20] Widespread use of the novel blood and urine markers in Asia or China has been hampered by cost and availability. Multi-parametric MRI has been shown to be promising in selecting significant cancers and enabling targeted biopsies, but there are still considerable false positives and false negatives, especially in Prostate multi-parametric magnetic resonance imaging (PI-RADS) 3 lesions. [21-22] It is more and more common for Chinese patients to have an MRI prostate done with elevated PSA, but most are performed without a standardized multi-parametric MRI scanning protocol and reporting system. The lack of qualified interpreters of the MRI images and the lack of targeted biopsy facilities currently limit the role of MRI in this region. Therefore, most biopsy decisions in Asia or China are still based on PSA alone.

Having a lower prostate cancer incidence in China and lower positive biopsy rates, a simple, easily accessible, inexpensive, and validated RC should be used to avoid significant number of unnecessary biopsies based on PSA only. The validated risk calculator in this study provides Chinese men with such a tool, with simple and commonly available clinical parameters, and without the extra costs and expertise required in novel biomarkers and/or imaging.

The main strength of this study is that this is the first large scale adaptation and external validation of a PCa risk calculator tailored for the clinical Chinese population. The discrimination and calibration was excellent in the validation cohort and supports using this RC in Chinese patients.

There are certain limitations to this study. Firstly, all patients in the development and external validation cohort were Chinese men, and whether this risk calculator could be applicable to other Asian men needs further validation. Secondly, this new ERSPC risk calculator is currently only applicable to patients with initial biopsies.

CONCLUSIONS

A recalibrated ERSPC risk calculator for the Hong Kong Chinese population was developed and demonstrated excellent predictive abilities in an external validation cohort of Chinese men. In future, the risk calculator tailored for Chinese men should be used for risk stratification before prostate biopsy and should replace purely PSA based decision

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CHAPTER 5

Additional benefit of using a risk based selection for prostate biopsy: an analysis of biopsy complications in the Rotterdam section of the European Randomized Study of Screening for Prostate Cancer (ERSPC)

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BJU Int. 2017 Sep;120(3):394-400.

ABSTRACT

Objective

To investigate biopsy complications and hospital admissions that could be reduced by the use of ERSPC risk calculators(RC).

Materials and Methods

All biopsies in the Rotterdam section of the ERSPC from 1993 to 2015 were included. Biopsy complications and hospital admission data were prospectively recorded in questionnaires that were completed 2 weeks after biopsy. The ERSPC RC3 and RC4 were applied to men attending the first and subsequent rounds of screening, respectively. Applying the predefined RC3/4 probability cut-offs for prostate cancer(PCa) risk of ≥12.5% and high grade PCa(HGPCa) risk ≥3%, we assessed the the number of complications, admissions and costs that could be reduced by avoiding biopsies in men below these cut-offs.

Results

10747 biopsies with complete questionnaires were included. A total of 7294(67.9%) complications, 3.9%(416/10747) post-biopsy fever, and 0.9%(92/10747) hospital admissions were recorded. Fever rate has been static over the years, but hospital admissions had tripled from 0.6%(1993-1996) to 2.1%(2009-2015). Among 7704 biopsies which fit the criteria of RC3 or 4, 35.8%(2757/7704) biopsies, 37.4%(1972/5268) complications, 38.4%(123/320) fever, and 42.3%(30/71) admissions could have been avoided by using one of the RCs. More complications could have been avoided in the case of RC4 or more recent biopsies(2009-2015). 35.9% of the total cost of biopsies and complication treatment could be saved.

Conclusion

A significant proportion of biopsy complications, hospital admissions, and costs could be reduced if biopsy decisions were based on ERSPC risk calculators instead of PSA only, and this effect was most prominent in more recent biopsies and in men with repeated biopsies or screening.

1. INTRODUCTION

The European Randomized study of Screening for Prostate Cancer (ERSPC) showed a reduction of prostate cancer mortality with PSA screening, but it was associated with substantial unnecessary biopsies, over-diagnosis and over-treatment. [1] Sepsis and other complications are common after prostate biopsies and they have been on the rise in recent years [2-3]. These complications are associated with increased morbidities, hospital admissions, and costs. [4] Hence, complications and especially those in unnecessary biopsies increase the morbidities and costs of screening.

Risk factors for post-biopsy infections are variable in different studies. The biopsy sepsis rates in the Rotterdam section of the ERSPC have been reported, and diabetes mellitus and prostate enlargement were significant risk factors for fever after biopsy [5]. A large Swedish cohort, on the other hand, showed that prior urinary tract infection, a higher Charlson comorbidity index, and diabetes mellitus were risk factors for post-biopsy infections. [6]

Risk factors form the basis for targeted infection prophylaxis in certain patient groups, but augmented or more potent antibiotics might eventually result in future antimicrobial resistance. [3] In addition, post-biopsy bleeding and/or pain are not being avoided with this approach.

The best way of reducing biopsy complications is to reduce the number of unnecessary biopsies. Externally validated risk calculators (RC) like the ERSPC RC and the Prostate Cancer Prevention Trial (PCPT) RC [7-9] have been developed to more accurately assess the risk of prostate cancer and as such reduce the number of unnecessary biopsies. The use of RC3/4 at initial or second screening was shown to reduce unnecessary biopsies by 33 to 37% while detecting all life threatening PCa cases [7].

In the current study we do not focus on prostate cancers detected in relation to biopsies saved but we assess the potential of pre-biopsy risk stratification using the ERSPC RCs in avoiding various biopsy complications and hospital admissions. In addition, we estimate the effect on associated costs.

2. MATERIAL AND METHODS

2.1 Study population and antibiotic prophylaxis

All prostate biopsies from 1993 to 2015 in the Rotterdam section of the ERSPC were included in this study. [10]. The standard antibiotic prophylaxis was given 2 hours before and 4 hours after a prostate biopsy. Oral Trimethoprim-sulfamethoxazole was used until 2008, and oral Ciprofloxacin thereafter. For patients considered at higher risk of infection, i.e. patients with diabetes on insulin, steroid, or prosthesis, a 5-day course of ciprofloxacin was given. For patients with history of endocarditis or artificial cardiac valves, intravenous Amoxicillin was given 1 hour prior to prostate biopsy on top of the standard regime.

2.2 Prospective assessment of complications

A questionnaire on complications was completed by the attending doctor when each man returned for the standard 2-week post-biopsy follow-up for pathology results. Complications after prostate biopsy in the questionnaire included fever, hematuria, hematospermia, pain (persistent after biopsy), and any hospital admission within the first 2 weeks. These complication data, together with baseline clinical information, were prospectively recorded into the study database. In the first part of this study we analyzed the complication and admission rates, and in addition assessed potential predictors of complications in 10747 biopsies with complication information available.

2.3 Applying the ERSPC risk calculators

In the second part of this study, the proportion of biopsies, complications, and admissions that could be avoided by applying the ERSPC risk calculators (RC) for men with a PSA value ≥3.0 ng/ml at initial and repeat biopsy was assessed. [7] RC3 was applied to men in the first round of screening. RC4 was applied to men in all subsequent rounds of screening (Rounds 2 to 5) independent of previous biopsy status. (www.prostatecancer-riskcalculator.com). [7-8] For both RC3 and RC4, a cutoff of 12.5% for prostate cancer (PCa) *and* 3% for high grade PCa (HGPCa) was used according to previously published data. [7] HGPCa was defined as PCa with clinical T-stage >T2b and/or Gleason score ≥7. [8] Complications, admissions, and costs that could have been reduced by avoiding biopsies in men with RC3/4 PCa risks less than 12.5% *and* HGPCa less than 3% were assessed. Data on healthcare costs that could have been saved by avoiding biopsies and hospital admissions were obtained from reimbursement data from the hospital finance department.

2.4 Statistical analyses

The baseline characteristics of men with or without post-biopsy fever and hospital admissions were compared, using chi-square tests for categorical variables, and T-tests (for normally distributed data) and Mann Whitney U tests (for non-normally distributed data) for continuous variables. Multivariate analyses for prediction of fever and hospital admissions were performed with variables including age (continuous), diabetes mellitus, heart disease, prior negative biopsy (PNB), fever in previous biopsy, and prostate volume (continuous). Statistical analyses were performed in IBM SPSS Statistics for Windows version 21(IBM Corp., Armonk, NY, USA). A 2-sided p-value of <0.05 was considered significant. This study conformed to the provisions of the Declaration of Helsinki, and was approved by the ethics committee of the institution (Clinical trial number ISRCTN49127736).

3. RESULTS

3.1 Patient characteristics and Biopsy complications

A total of 10970 biopsies from 7422 men were performed in the Rotterdam section of the ERSPC from 1993 to 2015. Evaluation of 10747 questionnaires with complete complication and hospital admission data showed that a least one complication (any complication) occurred in 67.9% (7294/10747) of biopsies. Post-biopsy fever occurred in 3.9% (416/10747) of biopsies, and hospital admission was required in 0.9% (92/10747) of biopsies. A comparison of baseline characteristics between men with and without fever, and men with and without admission, is listed in Table 1.

Table 1. Baseline characteristics of the ERSPC Rotterdam section who received a prostate biopsy.

	Total (n=10747)	Fever Vs No fever	Admission Vs No Admission
Age, yr, median (IQR)[a]	68.0 (64.0-71.5)	67.2 Vs 67.4, p=0.559[b]	68.1 Vs 67.4, p=0.136[b]
Prostate volume, ml, median (IQR)	45.0 (34.0-59.4)	52.6 Vs 49.5, p=0.005[b]	58.2 Vs 49.5, p<0.001[b]
Fever in previous biopsy, n(%)	100 (0.9%)	8.0% Vs 3.8%, p=0.032[c]	5.0% Vs 0.8%, p<0.001[c]
Diabetes, n(%)	692 (6.4%)	5.3% Vs 3.8%, p=0.036[c]	1.6% Vs 0.8%, p=0.032[c]
Heart disease, n(%)	1883 (17.5%)	3.9% Vs 3.9%, p=0.969[c]	1.0% Vs 0.8%, p=0.441[c]
Any complications, n(%)	7294 (67.9%)		
Fever, n(%)	416 (3.9%)		
Hematuria, n(%)	2733 (25.4%)		
Haematospermia, n(%)	5369 (50.0%)		
Pain, n(%)	490 (4.6%)		
Hospital admission, n(%)	92 (0.9%)		

[a]IQR = Inter-quartile range, [b]indepedent sample T-test, [c]Chi-square test.

3.2 Trends of post-biopsy fever and admissions over time

In figure 1, it is shown that from 1993 to 2015, the incidence of fever after biopsy has been quite stable in the range of 3.7-4.4%, but the hospital admission rates gradually increased from 0.6% (1993-1996) to 2.1% (2009-2015) (linear-by-linear association test, p<0.001), and admissions due to fever gradually increased from 0.5% (1993-1996) to 1.6% (2009-2015) (linear-by-linear association test, p<0.001) over the past 20 years.

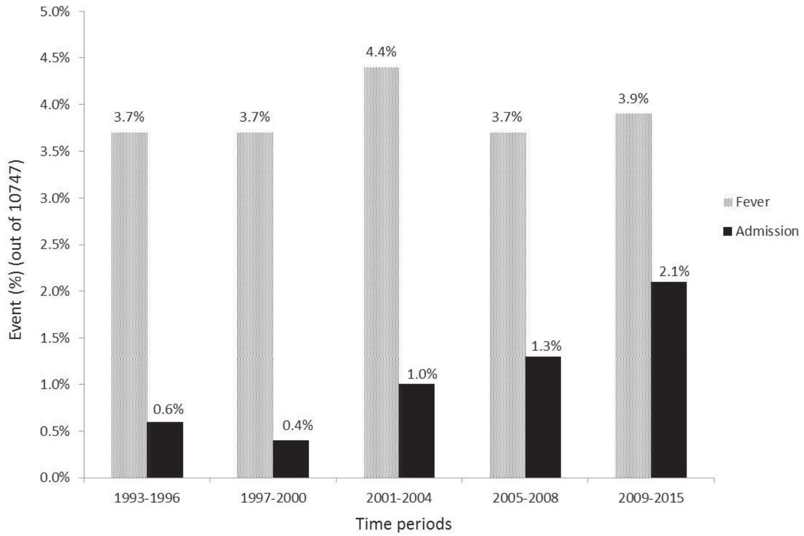

Figure 1. The change in post-biopsy fever and hospital admissions over time

3.3 Risk factors for post-biopsy fever and admissions

Multivariate analyses of potential predictors showed that diabetes mellitus and larger prostates (volume) were the only 2 significant predictors for post-biopsy fever, while larger prostates (volume), fever in previous biopsy, and more recent biopsies (biopsy year) were the 3 predictors for hospital admissions. (Table 2)

3.4 Applying the ERSPC risk calculators

Among the 10747 biopsies with completed questionnaire, we excluded 2218 biopsies in men with PSA <3ng/mL (biopsy done in side studies for various indications), 346 early repeat biopsies within 6-8 weeks for high grade prostatic intraepithelial neoplasia or atypical small acinar proliferation, 41 biopsies which lacked RC data, and 438 biopsies which were

Table 2. Multivariate analyses of post-biopsy fever and hospital admissions. (n=10747)

	Fever*	Admission (all cause)*
Age at biopsy (continuous)	0.98 (0.96-1.01); p=0.163	0.97 (0.92-1.02); p=0.221
Biopsy year (continuous)	1.01 (0.99-1.03); p=0.390	1.11 (1.06-1.16); p<0.001
Prostate volume (continuous)	1.01 (1.00-1.01); p=0.006	1.01 (1.00-1.02); p=0.003
Diabetes	1.42 (1.00-2.02); p=0.048	1.61 (0.85-3.06); p=0.147
Heart disease	1.02 (0.79-1.33); p=0.865	1.20 (0.72-2.02); p=0.481
Fever in previous biopsy	2.01 (0.97-4.19); p=0.061	4.52 (1.77-11.58); p=0.002

*Data presented in Odds ratios (95% confidence interval); p-values not performed at the year of screening. This resulted in 7704 evaluable biopsies for the RC analysis.

RC3 (first round of screening) and RC4 (all subsequent rounds) cutoffs of 12.5% for PCa and 3% for HGPCa were applied. When biopsies were not performed in men with risks lower than the cutoff, a reduction of 35.8% (2757/7704) biopsies, 37.4% (1972/5268) complications, 38.4% (123/320) fever, and 42.3% (30/71) hospital admissions could be established. (Table 3) The reduction in biopsies, complications and admissions were more prominent when RC4 was applied to men in the 2nd- 5th rounds of screening and/or previous negative biopsy.

Table 3. Biopsies, Complications, and Admissions that could be reduced by avoiding biopsies in applying ERSPC risk calculator 3 (RC3) and risk calculator 4 (RC4). (n=7704)

Events reduced by avoiding biopsy if RC3 or RC4: PCa[a] risk <12.5% AND HGPCa[b] risk <3%	Whole cohort (RC3 or RC4) n=7704	RC3 for first round of screening and without previous biopsies n=3083	RC4 for 2nd – 5th rounds of screening and/or previous negative biopsy (RC4) n=4621
Biopsy	35.8% (2757/7704)	27.1% (837/3083)	41.5% (1920/4621)
Any complications	37.4% (1972/5268)	28.2% (564/2000)	43.1% (1408/3268)
Fever	38.4% (123/320)	30.9% (38/123)	43.1% (85/197)
Hematuria	43.3% (893/2063)	32.1% (224/698)	49.0% (669/1365)
Haematospermia	35.8% (1363/3810)	27.4% (407/1483)	41.1% (956/2327)
Pain	39.0% (141/362)	33.3% (48/144)	42.7% (93/218)
Hospital admissions	42.3% (30/71)	15.4% (2/13)	48.3% (28/58)

[a]PCa = Prostate cancer, [b]HGPCa = High grade prostate cancer

3.5 Costs

The median number of days of admission was 5 (Interquartile range 4-6) days, and among the admitted patients, 1 patient stayed in the ICU for 2 days. The cost of each systematic prostate biopsy was €1276, the average daily cost of hospital admission for post-biopsy complication was €535, and each general practitioner visit was €175. When all 7704 men were subjected to biopsy, the total cost of biopsies, admissions and general practitioner visits was estimated to be €437.557 per year [(€1276 x 7704 + €535 x 5 x 71 + €175 x 249) divided by 23 years]. If biopsy decisions would have been made according to the ERSPC RC recommendations of 12.5% for PCa and 3% for HGPCa, the total costs of biopsy, admissions and general practitioner visits that could have been avoided was estimated to be €157.150 per year [(€1276 x 2757 + €535 x 5 x 30 + €175 x 93) divided by 23 years], a 35.9% cost reduction.

4. DISCUSSION

The current study showed that by using previously defined and validated ERSPC RC cutoffs in a screening cohort consisting up to 5 screening visits with a 4-year interval that, 35.8% of biopsies, 37.4% of biopsy complications and 42.3% of hospital admissions could be avoided in a screening cohort. An even higher proportion of these complications could be avoided in biopsies of more recent years (2009-2015), in men with multiple screening episodes and repeated biopsies. Therefore, besides avoiding unnecessary biopsies and potential overdiagnosis, using the ERSPC RC has the additional benefit of reducing morbidities due to (severe) biopsy complications. Up to date, this is the first study to describe this additional benefit of applying a risk based strategy in the decision to perform a prostate biopsy.

The original versions of ERSPC RC3 and RC4 including TRUS prostate volume, TRUS lesion and DRE abnormality were used in this study. (www.prostatecancer-riskcalculator.com) [7] When TRUS is not readily available in the Urology clinic, the DRE versions of RC3 and RC4 using DRE-estimated prostate volume (DRE-PV) were shown to be similarly effective in achieving a good prediction for PCa and HGPCa [8,11].

Most fever cases did not require hospital admission and were managed by general practitioners or emergency department doctors. Less than 1% of biopsied men required hospital admission within 2 weeks, and most hospitalizations were due to biopsy-related infections. Although only 0.9% of the whole cohort required hospital admission, these men usually required a period of intravenous antibiotics, resulting in a median hospital stay of 5 days. The post-biopsy fever rates were stable over the years (3.7-4.4%), but admissions increased more than 3 times from 0.6% (1993-1996) to 2.1% (2009-2015) (Figure 1). This might be explained by a significantly increasing proportion of diabetes mellitus (an independent predictor of biopsy fever in multivariate analysis) in men having biopsy over the years: 4.6% in 1993-1996, 5.1% in 1997-2000, 6.3% in 2001-2004, 9.9% in 2005-2008, and 10.3% in 2009-2015. Even though a proportion of diabetic patient already received a longer course of oral antibiotics after biopsy, the infection rate was still increasing. Larger prostate being more pronounced in the more recent rounds of screening (mean of 51.2ml in 1993-1996 and 56.4ml in 2009-2015) was also associated with more biopsy infections. Increasing age (mean of 66.5 years in 1993-1996 and 71.8 years in 2009-2015) was not associated with more infection in multivariate analysis. The increasing admissions in more recent years could be due to more severe infection at presentation and/or lower threshold in admitting older patients with more comorbidities.

Other complications described in this study included hematuria (25%), haematospermia (50%), and persistent pain after biopsy(5%). These were mostly self-limiting and did not require hospital admission. However, hematuria and haematospermia were very common and they added to the suffering of a significant proportion of men with biopsies done, in which more than 1/3 of them might be unnecessary. It has been described in a cohort of active surveillance patients that men were less likely to receive scheduled repeated biopsies when there were previous biopsy complications. [12] Although the current study was not on active surveillance patients, it could be postulated that the complications experienced in prior biopsies might deter men from receiving another biopsy even when the indication was stronger by that time. There was no biopsy-related mortality from 1993 to 2015, which confirmed the rare mortality rate in a previous systematic review. [3]

The multivariate analyses predicting infection and admission were updates from a previously published report in the same cohort from 1993-2011 (n=9241). [13] The multivariate analyses were repeated in 10747 biopsies 1993-2015 in the current study. For post-biopsy infections, diabetes and larger prostates were the only 2 significant risk factors as previously reported. [13] However, for hospital admission prediction, in addition to the previously reported risk factor of later year of biopsy, infection in previous biopsy episodes and larger prostates were also significant risk factors. The differences observed in the risk factors for hospital admissions would likely be related to a significant increase in admission rates (mostly related to severe infection) from 0.8% before 2011 to 2.9% after 2011.

Blood markers like Prostate health index (PHI), urine markers like Prostate Cancer Antigen 3 (PCA3), and multiparametric MRI (mpMRI) of the prostate with or without combination with risk calculators are possible alternatives to reduce unnecessary biopsies and potentially their related complications. [14-17] However, they all incur additional facilities or costs, and in the case of diagnostic mpMRI prostate, there are still significant variations in reporting quality despite the availability of standardized Prostate Imaging - Reporting and Data System (PI-RADS) reporting. [18]

The main strength of this study was the prospective collection and continual recording of complications and admission data within a large randomized screening cohort over 23 years.

There were certain limitations in this study. Some complications like retention of urine or per rectal bleeding were not included in the questionnaire and therefore data was not available. Although complication data and admission episodes were prospectively recorded, the admission details (length of stay and any further morbidity) and hospital costs were retrospectively traced. Furthermore, the average cost instead of specific cost of each patient was quoted.

CONCLUSION

A significant proportion of biopsy complications, hospital admissions, and associated costs could be reduced if biopsy decisions were done on the basis of an individual multivariate risk assessment using the ERSPC risk calculators. This effect was most prominent in men having had multiple biopsy sessions.

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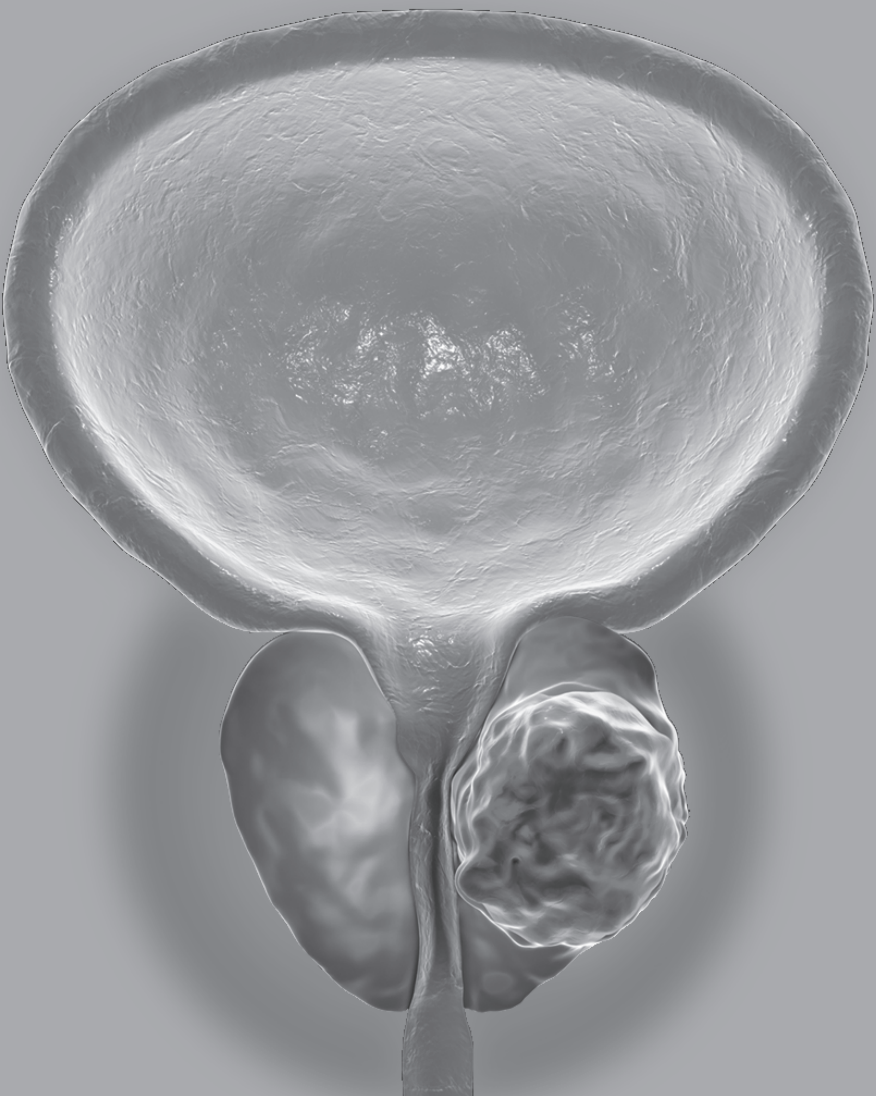

CHAPTER 6

The Prostate Health Index in predicting initial prostate biopsy outcomes in Asian men with prostate-specific antigen levels of 4–10 ng/mL

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ABSTRACT

Purpose

To investigate the role of the Prostate Health Index (*phi*) in prostate cancer (PCa) detection in patients with a prostate-specific antigen (PSA) level of 4–10ng/mL receiving their first prostatic biopsy in an Asian population.

Methods

This was a retrospective study of archived serum samples from patients enlisted in our tissue bank. Patients over 50 years old, with PSA level of 4–10ng/mL, a negative digital rectal examination, and received their first prostatic biopsy between April 2008 and April 2013, were recruited. The serum sample collected before biopsy was retrieved for the measurement of various PSA derivatives and the *phi* value was calculated for each patient. The performance of these parameters in predicting the prostatic biopsy results was assessed.

Results

230 consecutive patients, with 21(9.13%) diagnosed with PCa, were recruited for this study. Statistically significant differences between PCa patients and non-PCa patients were found for total PSA, PSA density, [-2]proPSA(p2PSA), free-to-total PSA ratio (%fPSA), p2PSA-to-free PSA ratio (%p2PSA), and *phi*. The areas under the curve of the receiver operating characteristic curve for total PSA, PSA density, %fPSA, %p2PSA, and *phi* were 0.547, 0.634, 0.654, 0.768, and 0.781, respectively. The *phi* was the best predictor of the prostatic biopsies results. At a sensitivity of 90%, the use of the *phi* could have avoided unnecessary biopsies in 104 (45.2%) patients.

Conclusions

Use of the *phi* could improve the accuracy of PCa detection in patients with an elevated PSA level and thus avoid unnecessary prostatic biopsies.

INTRODUCTION

Prostate cancer (PCa) is the second most common cancer in the world, and its incidence in the Asia-Pacific region is increasing. [1] Fortunately, the use of serum levels of prostate-specific antigen (PSA) as a diagnostic tool has increased the detection rate of PCa at an earlier stage, when management with various therapies can adequately control the disease. [2] Unfortunately, the level of PSA in serum is not an ideal cancer biomarker, because it can be elevated due to many other conditions (such as benign prostatic hyperplasia and prostatitis), and is therefore not cancer-specific. Thus, due to the false-positive results obtained by the PSA test during screening, many patients are subjected to an unnecessary transrectal ultrasound-guided prostatic biopsy (TRUSPB), which is an invasive procedure that can lead to significant morbidity, and even mortality. [3,4]

Many approaches have been explored to improve the performance of PSA in the detection of PCa, such as correlating the PSA level with the prostate volume (PSA density), the rate of change in PSA over time (PSA velocity), and the ratio of different non-complexed forms of PSA in the serum. [5] One of the most recent approaches has been to measure the PSA isoform, [-2]proPSA (p2PSA) and its derivatives, and calculate the Beckman Coulter Prostate Health Index (*phi*). [6-8] In 2012, the US Food and Drug Administration approved the use of the *phi* for the detection of PCa in men over 50 years of age with a serum PSA level of 2–10 ng/mL and negative digital rectal examination (DRE) findings. The initial clinical validation of this new marker to improve the detection of PCa compared with PSA was performed mainly on Caucasian populations. [9] To confirm the clinical efficiency of the *phi* in an Asian population, we compared the performance of the *phi* with that of other PSA derivatives in the detection of PCa in patients with a serum level of PSA between 4 and 10 ng/mL, who had been selected for an initial TRUSPB.

METHODS

Study design

This was a retrospective study on archived serum samples from patients enlisted in our prostate tissue bank. Patients with a total serum PSA level of 4–10 ng/mL (measured using a Roche Cobas e601 system with standardization against the WHO 96/670 reference standard) and negative DRE findings who received their first TRUSPB between April 2008 and April 2013 were recruited. As in most of the centres in our area, patients who are suspected of having PCa, because of either an elevated level of serum PSA > 4 ng/mL or an abnormal DRE, are recommended to have a TRUSPB for further assessment. In our centre, immediately before each patient undergoes a TRUSPB, additional informed consent is obtained for blood collection to establish a prostate disease tissue bank, which has been approved by our local institutional ethics committee. All of the studies were conducted according to the Declaration of Helsinki. If the patient agreed to participate in the study, then the blood was collected immediately before the biopsy. These archived sera are the basis of our study.

Men aged 50 years or older with a serum PSA level in the range of 4–10 ng/mL and negative DRE findings were included in the study. A previous history of TRUSPB was an exclusion criterion and all men who were included had been scheduled for an initial biopsy. At least 10 systematic prostatic biopsy cores were taken during the TRUSPB, and all of the clinical data were available for review. The 10 cores of prostatic biopsy were based on the classical sextant biopsy with two additional lateral biopsies on each side. We used this 10-core extended biopsy template for all our patients receiving their first TRUSPB. This template would be adequate for detecting PCa in men for their first biopsy, without excessive increases in complication rate. [10,11] Patients with a known history of PCa or a history of past prostatic surgery for any prostatic condition would be excluded. And patients with history of urinary tract infection, acute urinary retention, bladder stone and prostatic massage within three months before blood taking would be excluded. Patients had a history of use of a 5-α reductase inhibitor or any other drugs that have anti-androgenic properties (such as androgen receptor blockers, ketoconazole etc) at any time before blood collection were also excluded. Finally, patients whose serum samples had been archived for more than three years were not included.

After identifying the eligible subjects, their clinical data, serum samples collected before biopsy, and biopsy results were retrieved for the study.

Specimens and laboratory analysis

Blood samples collected from consenting patients were immediately stored at 0°C and then processed (centrifuged and refrigerated) within 3 h of blood collection. The sera were then frozen at –70°C or below for future research.

The measurement of serum PSA and its derivatives was performed with an Access2 automated immunoassay analyzer system (Beckman Coulter, Brea, CA, USA). The research staffs who operated the system were blinded to the clinical information of the patients. The assay used was a paramagnetic particle, chemiluminescent immunoassay for the quantitative determination of p2PSA. The levels of total PSA (tPSA), free PSA (fPSA), and p2PSA were determined by calibration to the Hybritech standard. All assays were performed using the same batch of calibrators, and all results were obtained by a single determination.

The free-to-total PSA ratio (%fPSA) and p2PSA-to-free PSA ratio (%p2PSA) were calculated. The Beckman Coulter Prostate Health Index (*phi*) was determined by the formula *phi* = (p2PSA/fPSA) × (square root of tPSA). The levels of these parameters were then compared between patients diagnosed with PCa (PCa patients) and those with no evidence of PCa (non-PCa patients). The receiver operating characteristic (ROC) curves of these parameters were also constructed and compared.

STATISTICAL METHODS

The PSA density was calculated by dividing the serum level of tPSA (measured by the Hybritech-calibrated Assess2 system) by the prostate volume (determined by transrectal ultrasound during the biopsy). The differences in mean age, prostate volume, and levels of various PSA derivatives between the PCa and non-PCa patients were assessed using the Student t-test for normal data and the Mann-Whitney U test for skewed data. All of the descriptive statistics and comparisons were performed using the SPSS v.20.0 software package (SPSS, Chicago, IL, USA). The areas under the ROC curves (AUC) and the sensitivity and specificity were calculated to assess the diagnostic performance of the various assays in terms of PCa detection. The AUCs of the ROC curves and the multivariable analysis were derived using MedCalc (Version 12.6.1.0-64 bit). A two-sided p value of <0.05 was considered to be significant in all of the analyses.

RESULTS

Between April 2008 and March 2013, 1,766 patients received an initial TRUSPB in our center, and 930 consented to give blood samples. Of these, 230 consecutive patients fulfilled the inclusion criteria and their clinical data and sera were retrieved for the study. Twenty-one patients (9.13%) were diagnosed as having PCa from the results of the initial biopsy. The baseline information of these patients is given in Table 1.

The values of the various PSA parameters are also summarized in Table 1. Patients with PCa had a smaller prostate than the non-PCa patients. Statistically significant differences between the PCa patients and non-PCa patients were noted for PSA density, p2PSA, %p2PSA, and *phi*. However, the tPSA, fPSA, and %fPSA levels of the two groups were not statistically significantly different (Table 1).

The AUCs of the ROC of tPSA, PSA density, %fPSA, %p2PSA, and *phi* were 0.547, 0.634, 0.654, 0.768, and 0.781, respectively (Figure 1). Of the various parameters, the *phi* showed the best performance in predicting the results of the initial prostatic biopsy in our population.

To assess the performance of the various parameters further, we set the sensitivity level at 90%, which eliminated two of the 21 cancer cases. The *phi* had the best specificity of 49.76% (95% confidence interval: 42.8–56.7) (Table 2). If we had applied the *phi* to the cohort during the initial assessment, 104 (45.2%) patients with no evidence of PCa after their initial TRUSPB would have avoided undergoing a biopsy. The two PCa cases that were eliminated from the analysis were both clinically T1c disease, with only one positive core (out of 10 biopsy cores) that was assessed as Gleason 3+3. Both of these were therefore considered to be low-risk cases. [12]

Table 1. Patient characteristics of the study population

Mean (Range)	Overall N=230	Non-cancer patients N=209	Cancer patients N=21	p-value
Age (Years)	65.9 (50-79)	65.7 (50-84)	69.2 (57-76)	0.172
Total PSA (ng/ml) *	6.285 (4 – 9.5)	6.260 (4 – 9.5)	7.424 (4.6 – 9.4)	0.378
Prostate volume (ml)	46.2 (11 – 163)	46.8 (11 – 163)	39.6 (16.3 – 97.4)	0.061
Total PSA **	6.745 (3.18 – 9.98)	6.721 (3.18 – 9.98)	6.985 (4.75 – 9.11)	0.451
PSA density (ng / ml2)	0.175 (0.044 – 0.513)	0.171 (0.044 – 0.513)	0.213 (0.073 – 0.414)	0.043
Free PSA (ng/ml)	1.31 (0.39 – 4.09)	1.32 (0.39 – 4.09)	1.24 (0.50 – 2.36)	0.566
Free to total PSA ratio (%fPSA, %)	19.688 (6.227 – 47.379)	19.839 (6.297 – 47.379)	18.188 (6.227 – 31.307)	0.275
p2PSA level (pg/ml)	14.42 (4.29 – 67.33)	14.02 (4.29 – 67.33)	18.42 (6.27 – 35.82)	0.020
p2PSA to free PSA ratio (%p2PSA, %)	1.141 (0.393 – 2.572)	1.105 (0.393 – 2.528)	1.493 (0.629 – 2.572)	<0.001
phi	29.30 (9.58 – 78.08)	28.20 (9.58 – 78.08)	39.45 (13.89 – 77.63)	<0.001

* Measured by a Roche Cobas e601 system calibrated with the WHO 96/670 reference standard.

** Measured by a Hybritech-calibrated Beckman Coulter Assess2 System.

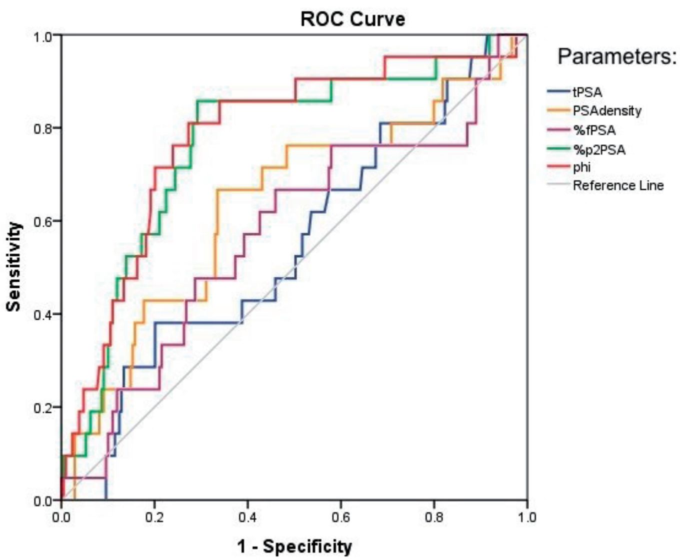

Figure 1. Receiver operating characteristic (ROC) curves of the various prostate-specific antigen (PSA) derivatives

Table 2. Performance characteristics at a pre-set sensitivity of 90% or not missing any Gleason 7-10 cancer.

	Cutoff for needing biopsy	**Specificity at 90% sensitivity (%, 95% CI)**	**Number of patients with no evidence of cancer that could have avoided a biopsy (Total 209)**
Total PSA (ng/ml)	>5.251	17.22 (12.4 – 23.0)	36
PSA density (ng/ml[2])	>0.102	18.18 (13.2 – 24.1)	38
Free to total PSA ratio (%)	<27.978	11.0 (7.1 – 16.1)	23
p2PSA (pg/ml)	>9.269	22.97 (17.4 – 29.3)	48
p2PSA to free PSA ratio (%)	>0.995	42.11 (35.3 – 49.1)	88
phi	>26.54	49.76 (42.8 – 56.7)	104

Multivariate analysis was used to assess the value of %p2PSA and *phi* in the diagnosis of PCa at TRUSPB, as suggested by Guazzoni et al. [7] Age, tPSA, prostate volume and %fPSA were put into the multivariate analysis as base prediction model. The p2PSA level free PSA and PSA density were omitted from the base model to avoid problems of multicollinearity. Both %p2PSA and the *phi* improved the AUC of the base multivariate model from 0.668 to 0.786 and 0.792, respectively. Because not every patient would have had a transrectal ultrasound for prostate volume before TRUSPB, we tested an additional base model using only clinical parameters: patient age, tPSA, and %fPSA. We then tested the effect of adding %p2PSA and the *phi* on the accuracy of diagnosis (Table 4). Both %p2PSA and the *phi* improved the AUC of this second base multivariate model from 0.623 to 0.783 and 0.787, respectively. Comparing the first and second base models after the inclusion of the *phi*, no significant difference in the AUC with or without prostate volume was observed (0.792 versus 0.787). Therefore, the measurement of prostate volume (for the determination of PSA density) may not improve the performance of %p2PSA and the *phi* in the diagnosis of PCa further.

We also compared the *phi* value between PCa patients with a Gleason score of 3+3 and those with Grade 4 or 5 components (i.e., Gleason sum = 7 or above). The mean *phi* levels for Gleason 6 and Gleason 7 or above were 35.28 (standard deviation = 10.12) and 52.77 (standard deviation = 14.81) (p = 0.007).

Table 3. Multivariate analyses of the predictive value of each of the parameters in the diagnosis of prostate cancer

			Multivariable analysis		
	AUC **95% CI of AUC**	**Univariate analysis** **OR (95%CI);** **p-value**	**Base model** **OR (95%CI);** **p-value**	**With %p2PSA** **OR (95%CI);** **p-value**	**With phi** **OR (95%CI);** **p-value**
Age	0.589 (0.476 – 0.702)	1.052 (0.978 – 1.133); 0.174	1.068/ (0.987 – 1.155); 0.101	1.076 (0.988 – 1.172); 0.093	1.076 (0.988 – 1.172); 0.093
tPSA	0.547 (0.421 – 0.674)	1.119 (0.836 – 1.499); 0.450	1.103 (0.814 – 1.494); 0.528	1.075 (0.791 – 1.461); 0.644	0.859 (0.607 – 1.215); 0.390
Free PSA*	0.538 (0.413 – 0.663)	0.736 (0.300 – 1.804); 0.503	--	--	--
%fPSA	0.572 (0.437 – 0.708)	0.965 (0.901 – 1.034); 0.311	0.974 (0.902 – 1.052); 0.507	0.982 (0.908 – 1.063); 0.658	0.982 (0.908 – 1.062); 0.651
Prostate volume	0.624 (0.501 – 0.747)	0.980 (0.954 – 1.006); 0.129	0.978 (0.950 – 1.007); 0.141	0.993 (0.964 – 1.023); 0.640	0.994 (0.965 – 1.023); 0.684
PSAD*	0.634 (0.501 – 0.768)	82.032 (1.113 – 6046.391); 0.045	--	--	--
p2PSA*	0.654 (0.523 – 0.786)	1.059 (1.009 – 1.111); 0.020	--	--	--
%p2PSA	0.768 (0.660 – 0.876)	8.497 (2.899 – 24.900); <0.001	--	8.153 (2.529 – 26.287); <0.001	--
Phi	0.781 (0.675 – 0.887)	1.078 (1.038-1.119); <0.001	--	--	1.082 (1.035 – 1.132); 0.001
AUC of the multivariable models (95%CI)			0.668 (0.540 – 0.795)	0.786 (0.677 – 0.894)	0.792 (0.668 – 0.895)

*These parameters were excluded from the multivariabale analysis to avoid multi-collinearity problems.

Table 4. Multivariate analyses of the predictive value of each of the parameters in the diagnosis of prostate cancer, with patient age, tPSA, %fPSA, %p2PSA and phi only

	AUC 95% CI of AUC	Univariable analysis OR (95%CI); p-value	Multivariable analysis Base model OR (95%CI); p-value	With %p2PSA OR (95%CI); p-value	With phi OR (95%CI); p-value
Age	0.594 (0.487 - 0.702)	1.057 (0.986 – 1.132); 0.119	1.068 (0.987 – 1.156); 0.100	1.062 (0.785 – 1.436); 0.091	1.076 (0.988 – 1.172); 0.092
tPSA	0.582 (0.459 - 0.704)	1.195 (0.934 – 1.529); 0.156	1.044 (0.780 – 1.398); 0.774	1.062 (0.785 – 1.436); 0.697	0.844 (0.603 – 1.179); 0.319
%fPSA	0.572 (0.437 – 0.708)	0.965 (0.901 – 1.034); 0.311	0.951 (0.884 – 1.022); 0.169	0.974 (0.908 – 1.044); 0.455	0.975 (0.909 – 1.045); 0.473
%p2PSA	0.784 (0.686 - 0.881)	9.705 (3.519 – 26.762); <0.001	--	8.856 (2.874 – 27.289); <0.001	--
phi	0.803 (0.706 - 0.899)	1.086 (1.047-1.126); <0.001	--		1.085 (1.039-1.133); <0.001
AUC of the Multivariable models (95% CI)			0.623 (0.493 – 0.752)	0.783 (0.676 – 0.890)	0.787 (0.683 – 0.891)

DISCUSSION

Despite its beneficial role in the detection of early stage PCa, several issues related to the use of PSA in the diagnosis of PCa remain unsettled. One is its lack of cancer specificity, which leads to a large number of patients with elevated PSA levels undergoing unnecessary TRUSPBs. The *phi* has been shown to give better results than tPSA and %fPSA in the diagnosis of PCa in patients with serum PSA levels ranging from 2 to 10 ng/mL. In a recent meta-analysis, at a sensitivity of 90%, the specificity of the *phi* was 32% (range, 26–43%) and the AUCs obtained by ROC analysis were between 0.703 and 0.77. [9] Most of the current data on the *phi* were based on studies in Caucasian populations, which have a higher incidence of PCa. According to Filella and Giménez, [9] the positive biopsy rate for patients with a PSA level of 2–10 ng/mL ranged from 39.9% to 57.2%. However, data on the application of the *phi* in Asian populations, which have a lower incidence of PCa, were sparse. Ito *et al.* reported the application of p2PSA and the *phi* in a Japanese population with levels of tPSA that ranged from 2 to 10 ng/mL, with or without abnormal DRE findings. [13] The results showed that the performance of the *phi* in diagnosing PCa was superior to that of tPSA and %fPSA at all levels of sensitivity.

Our results showed that the *phi* also performed better than the other parameters, even with a positive biopsy rate of around 10%. The AUC of the ROC analysis of *phi* was 0.781, which was comparable with that reported in the literature. [9] Compared with the report from Ito *et al.*, our population had a lower positive biopsy rate (9.13% versus 18.3% in patients with normal DRE findings). [13] Nevertheless, both studies support the use of *phi* in Asian populations to improve the accuracy of PCa diagnosis.

In addition to its role in the diagnosis of PCa, the use of *phi* might also help to predict the pathology and tumor aggressiveness of PCa. [6,14] In our study, a significant difference was observed between the *phi* level in patients with a Gleason score of 3+3 and those with Gleason 4 or 5 components. However, because of the small sample size (only 21 cases of PCa, five of which had Gleason 4 or 5 components), more meaningful analysis of the correlation with pathology was difficult. Therefore, further studies of the role of the *phi* in predicting pathology results in Asian populations are needed.

First introduced by Benson et al. in 1992, PSA density is another simple approach that improves the diagnostic and prognostic value of PSA. [5] While ultrasound prostate size assessment was routinely used in some part of the world, unfortunately, it was not a routine procedure during either PCa screening or the assessment of lower urinary tract symptoms in our local hospitals. Thus, the determination of PSA density implies an additional procedure in our centers. Moreover, from our results, *phi* alone had a better performance than PSA density in diagnosis prostate cancer in our study population. Furthermore, when we compared the use of two different base models for multivariate analysis using the *phi*, the inclusion of PSA density or a measurement of prostate volume produced minimal further improvements in the AUC in the multivariate model. Therefore, use of the *phi* would provide a more accurate prediction of prostate cancer and also might help to save the need of prostate size measurement during the initial assessment of patients in some centres.

During assessment of the effect of the *phi* on the diagnosis of PCa, it might be prudent to assess its financial impact on the healthcare system in addition to its diagnostic performance. From our results, the use of the *phi* could have avoided a large proportion of unnecessary TRUSPBs (45%), even when the sensitivity level was set at 90%. The financial savings on unnecessary TRUSPBs would need to be set against the additional cost of testing each patient. Nichol et al. used a mathematical model to calculate the cost-effectiveness of an additional *phi* measurement over a 25-year cycle of annual screening in the US healthcare system, [15] and concluded that the addition of a *phi* measurement to routine PSA screening was more cost-effective than PSA testing alone. However, this conclusion might not be applicable to other healthcare systems or non-annual screening situations. Moreover, as many different tests are available to improve the diagnostic yield of TRUSPB, a comparison of the various approaches, such as the *phi*, PSAD, and even prostate cancer antigen 3, [16,17] would be helpful to determine the most cost-effective approach in clinical management.

One of the drawbacks of our study is its retrospective nature and the use of stored blood samples. In this study, as all patients' data and blood were collected prospectively for prostate tissue bank and we hoped this would minimize potential bias. Moreover, our standard practice ensured that all of the blood samples were handled immediately after collection (within 3 h) and stored at –70ºC until further use. [18] We also limited the study to samples that had been in storage for less than 3 years, and thus the use of stored samples hopefully did not affect the assessment of the PSA derivatives. However, further prospective studies may be needed to verify our results.

Another problem is the difference in the assays used to measure serum levels of tPSA. The initial PSA measurement (which was an inclusion criteria) was made with our own hospital laboratory system, which is calibrated according to the WHO 96/670 reference standard. However, in the subsequent study, the measurement of PSA and its derivatives was performed with a Beckman Coulter Access2 system that was calibrated to a Hybritech Tandem-R calibrator. This may have led to some discrepancy in the two tPSA levels. [19] Thus, although the inclusion criterion was set as patients with a tPSA level of 4–10 ng/mL, the tPSA range measured by the Access2 system was 3.18–9.98 ng/mL. We understood that there were many different commercial assays used for PSA measurement available, and they may differ slightly in their calibration and also measured PSA values. In real life clinical practice, different centres may use different PSA measuring systems. Therefore, our main study objective was to assess the role of *phi* as a separate tool in PCa diagnosis among patients with PSA level between 4 to 10 ng/mL in our current practise. However, in order to ensure that measurements were comparable in all of the analyses (including PSA density), those parameters obtained from the Access2 system were used for comparison alone. The PSA level measured by the Roche Cobas e601 system was only used in the inclusion criteria. Nevertheless, our data showed a promising role for *phi* in improving the accuracy of the need for TRUSPB in our population.

CONCLUSION

As demonstrated in other studies, the use of p2PSA and its derivatives improves the accuracy of the detection of PCa in patients with an elevated level of PSA among an Asian population that has a lower incidence of this tumor. Among the various parameters, the *phi* showed the best performance, and its use could significantly decrease the number of patients who are selected to undergo a prostatic biopsy.

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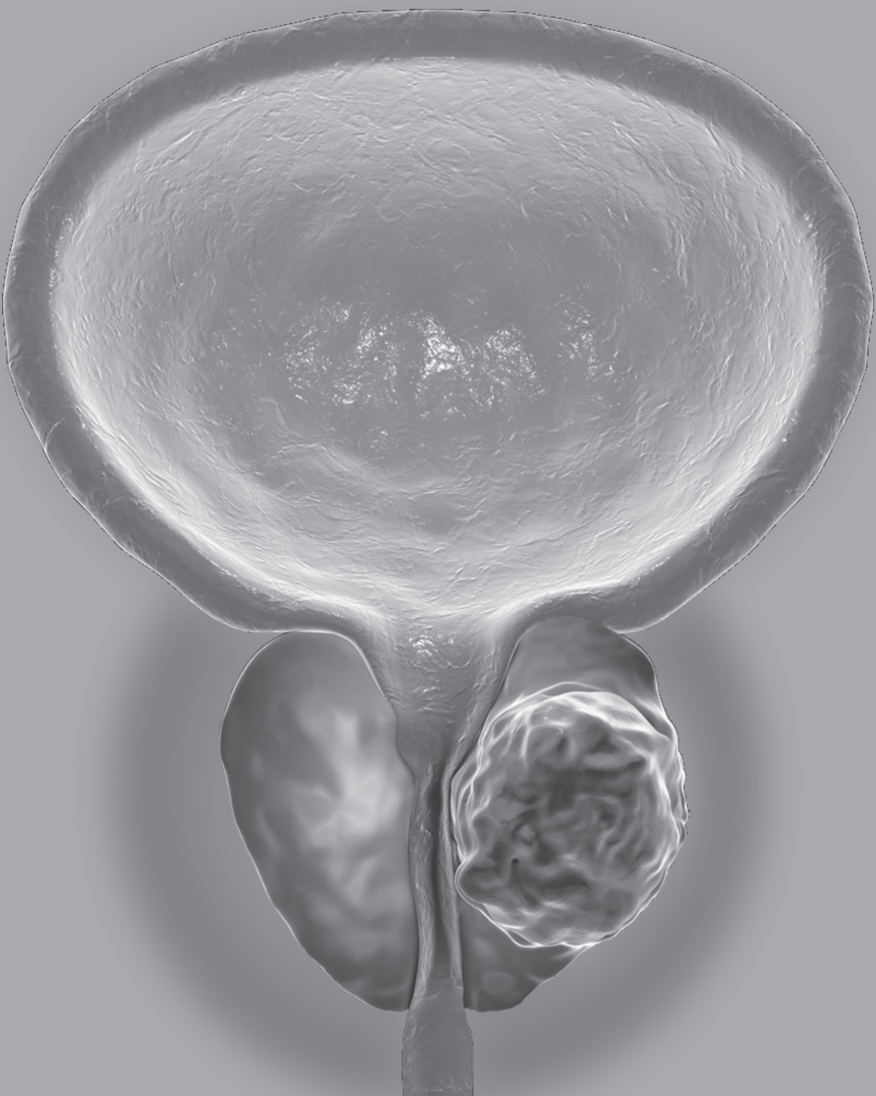

CHAPTER 7

Extended Use of Prostate Health Index (PHI) and %p2PSA in Chinese Men with PSA 10-20 ng/mL and Normal Digital Rectal Examination

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ABSTRACT

Purpose:

The rate of prostate cancer detection in Chinese men with PSA 10-20ng/mL was comparable to that of the Western population with PSA 4-10ng/mL. We investigated the extended use of Prostate Health index (PHI) and %p2PSA in Chinese men with PSA 10-20ng/mL and normal digital rectal examination (DRE).

Materials and Methods:

All consecutive Chinese men with PSA 10-20ng/mL and normal DRE who agreed for transrectal ultrasound (TRUS)-guided 10-core prostate biopsy were recruited. Blood samples were taken immediately before TRUS-guided prostate biopsy. The performances of total PSA(tPSA), %free PSA(%fPSA), %p2PSA and Prostate Health Index(PHI) were compared using logistic regression, receiver operating characteristics(ROC), and decision curve analyses(DCA).

Results:

From 2008 to 2015, 312 consecutive Chinese men were included. Among them, 53 out of 312(17.0%) men were diagnosed to have prostate cancer on biopsy. The proportions of men with positive biopsies were 6.7% in PHI<35, 22.8% in PHI 35-55, and 54.5% in PHI>55(chi-square test, p<0.001). The AUC of the base model including age, tPSA and status of initial/repeated biopsy was 0.64. Adding %p2PSA and PHI to the base model improved the AUC to 0.79(p<0.001) and 0.78(p<0.001) respectively, and provided net clinical benefit in DCA. The positive biopsy rates of Gleason 7 or above prostate cancers were 2.2% for PHI<35, 7.9% for PHI 35-55, and 36.4% for PHI>55(chi-square test, p<0.001). By utilizing the PHI cutoff of 35 to men with PSA 10-20ng/mL and normal DRE, 57.1% (178/312) biopsies could be avoided.

Conclusions:

Both PHI and %p2PSA performed well in predicting prostate cancer and high grade prostate cancer. The use of PHI and %p2PSA should be extended to Chinese men with PSA 10-20ng/mL and normal DRE.

INTRODUCTION

Prostate specific antigen (PSA) has been widely used for a screening tool for early prostate cancer detection. The European Randomized Study of Screening for Prostate Cancer (ERSPC) showed that PSA screening could reduce prostate cancer-specific mortality. [1] However, PSA has a poor specificity at the common cutoff of 4ng/mL,[2] and this may lead to many unnecessary negative prostate biopsies and biopsy-related morbidities. There is a need for a better tool for early prostate cancer detection, and prostate health index (PHI) is one of the more promising biomarkers being investigated.

Previous studies showed that PHI and the percentage of prostate-specific antigen isoform [-2]proPSA (p2PSA) were more accurate than total PSA (tPSA) or %free PSA (%fPSA) in predicting prostate cancer.[3] In 2012, the United States Food and Drug Administration (FDA) has approved the use of PHI and p2PSA in men older than 50 years old with a total PSA 4-10 ng/mL and normal DRE to reduce unnecessary prostate biopsies. However, the incidence of prostate cancer varies widely between different countries and ethnicities.[4] In the Western population, the cancer detection rate was 20.7% for patients with normal DRE and PSA of 4.1-9.9ng/mL.[5] Whereas in our locality, the rates of prostate cancer detection in Chinese men with normal DRE were 13.4% for PSA 4-10 ng/mL and 21.8% for PSA 10.1-20 ng/mL.[6] At the PSA level of 10-20ng/mL, the rate of prostate cancer detection in Chinese men is more comparable to that of the Western population at the PSA level of 4-10ng/mL. We postulated that the use of PHI and p2PSA could be extended to PSA level of 10-20ng/mL in Chinese men, and this may be more clinically applicable and beneficial.

Na *et al.* previously reported the performances of PHI and p2PSA in Chinese men with PSA 10.1-20ng/mL.[7] However, the cohort was relatively heterogeneous as patients with abnormal DRE were also included in this study. The true performances of PHI and p2PSA in patients with PSA 10-20ng/mL and normal DRE remained undetermined. In this current study, we investigated the diagnostic performances of PHI and %p2PSA in a homogeneous cohort of Chinese men with PSA 10-20 ng/mL and normal DRE.

MATERIALS AND METHODS

Study Design

All consecutive patients with PSA 10-20ng/mL and normal DRE who agreed to undergo transrectal ultrasound-guided (TRUS) prostate biopsy were recruited for prospective blood sample collection and informed consents were signed. There were 391 men with PSA 10-20ng/ml, and 79 men with PSA 10-20 ng/ml and abnormal DRE were excluded. Blood samples from the resulting 312 consecutive patients with PSA 10-20 ng/ml and normal

DRE were collected prospectively immediately before TRUS biopsy from November 2008 to July 2015.

Blood samples were centrifuged within 3 hours after blood taking, and the serum was stored at -80°C. The bloods were subsequently analyzed for tPSA, fPSA, and p2PSA using the Beckman Coulter Access 2 Immunoassay System (Beckman Coulter Inc., Brea, CA, USA) and according to the criteria described by Semjonow et al.[8] Men with known history of prostate cancer, abnormal digital rectal examination (DRE), usage of androgen deprivation therapy or 5 alpha-reductase inhibitor before blood taking would be excluded from this study.

Patients had TRUS prostate biopsy with 10 biopsy cores taken at peripheral portions of the prostate gland. The biopsy specimens were evaluated by experienced genitourinary pathologists. Prostate cancer was graded according to International Society of Urological Pathology 2005 consensus.[9] This study was conducted in a university hospital and the study protocol was approved by the Joint Chinese University of Hong Kong-New Territories East Cluster Clinical Research Ethics committee. This study conforms to the provisions of the Declaration of Helsinki (as revised in Tokyo 2008).

Study outcomes

The primary outcome of the study was to compare the diagnostic accuracies of %p2PSA and PHI with tPSA and %fPSA in predicting prostate cancer, as determined by the area under curves (AUC) of the receiver operating characteristic (ROC) curves. All PSA values were derived from Hybritech calibration. The ability of %p2PSA and PHI in predicting high grade prostate cancers (Gleason score 7 or above) [1] were also analyzed. %p2PSA was calculated by p2PSA (pg/mL) / free PSA (ng/mL) / 1000. PHI was calculated using the following formula: (p2PSA/free PSA) × √total PSA.

Sample Size Calculation

In the Chinese study by Na *et al.*,[7] regardless of the DRE findings, a difference in AUC of 0.23 between PHI and tPSA was demonstrated in patients with PSA 10-20ng/mL. In our previous study[10] on patients with PSA 4-10ng/mL and normal DRE, a difference in AUC of 0.234 between PHI and tPSA was demonstrated. In this current study, in order to detect a difference in AUC of 0.20 with alpha error 0.05 and 80% power, an estimated sample size of 250 is required.

Statistical Analyses

T-test and Mann-Whitney U test were used to compare normally and non-normally distributed continuous variables, respectively. Chi-square test was used to compare categorical variables. Univariate and multivariate logistic regression was used to predict status of prostate cancer and high grade prostate cancer. The defined base model in multivariate analysis included age, tPSA, and status of initial/repeated biopsy. Using the non-parameteric method of DeLong, the AUC of the ROC curves were compared between the defined base model, base model + %fPSA, base model + %p2PSA, and base model + PHI. Decision curve analysis (DCA)[11] was used to evaluate whether adding PHI or %p2PSA to the base model would yield net clinical benefit. The decision curves were plotted with y-axis being the net clinical benefit and the x-axis being the threshold probability. The threshold probability is the probability of the outcome (diagnosis of prostate cancer) that the patient would opt for prostate biopsy.

All statistical analyses were performed using IBM SPSS Statistics for Windows version 22 (IBM Corp., Armonk, NY, USA). The R package "pROC" [12] was used to compare ROC curves and decision analysis curves were plotted with R version 3.1.1 (The R Foundation for statistical computing, Vienna, Austria). A 2-sided p-value of <0.05 was considered significant.

RESULTS

Out of the 312 men who fit the inclusion criteria, 260 samples were initial biopsies and 52 were repeated biopsies. 53 patients (17.0%) were diagnosed to have prostate cancer after TRUS biopsy. The baseline characteristics of the cohort were listed in Table 1. The mean age was 68.1 ± 6.2 years old, and patients with prostate cancer had significantly older age. The tPSA values between prostate cancer patients and non-cancer patients had no significant difference. %p2PSA and PHI were significantly higher in prostate cancer patients. (Table 1)

Table 1. Baseline characteristics

Mean ± SD Range	Overall n=312	Non Cancer n=259	Cancer patients n=53	p-value
Age	68.1 ± 6.2 51-82	67.6 ± 6.1 51-82	70.3 ± 5.9 58-81	0.005
Total PSA(tPSA)	13.27 ± 2.71 9.95 – 20.01	13.36 ± 2.67 9.95 – 20.01	12.82 ± 2.89 10.07 – 19.58	0.182
Prostate volume	64.0 ± 28.5 12 – 179	67.3 ± 28.0 20 – 179	48.0 ± 25.7 12 – 117	<0.001
Repeated Biopsy (%)	52 (16.7%)	45 (17.4%)	7 (13.2%)	0.458
%fPSA	0.21 ± 0.11 0.05 – 1.08	0.22 ± 0.11 0.06 – 1.08	0.17 ± 0.73 0.05 – 0.42	<0.001
%p2PSA	1.05 ± 0.53 0.12 – 4.66	0.94 ± 0.37 0.12 – 3.01	1.55 ± 0.83 0.29 – 4.66	<0.001
PHI	37.53 ± 19.64 4.16 – 179.28	33.96 ± 13.78 4.16 – 108.33	54.95 ± 31.51 13.04 – 179.28	<0.001

Table 2. Positive biopsy rates (any grade prostate cancer) for different Prostate health index (PHI) and %p2PSA ranges

PHI	<35	35-55	>55	Total	p-value
Whole cohort	12/178 (6.7%)	23/101 (22.8%)	18/33 (54.5%)	312	<0.001
Initial biopsies	11/146 (7.5%)	30/85 (23.5%)	15/29 (51.7%)	260	<0.001
Repeated biopsies	1/32 (3.1%)	3/16 (18.8%)	3/4 (75.0%)	52	0.001
%p2PSA	**<1%**	**1-1.5%**	**>1.5%**	**Total**	**p-value**
Whole cohort	13/183 (7.1%)	21/93 (22.6%)	19/36 (52.8%)	312	<0.001
Initial biopsies	13/150 (8.7%)	17/78 (21.8%)	16/32 (50.0%)	260	<0.001
Repeated biopsies	0/33 (0%)	4/15 (26.7%)	3/4 (75.0%)	52	<0.001

The rates of prostate cancer detection for different PHI ranges were 6.7% for PHI <35, 22.8% for PHI 35-55, and 54.5% for PHI >55 (p<0.001) (Table 2). The rates of prostate cancer detection for different %p2PSA ranges were 7.1% for %p2PSA <1%, 22.6% for %p2PSA 1-1.5%, and 52.8% for %p2PSA >1.5% (p<0.001) (Table 2). Similar trends for initial and repeated biopsies were observed for both PHI and %p2PSA, except that for PHI < 35 and %p2PSA < 1%, the positive biopsy rates were particularly low at 3.1% and 0% respectively (Table 2).

Concerning the prediction of prostate cancer, the AUC for tPSA, %fPSA, %p2PSA and PHI were 0.58, 0.69, 0.76, and 0.73 respectively upon univariate analyses (Table 3). Upon multivariate analyses, using the base model including age, tPSA and status of initial/repeated biopsy, the AUC was 0.64 (95% CI 0.56-0.72) (Table 3). Adding %fPSA to the base model increased the AUC to 0.75 (95% CI 0.67-0.82, p=0.007). Adding %p2PSA to the base model increased the AUC to 0.79 (95% CI 0.71-0.86, p<0.001), and adding PHI to the base model increased the AUC to 0.78 (95% CI 0.70-0.86, p<0.001).

With the concern of any interaction between PSA and other PSA derivatives in the multivariate models, interaction tests have been performed. There was no significant interaction between PSA and %fPSA (p=0.275), PSA and %p2PSA (p=0.510), and PSA and PHI (p=0.538). In addition, all 3 models (base model + %fPSA, base model + %p2PSA, and base model + PHI) had lower AUC values when PSA was removed from each model. Therefore, PSA should remain in the 3 models.

Upon decision curve analyses (DCA) in predicting prostate cancer diagnosis (Figure 1), %p2PSA and PHI demonstrated net clinical benefit over tPSA or %fPSA over whole range of threshold probabilities. Comparing the different models upon DCA (Figure 2), adding

Table 3. Multivariate analyses for prostate cancer diagnosis

			Multivariate analysis			
	ROC AUC (95% CI)	**Univariate analysis OR (95%CI); p-value**	**Base model OR (95%CI); p-value**	**With %fPSA OR (95%CI); p-value**	**With %p2PSA OR (95%CI); p-value**	**With PHI OR (95%CI); p-value**
Age	0.62 (0.54 – 0.70)	1.07 (1.02 – 1.13); p=0.006	1.08 (1.02 – 1.14); p=0.004	1.11 (1.05 – 1.17); p<0.001	1.06 (1.00 – 1.12); p=0.055	1.06 (1.00 – 1.12); p=0.060
tPSA	0.58 (0.49 – 0.67)	0.92 (0.82 – 1.04); p=0.183	0.91 (0.81 – 1.02); p=0.102	0.91 (0.81 – 1.03); p=0.131	0.92 (0.81 – 1.04); p=0.193	0.85 (0.74 – 0.97); p=0.014
Repeated Biopsy	0.52 (0.44 – 0.60)	0.72 (0.31 – 1.71); p=0.460	0.75 (0.36 – 2.09); p=0.754	0.86 (0.35 – 2.12); p=0.743	0.79 (0.30 – 2.11); p=0.643	0.82 (0.31 – 2.16); p=0.690
%fPSA	0.69 (0.61 – 0.77)	1.27 (1.14 – 1.42); P<0.001	--	1.33 (1.18 – 1.49); p<0.001	--	---
%p2PSA	0.76 (0.68 – 0.84)	7.14 (3.80 – 13.44); p<0.001	--	--	6.43 (3.41 – 12.11); p<0.001	--
PHI	0.73 (0.65 – 0.82)	1.05 (1.03 – 1.07); p<0.001	--	--	--	1.05 (1.03 – 1.07); p<0.001
AUC of the multivariable models (95%CI)			0.64 (0.56 – 0.72)	0.75 (0.67 – 0.82)	0.79 (0.71 – 0.86)	0.78 (0.70 – 0.86)
p-value, comparing with AUC of base model			--	0.007	<0.001	<0.001

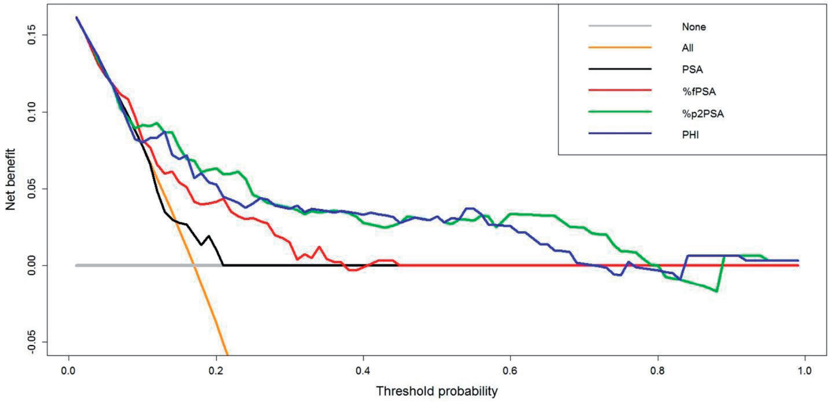

Figure 1. Decision curve analysis for prediction of prostate cancer diagnosis, comparing total PSA, %free-to-total PSA (%fPSA), %p2PSA, and PHI. X-axis (threshold probability) is the probability of prostate cancer diagnosis that the patient would opt for prostate biopsy. Y-axis is the net clinical benefit for different models.

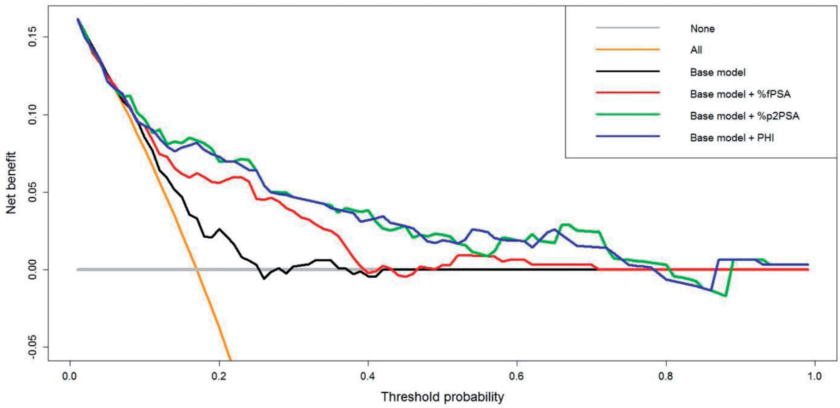

Figure 2. Decision curve analysis for prediction of prostate cancer diagnosis, comparing base model, base model + %free-to-total PSA (%fPSA), base model + %p2PSA, and base model + PHI. Base model included age, total PSA, and status of initial / repeated biopsy. X-axis (threshold probability) is the probability of prostate cancer diagnosis that the patient would opt for prostate biopsy. Y-axis is the net clinical benefit for different models.

%p2PSA or PHI to the base model demonstrated net clinical benefit over whole range of threshold probabilities.

PHI and %p2PSA predicted high grade (Gleason 7 or above) prostate cancers in the PSA range of 10-20ng/mL. The positive biopsy rate of high grade prostate cancers was 7.7% (24/312) for the whole cohort. Dividing into different PHI ranges, the proportion of high grade prostate cancers were 2.2% (4/178) for PHI <35, 7.9% (8/101) for PHI 35-55, and 36.4% (12/33) for PHI > 55 (chi-square test, p<0.001). The AUCs for high grade prostate cancers were 0.62 for tPSA, 0.68 for base model, 0.77 for base model +%fPSA, 0.83 for base model + %p2PSA, and 0.84 for base model + PHI.

By utilizing the PHI cutoff of 35 to men with PSA 10-20ng/mL and normal DRE, 57.1% (178/312) biopsies could be avoided with the cost of missing 6.7% (12/178) any grade prostate cancer and 2.2% (4/178) high grade prostate cancer in men with PHI<35.

All Gleason scores in the current study were derived from biopsy pathology. There were 15 out of 53 (28.3%) cancer cases who had radical prostatectomy performed, and others treatments included radiotherapy with or without androgen deprivation therapy (34.0%), active surveillance (3.8%), watchful waiting / refusal of treatment (18.9%), and androgen deprivation therapy only (13.2%). Among the 15 cases with radical prostatectomies done, 8 were biopsy Gleason 6 cancers and none of them had any upgrading of Gleason score in final pathology. For the 2 prostatectomy cases with PHI < 35, there was one Gleason 6 and one Gleason 8 on biopsy, but both were organ confined disease (pT2) in final pathology. On the other hand, 3 out of 13 prostatectomy cases with PHI >35 had pT3 disease.

DISCUSSION

The rates of prostate cancer detection in Caucasians in the classical grey-zone of PSA 4-10 ng/mL ranged from 26-47%.[4] Different markers for predicting prostate cancer including free PSA [2], PSA density [13,14], PCA3 [15,16], p2PSA and PHI [3] mainly targeted patients with PSA <10ng/mL as the rate of prostate cancer detection in this range is lower and the use of these markers could help reduce unnecessary prostate biopsies. Compared to Caucasians, Chinese men have much lower rates of positive biopsies across different PSA ranges.[6] In our current study on Chinese men with PSA 10-20ng/mL and normal DRE, the overall prostate cancer detection rate was 17.2%, which is comparable to that of the Western population at PSA level of 4-10ng/mL.[5] Another recent Chinese cohort showed a higher positive biopsy rate of 36.5% for men with 10-20 ng/mL (about 30% abnormal DRE) [7], but that was still similar to that in Caucasian with PSA 4-10ng/mL. Although PHI was classically indicated in men with PSA 4-10 ng/mL and normal DRE, we believe PHI may play an important role at PSA 10-20ng/mL in the Chinese population, and the current study is the first to address this specific group of men.

A previous study on Chinese men reported better performance of p2PSA and PHI than total or free PSA across a wide range of PSA. However, about 30% of the cohort had abnormal DRE and the results should be interpreted with caution.[7] As the risk of prostate cancer in those with abnormal DRE is much higher (52% in the range of PSA 10-20ng/mL),[6] prostate biopsy should be offered directly instead of PHI. The performances of p2PSA and

PHI may also be different in men with abnormal DRE. The true performances of PHI and p2PSA in patients with PSA 10-20ng/mL and normal DRE remained undetermined. In the current study, our analyses were based on a homogeneous cohort of Chinese men with PSA 10-20ng/mL and normal DRE, and we believe the results would be of significant value.

The current study demonstrated the role of %p2PSA and PHI in predicting prostate cancer diagnosis in a Chinese cohort with PSA 10-20 with normal DRE. For the group of patients with %p2PSA <1% (n=183) and PHI < 35 (n=178), the rates of prostate cancer detection were only 7.1% and 6.7% respectively. Upon univariate analyses, the AUCs of %p2PSA and PHI were better than tPSA and %fPSA. In the multivariate logistic regression model, adding %p2PSA or PHI to the pre-defined base model (Age, tPSA, and status of initial/repeat biopsy) significantly increased the predictive accuracy from 0.64 to 0.78-0.79. Our results showed that p2PSA and PHI could help stratify the risk of prostate cancer in Chinese men with PSA 10-20 ng/mL with normal DRE. In Chinese men with PSA 10-20 ng/mL, biopsy decisions should not be based on PSA alone, but should be based on the additional PHI & p2PSA information after personalized counselling by a Urologist.

PHI and p2PSA were associated with more aggressive pathologies in the tPSA range of 4-10 ng/mL in previously published studies. [17,18] In the current study, %p2PSA and PHI were also associated with more aggressive prostate cancers in the range of PSA 10-20. The positive biopsy rates of Gleason 7 or above prostate cancers for PHI ranges of <35, 35-55, and >55 were 2.2%, 7.9%, and 36.4%, respectively. PHI could serve as a guide for men who wish to be treated only if there is aggressive prostate cancer.

Analyses of PCa and HGPCa in the current study were derived from biopsy pathology but not from prostatectomy pathology, as only 28.3% (15/53) PCa men opt for radical prostatectomy in this cohort. Among the 15 cases with prostatectomy pathology, 2 had PHI <35 and 13 had PHI >35. None of the 2 cases with PHI <35 had pT3 disease, while 3 out of 13 cases with PHI > 35 had pT3 disease. These findings were in line with previous evidence showing PHI was associated with more aggressive prostatectomy pathology. [19] Furthermore, none of the 15 prostatectomy pathology showed upgrading of Gleason score from biopsy pathology, and this might support the fact that biopsy pathology was representative in the current study. A lack of final pathology in all cancer cases, however, was definitely a limitation of the study.

In contrast to Caucasian men, Asian men have very different prostate cancer epidemiology. The incidence of prostate cancer in Caucasian men was 5-10 times more than that in many regions of Asia and 10 times of that in Chinese men. [20] Most prostate cancers in Caucasians were diagnosed at an early stage, whereas in China, 65% PCa were diagnosed with PSA >10 ng/mL, and 45% PCa were either locally advanced or metastatic. Nevertheless, there were variations in Asia, and only about 35-40% prostate cancers were diagnosed with PSA >10ng/mL in Hong Kong, Singapore, and Korea. [20] The above differences in cancer epidemiology in Caucasian and Asian might be explained by lifestyle and genetic differences. In general, Asians consume more vegetables and less meat in their diet compared with Western population. [20] In terms of genetic differences, there were significant variations in single nucleotide polymorphisms. [20] The rates of TMPRSS2-ERG gene fusion [21] and PTEN inactivation [22] were also lower in Asian or Chinese population compared with Caucasians.

The strengths of this study included the prospective collection of blood samples of all consecutive patients, the emphasis on a homogeneous patient group with PSA 10-20 and normal DRE, the analyses of blood samples according to guidelines recommended by Semjonow et al,[8] the use of standardized systemic 10-core prostate biopsy, and the interpretation of all biopsy specimens by experienced genitourinary pathologists in our institution. The limitations of this study included single institution data, the lack of prostatectomy pathology in most cases, and the lack of comparison with other predictive models or investigation modalities.

CONCLUSIONS

Both PHI and %p2PSA performed well in predicting prostate cancer and high grade prostate cancer. The use of PHI and %p2PSA should be extended to Chinese men with PSA 10-20ng/mL and normal DRE.

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CHAPTER 8

Prostate Health Index (PHI) and %p2PSA predict aggressive prostate cancer pathology in Chinese patients undergoing radical prostatectomy

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ABSTRACT

Purpose

To investigate the performance of prostate health index(PHI) and %p2PSA in predicting pathological outcomes at radical prostatectomy(RP) in a Chinese population.

Methods

This is a prospective study on 135 prostate cancer patients with radical prostatectomy performed. The accuracy of pre-operative %p2PSA (=p2PSA / free PSA) and PHI [=(p2PSA/free PSA)x√PSA] in predicting pathological outcomes of RP including pathological T3(pT3), pathologic Gleason score(pGS)≥7 , GS upgrade at RP, Tumor volume>0.5ml, and Epstein significant tumor were calculated using multivariate analyses and area under curve(AUC). The base model in multivariate analysis included age, PSA, abnormal digital rectal examination (DRE), and biopsy Gleason score(GS).

Results

PHI was significantly higher in patients with pT3 or pGS≥7(p<0.001), pT3 disease(p=0.001), pGS≥7(p<0.001), GS upgrade(p<0.001), tumor volume >0.5ml(p<0.001), and Epstein significant tumor(p=0.001). %p2PSA was also significantly higher in all the above outcomes. The risk of pT3 or pGS≥7 was 16.1% for PHI<35 and 60.8% for PHI>35 (sensitivity 84.2%, specificity of 60.3%), and the risk of tumor volume >0.5ml was 25.5% for PHI<35 and 72.6% for PHI>35 (sensitivity 79.1%, specificity 67.2%). In multivariate analysis, adding %p2PSA or PHI to the base model significantly improved the accuracy(AUC) in predicting pT3 or pGS≥7(by 7.2-7.9%), tumor volume>0.5ml(by 10.3-12.8%), and Epstein significant tumor(by 13.9-15.9%). Net clinical benefit was observed in decision curve analyses for prediction of both tumor volume >0.5ml, and pT3 or pGS≥7.

Conclusions

Both PHI and %p2PSA predict aggressive and significant pathologies in radical prostatectomy in Chinese men. This enabled identification of non-aggressive cancers for better counselling on active surveillance or treatment.

INTRODUCTION

The Prostate health index (PHI) or percentage of prostate-specific antigen isoform [-2] proPSA was shown to be more accurate than PSA, %free PSA (%fPSA), or PSA density in predicting diagnosis of prostate cancer in prostate biopsies for patients with PSA less than 10ng/mL.[1-8] PHI or %p2PSA was also associated with higher gleason scores in prostate biopsies.[1, 2, 4, 7] The associations of PHI or %p2PSA with radical prostatectomy (RP) pathology have only been reported in European population.[1, 9-11] It was reported that higher PHI or %p2PSA values predicted pT3 disease, higher pathologic Gleason score (pGS), upgrading of Gleason score, and higher tumor volume.[9, 11]

The incidence of prostate cancer is increasing in Asian countries[12] with aging population and widespread use of PSA testing, and this is associated with more and more over-diagnosis and over-treatment of indolent prostate cancers. We need better markers to differentiate aggressive prostate cancers from less aggressive ones in order to better counsel our patient for appropriate treatment options including radical treatment and active surveillance. In this study, we aim to investigate the performance of PHI or %p2PSA in predicting RP pathological outcomes in a Chinese population.

METHODS

This is a prospective cohort of a single hospital including all patients with biopsy proven prostate cancer planning for robotic assisted laparoscopic radical prostatectomy (RP) performed between August 2011 and July 2015. All cancers were diagnosed with transrectal ultrasound guided systematic 10-core biopsies. Study bloods were taken 1 day before RP to allow more accurate correlation with final pathology, as the waiting time between pre-biopsy PSA and RP was at a mean of 31.3 weeks. They were subsequently analyzed for PSA, fPSA, and p2PSA. Patients with digital rectal examination (DRE), androgen deprivation therapy, or 5 alpha-reductase inhibitor before blood taking would be excluded from this study.

The primary objective of this study was to investigate the accuracy of PHI and %p2PSA in predicting final RP pathology. They included status of pT3 or pathological Gleason score (pGS) ≥7, pT3, pGS≥7, upgrading of GS (pGS higher than biopsy GS), tumor volume >0.5ml, and Epstein significant tumor (≥pT3, pGS≥7, or tumor volume >0.2ml).[13, 14] Clinical data included age at surgery, digital rectal examination (DRE), biopsy Gleason score, PSA, fPSA, %fPSA (fPSA/PSA x 100), p2PSA, %p2PSA [(p2PSA)/(fPSAx100)x1000] and PHI [(p2PSA/fPSA)x√PSA]. Blood samples were taken at least 6 weeks from prostate biopsy as recommended in the Beckman Coulter Access Hybritech p2PSA Instructions for use. Bloods were processed by the Beckman Coulter Access 2 Immunoassay System (Beckman Coulter Inc., Brea, CA, USA) and according to the criteria described by Semjonow et al.[15]

RP pathological outcomes included pathologic Gleason score (pGS), pathologic T-stage, and tumor volume. All pathologic outcomes (biopsy and surgery) were reported by genitourinary pathologists blinded to all blood results. Prostate cancer was graded according to International Society of Urological Pathology 2005 consensus.[16] The study was approved by the hospital ethics committee and conformed to the provisions of the Declaration of Helsinki. Informed consents were signed by all patients.

T-test and Mann-Whitney U test were used to compare normally and non-normally distributed continuous variables, respectively. Chi-square or Fisher's exact test were used to compare categorical variables. Univariate and multivariate logistic regression was used to predict status of pT3 or pGS≥7, tumor volume >0.5ml, and Epstein significant tumor. Odd ratios (ORs) with 95% confidence intervals (CIs) were calculated. Area under curve (AUC) of receiver operating characteristics (ROC) was used to calculate predictive accuracy in each univariate and multivariate analysis. The defined base model in multivariate analysis included age, PSA, biopsy GS, and abnormal digital rectal examination (DRE). The performance (in terms of AUC) of the base model alone was compared with the addition of %fPSA, %p2PSA or PHI to the base model. Decision curve analysis (DCA)[17] was used to evaluate whether adding PHI or %p2PSA to the base model would lead to net clinical benefit. The decision curves were plotted with y-axis being the net clinical benefit and the x-axis being the threshold probability. The threshold probability is the probability of the outcome (pT3 or pGS≥7, or Tumor volume>0.5mL) that the patient or doctor would opt for RP, and this threshold can vary widely between different patients or doctors.

All statistical analyses were performed using IBM SPSS Statistics for Windows version 21 (IBM Corp., Armonk, NY, USA). Decision curves were plotted with R version 3.0.3 (The R Foundation for statistical computing, Vienna, Austria). A 2-sided p-value of <0.05 was considered significant.

RESULTS

Baseline characteristics of the 135 included patients were listed in Table 1. In our cohort, the indication of PSA was either lower urinary tract symptoms (LUTS) in 76.3% (103/135), opportunistic screening (PSA taken for non-urinary tract symptoms) in 23.0% (31/135), or abnormal digital rectal examination (DRE) without LUTS in 0.7% (1/135). The indication of all prostate biopsies were related to elevated PSA >4 ng/mL with or without abnormal DRE. All study bloods were taken 1 day before operation and at a mean of 24.9 weeks (range 6-115 weeks) after prostate biopsy. The time from pre-biopsy PSA to RP was at a mean of 31.3 weeks (range 8-144 weeks, SD 19.8 weeks). PSA 1 day before RP (mean 12.2 ng/mL, median 9.0 ng/mL) was significantly higher than the pre-biopsy PSA (mean 10.6 ng/mL, median 8.5 ng/mL) (p<0.001, paired t-test).

Table 1. Clinical and pathological characteristics of patients

Parameters (Median & Interquartile range)	Whole cohort (n=135)
Age (years)	65.5 ± 5.4 (mean ± SD)
Total PSA (ng/mL)	9.0 (6.3-15.3)
Free to total PSA (%)	15.32 (11.22 – 19.97)
TRUS biopsy Gleason Score	
≤6	99 (76.2%)
7	20 (15.4%)
8	8 (6.2%)
9	3 (2.3%)
Abnormal DRE	27 (20.8%)
%p2PSA (%)	1.28 (1.08 – 1.76)
Prostate health index (PHI)	38.05 (30.22 – 57.38)
pT3	40/135 (29.6%)
Pathological Gleason score (pGS) ≥7	36/135 (26.7%)
pT3 or pGS≥7	57/135 (42.2%)
Upgrade of Gleason score (GS)	24/135 (17.8%)
Tumor volume >0.5	67/128 (52.3%)
Epstein significant tumor	101/133 (75.9%)

There were 42.2% (57/135) with pT3 or pGS≥7, 17.8% (24/135) with upgrade of GS at final pathology, 52.3% (67/128) with tumor volume >0.5ml, and 75.9% (101/133) patients with Epstein significant tumor. Mean PHI values were significantly higher for ≥pT3 or pGS≥7 (70.4 Vs 35.9, T-test, p<0.001), ≥pT3 (71.0 Vs 41.8, T-test, p=0.001), pGS≥7 (84.6 Vs 38.1, T-test, p<0.001), GS upgrade (85.5 Vs 42.9, T-test, p<0.001), Tumor volume ≥0.5ml (62.2 Vs 31.1, T-test, p<0.001), and Epstein significant tumor (58.5 Vs 27.1, T-test, p=0.001) (Supplementary Figure 1). Mean %p2PSA values were significantly higher for ≥pT3 or pGS≥7(1.77% Vs 1.25%, T-test, p=0.001), ≥pT3 (1.80% Vs 13.3%, T-test, p=0.007), pGS≥7 (1.96% Vs 1.30%, T-test, p<0.001), GS upgrade (2.02% Vs 1.36%, T-test, p=0.001), Tumor volume ≥0.5ml (1.67% Vs 1.15%, T-test, p<0.001), and Epstein significant tumor (1.63% Vs 1.00%, T-test, p=0.001).

The risk of pT3 or pGS≥7 increased from 16.1% with PHI<35 to 60.8% with PHI>35 (chi-square, p<0.001, sensitivity 84.2%, specificity of 60.3%). The risk of Epstein significant tumor increased from 55.6% with PHI<35 to 89.9% with PHI>35 (chi-square, p<0.001, sensitivity 70.3%, specificity 75.0%), and the risk of tumor volume >0.5ml increased from 25.5% with PHI<35 to 72.6% with PHI>35 (chi-square, p<0.001, sensitivity 79.1%, specificity 67.2%).

Univariate and Multivariate logistic regression analyses were performed for predictions of pT3 or pGS≥7 (table 2), tumor volume > 0.5ml (Table 3), and Epstein significant tumor

Table 2. Univariable and multivariable analysis for pT3 (pathological T3 stage) or pGS (pathological gleason score) ≥7

			Multivariable analysis			
	AUC 95% CI of AUC	**Univariate analysis OR (95%CI); p-value**	**Base model Adjust OR (95%CI); p-value**	**Base model + %fPSA Adjust OR (95%CI); p-value**	**Base model + %p2PSA Adjust OR (95%CI); p-value**	**Base model + PHI Adjust OR (95%CI); p-value**
Age	0.504 (0.402 – 0.605)	0.997 (0.933 – 1.066); p=0.935	0.970 (0.902 – 1.043); p=0.407	0.986 (0.914 – 1.063); p=0.711	0.975 (0.903 – 1.052); p=0.513	0.975 (0.904 – 1.051); p=0.506
PSA[a]	0.680 (0.584 – 0.776)	1.114 (1.050 – 1.183); P<0.001	1.117 (1.050 – 1.188); P<0.001	1.106 (1.039 – 1.177); p=0.001	1.121 (1.048 – 1.199); p=0.001	1.046 (0.972 – 1.125); p=0.228
Abnormal DRE[b]	0.565 (0.465 – 0.665)	2.200 (0.928 – 5.214); p=0.073	1.518 (0.587 – 3.923); p=0.389	1.498 (0.565 – 3.970); p=0.416	1.283 (0.461 – 3.574); p=0.406	1.376 (0.500 – 3.788); p=0.537
Biopsy GS[c]	0.581 (0.481 – 0.681)	1.891 (1.101 – 3.248); p=0.021	1.916 (1.079 – 3.401); p=0.026	1.813 (1.004 – 3.271); p=0.048	1.835 (0.997 – 3.378); p=0.051	1.750 (0.962 – 3.181); p=0.067
%fPSA[d]	0.717 (0.628 – 0.805)	0.895 (0.839 – 0.955); p=0.001	--	0.924 (0.872 – 0.980); p=0.008	--	--
%p2PSA	0.688 (0.597 – 0.779)	3.208 (1.567 – 6.567); p=0.001	--	--	3.287 (1.500 – 7.202); p=0.003	--
PHI[e]	0.800 (0.725 – 0.875)	1.042 (1.022 – 1.062); p<0.001	--	--	--	1.033 (1.008 – 1.057); p=0.008
AUC of the multivariable models (95%CI)			0.717 (0.626 – 0.809)	0.757 (0.671 – 0.842)	0.796 (0.721 – 0.871)	0.789 (0.712 – 0.865)

[a]PSA = Prostate-specific antigen, [b]DRE = Digital rectal examination, [c]GS = Gleason score, [d]%fPSA = Percent free to total PSA, [e]PHI = prostate health index

Table 3. Univariable and multivariable analysis for tumor volume >0.5ml

			Multivariable analysis			
	AUC 95% CI of AUC	**Univariate analysis OR (95%CI); p-value**	**Base model Adjust OR (95%CI); p-value**	**Base model + %fPSA Adjust OR (95%CI); p-value**	**Base model + %p2psa Adjust OR (95%CI); p-value**	**Base model + PHI Adjust OR (95%CI); p-value**
Age	0.634 (0.535 – 0.732)	1.083 (1.009 – 1.162); p=0.027	1.069 (0.994 – 1.150); p=0.072	1.084 (1.004 – 1.169); p=0.038	1.090 (1.006 – 1.182); p=0.036	1.095 (1.007 – 1.191); p=0.034
PSA[a]	0.683 (0.590 – 0.776)	1.130 (1.053 – 1.213); P=0.001	1.121 (1.043 – 1.204); p=0.002	1.111 (1.035 – 1.193); p=0.003	1.159 (1.058 – 1.269); p=0.001	0.987 (0.901 – 1.081); p=0.775
Abnormal DRE[b]	0.567 (0.467 – 0.668)	2.344 (0.932 – 5.894); p=0.070	1.818 (0.678 – 4.874); p=0.235	1.748 (0.639 – 4.778); p=0.277	1.440 (0.467 – 4.443); p=0.526	1.638 (0.524 – 5.118); p=0.396
Biopsy GS[c]	0.555 (0.454 – 0.657)	1.315 (0.785 – 2.201); p=0.298	1.216 (0.699 – 2.113); p=0.489	1.145 (0.651 – 2.014); p=0.638	1.050 (0.565 – 1.951); p=0.878	0.920 (0.475 – 1.784); p=0.806
%fPSA[d]	0.651 (0.555 – 0.747)	0.939 (0.888 – 0.992); p=0.026	--	0.944 (0.889 – 1.002); p=0.059	--	--
%p2PSA	0.724 (0.634 – 0.813)	4.882 (2.109 – 11.301); p=0.001	--	--	7.661 (2.702 – 21.724); p<0.001	--
PHI[e]	0.818 (0.746 – 0.890)	1.079 (1.043 – 1.116); p<0.001	--	--	--	1.086 (1.042 – 1.132); p<0.001
AUC of the multivariable models (95%CI)			0.717 (0.628 – 0.806)	0.739 (0.654 – 0.825)	0.820 (0.749 – 0.891)	0.845 (0.780 – 0.910)

[a]PSA = Prostate-specific antigen, [b]DRE = Digital rectal examination, [c]GS = Gleason score, [d]%fPSA = Percent free to total PSA, [e]PHI = prostate health index

Table 4. Univariable and multivariable analysis for Epstein significant tumor

			Multivariable analysis			
	AUC 95% CI of AUC	Univariate analysis OR (95%CI); p-value	Base model Adjust OR (95%CI); p-value	Base model + %fPSA Adjust OR (95%CI); p-value	Base model + %p2PSA Adjust OR (95%CI); p-value	Base model + PHI Adjust OR (95%CI); p-value
Age	0.597 (0.480 – 0.714)	1.055 (0.974 – 1.144); p=0.190	1.055 (0.973 – 1.144); p=0.191	1.079 (0.989 – 1.176); p=0.194	1.069 (0.973 – 1.175); p=0.165	1.074 (0.974 – 1.184); p=0.154
PSA[a]	0.610 (0.498 – 0.723)	1.075 (0.999 – 1.157); P=0.053	1.064 (0.992 – 1.142); P=0.084	1.052 (0.977 – 1.132); p=0.179	1.119 (1.006 – 1.246); p=0.039	0.904 (0.811 – 1.007); p=0.067
Abnormal DRE[b]	0.519 (0.401 – 0.637)	1.276 (0.435 – 3.746); p=0.657	0.790 (0.264 – 2.368); p=0.674	0.716 (0.223 – 2.296); p=0.574	0.489 (0.133 – 1.804); p=0.283	0.596 (0.161 – 2.207); p=0.439
Biopsy GS[c]	0.589 (0.482 – 0.697)	2.557 (0.977 – 6.689); p=0.056	2.507 (0.968 – 6.491) p=0.058	2.701 (0.948 – 7.695); p=0.063	2.572 (0.920 – 7.190); p=0.072	
%fPSA[d]	0.727 (0.636 – 0.819)	0.908 (0.854 – 0.967); p=0.002	--	0.907 (0.851 – 0.966); p=0.002	--	--
%p2PSA	0.769 (0.671 – 0.866)	9.533 (2.942 – 30.889); P<0.001	--	--	19.852 (4.671 – 84.366); p<0.001	--
PHI[e]	0.817 (0.739 – 0.895)	1.110 (1.054 – 1.169); p<0.001	--	--	--	1.139 (1.072 – 1.210); p<0.001
AUC of the multivariable models (95%CI)			0.702 (0.606 – 0.798)	0.764 (0.676 – 0.853)	0.841 (0.769 – 0.913)	0.861 (0.796 – 0.925)

[a]PSA = Prostate-specific antigen, [b]DRE = Digital rectal examination, [c]GS = Gleason score, [d]%fPSA = Percent free to total PSA, [e]PHI = prostate health index

(Table 4). In univariate analysis, PSA, biopsy GS, %fPSA, %p2PSA and PHI were all predictors for pT3 or pGS≥7. In multivariate analysis for prediction of pT3 or pGS≥7, %fPSA (OR 0.92, 95% CI 0.87-0.98), %p2PSA (OR 3.29, 95% CI 1.50-7.20), and PHI (OR 1.03, 95% CI 1.01-1.06) were all independent predictors. Adding %fPSA, %p2PSA, or PHI to the base model (age, PSA, abnormal DRE, biopsy GS) improved the AUC from 71.7% to 75.7%, 79.6%, and 78.9% respectively.

For prediction of tumor volume >0.5ml (Table 3), %p2PSA and PHI (but not %fPSA) were independent predictors, and adding %p2PSA or PHI to the base model improved the AUC from 71.7% to 82.0% and 84.5% respectively. For prediction of Epstein significant tumor (Table 4), adding %fPSA, %p2PSA or PHI to the base model improved AUC from 70.2% to 76.4%, 84.1%, and 86.1% respectively.

The DCA curves were plotted for tumor volume >0.5ml and pT3 or pGS≥7. Net clinical benefit was observed in using PHI (comparing with %fPSA and PSA) to predict tumor volume >0.5ml (Figure 1) across the whole range of threshold probability beyond 20% (the probability of tumor volume >0.5ml that the patient would opt for treatment). Net clinical benefit was also observed in using PHI for prediction of pT3 or pGS≥7 (Figure not shown) between the threshold probability of 20% and 45%.

Low and very low risk patients according to NCCN criteria were analyzed in subgroups for the effect of PHI on upgrading and upstaging. There were 29 low risk and 25 very low risk patients. 6 out of 29 low risk patients had upgrade of Gleason score, with upgraded patients having a significantly higher PHI values (42.8 Vs 31.9, p=0.032, T-test). Only 2 out of 25 very low risk patients had an upgrade of Gleason score, and analysis was not

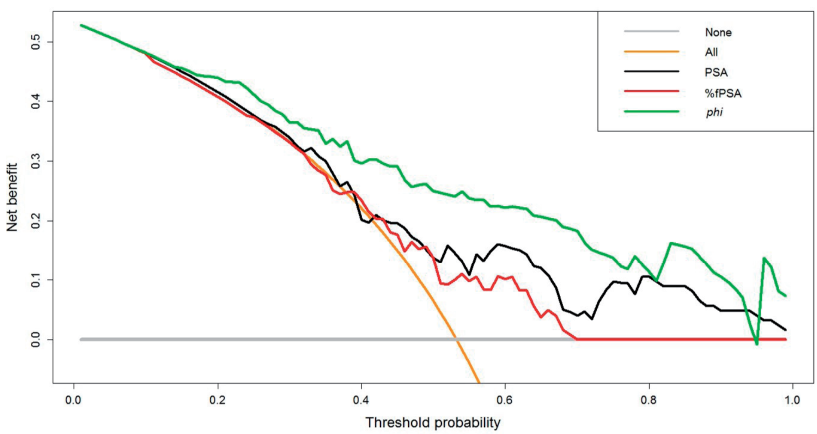

Figure 1. Decision curve analysis for prediction of tumor volume >0.5 ml, comparing PSA, %fPSA, and PHI. The x-axis (threshold probability) is probability of tumor volume >0.5 ml that patient would opt for treatment; y-axis is net clinical benefit of different models

meaningful due to small event number. 22 out of 29 (75.9%) low risk patients had upstage to pT2b or above, with upstaged patients having significantly higher phi values (36.8 Vs 26.0, p=0.023, T-test). 20 out of 25 (80.0%) very low risk patients had upstage to pT2b or above, but the difference in PHI values did not reach statistical significance.

DISCUSSION

This study investigated the association of PHI and %p2PSA with RP final pathology in a Chinese cohort. Our results supported that PHI or %p2PSA could predict RP pathological outcomes including pT3, pGS, upgrade of GS, tumor volume >0.5ml and Epstein significant tumor. A commonly used PHI diagnostic cutoff [4] of 35 was also associated with an increase in risk of pT3 or pGS≥7 disease from 16.1% to 60.8%, and an increase in risk of significant tumor volume (0.5ml) from 25.5% to 72.6%.

In multivariate analyses, adding PHI or %p2PSA to the base model (age, PSA, abnormal DRE, and biopsy GS) improved AUC for predicting pT3 or pGS≥7 by 7.2% and 7.9% respectively, improved AUC for predicting significant tumor volume (0.5ml) by 12.8% and 10.3% respectively, and improved AUC for predicting Epstein significant tumor by 15.9% and 13.9% respectively. To date, this is the first study to investigate association of PHI or %p2PSA with radical prostatectomy final pathology in Chinese men.

There were 4 previously published papers on relationship of p2PSA or PHI with surgical pathology, and all of them were performed in European men.[1, 9-11] The RP pathologic outcomes of a study on Dutch and Austrian men showed that PHI value was significantly higher in Dutch men with pathologic GS ≥7 (42.4 Vs 36.3) but not in Austrian men, and there was no significant difference in %p2PSA values for GS ≥7 in both Dutch and Austrian men.[1] A study on Italian men reported that PHI and %p2PSA accurately predicted RP pathological outcomes including pT3 status (by AUC 2.4-2.5%), pathologic Gleason sum (by AUC 6.0%), Gleason sum upgrading (by AUC 5.1-5.7%), and tumor volume <0.5ml (by AUC 3.8-4.2%) in multivariate analyses.[9] A study on German men reported that PHI or %p2PSA were not independent predictors of RP pathological outcomes in multivariate analysis, but using a p2PSA cutoff of 22.5pg/ml could slightly improve the predictive accuracy of pT3 disease (by 3.6% in AUC) but not pGS.[10] A multi-centre European study had shown PHI or %p2PSA could improve AUC by 1.2% and 2.3%, respectively, over base model in predicting pT3 or pGS ≥7 in multivariate analyses.[11] In the current study, the absolute improvements of AUC in prediction of various pathologic outcomes in Chinese men were more pronounced compared with that in European men. This might be due to differences in prostate cancer epidemiology (incidence of prostate cancer and aggressive prostate cancer) and ethnicity in performance of PHI or %p2PSA.

As the primary objective of the current study was to correlate PHI & %p2PSA with prostatectomy pathology, all study bloods were taken 1 day before surgery to allow more accurate prediction. In application of the PSA isoforms at the time of screening (systematic or opportunistic), a higher %p2PSA or PHI would allow better prediction of the likelihood of more advanced prostate cancer at that moment, and patients could be better counselled on biopsy and treatment options.

Combining with existing markers including age, PSA, %fPSA, biopsy GS, and abnormal DRE, PHI or %p2PSA could improve the accuracy in predicting indolent tumor in terms of ≤pT2c and pGS≤6, Epstein insignificant tumor or tumor volume <0.5ml. As more and more non-aggressive prostate cancers are diagnosed in the PSA era, accurate prediction of non-aggressive tumors could aid in patient counselling on selection of appropriate intervention including radical treatment or active surveillance. As the definition of insignificant tumor in RP specimen is controversial[18-20], we used 3 different definitions for this purpose (≤pT2c and pGS≤6, Epstein insignificant tumor, or tumor volume <0.5ml).

In decision curve analyses with PHI, net clinical benefit was seen for pT3 or pGS≥7 in the range of threshold probability of 20-45%, and in the whole range of threshold probability for tumor volume >0.5ml. On the contrary, the decision curve analyses in the studies by Guazzoni et al[9] and Fossati et al[11] showed no significant net clinical benefit. We postulate that the difference might be due to much higher proportion (up to 70%) of patients having clinically aggressive disease (pT3 or pGS≥7) in the two European cohorts, comparing with only 42.2% in the current Chinese cohort. It should be emphasized that, at similar median PSA levels (Guazzoni[9] 5.89 ng/mL, Fossati[11] 5.25 ng/mL, Current study 9.0 ng/mL) and proportion of abnormal DRE (Guazzoni[9] 13%, Fossati[11] 30%, Current study 20.8%), the proportion of clinically aggressive prostate cancers were much higher in Caucasian than in Chinese. Incorporating PHI or %p2PSA to existing markers provided net clinical benefit in predicting pT3 or pGS≥7 in Chinese population with lower incidence of clinically aggressive disease.

The strengths of the study included the prospective collection of clinical data and blood samples, the adherence of blood processing to recommended protocol[15], the analyses of final RP pathology instead of biopsy pathology, the reporting of pathologic outcomes by experienced genitourinary pathologists, and the use of both multivariate analyses and decision curve analyses for assessment of statistical and clinical significance. The weaknesses of this study included relatively small sample size and lack of comparison with other nomograms, imagings, or markers. In conclusion, addition of PHI or %p2PSA to existing markers improved predictive accuracy of RP pathological outcomes in Chinese patients, and enabled more accurate prediction of non-aggressive cancers for better counselling on intervention.

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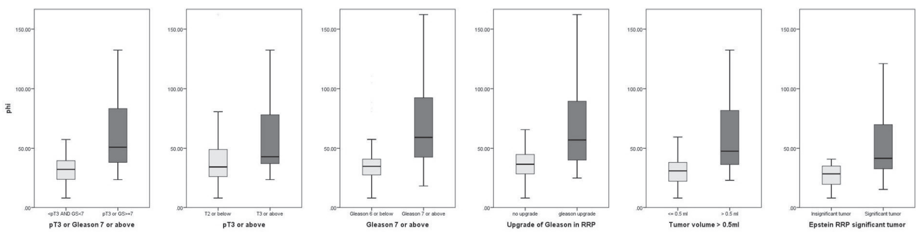
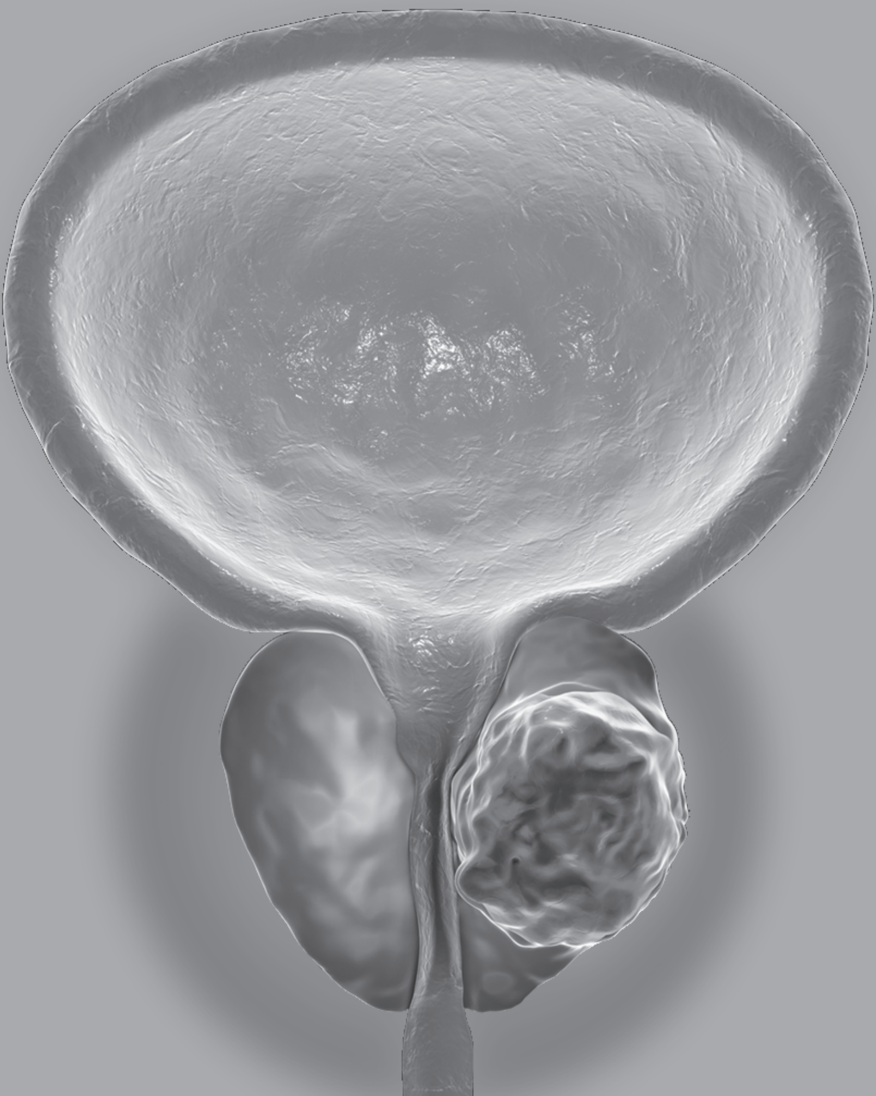
SUPPLEMENT



Supplementary Figure 1. Boxplot of PHI values for different pathologic outcomes.



CHAPTER 9

A multi-centre evaluation of the role of Prostate health index (PHI) in regions with a different prevalence of prostate cancer: adjustment of PHI reference ranges is needed for European and Asian settings

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ABSTRACT

Asian have a lower incidence of prostate cancer(PCa). This study aims to compare the performance of Prostate health index(PHI) in different ethnic groups. 2488 men (1688 Asian and 800 European men from 9 sites) with PSA 2-20ng/mL, PHI test results and transrectal ultrasound-guided biopsy performed were included. 1652 men had PSA 2-10ng/mL, normal digital rectal examination(DRE) and underwent initial biopsy. The proportions of PCa(Gleason≥6) and higher grade PCa(HGPCa, Gleason≥7) across different PHI ranges were compared. The performance of PSA and PHI were compared using area under curve(AUC) and decision curve analyses(DCA). In Asian men, HGPCa was diagnosed in 1.0%(PHI<25), 1.9%(PHI 25-35), 13%(PHI 35-55), and 30%(PHI>55) of men. At 90% sensitivity for HGPCa(PHI>30), 56% biopsies and 33% Gleason 6 cancer diagnoses could have been avoided. In European men, HGPCa was diagnosed in 4.1%(PHI<25), 4.3%(PHI 25-35), 30%(PHI 35-55), and 34%(PHI>55) of men. At 90% sensitivity for HGPCa(PHI>40), 40% biopsies and 31% Gleason 6 cancer diagnoses could have been avoided. AUC and DCA confirmed benefit of PHI over PSA. The benefit of PHI was also seen at repeat biopsy(n=397) or PSA 10-20ng/ml(n=439). PHI is effective in cancer risk stratification in both European and Asian men. Population-specific PHI reference ranges should however be used.

PATIENT SUMMARY

The blood test Prostate Health Index(PHI) helps to identify men at higher risk of prostate cancer in both Asian and European, and could significantly reduce unnecessary biopsies and over-diagnosis of prostate cancer. Different PHI reference ranges should be used for different ethnic groups.

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

This is a European and Asian multicentre study including 9 clinical sites. European sites include Paris and Rennes(France), Hamburg and Muenster(Germany). 90-98% men are Caucasian in the European cohorts. Asian sites include Asian men from Hong Kong and Shanghai(China), Singapore, Tai Chung and Taipei(Taiwan). Men with PSA 2-20ng/ml(Hybritech calibration) and 10-12 core transrectal ultrasound(TRUS) guided systematic prostate biopsies performed were included. A pre-biopsy blood was taken, centrifuged within 3 hours, immediately stored at −80°C, and subsequently analyzed for PSA, fPSA, and [-2]proPSA(p2PSA)(Beckman Coulter immunoassay system, Fullerton, CA, USA).[7] Prostate Health Index(PHI) was calculated using the formula p2PSA/fPSA x√PSA. Outcomes included PCa and higher grade PCa(HGPCa, Gleason 3+4 or above). 2488 men(1688 Asian and 800 European) with PSA 2-20ng/mL and normal DRE were included for analyses.

The cohort was divided into 3 different groups for separate analyses:
Group 1(n=1652): PSA 2-10ng/mL, normal DRE, and initial biopsies,
Group 2(n=397): PSA 2-10ng/mL, normal DRE and repeat biopsies,
Group 3(n=439): PSA 10-20ng/mL and normal DRE.

The baseline characteristics of the European and Asian cohorts in Group 1 are listed in Supplementary Table 1. The European cohorts have a higher percentage of repeat biopsies and median PHI, a lower PSA level, and similar median prostate size compared with the Asian cohorts. The PCa detection rates in European and Asian men(Group 1) for different PHI ranges are listed in Table 1. PCa and HGPCa risks in European men were 4 times higher as compared to Asian men(Chi-square test,p<0.001).

Table 1. Prostate cancers in different Prostate health index (PHI) ranges, for men with PSA 2-10 ng/mL, normal DRE and initial biopsies (Group 1).

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

*Chi-square tests for Cancer Vs PHI ranges (PHI <25, PHI 25-35, PHI 35-55, and PHI >55)

The AUC of ROC curves when predicting PCa are listed in Supplementary Table 2. In predicting PCa and Gleason≥7 PCa, PHI had the highest AUC in both European and Asian cohorts, except for Gleason≥3+4 PCa in European men where PHI performed similar to PSA density.

Table 2, based on men in Group 1, depicts sensitivity, specificity, and the number of prostate biopsies that could have been saved for different PHI cutoffs in relation to HGPCa. The number of HGPCa missed and Gleason 6 cancer diagnoses avoided is listed for each cutoff. In European men, at 90% sensitivity for HGPCa(PHI 40), 40% biopsies and 31% Gleason 6 cancer diagnoses could have been avoided. In Asian men, at 90% sensitivity for HGPCa(PHI 30), 56% biopsies and 33% Gleason 6 cancer diagnoses could have been avoided. In the case of Gleason ≥4+3 PCa, PHI cutoff was 40 at 90% sensitivity in European, while saving 40%(201/503) biopsies and 31%(45/147) Gleason 6 cancers. For Asian Gleason≥4+3 PCa, PHI cutoff was 30 at 90% sensitivity, while saving 53%(605/1149) biopsies and 26%(22/85) Gleason 6 cancers.

Group 2 included 397 men with PSA 2-10, normal DRE, and repeat biopsies. 75% of men were European. Median PSA was 5.9(IQR 4.5-7.4)ng/mL. Supplementary Table 3 shows PCa diagnosis at different PHI ranges. The AUC's for PCa are: PHI 0.78, PHI density 0.73, PSA density 0.58, and PSA 0.44. The AUC's for HGPCa are: PHI 0.78, PHI density 0.74, PSA density 0.66, and PSA 0.52.

Group 3 included 439 Asian men with PSA 10-20ng/mL and normal DRE. The small number(n=33, 7%) of European men were not included in the analysis. Median PSA was 13(IQR 11-15)ng/mL. Supplementary Table 3 shows PCa diagnosis at different PHI ranges.

Table 2. Biopsies and Gleason 6 cancers that can be reduced with different PHI cutoffs (for Gleason 7 or above cancers) in European and Asian cohorts.

	PHI cutoff	**Sensitivity (for HGPCa)**	**Specificity (for HGPCa)**	**Biopsy saved if all below cutoff NOT biopsied (% of all biopsies, n=503)**	**Gleason ≥7 cancers missed (% of all Gleason ≥7 cancers, n=115)**	**Gleason 6 cancer diagnosis reduced (% of all Gleason 6 cancers, n=147)**
	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%)**
European (n=503)	**55**	**53%**	**72%**	**343 (68%)**	**60 (52%)**	**87 (59%)**
Asian (n=1149)	PHI cutoff	Sensitivity (for HGPCa)	Specificity (for HGPCa)	Biopsy saved if all below cutoff NOT biopsied (% of all biopsies, n=1149)	Gleason ≥7 cancers missed (% of all Gleason ≥7 cancers, n=66)	Gleason 6 cancers diagnosis reduced (% of all Gleason 6 cancers, n=85)
	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%)

The AUC's for PCa are: PHI 0.76, PHI density 0.77, PSA density 0.67, PSA 0.47. The AUC's for HGPCa are: PHI 0.77, PHI density 0.81, PSA density 0.75, and PSA 0.44.

DCA curves for different biopsy indication scenarios are shown in Supplementary Figure 1. In all scenarios, net clinical benefit of PHI was higher as compared to all other markers, except in Group 1 European cohorts(Figure 1d) where PHI showed similar performance to PSA density in predicting HGPCa.

We created forest plots showing the odd's ratio of PHI in the different centres for the different outcomes in Group 1. These forest plots showed substantial heterogeneity of the effect of PHI when predicting the presence of cancer. The grouping factor Asia/Europe was able to explain the observed heterogeneity partly. For the outcomes any PCa and Gleason ≥4+3 there was no statistically significant residual heterogeneity, while there was some residual heterogeneity for Gleason≥3+4. After subdividing Europe into the countries there was no statistically significant residual heterogeneity. Therefore we presented results grouped by continent across all outcomes.

Men in the European cohort had a 4 times higher risk of PCa and HGPCa as compared to Asian men. Baseline age and PSA was higher in Asian while prostate size was comparable. All 9 cohorts were clinically referred patients and not from any structured PSA screening program. The differences in cancer risk are likely related to ethnical differences.

Druskin et al. reported PHI density(AUC 0.82) having better performance than PHI(AUC 0.79) in predicting clinically significant PCa.[8] In the current study, PHI density did not perform better than PHI in most scenarios except Group 3. The larger sample size and multi-ethnicity in the current study may be more representative concerning the usefulness of PHI density.

Other well performing tools for PCa diagnosis (e.g. risk calculators) include PSA density, requiring an estimate of prostate volumes.[9] Multiparametric MRI prostate improves diagnosis of clinically significant prostate cancer[10], but in general is related to higher costs and requires radiological expertise. MRI and PHI is shown to be complementary to each other as each modality missed some significant PCa.[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 likely go down with time, the role of PHI as a screening tool is worth investigating.

There are certain strengths in the current study, which include the largest sample size to date for PHI research, and the involvement of different ethnic groups from 9 sites. The limitations include: 1. Very few prostate MRIs done and potential under-diagnosis, 2. Lack of biopsy information like number of positive cores or percentage of cancer in each core, 3. No cost effectiveness analysis as the costs in each site are different.

In conclusion, PHI was shown to be more effective than PSA density, %fPSA, or PSA in predicting PCa in all subgroups including PSA 2-10ng/mL, PSA 10-20ng/mL, or any history of prior negative biopsy. By using PHI, more biopsies could have been avoided in Asian men(56% vs 40%) while reducing 30% Gleason 6 diagnoses in both groups. Population-specific PHI reference ranges and cutoff values should be formulated.

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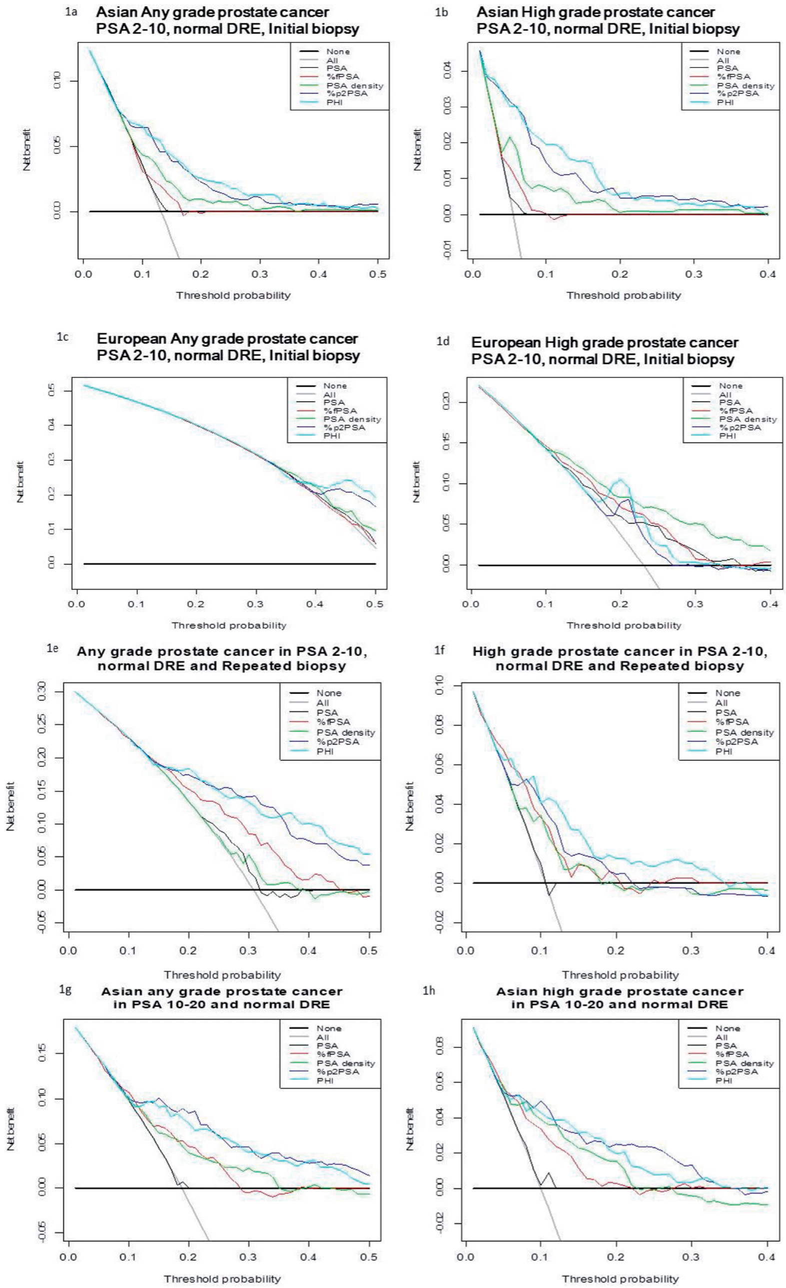
SUPPLEMENT



Supplementary Figure 1. Decision curve analyses of different scenarios (1a-1h).

Supplementary Table 1. Baseline characteristics of men with PSA 2-10, normal DRE, and initial biopsies.

	European N=503	**Asian N=1149**	**p-value**
Age at TRUS biopsy, median (IQR)	63 (58-68)	65 (61-71)	<0.001
TRUS volume (ml), median (IQR)*	41 (31-54)	43 (32-58)	0.449
PSA (ng/ml), median (IQR)	5.0 (4.0-6.4)	6.4 (5.3-7.8)	<0.001
% Free PSA, median (IQR)	0.14 (0.10-0.18)	0.19 (0.14-0.24)	<0.001
%p2PSA (%), median (IQR)	2.1 (1.5-2.7)	1.1 (0.90-1.5)	<0.001
PHI, median (IQR)	45 (33-62)	29 (23-37)	<0.001
PCa	262 (52%)	151 (13%)	<0.001
HGPCa	115 (23%)	66 (5.7%)	<0.001

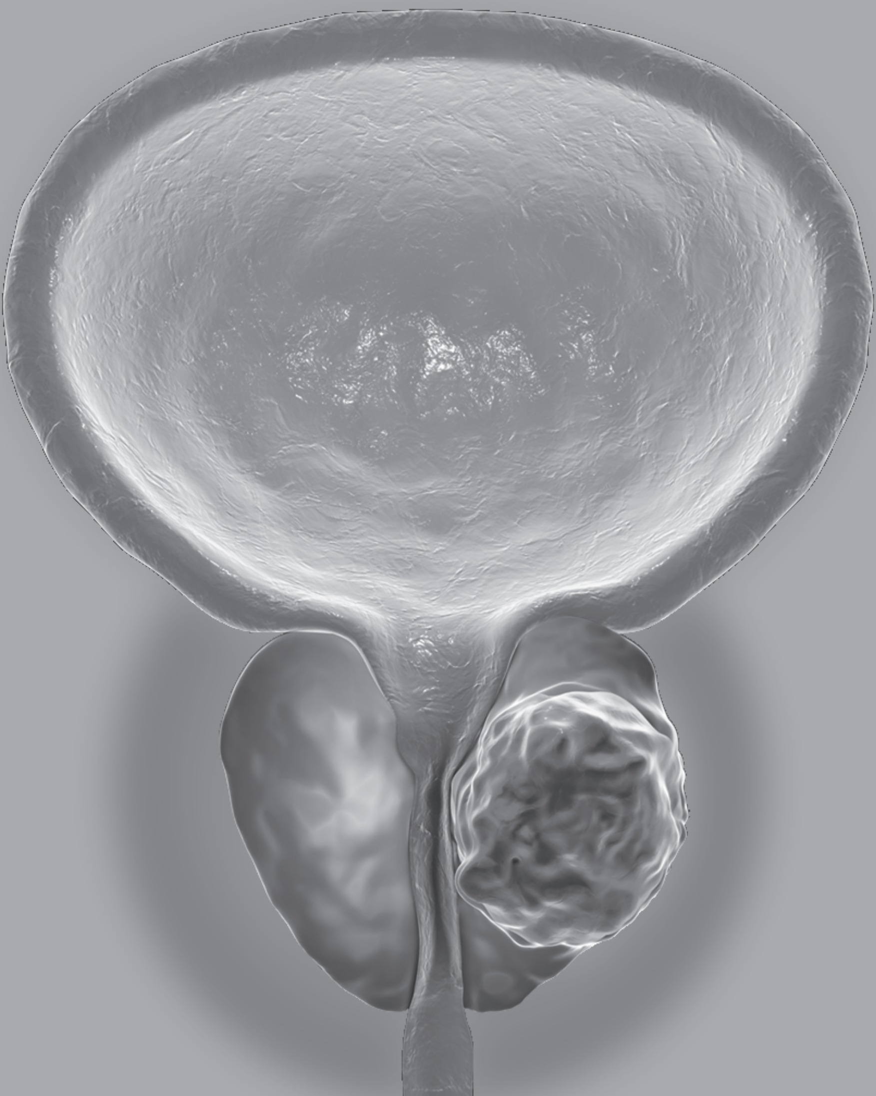
*TRUS volume measured by Ellipsoid formula. Missing data in TRUS volume: 1 in European, 74 in Asian.

Supplementary Table 2. Area-under-curve (AUC) in predicting prostate cancer (Group 1).

	Any grade PCa		Gleason ≥ 3+4 PCa		Gleason ≥ 4+3 PCa	
AUC (95% CI)	**European**	**Asian**	**European**	**Asian**	**European**	**Asian**
PSA	0.56 (0.51-0.61)	0.51 (0.46-0.56)	0.63 (0.58-0.69)	0.54 (0.46-0.62)	0.60 (0.50-0.69)	0.44 (0.32-0.62)
%free PSA	0.59 (0.54-0.64)	0.58 (0.53-0.63)	0.66 (0.60-0.71)	0.63 (0.55-0.70)	0.62 (0.52-0.71)	0.59 (0.48-0.70)
PSA density	0.63 (0.58-0.67)	0.66 (0.61-0.71)	0.72 (0.67-0.77)	0.70 (0.63-0.78)	0.64 (0.55-0.73)	0.57 (0.44-0.69)
%p2PSA	0.69 (0.64-0.74)	0.73 (0.69-0.78)	0.67 (0.61-0.72)	0.83 (0.78-0.89)	0.65 (0.56-0.74)	0.79 (0.69-0.88)
PHI	0.71 (0.66-0.76)	0.74 (0.70-0.79)	0.71 (0.66-0.76)	0.84 (0.78-0.89)	0.68 (0.60-0.77)	0.79 (0.69-0.88)
PHI density	0.69 (0.64-0.73)	0.74 (0.70-0.79)	0.72 (0.68-0.76)	0.82 (0.76-0.88)	0.66 (0.58-0.74)	0.73 (0.63-0.84)

Supplementary Table 3. Prostate cancers (PCa) and High grade prostate cancers (HGPCa) in different Prostate health index (PHI) ranges for Groups 2 and 3.

Group	Racial distribution	PHI	<25	25-35	35-55	>55	Total	p-value
Group 2: PSA 2-10, normal DRE, Repeated biopsy N=397	25% Asian 75% European	PCa	13% (8/64)	12% (14/115)	35% (50/144)	68% (50/74)	31% (122/397)	<0.001
		HGPCa	0% (0/64)	5.2% (6/115)	10% (15/144)	28% (21/74)	11% (42/397)	<0.001
Group 3: PSA 10-20, Normal DRE N=439	100% Asian	PCa	9.0% (7/78)	5.5% (8/145)	20% (27/137)	51% (40/79)	19% (82/439)	<0.001
		HGPCa	2.6% (2/78)	3.4% (5/145)	8.8% (12/137)	30% (24/79)	9.8% (43/439)	<0.001



CHAPTER 10

Prostate health index (PHI) and Prostate specific antigen (PSA) predictive models for prostate cancer in the Chinese population and the role of digital rectal examination estimated prostate volume

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ABSTRACT

Purpose

To investigate PSA and PHI(prostate health index)-based models for prediction of prostate cancer(PCa) and the feasibility of using DRE estimated prostate volume(DRE-PV) in the models.

Methods

This study included 569 Chinese men with PSA 4-10ng/mL and non-suspicious DRE with transrectal ultrasound(TRUS) 10-core prostate biopsies performed between April 2008 and July 2015. DRE-PV was estimated using 3 pre-defined classes: 25ml, 40ml or 60ml. The performance of PSA-based and PHI-based predictive models including age, DRE-PV, and TRUS prostate volume(TRUS-PV) were analyzed using logistic regression and area under the receiver operating curves(AUC), in both the whole cohort and the screening age group of 55-75.

Results

PCa and high grade PCa(HGPCa) was diagnosed in 10.9%(62/569) and 2.8%(16/569) men, respectively. The performance of DRE-PV based models was similar to TRUS-PV based models. In the age group 55-75, the AUCs for PCa of PSA alone, PSA with DRE-PV and Age, PHI alone, PHI with DRE-PV and Age, and PHI with TRUS-PV and Age were 0.54, 0.71, 0.76, 0.78, and 0.78, respectively. The corresponding AUCs for HGPCa were higher(0.60, 0.70, 0.85, 0.83, and 0.83). At 10% and 20% risk threshold for PCa, 38.4% and 55.4% biopsies could be avoided in the PHI-based model, respectively.

Conclusions

PHI had better performance over PSA-based models and could reduce unnecessary biopsies. A DRE assessed PV can replace TRUS assessed PV in multivariate prediction models to facilitate clinical use.

INTRODUCTION

Prostate specific antigen(PSA) is widely used as a screening tool for prostate cancer(PCa), either in a systematic or opportunistic manner. However, due to its poor predictive ability, the sole use of PSA resulted in a lot of unnecessary biopsies and treatments [1-2]. Incorporation of clinical parameters in a multivariate risk stratification can improve the performance of screening [3-5]. Commonly used risk calculators used parameters including age, digital rectal examination(DRE) finding, prostate volume, ultrasound lesion, and history of prior negative biopsy [3-5].

Prostate health index(PHI) was shown to be a significantly better marker than PSA or free PSA in predicting PCa and high grade prostate cancers(HGPCa), and using PHI could further reduce unnecessary biopsies [6-8]. Similar to the case of PSA-based risk calculators, combining PHI with other clinical parameters could further improve the prediction of PCa [9-10].

Transrectal ultrasound(TRUS) prostate volume(PV) was shown to improve risk stratification in PSA or PHI-based risk calculators [4,11]. In real life practice, prostate volume measurement by TRUS is an extra procedure and is not convenient as a part of screening. DRE is a routinely performed examination in men at risk of PCa. It has been shown in the ERSPC risk calculator that using DRE estimation of prostate size as part of the risk stratification resulted in similar cancer prediction compared with TRUS detected prostate volume in Caucasian [4].

The positive biopsy rate in the 'diagnostic gray zone' of PSA 4-10ng/mL varied across different ethnic groups and countries [12]. Studies have shown that positive biopsy rates were about 30%(range 26-47%) in Caucasians [12], and only 15-25% in Asian [13]. In a contemporary Hong Kong Chinese cohort of men with PSA 4-10ng/mL and normal DRE, the positive biopsy rate was as low as 13.4% [14]. In these patient groups, up to 85% of biopsies were unnecessary, and therefore better risk stratification specific to Asian or Chinese is needed.

In this study, we assessed the role of DRE estimated prostate volume in PSA and PHI-based PCa risk prediction models in a cohort of Chinese men.

MATERIALS AND METHODS

This is a prospective cohort recruiting consecutive patients with PSA 4-10ng/mL and non-suspicious digital rectal examination(DRE), with or without lower urinary tract symptoms, who consented before prostate biopsy. The blood samples were processed according to the criteria described by Semjonow et al [15]. The bloods were centrifuged within 3 hours, immediately stored at -80°C, and subsequently analyzed for PSA, free PSA and p2PSA using the Beckman Coulter Access 2 Immunoassay System(Beckman Coulter Inc., Brea, CA, USA). The exclusion criteria included patients with known history of prostate cancer, any suspicious DRE finding, and use of androgen deprivation therapy or 5 alpha-reductase inhibitors before the study. Patients with abnormal or suspicious DRE were excluded as PHI was approved by the United States Food and Drug Administration(FDA) for patients with normal DRE.

Immediately after blood taking, patients were placed in left lateral decubitus position with DRE performed by a Urology resident. DRE prostate volume(DRE-PV) was estimated by the doctor and recorded by a nurse at that moment. For cases before 2012, the exact estimated DRE-PV was subsequently reclassified into one of the 3 classes: <30ml(coded as 25ml), 30-50ml(coded as 40ml), or >50ml(coded as 60ml). Since 2012, the DRE-PV was directly recorded into one of the 3 classes as stated above. After DRE, TRUS prostate volume(TRUS-PV) was measured using the ellipsoid formula. A systematic 10-core TRUS guided prostate biopsy was then performed according to the standardized protocol. The biopsies were evaluated by genitourinary pathologists blinded to the blood results. PCa were graded according to the International Society of Urological Pathology 2005 consensus [16]. This study conformed to the provisions of the Declaration of Helsinki, and was approved by the ethics committee of our hospital. Informed consent was signed by each patient.

The primary objective of this study was to compare the performance of various parameters in predicting PCa and HGPCa(Gleason score 7 or above). The parameters included PSA(Hybritech calibration), Prostate health index(PHI), and other clinical parameters including age, previous negative biopsy(PNBx), TRUS-PV, and DRE-PV. %free PSA(%fPSA) was calculated by dividing free PSA by total PSA. %p2PSA was calculated using the formula p2PSA/freePSA. Prostate health index (PHI) was calculated using the formula (p2PSA/freePSA)x $\sqrt{PSA}$.

Statistically significant differences in patient characteristics between cancer and non-cancer patients were assessed using the Mann-Whitney U test for continuous data and the chi-square test for categorical data. Commonly used PHI cutoffs of 25, 35, and 55 as suggested by Catalona [6] were used to stratify the risk of PCa and HGPCa. Multivariate analyses were performed for both PSA and PHI, including base parameters of age, DRE-PV, and PNBx. The areas under the curves(AUC) of the receiver operating characteristic(ROC) were listed for different models, and the regression models were compared using the likelihood ratio test. Predictors including PSA, %fPSA, %p2PSA, PHI, TRUS-PV, and DRE-PV were 2-log transformed before regression and AUC analyses. Analyses were performed separately for the whole cohort and for the screening age of 55-75 years, and results were mainly presented in the latter group in which application of screening tests is most appropriate. IBM SPSS Statistics for Windows version 22(IBM Corp., Armonk, NY, USA) was used for statistical analyses. A 2-sided p-value of <0.05 was considered significant.

RESULTS

Between April 2008 and July 2015, 2779 TRUS biopsies were performed, with 1314 patients with PSA 4-10ng/mL and non-suspicious DRE. Among them, 569 patients consented for extra blood taking before TRUS biopsy and were included in the current study. Complete clinical parameter data and TRUS biopsies were available. The baseline demographic information of the whole cohort(n=569), the screening age group of 55-75 years(n=505), and cancer and non-cancer patients are listed in Table 1. PCa was diagnosed in 62 out of 569(10.9%) patients in the whole cohort, and in 56 out of 505(11.1%) men in the age group of 55-75. Similar data for HGPCa were 16 out of 569 men (2.8%) and 16 out of 505 men (3.2%) respectively. There was no significant difference in clinical and blood based parameters between the whole cohort and the group with age 55-75. In PCa patients, age, %fPSA, %p2PSA, and PHI were significantly higher, while TRUS-PV and DRE-PV were significantly lower (Table 1). The PSA values between cancer and non-cancer patients were not significantly different. For the comparison of patients who consented for extra

Table 1. Baseline characteristics

Median IQR[a]	Age 55-75 n=505	Overall n=569	Non Cancer n=507	Cancer patients n=62	p-value
Age (years)	66 62 - 70	66 61 - 71	66 61 - 71	69 64 - 73	0.005 [g]
PSA (ng/mL)	6.70 5.63 - 7.97	6.73 5.64 – 8.03	6.74 5.59 – 8.02	6.59 5.96 – 8.35	0.532 [g]
TRUS-PV[b] (ml)	46.0 34.5 - 60.7	46.0 33.9 – 60.9	47.6 35.6 – 62.3	34.0 26.0 – 46.3	<0.001 [g]
DRE-PV[c] (ml)					<0.001 [h]
<30ml (25ml)	120 (23.8%)	142 (25.0%)	116(22.9%)	26 (41.9%)	
30-50ml (40ml)	198 (39.2%)	218 (38.3%)	192(37.9%)	26 (41.9%)	
>50ml (60ml)	187 (37.0%)	209 (36.7%)	199(39.3%)	10 (16.1%)	
Repeated Biopsy (%)	72 (14.3%)	81 (14.1%)	76 (15.0%)	5 (8.1%)	0.141 [h]
%fPSA[d] (%)	0.19 0.15 – 0.25	0.20 0.15 – 0.25	0.20 0.15-0.25	0.16 0.13 – 0.21	0.003 [g]
%p2PSA[e] (%)	1.12 0.90 – 1.38	1.12 0.89 – 1.40	1.08 0.86 – 1.34	1.46 1.21 – 1.75	<0.001 [g]
PHI[f]	28.7 23.2 – 35.7	28.5 23.0 - 35.8	27.6 22.6 – 33.9	38.2 30.1 – 44.6	<0.001 [g]

[a] IQR = Inter-quartile range, [b] TRUS-PV = Transrectal ultrasound prostate volume, [c] DRE-PV = Digital rectal examination prostate volume, [d] %fPSA = free PSA / total PSA, [e] %p2PSA = p2PSA / free PSA, [f] PHI = prostate health index. [g] Mann-Whitney U-test, between cancer and non-cancer patients. [h] Chi-square test, between cancer and non-cancer patients.

Table 2. Prostate cancers and High grade prostate cancers in different Prostate health index (PHI) ranges (Whole cohort)

PHI	<25	25-35	35-55	>55	Total	p-value
Prostate cancer	7/192 (3.6%)	17/225 (7.6%)	30/131 (22.9%)	8/21 (38.1%)	569	<0.001
High grade prostate cancer	1/192 (0.5%)	2/225 (0.9%)	9/131 (6.9%)	4/21 (19.0%)	569	<0.001
Gleason scores of high grade prostate cancer	3+5 (n=1)	3+4 (n=1) 3+5 (n=1)	3+4 (n=5) 3+5 (n=1) 4+5 (n=3)	3+4 (n=3) 4+5 (n=1)		

PHI blood taking before TRUS biopsy with those who did not, the baseline characteristics including age, PSA, TRUS-PV, PCa rates and HGPCa rates had no significant difference.

Numbers of PCa and HGPCa diagnosed within the various commonly used PHI ranges are shown in Table 2(whole cohort). Using PHI 35 as a cutoff stratified the risk of PCa to 5.8%(24/417) in PHI <35 and 25.0%(38/152) in PHI >35. Similarly, PHI 35 cutoff stratified the risk of HGPCa to 0.7%(3/417) in PHI <35 and 8.6%(13/152) in PHI >35.

The AUCs of PSA and PHI-based predictive models incorporating TRUS-PV, DRE-PV, and age for the group 55-75 years were shown in Table 3. Adding TRUS-PV and age to PSA improved the AUC of predicting PCa from 0.54 to 0.72 (likelihood ratio test, p<0.001), and improved that of predicting HGPCa from 0.60 to 0.71 (likelihood ratio test, p=0.003). Substituting TRUS-PV with DRE-PV in PSA-based models showed similar improvement of AUC compared to PSA alone.

PHI achieved the AUC of 0.76 for PCa and was better than the PSA-based models (Table 3). Adding Age and DRE-PV to PHI (model 10) further improved the AUC of predicting PCa from 0.76 to 0.78 (likelihood ratio test, p=0.009). Substituting PHI in model 10(PHI + DRE-PV + Age) with %fPSA or %p2PSA resulted in AUC of 0.71 and 0.77 respectively, while adding PSA to model 10 resulted in no additional benefit to the AUC of 0.78.

For HGPCa, adding DRE-PV and age to PSA-based model improved the AUC from 0.60 to 0.70 (likelihood ratio test, p=0.017)(Table 3). The highest AUC observed was 0.85 with PHI alone, and there was no additional benefit in AUC in adding age and/or DRE-PV to PHI (Table 3).

The number of biopsies that can be reduced at different risk thresholds for PCa and HGPCa in the age group of 55-75 were shown in Table 4. The model with PHI, DRE-PV and Age could reduce the most number of biopsies comparing with other models. At 20% risk threshold for PCa and HGPCa, 55.4% and 80.2% of the biopsies could be avoided, respectively. The results in Table 3-5 for age 55-75 had no significant difference compared with that in the whole cohort.

Table 3: Areas under the curve of the calculated probabilities of the different predictive models with Transrectal ultrasound or digital rectal examination estimated prostate volumes (in age 55-75)

	Prediction of prostate cancers			Prediction of high grade prostate cancers		
Model	**AUC**[a]	**95% CI**[b]	**p-values***	**AUC**[a]	**95% CI**[b]	**p-values**[f]
1. PSA	0.54	0.47-0.62	reference	0.60	0.48-0.72	reference
2. PSA + TRUS-PV[c]	0.68	0.61-0.76	Model 1 Vs 2, p<0.001	0.71	0.56-0.87	Model 1 Vs 2, p<0.001
3. PSA + DRE-PV[d]	0.68	0.61-0.75	Model 1 Vs 3, p<0.001	0.71	0.57-0.86	Model 1 Vs 3, p=0.010
4. PSA + TRUS-PV + Age	0.72	0.64-0.79	Model 1 Vs 4, p<0.001	0.71	0.54-0.88	Model 1 Vs 4, p=0.003
5. PSA + DRE-PV + Age	0.71	0.63-0.78	Model 1 Vs 5, p<0.001	0.70	0.54-0.86	Model 1 Vs 5, p=0.017
6. PHI[e]	0.76	0.70-0.83	Model 1 Vs 6, p<0.001	0.85	0.75-0.96	Model 1 Vs 6, p<0.001
7. PHI + TRUS-PV	0.77	0.71-0.84	Model 6 Vs 7, p=0.008	0.84	0.72-0.97	Model 6 Vs 7, p=1.000
8. PHI + DRE-PV	0.77	0.70-0.84	Model 6 Vs 8, p=0.064	0.84	0.72-0.97	Model 6 Vs 8, p=1.000
9. PHI + TRUS-PV + Age	0.78	0.72-0.85	Model 6 Vs 9, p=0.002	0.83	0.70-0.95	Model 6 Vs 9, p=1.000
10. PHI + DRE-PV + Age	0.78	0.72-0.85	Model 6 Vs 10, p=0.009 Model 5 Vs 10, p<0.001	0.83	0.71-0.96	Model 6 Vs 10, p=1.000

[a]AUC = area under the curve, [b]CI = confidence interval, [c]TRUS-PV = Transrectal ultrasound prostate volume, [d]DRE-PV = Digital rectal examination prostate volume (divided into <30ml, 30-50ml, and >50ml), [e]PHI = Prostate health index. [f]Likelihood ratio test.

Table 4. Number of biopsies that can be reduced compared to all-biopsy strategy in age 55-75 (n=505) for PSA and PHI-based calculators

	Number of biopsies reduced (%)			
All cancer				
Risk threshold	PSA	PSA + DRE-PV[a] + Age	PHI[b]	PHI + DRE-PV + Age
5%	55 (10.9%)	78 (15.4%)	110 (21.8%)	140 (27.7%)
10%	81 (16.0%)	124 (24.6%)	153 (30.3%)	194 (38.4%)
20%	105 (20.8%)	189 (37.4%)	240 (47.5%)	280 (55.4%)
30%	111 (22.0%)	285 (56.4%)	284 (56.2%)	317 (62.8%)
40%	127 (25.1%)	328 (65.0%)	309 (61.1%)	358 (70.9%)
High grade cancer				
Risk threshold	PSA	PSA + DRE-PV + Age	PHI	PHI + DRE-PV + Age
10%	94 (18.6%)	72 (14.3%)	261 (51.7%)	248 (49.1%)
20%	125 (24.8%)	232 (45.9%)	363 (71.9%)	405 (80.2%)
30%	144 (28.5%)	347 (68.7%)	371 (73.5%)	418 (82.8%)
40%	159 (31.5%)	360 (71.3%)	396 (78.4%)	450 (89.1%)

[a]DRE-PV = DRE estimated prostate volume, [b]PHI = prostate health index

The box plots of TRUS-PV against DRE-PV classes were shown in Fig 1. Although the 3 defined DRE-PV classes of 25, 40 and 60ml underestimated the median TRUS-PV of 27.3, 43.0, and 68.0ml, respectively($p<0.001$ in all 3 classes), most performances of DRE-PV in the predictive models (Table 3) were similar to that of TRUS-PV.

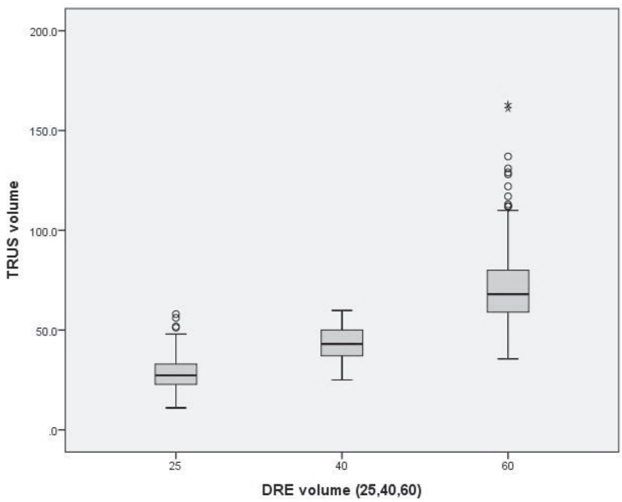

Figure 1. Box plots of TRUS prostate volume against DRE prostate volume

DISCUSSION

Prostate volume has been shown to be useful in improving performances of a number of PSA and PHI-based risk models [4-5, 9-10]. In this study, the value of using DRE prostate size estimation in the predictive models was confirmed in a contemporary Chinese cohort with 10-core biopsy done.

Although it has been shown that DRE estimation of TRUS prostate volume was only moderately well [17], dividing DRE-PV into 3 classes(25, 40, and 60ml) in the ERSPC risk calculators was found to perform as good as TRUS-PV [4]. DRE-PV in the current study performed well in both PSA and PHI-based predictive models, and its performance was comparable, if not identical, to the performance of models using TRUS-PV. All DRE-PV was performed by Urology residents in our hospital with 1-5 years of experience, and therefore it is likely that the DRE estimation would be generalizable to other doctors who perform DRE of the prostate regularly. TRUS-PV could be replaced by DRE-PV at screening, and would be more convenient in both PSA-based and PHI-based scenarios in a clinic setting.

The performance of PSA in predicting PCa in this cohort with PSA 4-10 ng/mL was poor(AUC 0.54). If only PSA was available, adding Age and Prostate volume(either TRUS or DRE) to a PSA-based model was essential to improve the AUC significantly from 0.54 to 0.72.

The AUC of PHI alone in predicting PCa was 0.76 and was better than PSA alone(0.54) or a PSA-based model(0.71-0.72). In PHI-based models, adding clinical parameters including age and DRE volumes slightly improved AUC from 0.76 to 0.78. Therefore, in the presence of PHI, the role of TRUS-PV or DRE-PV, or the ability of DRE-PV substituting TRUS-PV, would be less important than that in PSA models.

When age and DRE volumes were added, the AUC of the PHI-based model(0.78) was significantly better than that in the PSA-based model(0.71) (likelihood ratio test, $p<0.001$). Therefore, when PHI is available, PSA or PSA-based models should not be used for risk stratification. Previous negative biopsy(PNBx) did not add further benefit in terms of AUC to any predictive model(Data not shown).

PHI-based model reduced the most number of unnecessary biopsies compared with other models. More than half of the biopsies could have been avoided if the risk threshold for PCa was 20%. The effect was more pronounced in the case of HGPCa, in which 49.1% and 80.2% biopsies would have been avoided at risk thresholds of 10% and 20% respectively.

Both the whole cohort with age 36-86(n=569) and the group with age 55-75(n=505) were analyzed in this study. The majority of the analyzed results were presented in the age 55-75 group as this represented the age group where screening for prostate cancer, be it systematic or opportunistic, is most commonly done. Nevertheless, all analyses showed similar results for the 2 groups.

It has to be noted that a small percentage of high grade prostate cancers were found in PHI < 25 (n=1, Gleason 3+5), and PHI 25-35 (n=2, Gleason 3+4 and 3+5) (Table 2). Men should be counselled of this small risk of HGPCa even when PHI is <35. Subgroup analysis for different Gleason scores of HGPCa was not performed due to the small HGPCa number of 16 in this study.

Out of the 62 patients with PCa diagnosed, 33(53.2%) had radical prostatectomy performed. In PHI <35, 2 out of 13(15.4%) radical prostatectomies showed HGPCa in final pathology. In PHI >35, 8 out of 20(40.0%) radical prostatectomies showed HGPCa.

Asian men have very different PCa epidemiology compared with Western men. The PCa incidence (per 100,000) in Western men is 5-10 times more than that in most parts of Asia and 10 times more than that in Chinese men, but incidence in Asia has been increasing rapidly in recent years. [13] With the widespread use of PSA as a means of early detection, most PCa in Western were diagnosed at an early stage. This is in contrast to the situation in China, where 65% PCa were diagnosed with PSA > 10 ng/mL, and 45% PCa were either locally advanced or metastatic. However, in certain parts of China like Hong Kong and Macau, only 35% PCa were diagnosed with PSA > 10ng/mL. [13] The positive biopsy rates of PCa for PSA 4-10 ng/mL were also lower in Asian men (15-25%) [13] compared with Western men (around 30%) [12]. The above differences might be explained by genetic and lifestyle differences. The reported incidence of TMPRSS2-ERG gene fusion [18] and PTEN inactivation [19] were both lower in Asian or Chinese population, and there were significant differences in single nucleotide polymorphisms compared with Caucasians. [13] In terms of diet, Asians in general consume more vegetables and less meat than Caucasians. [13]

The strengths of this study included the validation of DRE-PV in replacing TRUS-PV in different models, the analysis in a homogeneous group of patients with PSA 4-10ng/mL with non-suspicious DRE, the collection of blood samples right before prostate biopsy, a standardized blood processing according to Semjonow et al [15], a standardized systematic 10-core biopsy protocol [20], and the analysis of all biopsy specimen by experienced genitourinary pathologists.

The PCa and HGPCa rates in the current study were much lower than that in Caucasian studies and some Asian studies [12-13]. This was related to exclusion of patients with abnormal DRE, and the actual situation of lower positive biopsy rate of PCa and HGPCa in Chinese patients. Including patients with or without PHI data in the current institution, the rate of HGPCa in men with PSA 4-10 ng/mL and normal DRE was 2.6%(53/2022), and was similar to the group with PHI data in this study(2.8%). According to another paper on PCa risks in Chinese men, the proportion of men with PSA 4-10ng/mL and normal DRE diagnosed with HGPCa and PCa were 3.8% and 13.4%, respectively [14]. They were similar to the rates in the current study (HGPCa 2.8% and PCa 10.9%). In patients with PSA 4-10ng/mL and abnormal DRE, the rates of HGPCa and PCa were 17.8% and 30.2%, respectively [14].

All men in our centre received 10 core systematic biopsy since 2008, as the EAU guidelines on prostate cancer has been recommending a systematic prostate biopsy of 10-12 cores in recent years until the latest version in 2016. [21] A study by Yoon et al [20] has shown that the positive biopsy rates of 10 and 12 cores are similar at 26.4% and 28.4% respectively (p=0.378) in a group of men with mean PSA of 10.9 +/- 15.3 ng/mL. In our study, it is possible that men with larger prostates might have an underestimated positive biopsy rate, but it is very unlikely to have a real impact on outcome considering that our PSA range was PSA of 4-10 ng/mL.

Other weaknesses of this study included limited sample size, single institution data, and the fact that the results could not be applied to patients with abnormal DRE. A limited sample size and single institution data in our study implied that the PSA and PHI-based models need to be externally validated in another Chinese or Asian population before implementation.

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CHAPTER 11

A prospective evaluation of prostate health index (PHI) in guiding prostate biopsy decisions in a large clinical cohort of Hong Kong Chinese men with 2 years of follow-up data

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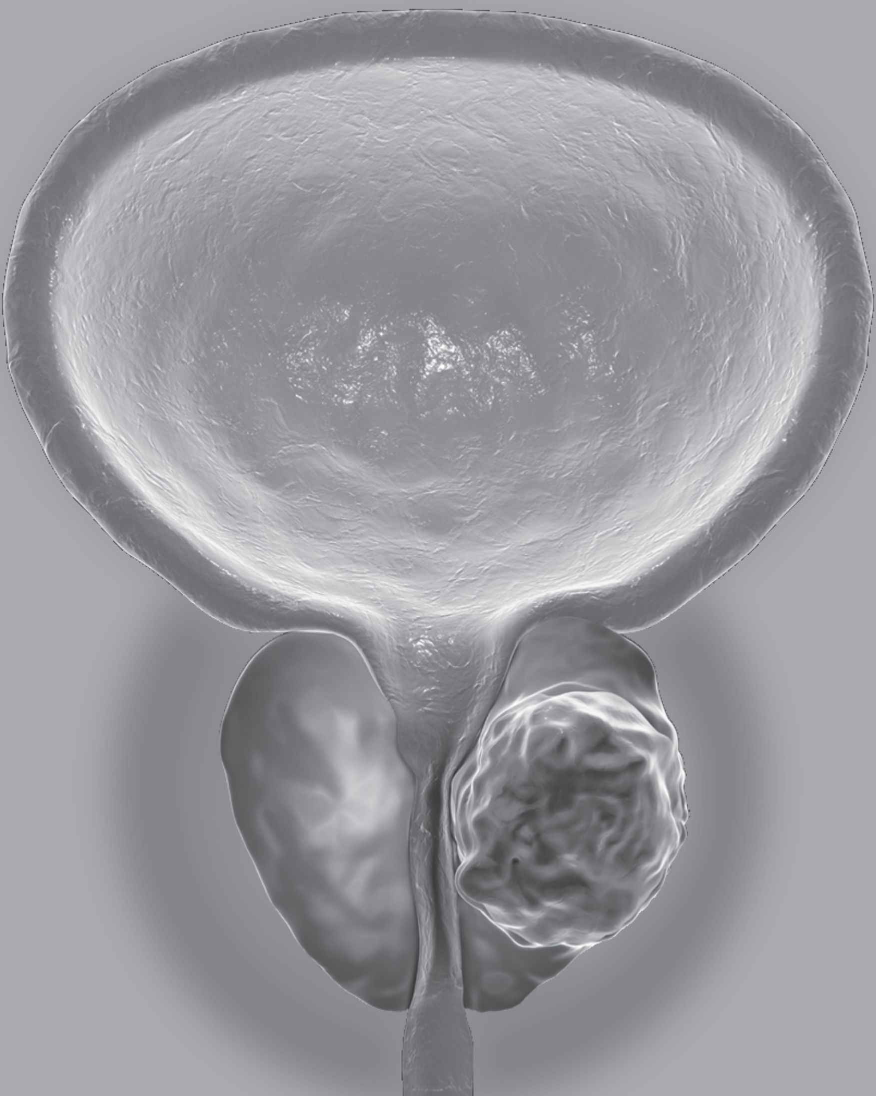
Manuscript in preparation



CHAPTER 12

General Discussion

In Chapter 1 - General introduction, the two main objectives of this thesis are stated. The first objective of this thesis is to determine how harms of prostate cancer screening can be reduced by using PSA-based risk stratification tools, and how these tools can be applied to Asian populations. The second objective of this thesis is to investigate the role of the serum biomarker Prostate Health Index (PHI) in prostate cancer diagnosis in Asian populations.

Part 1: By using PSA-based risk stratification tools, can we reduce harms of prostate cancer screening? Can these tools be applied to Asian populations?

Can we screen but still reduce overdiagnosis?

Screening for cancer aims to find cancers as early as possible when the chance of cure is highest and as such involves healthy people who don't have any symptoms at that point in time. Overdiagnosis is the diagnosis of a latent disease that would not have been diagnosed during a person's lifetime (and would not have affected the person at all) without screening. Whether the diagnosis of a cancer in a particular patient can be considered as overdiagnosis is an interaction of how latent the disease is and how long the patient will live (life expectancy). A relatively rapid growing cancer might not necessarily harm the patient or be the cause of death if the patient had a short remaining lifetime. On the other hand, a slow growing cancer might harm the patient if he or she lives long enough. (Figure 1)

Knowledge on the natural history of prostate cancer is important to understand the impact on life expectancy and quality of life of localized prostate cancer if it is left untreated. In a long term observational study by Johanssen et al, 223 Swedish men with localized prostate cancer diagnosed in 1977-1984 (pre-PSA era) without initial active treatment were observed. [1] Most men did not suffer from prostate cancer in the first 15 years, but progres-

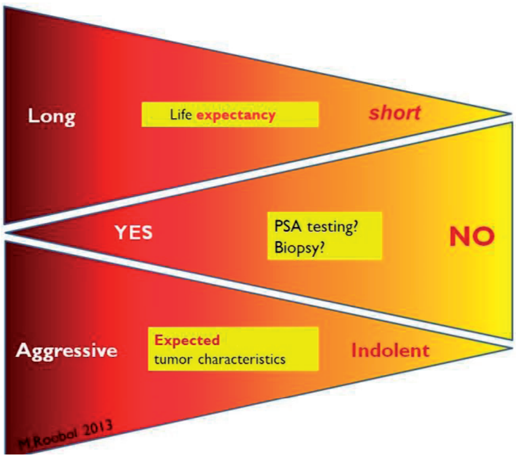


Figure 1. Prostate cancer screening in association with life expectancy and disease course

sion and prostate cancer death increased rapidly at 15-20 years in those who were still alive. After 30 years of follow-up and death of 99% of men in the cohort, it was observed that 17% of men died from prostate cancer, usually between 15-25 years after diagnosis. [2]

The control arms of randomized trials on surgery versus observation also gave us insights to the natural history of localized prostate cancer. The Scandinavian Prostate Cancer Group 4 (SPCG4) in the pre-PSA era randomized 699 men between 1989 and 1999 to radical surgery versus watchful waiting. [3] Prostate cancer mortality was 20% at 15 years of follow-up in the watchful waiting group. The Prostate Cancer Intervention Versus Observation Trial (PIVOT) in the early PSA era randomized 731 men between 1994 and 2002. [4] Most men in PIVOT had low to intermediate risk disease. In the observation arm, prostate cancer mortality was about 20% at 15 years, and in the low risk subgroup, cancer mortality was less than 5% at 15 years. In short, localized prostate cancer has excellent 15-year cancer specific survival without initial curative intent treatment, and the benefit of treatment was mostly observed in younger (<65) and non-low risk prostate cancer patients. [3]

Screening of prostate cancer with a PSA cutoff of 3 ng/mL in the European Randomized study of Screening for Prostate Cancer (ERSPC) showed a 20% reduction of prostate cancer mortality and a 30% reduction of metastatic disease at 9 years follow-up. [5, 6] However, overdiagnosis of low risk prostate cancer was significant. Applying mathematical simulation models in the Rotterdam section of the ERSPC data, using an algorithm of screening men at 55-70 years every 4 years would lead to 40% overdiagnosis. [7]

In a cost-effectiveness study using the Microstimulation Screening Analysis (MISCAN) model, screening for prostate cancer every 2 years for 3 times between the age of 55 and 59 would result in the best incremental cost-effectiveness ratio. The upper age limit of screening to maintain a similar cost-effectiveness ratio could be increased to 72 if better quality of life could be achieved by applying active surveillance for low risk prostate cancer. [8] From a decision process model, Zhang et al. suggested the optimal stopping age of PSA testing was 76 from the patients' perspective (Quality adjusted life years, QALYs) and 71 from the societal perspective (cost-effectiveness). [9]

In view of the rising life expectancy, the uncertainty of remaining lifetime of an individual, the improvement of treatment outcomes and complication profile, and availability of numerous life-prolonging therapy even in case of metastatic disease, it is difficult to set a specific age limit to stop screening for prostate cancer. Instead, an individual assessment with proper counseling and shared decision-making would be more appropriate in the current era.

Prostate cancer is particularly amenable to overdiagnosis as there is a considerable reservoir of so-called latent disease which can be detected by a relatively simple procedure, the systematic prostate biopsy. Although obvious as it may seem, prostate cancer screening is frequently mixed up with PSA based screening. While systematic large scale screening for prostate cancer by a PSA-only approach may not be appropriate, it does not mean that there should be no prostate cancer screening at all. The issue is not that black and white.

To improve the efficacy of prostate cancer screening, men at a higher risk of prostate cancer can be selected, and they include men with positive family history, genetic disposition to prostate cancer, and ethnically Black men.

Men with a positive family history of prostate cancer are at a relative risk of 2.5-4.4 in those with 1-2 affected first-degree relatives, and is also associated with an earlier onset of disease (before 65 years old). [10, 11] Genetic mutations identified in Genome-wide association studies (GWAS) could explain 25-33% familial risks of prostate cancer, but it is not cost-effective to screen all susceptible loci and the harm-to-benefit ratio is unknown. [12, 13] The risk of prostate cancer in ethnically black men can be more than double of that in Caucasian in the same region, while risk of prostate cancer death can be similar or higher depending on regions being studied. [14, 15]

Better tools for detection of (potentially aggressive) prostate cancer have emerged since the PSA era, which include multivariate approaches, i.e. combining relevant information from multiple sources like e.g. clinical data, blood, urine markers, genetic tools, and novel imaging techniques. Such an approach may help to reduce unnecessary testing (e.g. biopsy) and over-diagnosis of non-lethal cancers, while, and this is crucial, not missing the diagnosis of a potentially lethal prostate cancer. [16-21] (Figure 2)

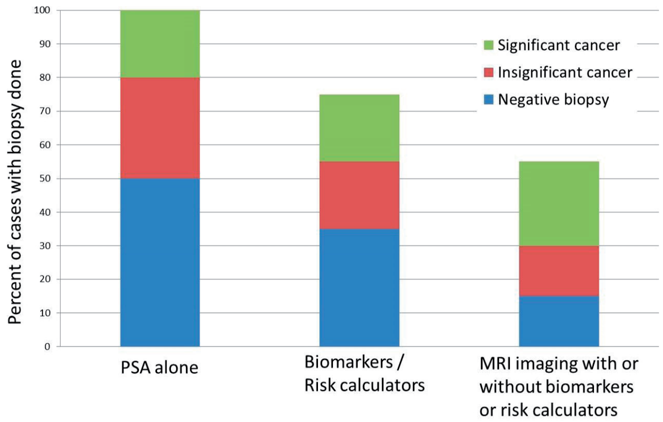


Figure 2. Effect of using biomarkers, risk calculators and/or MRI imaging in biopsy and outcomes

Life expectancy and prostate cancer screening

According to data from World Health Organization (WHO), the worldwide life expectancy at birth has been on the rise in the past decades from 67.7 in 2000 to 72.2 years in 2017. In Caucasian men who reached 70 years of age, the life expectancy in North America and Western Europe ranges from 14-16 years. Figure 3 shows an example of life expectancy data

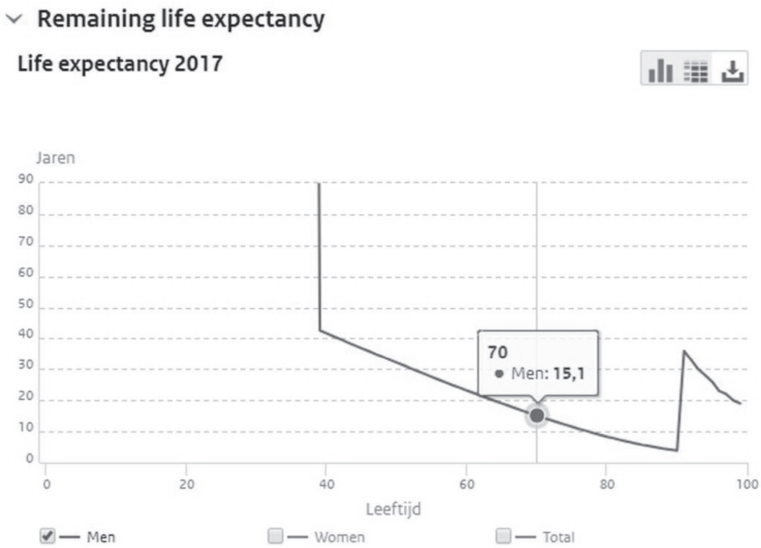


Figure 3. Remaining life expectancy in the Dutch men

in the Netherlands. Dutch men at 70 years old have 15 years of life expectancy, and those with higher education level had 4 extra years of life expectancy. [22] (Figure 3)

In Asian men who reached 70 years of age, the life expectancies in India, China, South Korea, Singapore and Japan are 11.2, 11.5, 14.6, 15.3 and 15.7 years. [23] However, life expectancy of urban and rural areas in Asian countries can have great variations. In China, in more developed cities like Hong Kong, the life expectancies of men at 70, 75 and 78 years old are 16.0, 12.5, and 10.6 years. [24] A 70 year-old men in the urban regions like Beijing, Shanghai, Hong Kong, Macau, Tianjin, or Zhejiang would have about 15 years of life expectancy. In less developed regions of China, the life expectancy is in general 5-8 years less. [25] There is also evidence that higher education level is associated with longer life expectancy. [22] Therefore, eligibility for prostate cancer screening (or age to stop screening) needs to be individualized in the context of life expectancy. While men at 70 years old in urban Asia have about 15 years of life expectancy and therefore should still be eligible for prostate cancer screening, those in rural Asia may have less than 10 years of life expectancy at 70 years old. Furthermore, screening should be done not only on the basis of a PSA test but additional risk stratification using risk calculators, biomarkers and/or MRI to avoid unnecessary prostate biopsy and diagnosis of indolent prostate cancer. (Figure 4, Figure 5)

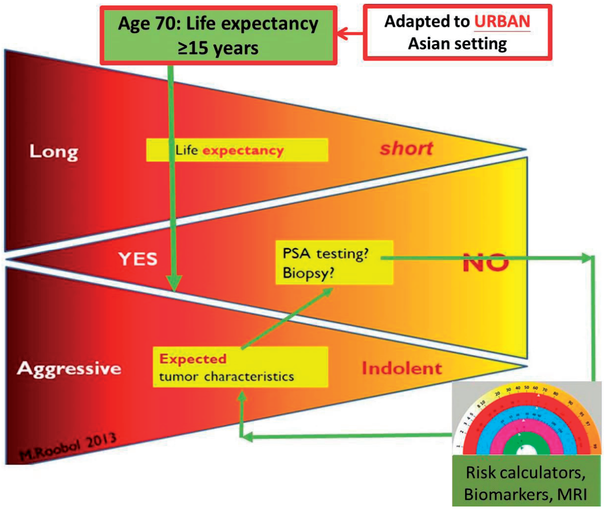


Figure 4. Prostate cancer screening in Urban Asian setting in association with life expectancy at 70 years old and disease course in the context of PSA, biomarkers and MRI.

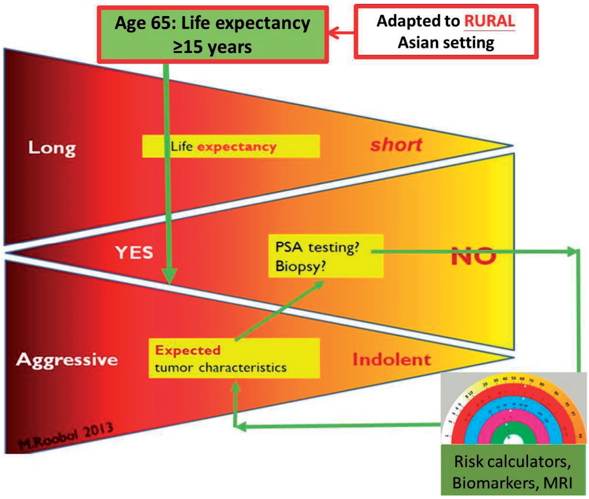


Figure 5. Prostate cancer screening in Rural Asian setting in association with life expectancy at 65 years old and disease course in the context of PSA, biomarkers and MRI.

To reduce harms of prostate cancer screening by using PSA-based risk stratification tools in Asian men?

Part of the harms of prostate cancer screening included unnecessary prostate biopsies in men with no cancer and the associated biopsy complications. PSA-based risk stratification tools (e.g. PSA density, Prostate cancer risk calculators) can reduce such harms.

PSA density

PSA density, calculated with PSA divided by prostate volume, was first reported by Benson et al in 1992 to have better ability to predict prostate cancer than PSA. [26] A further study in 3140 men showed that in the PSA range of 4-20 ng/mL, PSA density could improve cancer risk stratification compared with PSA alone. [27] Bazinet et al suggested PSA density of 0.15 for PSA 4-10 ng/mL [28], but Catalona et al showed in a cohort of almost 5000 men with sextant biopsy, that adding prostate volume significantly improved positive predictive value, but almost half of cancers might be missed by using PSA density cutoff of 0.15. [29]

In chapter 3 of this thesis, the role of PSA density was being explored in 854 Asian men with elevated PSA > 4ng/mL in 2009-2012. [30] The cohort was divided into obese and non-obese men, with obese man having similar PSA levels (8.2 Vs 7.9 ng/mL, p=0.416) but larger prostate sizes (63ml Vs 52ml, p<0.001). The performance of PSA density was significantly better than PSA in obese men (AUC 0.73 Vs 0.51) but only slightly better than PSA in non-obese men (AUC 0.65 Vs 0.62). The risk of prostate cancer in obese men with PSA density > 0.15 was 4 times the risk in men with PSA density < 0.15, while it was only 2 times the risk in non-obese men. The study demonstrated value of PSA value in Asian men and in obese Asian men in particular. [30]

Teoh et al reported the performance of PSA density in another cohort of 2600 Chinese men in Hong Kong in 2000-2013, confirming the superiority of PSA density over PSA. [31] At PSA density 0.15, 90% sensitivity and 42% specificity for any grade prostate cancer was achieved.

Although prostate volume can be easily measured by ultrasound in the clinic, transrectal ultrasound (TRUS) still involves an extra procedure and cost. Using Digital rectal examination (DRE) to estimate prostate size accurately is difficult, but when DRE-estimated prostate volume was categorized to 25, 40 and 60ml in a study by Roobol et al, the corresponding TRUS-measured volumes were found to be very similar at 27, 46, and 69ml, respectively. [16] Another study done in Asian (Chinese) men (Chapter 10 of this thesis) [32] prospectively validated the DRE-estimated prostate volume in 569 men by Urology residents, and the corresponding TRUS-measured volumes were 27, 43, and 68ml, which were almost identical to the result obtained from the Caucasian study [16]. The AUCs of the models with PSA+DRE prostate volume Vs PSA + TRUS prostate volume in predicting prostate cancer (and high-grade prostate cancer) were completely identical. [32]

In the current era of MRI imaging for prostate cancer diagnosis, PSA density could also help to stratify men who need a prostate biopsy (or a repeat biopsy in active surveillance). Washino et al showed that in patients with MRI prostates of PI-RADS ≤ 3 AND PSA density < 0.15, no clinically significant prostate cancer was being diagnosed. [33] Therefore, PSA density still has a definite value in improving performance of PSA in the contemporary era.

Prostate cancer risk calculator

By adding clinical factors to PSA, a multivariate approach to risk stratification can be used to better predict prostate risk and reduce unnecessary biopsies. Among the many risk calculators for prostate cancer prediction, the ERSPC risk calculator was shown to have excellent performance. [34] The ERSPC risk calculators added clinical risk factors including prostate volume, DRE finding and TRUS finding to PSA to improve the performance of PSA-based screening [35], and it has been externally validated. [36, 37] A risk-based strategy was proposed to select appropriate men for biopsy. By using a positive biopsy probability cutoff of 12.5%, 33% biopsies and 13% indolent cancer diagnosis would have been avoided. [38]

The ERSPC risk calculator (RC3 for initial biopsy) was being externally validated in a 3000-men cohort in Hong Kong. [39] (Chapter 4) The AUCs were 0.75 and 0.84 for prostate cancer and high grade prostate cancer, respectively, but there were overestimation of 10–40% for PCa and 10–30% for HGPCa across the whole range of predicted probabilities at calibration. Adaptations of the formulas (by setting-specific adjustments to the intercept constant) were performed and the recalibrated models were applied to the validation cohort of Chinese men in another hospital (n = 2214). The adapted ERSPC risk calculator showed excellent calibration and net clinical benefit over the original ERSPC RC3 in Chinese men. Therefore, the adapted form of ERSPC risk calculator could be applied in the Asian setting using easily available factors: PSA, DRE finding, and prostate volume. The adaptation to Asian setting is very important as estimating the cancer risk in Asian men using Caucasian-validated risk calculator would result in gross over-estimation of cancer risk and even more unnecessary biopsies.

Prostate biopsy complications can be reduced by applying PSA-based risk stratification tools

The other reason that renders prostate cancer screening harmful is the complications associated with prostate biopsy as a result of an elevated PSA. The complications include pain, haematuria, per rectal bleeding, haematospermia, acute retention of urine, and post TRUS biopsy sepsis. Post TRUS biopsy sepsis was infamous for its associated severe morbidities, potential intensive care requirements, and very rarely mortality. [40]

Unnecessary biopsies could be reduced by using a risk prediction models like the ERSPC or PCPT risk calculators. [18, 34] The proportion of biopsy complications that could be reduced have not been described previously. Chapter 5 of this thesis reviewed the biopsy complications of 10747 screened men in Rotterdam section of ERSPC in 1993-2015. [41] 67.4% of biopsies had at least one complication, 3.9% had fever and 0.9% required hospital admission. The fever rate was found to be static over the years, but the hospital admission rate tripled from 0.6% (1993–1996) to 2.1% (2009–2015) in recent years, implying more severe infection in more recent biopsies. This might be related to a doubled prevalence of the sepsis risk factor diabetes mellitus in the later rounds of screening. [42, 43]

Among 7704 biopsies which fit the criteria for ERSPC risk calculators (RC3 for first round of screening, RC4 for subsequent rounds of screening), 35.8% of biopsies (2757/7704), 37.4% of complications (1972/5268), 39.4% of fever events (128/325) and 42.3% of admissions (30/71) could have been avoided by using the recommended risk-based thresholds of < 12.5% risk for any prostate cancer and < 3% risk for high grade cancer. [38, 41]

Although obvious as it may seem, i.e. complications reduced by not performing the procedure, the harms of unnecessary biopsies need to be emphasized again and again. None of the risk calculators or novel tools in prostate cancer diagnosis is perfect, but they all performed much better than PSA alone. Therefore, for the sake of our patients, biopsy decisions based on PSA alone should be abandoned.

Conclusion of the first part of thesis

In using PSA-based tools like PSA density or risk calculators, we can better select men at a higher risk of potentially life threatening prostate cancer and as such candidates for further assessment (e.g. MRI and or prostate biopsy). When we apply risk assessment tools developed on predominantly Caucasian patient cohorts in Asian men with lower risk of prostate cancer, adaptations of the risk calculators are needed to avoid over-estimating cancer risks, which in turn might result in the opposite of what we want to achieve, i.e. more unnecessary biopsies.

Part 2: The use of Prostate Health Index (PHI) in prostate cancer diagnosis in Asian populations

What are the performance characteristics of PHI in the Asian setting and do we need a different PHI reference range for Asian and Caucasian?

The Prostate Health Index (PHI), a mathematical formula combining total PSA, free PSA and [-2] proPSA (or p2PSA), has been shown to have a better sensitivity, specificity and AUC compared with PSA and %freePSA in Caucasian men with PSA 2-10 ng/mL since. [44-46] The PHI blood test was approved by FDA in 2012 for use in men > 50 years old with PSA 4-10 ng/mL and normal DRE. [47] Numerous subsequent studies in other Caucasian population have confirmed the benefits of using PHI in men with elevated PSA < 10 ng/mL. [48]

While the reason that proPSA is elevated in prostate cancer tissues is not entirely understood, it is postulated that decreased processing of PSA in cancer cells might contribute to an increased level of proPSA and [-2]proPSA in particular. In prostate cancer cells, a loss of cellular architecture or cellular disruption may explain the increased leakage of the enzymatically inactive proPSA forms of the free PSA into the blood stream, and therefore elevated levels of these proPSA detected in blood. [49, 50]

As mentioned in the Introduction (Chapter 1), Asian population have a significantly lower incidence of prostate cancer and lower prostate cancer detection rate in the PSA gray zone of 4-10 ng/mL Therefore it is clinically important to validate the value of PHI in Asian men.

PHI in Asian men

Chapter 6 described the first PHI study done in Asian men. [51] In 230 Hong Kong Chinese men with PSA 4-10 ng/mL and normal DRE, bloods were taken immediately before an initial ≥10-core systematic prostate biopsy and analyzed for PSA, free PSA and p2PSA. The specificity of PHI was about 3 times that of PSA (50% Vs 17%). The AUC of PHI, PSA density, %freePSA and PSA was 0.78, 0.63, 0.57, and 0.55, respectively. At 90% sensitivity of PHI (cutoff 26.5) for Gleason ≥7 cancers, 45% unnecessary biopsies could be avoided. In this study with mean PSA of 6.3 ng/mL and prostate volume of 46ml, only 21 (9.3%) men were diagnosed to have prostate cancer. [51] This was similar to the usual 11% cancer detection rate in the same institution in Hong Kong Chinese men with PSA 4-10 ng/mL and normal DRE.

In a subsequent study in Shanghai Chinese men, superiority of PHI over PSA was also shown (AUC 0.73 Vs 0.53) in the subset of PSA 2-10 ng/mL with 30% abnormal DRE and 17.6% cancer detection rate. [52] Ito et al reported in a cohort of Japanese men with PSA 2-10 ng/mL and 22% cancer detection rate, 28% biopsies could be avoided by using PHI at a sensitivity of 95%. [53]

PHI in Asian men with PSA > 10 ng/mL

Chapter 7 described the use of blood test PHI in a cohort of 312 Chinese men with PSA 10-20 (mean 13.3) ng/mL and normal DRE. [54]. The AUC for any cancer detection for PSA, %fPSA, %p2PSA and PHI was 0.58, 0.69, 0.76 and 0.73. Using PHI or %p2PSA was shown to provide net clinical benefit over PSA and %freePSA over the whole range of probability threshold. Adding age, PSA and repeated biopsy to a multivariate model with %p2PSA or PHI increased the AUC (prostate cancer) to 0.78-0.79, and AUC (high grade prostate cancer) to 0.83-0.84. [54] The cancer detection rates in different PHI ranges were shown in Table 1.

Table 1. Cancer detection rates in different Prostate Health Index (PHI) ranges in men with PSA 10-20 ng/mL and normal DRE Cancer, adapted from Chapter 7.

Prostate Health Index	<35	35-55	>55	Total
Any prostate cancer	**12/178 (6.7%)**	**23/101 (22.8%)**	**18/33 (54.5%)**	312
Initial biopsies	11/146 (7.5%)	30/85 (23.5%)	15/29 (51.7%)	260
Repeated biopsies	1/32 (3.1%)	3/16 (18.8%)	3/4 (75.0%)	52
High grade prostate cancer	**4/178 (2.2%)**	**8/101 (7.9%)**	**12/33 (36.4%)**	312

As observed in this study with median PSA of 13.4 ng/mL and PSA density of 0.21, the cancer and high-grade cancer detection rates were only 17.0% and 7.7%, respectively. They were still lower than the reported cancer detection rate in Caucasian studies with PSA 2-10 ng/mL. Another study in Chinese men with a subset of men with PSA 10-20 ng/mL and 30% abnormal DRE showed that the AUC of PHI was 0.79 for PHI and 0.57 for PSA. [55] Therefore, the use of PHI can be extended to Asian men with PSA 10-20 ng/mL.

PHI predicts aggressive prostate cancer

A high PHI value not only predicts prostate cancer but also high grade prostate cancer. A study by Catalona et al showed that there were 42% Gleason 7 cancers on prostate biopsy in a high PHI group (PHI > 55) but only 26% in a low PHI group (PHI < 25). [44] In the era of systematic biopsy, discrepancy of Gleason score on biopsy and radical prostatectomy is common. PHI and p2PSA was also associated with more aggressive prostate cancer in radical prostatectomy specimens in a number of studies in Caucasian men. A study in Italian men %p2PSA and PHI improved the prediction of pT3 (by 2.5%), pathologic Gleason sum (by 6.0%), Gleason sum upgrading (by 5.7%) and indolent cancer with tumor volume < 0.5ml (by 4.2%) in multivariate analyses. [56] However, a study in a German cohort showed that PHI or p2PSA were not independent predictors of worse pathology outcomes in radical prostatectomy upon multivariate analyses, but using a p2PSA cutoff of 22.5 pg/mL could modestly improve pT3 prediction by 3.6% in AUC. [57] A multicentre European study showed PHI or %p2PSA improved AUC for pT3 or Gleason score ≥7 by 1.2-2.3% in multivariate analyses. [58]

Chapter 8 described the first report on the association of PHI and aggressive prostatectomy pathology in an Asian cohort. [59] PHI or %p2PSA was significantly higher in patients with pT3 disease, pathologic Gleason score ≥7, Gleason score upgrade, tumor volume >0.5 ml, and Epstein criteria for significant tumor (all p=0.001). The risk of pT3 or pathologic Gleason score ≥7 was 16.1% for PHI < 35 and 60.8% for PHI > 35 (specificity 84%). In multivariate analyses, adding PHI or %p2PSA to the base model (including

Age, PSA, abnormal DRE, and biopsy Gleason score) improved the prediction of pT3 or pathologic Gleason score ≥7 by 7.2-7.9% on AUC. Decision curve analyses showed a net clinical benefit in using PHI in prediction of tumor volume > 0.5ml, or pT3 or pathologic Gleason score ≥7. [59] Therefore, PHI or %p2PSA could be used to predict men with more aggressive final pathology in Asian men.

As PHI predicts final pathology, there could be a role for PHI to be included as marker for patients on active surveillance to receive active treatment if aggressive pathology is likely in case of high PHI values. Caucasian and Japanese studies have reported that [-2]proPSA could predict biopsy reclassification in men on active surveillance. [60, 61] In a study in 140 Chinese men who fit Prostate Cancer Research International: Active Surveillance (PRIAS) criteria, a low PHI was found to predict organ-confined disease. [62] Therefore, a baseline PHI could provide useful information before consideration of active surveillance.

Different PHI reference ranges for Caucasian and Asian.

As mentioned in Introduction (Chapter 1), the meaning of a mildly elevated PSA of 4-10 ng/mL is different in Caucasian and Asian. It was shown in Chapter 6 that in a cohort of Hong Kong Chinese men, only about 10% men with PSA 4-10 ng/mL and normal DRE was diagnosed with prostate cancer on 10-core systematic biopsy. [51] When PHI was available in the public health care system in Hong Kong since 2016, the reference range used in the PHI laboratory reports was the one published by Catalona et al. [44] (Figure 6)

Date Collected: 30/05/2016 13:06
Date Arrived: 31/05/2016 14:07

Prostate Health Index Profile

			Reference Range
Hybritech Total PSA	5.7	ng/mL	<4.0
Hybritech Free PSA	1.62	ng/mL	
Percent of Free PSA	28.6	%	Remark 1
Hybritech p2PSA	25.0	pg/mL	
Prostate Health Index (phi)	36.6		Remark 2

Remarks:

1. Probability of prostate cancer by % free PSA in patient with total PSA between 4 to 10 ng/mL

Percent Free PSA	0-10%	10-15%	15-20%	20-25%	>25%
Prostate Cancer Probability (% Pca)	56%	28%	20%	16%	8%

Source: A37210 Beckman Coulter Access Hybritech free PSA instructions for use 2011.

2. Probability of prostate cancer by phi in patient with total PSA between 2 to 10 ng/mL

Prostate Health index (phi)	0-24.9	25.0-34.9	35.0-54.9	55.0+
Prostate Cancer Probability (% Pca)	11.0%	18.1%	32.7%	52.1%

Source: Catalona WJ. Partin A. Sanda MG et al.

Figure 6. Prostate Health Index lab report in Hong Kong in May, 2016

From the Caucasian reference range, about 11% had prostate cancer in the lowest PHI range (lowest cancer risk) of PHI < 25, which is similar to the overall risk of cancer in Hong Kong Chinese men (10-15%) with PSA 4-10 ng/mL. Such reference range results in an overestimation of cancer risk and may lead to even more unnecessary biopsies. Therefore, it is inappropriate for use in Asian or Chinese men.

Chapter 9 is a multi-centre evaluation of the role of PHI in regions with different prevalences of prostate cancers. [19] The performance of PHI in 4 European cities in France and Germany and 5 Asian cities in China, Taiwan and Singapore with a total of 2488 men with biopsies done were compared. In men with PSA 2-10 ng/mL and normal DRE, there was a 4-fold difference in positive biopsy rates in Caucasian Vs Asian men (52% Vs 13%). In men at a lower PHI range of < 35, cancer risks were 28.5% in Caucasian and 6.3% in Asian, and Gleason ≥7 cancer risks were 4.2% Vs 1.5%. This study suggests a different PHI reference range should be used for different ethnic groups, especially in situation where cancer epidemiology was very different.

Among European men, at 90% sensitivity for Gleason ≥7 cancers (PHI 40), 40% of biopsies and 31% of Gleason 6 PC diagnoses could have been avoided. Among Asian men, at 90% sensitivity for Gleason ≥7 cancer (PHI 30), 56% of biopsies and 33% of Gleason 6 PC diagnoses could have been avoided. (Table 2, Chapter 6) [19] Therefore, the use of the PHI blood test could reduce more than half of unnecessary initial biopsies in Asian men with elevated PSA 2-10 ng/mL and normal DRE.

Back in Hong Kong, we have generated a PHI reference range from 569 Hong Kong Chinese men with PSA 4-10 ng/mL, normal DRE and prostate biopsy done. (Chapter 10) [32] Since 2017, a new PHI reference range for Hong Kong Chinese has been added in the PHI lab report. (Figure 7) Hopefully this could provide accurate risk estimation for men with PSA and PHI taken.

In the letter to the editor for the paper in Chapter 10 [19], Heidegger and Pichler queried the lack of detailed cancer information in Gleason 6 cancers including number of positive cores and percentage involvement in each core. The co-authors and I fully agreed to

Table 2. Comparison of prostate cancer prevalence, life expectancy and benefit harm ratio of cancer screening in Asian, Black and Caucasian.

	Prevalence	Metastatic disease at presentation	Life expectancy	PSA screening-Benefit harm ratio	Optimized screening#-Benefit harm ratio
Asian	*	**	**/***	*	***
Black	***	***	**	**	***
Caucasian	**	*	***	**	***

Optimized screening = PSA screening followed by risk stratification tool optimized for particular population

Reference: 18C7621646

Date Collected: 16/08/2018 13:59 Reference Interval

Date Arrived: 17/08/2018 16:08

Prostate Health Index Profile

Hybritech Total PSA	9.4 H ng/mL	<4.0
Hybritech Free PSA	1.76 ng/mL	
Percent of Free PSA	18.6 %	Remark 1
Hybritech p2PSA	11.3 pg/mL	
Prostate Health Index (phi)	19.7	Remarks 2 & 3

Remarks:

1. Probability of prostate cancer by % free PSA in patient with total PSA between 4 to 10 ng/mL

Percent Free PSA	0-10%	10-15%	15-20%	20-25%	>25%
Prostate Cancer Probability (% Pca)	56%	28%	20%	16%	8%

Source: A37210 Beckman Coulter Access Hybritech free PSA instructions for use 2011.

2. Probability of prostate cancer by phi in patient with total PSA between 2 to 10 ng/mL

Prostate Health index (phi)	0-24.9	25.0-34.9	35.0-54.9	55.0+
Prostate Cancer Probability (% Pca)	11.0%	18.1%	32.7%	52.1%

Source: Catalona WJ. Partin A. Sanda MG et al.

3. Probability of prostate cancer by phi in Chinese with total PSA between 4 to 10 ng/mL

Prostate Health index (phi)	0-24.9	25.0-34.9	35.0-54.9	55.0+
Prostate Cancer	3.6%	7.6%	22.9%	38.1%
High-grade Prostate Cancer	0.5%	0.9%	6.9%	19.0%

Source: PK Chiu. CF Ng et al.

Figure 7. Prostate Health Index lab report in Hong Kong in August, 2018.

the comment and having such information could potentially change some Gleason 6 cancers to significant. They also mentioned about the impact of MRI prostate in cancer diagnosis and a pre-biopsy MRI is currently being recommended in EAU guideline since March 2019. The authors and I are fully aware of the role of MRI, but the patients in the study were recruited years before the recent EAU recommendation and most of them did not have a pre-biopsy MRI. All of the above have been mentioned in the discussion part of the original manuscript and therefore we did not provide a reply to the letter. [63]

In the editorial for the paper (Chapter 10) by Zlotta and Kuk, comments were made concerning the potential underestimation of cancer incidence in Asia. The authors including myself agreed that cancer incidence has been climbing up in Asia in recent years, which might be related to more PSA testing and more awareness to prostate cancer. However, the current absolute number of prostate cancer being diagnosed and also the positive biopsy rates in PSA 4-10 ng/mL were still much lower than that in Caucasian. The suggestion of whether prostate cancers are developed at a later age in Asian is an aspect which we should explore further. A prostate cancer study in including PSA, PHI and MRI prostate is currently in progress in Hong Kong Chinese men, and hopefully the results would give us more insights into the epidemiology and the optimal screening strategy for prostate cancer. (Clinicaltrials NCT03891732)

Adding PHI to PSA based predictive models

In chapters 6-9, the value of PHI in Asian men and the need of a separate reference range have been described. PHI could be added in a predictive model to further improve its performance. Lughezzani et al developed a nomogram by adding PHI to clinical parameters including age, prostate volume, DRE, and history of prior negative biopsy. [64] Adding PHI to the baseline model with the 4 clinical factors improved AUC from 0.73 to 0.80, and it was externally validated in another clinical cohort, showing AUC of 0.75 and clinical benefit on decision curve analyses. [65] Roobol et al added PHI to the original ERSPC risk calculators RC3 and RC4 for initial and repeated screening settings (with DRE finding and DRE estimated prostate volume), and showed that the performance of the recalibrated ERSPC-based risk calculator including PHI (AUC 0.75 for any cancer, and 0.69 for high grade cancer) was similar to the one developed by Lughezzani et al. [66]

In chapter 10, PHI was compared with PSA-based and PHI-based predictive models in a Chinese cohort of men with PSA 4-10 ng/mL and normal DRE. [32] Adding age and prostate volume to PSA improved the AUC of cancer detection from 0.54 to 0.71 (DRE-estimated prostate volume) or 0.72 (TRUS measured prostate volume), and about 25% biopsies could be avoided at 90% sensitivity for any cancer. This confirmed again the importance of a multivariable predictive model. The AUC for PHI alone in the same cohort was 0.76 and already better than the PSA-based predictive model (0.72), and if age and DRE-estimated prostate volume was added to PHI, the AUC further improved from 0.76 to 0.78 ($p<0.001$). [32] For high grade prostate cancer, however, PHI alone had a high AUC of 0.85 and adding age and prostate volume did not further improve the AUC.

Zhu et al used the same factors of PHI, Age and TRUS estimated prostate volume and generated a PHI-based risk calculator for prostate cancer in Shanghai Chinese men with PSA < 10 with normal DRE. [67] It was externally validated in a Hong Kong Chinese cohort with PSA 4-10 ng/mL, normal DRE and a cancer detection rate of 9.1%. An AUC of 0.79 and good calibration was achieved. [67]

Therefore, similar to PSA and PSA-based predictive models, simple and easily available clinical factors like age, DRE finding and prostate size could be added into a PHI-based predictive model to improve performance. However, the magnitude of added benefit of including these clinical factors to PHI was less than that of adding them to PSA.

PHI use in a real-life Asian setting

There have been numerous validation studies of PHI showing the proportion of biopsies that can ***potentially*** be avoided by using a particular cutoff. [19, 48] However, the impact of a test in actual clinical practice is important to prove the effectiveness in its application.

There was only 1 publication so far reviewing the use of PHI in real-world scenarios. It included 345 Caucasian men in academic centres with a median PSA of 5.8ng/mL and >90% normal DRE. Compared with a historical cohort without PHI, men who decided not for biopsy increased from 52% to 61%, negative biopsy reduced from 25.5% to 17.5%, and Gleason Grade group ≥2 cancers remained unchanged at 13.5%. [68] However, this showed the effectiveness of applying PHI at one time point only.

Chapter 11 (Manuscript under submission) showed the impact of routine PHI on consecutive Chinese men in actual clinical practice in academic and non-academic centres in Hong Kong. Out of 2839 men with a median PSA of 6.1 (IQR 4.6-8.1)ng/mL, 11.5% with PHI <35 and 46.4% with PHI >35 decided for an immediate biopsy. PHI was shown to be the strongest predictor (OR 7.1, p<0.001) for an immediate biopsy decision, followed by younger age, prior negative biopsy, and a higher PSA level. The positive biopsy rates increased from 10.9% (historical cohort) to 28.3%, and Gleason grade group ≥2 cancers increased from 2.8% to 14.7%.

The second part of Chapter 11 illustrates 2 year follow-up data in the first 1392 noncancerous men with a median of 2.2 (range 2.0-2.6) years of follow-up. 9.8% (110/1127) in PHI<35 and 26.4% (70/265) in PHI>35 subsequently had a biopsy along follow-up (p<0.001), resulting in 11.0% (12/109) and 28.6% (20/70) Gleason Grade group ≥2 diagnosis, respectively (p=0.003). In men with PHI >55 with subsequent biopsies done within 2 years, 78% of biopsies revealed Gleason Grade group ≥2 cancers. This is the first PHI study to have longer term follow-up data available, and men with higher PHI ranges of >35, and >55 in particular, should be strongly encouraged to receive early biopsy.

Conclusion of the second part of thesis

PHI could predict prostate cancer and aggressive prostate cancer in Asian men with elevated PSA, but an Asian-specifi c PHI reference range needs to be used to avoid overestimation of cancer risks and further unnecessary biopsies. A multivariate approach including PHI could further improve prostate cancer prediction. PHI is also shown to be eff ective in real-life application. (Figure 8)

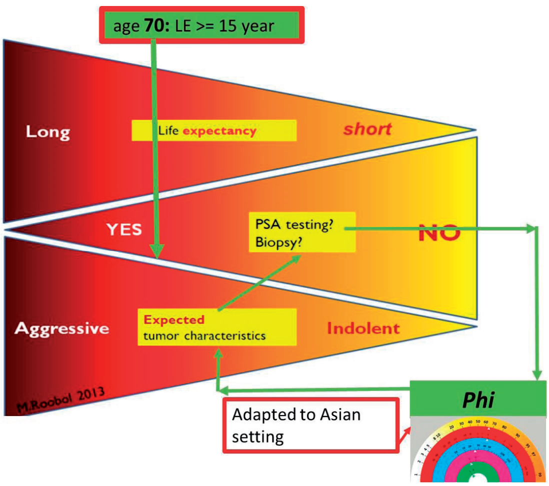


Figure 8. Biopsy decision in Asian men according to PHI result

Future perspectives

To screen, or not to screen, that is the question. It is always a balance of benefits and harms. The US Preventive Services Task Force (USPSTF) recommended against PSA-based prostate cancer screening in 2012 [69] as a result of conflicting results on prostate cancer mortality and harms of overdiagnosis from the randomized controlled trials. [5, 70, 71] This had led to widespread change of PSA screening practice in general practitioners, and cancer statistics from the United States have shown for the first time since 1990 an increase in prostate cancer mortality in 2016. [72] The updated analyses of ERSPC trial with longer follow-up time showed that, in addition to maintained prostate cancer mortality reduction of 20%, the number needed to screen (NNS) to prevent one cancer mortality reduced from 742 (at 13 year follow-up) to 570 (at 16 year follow-up). The number needed to treat (NNT) also reduced further from 26 to 18. [73, 74] The 19-year follow-up data in a section of the ERSPC in Rotterdam comprising one of the earliest study cohorts showed the trend of 54% reduction in metastatic disease and 52% reduction in of prostate cancer death with a longer follow-up. [75] The 18-year follow-up data in the Goteborg trial reported NNS of 139 and NNT of 13 for organized screening every 2 years. It also showed that opportunistic PSA testing was much less effective than organized screening in terms of reducing prostate cancer mortality reduction and overdiagnosis problem. [76] The USPSTF updated their recommendation in 2018 for men aged 55-69 years to an individual patient-based decision after a doctor's counselling. [77]

The benefits of organized prostate cancer screening could be seen, but the harms of over-investigation (biopsy), over-diagnosis and over-treatment of indolent cancers need to be reduced before screening could be applied on a population level. While the optimal screening strategy remains to be defined, it was shown that more intensive screening was associated with more overdiagnosis. [78] However, we have more than PSA and DRE in the modern era of prostate cancer detection. While a man with PSA > 3 ng/mL would be offered a sextant prostate biopsy in the ERSPC trial, it should no longer be the case in the current era. We have numerous tools to help us to stratify the risk of a man with elevated PSA, especially in the PSA gray zone of 4-10 ng/mL where most men with elevated PSA would fall into. The use of well-performing risk calculators like the ERSPC risk calculator could reduce unnecessary biopsies, but validation and calibration is needed to improve performance in specific ethnic groups. [36, 38, 39] Novel urine tests like PCA3 (with or without TMPRSS2:ERG) and Urine molecular biomarker-based risk score (SelectMDx) [79-81], and blood tests like PHI and a 4-Kallikrein panel(4K) [44, 82] could help to predict significant prostate cancers, reduce a significant proportion of unnecessary biopsies and diagnosis of indolent Gleason 6 prostate cancers. The cost of such tests would go down eventually, and as discussed in an earlier part of this chapter, the cost of a PHI test was reduced by 80% in a matter of few years. The use of multiparametric MRI prostate (including T1W, T2W, DWI and DCE sequences) accompanied with high quality imaging in men with elevated PSA could reduce unnecessary biopsies and diagnosis of insignificant cancers, allow targeted biopsy (and reduce systematic biopsies) and improve detection of significant prostate cancer. [20, 21, 83] Radiological expertise and standardized MRI reporting is however required to maximize the benefits of MRI. The availability and cost of a multiparametric MRI prostate is also a concern for most places in the world. A shorter biparametric MRI protocol including only T2W and DWI sequences was shown in a meta-analysis to have similar performance compared with multiparametric protocol, and could avoid gadolinium contrast and reduce scanning time and cost. [84]

In Asia, the incidence of prostate cancer and the cancer detection rate for elevated PSA is lower than in Caucasian, but the proportion of metastatic prostate cancer at diagnosis is higher. The proportion of metastatic disease is inversely proportional to the degree of cancer screening, and therefore there is a need for screening in regions with higher proportion of metastatic disease like Asia. While the number needed to screen to detect a significant cancer might be higher in Asian men, there is a greater need for the use of risk-stratification tools to better select men for biopsy in order to reduce the **number needed to biopsy** to detect a significant cancer. As shown in chapter 9 of this thesis, the proportion of unnecessary biopsies that can be reduced by using biomarkers like PHI can be higher in Asian than Caucasian. Therefore, the best screening protocol (Age range and Screening method) for a particular ethnic group or population need to be tailor-made or adapted from existing protocols for another population. (Table 2)

I believe the combination of PSA, clinical risk factors and a low-cost biomarker would form the basis of future prostate cancer screening to help select men at risk of significant prostate cancer to receive MRI prostate and biopsy. A combination of MRI and risk calculators or a combination of MRI and biomarkers could potentially further reduce unnecessary biopsies. [85, 86] Currently, a smart phone app like the Rotterdam prostate cancer risk calculator can help doctors to calculate the risk easily. [87, 88] In the future, the patient should have all tests done in a one-stop clinic and the Urologist should have the risk of cancer automatically generated on the computer screen to facilitate counselling.

Another harm of screening is about biopsy complications. The most fearsome complication of a transrectal ultrasound guided biopsy of the prostate is sepsis, and unfortunately the sepsis associated with resistant bacteria is on the rise. [40] Transperineal prostate biopsy could reduce the risk of sepsis to 0.1-0.3% and eliminate per rectal bleeding, but was traditionally associated with the need of spinal or general anaesthesia, and a higher risk of urinary retention after biopsy. [89] However, the feasibility of doing transperineal prostate biopsy under local anaesthesia with low rate of infection and urinary retention has recently been reported. [90, 91] A 'Trexit' initiative from London to change all prostate biopsies in United

Kingdom from transrectal to transperineal is underway, and severe sepsis after a prostate biopsy could potentially be reduced to near zero in the future. [92]

The problem of overdiagnosis of insignificant prostate cancer could partly be alleviated by the use of the novel diagnostic tools and biopsy being limited to man at high risk of significant cancer. However, when insignificant cancer was diagnosed on biopsy, the patient should be put on active surveillance to reduce over-treatment. [93] It is however important to note that a significant proportion of men on active surveillance without clinical progression would change to active treatment in 2-3 years, so instead of putting a lot of men to active surveillance, it remains important to reduce overdiagnosis in the first place. [93] In well selected men with intermediate prostate cancer, focal therapy could be used to treat the cancer and avoid the complications of a radical prostatectomy or radiotherapy. In a large series of men who received high-intensity focused ultrasound (HIFU) using focal or hemi-ablation technique, a high freedom from radical treatment rate of 91% and 81% at 5 and 8 years was observed. [94]

With a smarter approach to prostate cancer screening and avoidance of treatment in low risk cancers, the amount of harm observed in the screening trials could be greatly reduced. This would improve the benefit to harm ratio in prostate cancer screening. The European Association of Urology (EAU) has released an updated policy paper on PSA screening for prostate cancer in January 2019, with the aim to reopen discussion on the need of population-based prostate cancer screening program in European Union. [95]

Hopefully, the day will come when all eligible men can be screened for prostate cancer with a population-specific protocol, only men at high risk of significant prostate cancer (on multivariate risk assessment tools incorporating biomarkers and imaging) should be biopsied, only significant prostate cancers should be treated (by focal therapy if possible), and no more metastatic prostate cancer.

In fact, 'To screen, or not to screen', is NOT the question.

The question should be, how should we screen?

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SUMMARY

Chapter 1 (General Introduction) gives an overview of all available information regarding PSA-based screening for prostate cancer. The development of PSA-based risk stratification tools including PSA density, the Rotterdam Prostate Cancer Risk Calculator, and Prostate Health Index (PHI) is discussed and viewed in the setting of the epidemiological differences of prostate cancer in western and Asian populations. On the basis of this information research questions were formulated, addressed (Chapter 2-11 and discussed Chapter 12 (General discussion)).

Part 1: By using PSA-based risk stratification tools, can we reduce harms of prostate cancer screening? Can these tools be applied to Asian populations?

Chapter 2 consists of a review on PSA-based prostate cancer screening discussing the coinciding problems of overdiagnosis and potential ways to reduce these problems. Available data show that there are men that could benefit from screening and that long-term follow-up data of the largest RCT (ERSPC) show that the number needed to screen and number needed to treat to avoid a prostate cancer death continues to drop and comes into the range of e.g. breast cancer screening programs. Appropriate use of risk-stratification tools including risk calculators, blood and urine biomarkers, and MRI imaging could selectively identify men that could benefit from screening and as such have the ability to improve the benefit-to-harm ratio of screening.

The role of PSA density in Asian men is being explored in **Chapter 3**. PSA density has a better performance than PSA alone in prostate cancer detection in Asian men, and the effect was found to be more prominent in obese men. Obese men with an elevated PSA density > 0.15 were found to have four times the risk of prostate cancer in similar PSA levels.

With respect to the use of risk-stratification tools, the Rotterdam Prostate Cancer Risk Calculator has shown to predict prostate cancer and high-grade prostate cancer better than PSA alone. The Rotterdam Prostate Cancer Risk Calculator has been validated in multiple Caucasian cohorts. **Chapter 4** showed that the Rotterdam Prostate Cancer Risk Calculator performed well in Asian men, but overestimation of cancer risk was observed. After simple adaptation of the formula, the recalibrated Rotterdam Prostate Cancer Risk Calculator formula showed excellent calibration in another Asian validation cohort with accurate prediction of cancer risks. As shown in **Chapter 5**, by applying the Rotterdam Prostate Cancer Risk Calculator, 36% of unnecessary biopsies, 39% of post-biopsy fever, and 42% of hospital admissions could be avoided. This is especially important in the face of the increasing post-biopsy sepsis rates.

Part 2: The use of Prostate Health Index (PHI) in prostate cancer diagnosis in Asian populations

The blood test Prostate Health Index (PHI) was shown to improve prostate cancer detection in Caucasian men. In Chapter 1 (General introduction), the lower prevalence of prostate cancer in Asian men was discussed, and in Chapter 4, it was shown that the Rotterdam Prostate Cancer Risk Calculator needs to be adjusted before application in Asian men. Whether the PHI blood test can be applied to Asian men was unknown.

In **Chapter 6**, the first application of the PHI test in Asian men was performed in men with PSA 4-10 ng/mL with normal DRE, with PHI having three times the specificity compared to PSA, and avoiding 45% of biopsies at 90% sensitivity for high-grade prostate cancer. The use of PHI was further extended to Asian men with PSA 10-20 ng/mL and normal DRE in **Chapter 7**. It was shown that in Asian men with lower prevalence of cancer, PHI performed much better than PSA or percentage free PSA even in the case of PSA 10-20 ng/mL. Chapters 6 and 7 showed that PHI correlates with risk of prostate cancer in Asian men, while **Chapter 8** shows that PHI predicts aggressive pathology. In men with PHI levels of >35, the risk of pT3 or Gleason score ≥7 disease was 60.8%, compared with just 16.1% in men with PHI < 35. Therefore, in addition to biopsy decision, a PHI test could also guide treatment decisions (active surveillance vs. radical treatment).

The PHI reference range showed the risk of prostate cancer in different PHI ranges as supported by Caucasian data. **Chapter 9** is a multi-center evaluation of the role of PHI in regions with different prevalences of prostate cancer, including men from four European cities and four Asian cities. In men with PSA < 10 ng/mL, a four-fold difference in prostate cancer risk was observed between European and Asian men, and gross differences were observed in the cancer rates at different PHI ranges also. An ethnic specific PHI reference range should be used for Asian men to avoid over-estimation of cancer risk and even more unnecessary biopsies. In using 90% sensitivity for high-grade prostate cancer, 56% of unnecessary biopsies and 33% of Gleason 6 cancers could be reduced in Asian men, compared to 40% and 31% in European, respectively.

As for the Rotterdam Prostate Cancer Risk Calculator, adding multivariable clinical factors to PSA improved cancer prediction. In **Chapter 10** it was shown that this was similar in Asian men. Taking into account multiple factors next to PHI, e.g. DRE, prostate size and age, improved the capability of selectively identifying men with an elevated risk of having prostate cancer. For higher-grade cancers such an effect was not seen. Also in Asian men with relatively high PSA levels (10-20 ng/mL) further risk stratification was possible by (Chapter 7) including age, PSA and history of negative biopsy in the decision to biopsy.

While most papers on novel prostate cancer biomarkers report on the theoretical percentage of biopsies that could be reduced at a certain cutoff, the impact of a test in actual clinical practice is not commonly reported. In **Chapter 11**, the clinical impact of introducing PHI in routine clinical care in Hong Kong-Chinese men with elevated PSA is reported. In men with PSA 2-10 ng/mL, 82.0% of men decided not to undergo immediate biopsy after knowing their PHI results. By selecting higher risk men for biopsy with PHI, the percentage of prostate cancer diagnoses with Gleason 3+3 or 3+4 increased from 2.8% (data from a purely PSA-based strategy) to 14.7%. For men with more than two years of follow-up after an initial PHI test, 9.8% with PHI <35 and 26.4% with PHI >35 subsequently had a biopsy, resulting in 11.0% and 28.6% Gleason ≥3+4 diagnosis, respectively. By incorporating PHI into the routine clinical pathway, more than 80% of biopsies were avoided and high grade prostate cancer detection rate improved as compared to a PSA driven strategy. A higher baseline PHI was correlated to subsequent biopsy outcome and as such can serve as a tool to individualize the frequency of follow-up visits.

SAMENVATTING

In **hoofdstuk 1** wordt een overzicht gegeven van de beschikbare informatie omtrent vroege opsporing van prostaatkanker. Verder wordt de ontwikkeling van risicostratificatiemiddelen, zoals de PSA-density, de Prostaatwijzer en de Prostate Health Index (PHI, bloedtest) beschreven. Daarbij wordt de vraag gesteld welke epidemiologische verschillen met betrekking tot prostaatkanker er bestaan tussen Westerse (Kaukasische) en Aziatische populaties. Op basis hiervan worden de onderzoeksvragen geformuleerd die ten grondslag liggen aan dit proefschrift en zullen worden beantwoord in de hoofdstukken 2-11 en bediscussieerd in hoofdstuk 12 (Discussie).

Deel 1: Kunnen we door het gebruik van risicostratificatiemiddelen de nadelen van vroege opsporing van prostaatkanker verminderen? Kunnen deze risicostratificatiemiddelen ook één-op-één worden toegepast binnen een Aziatische populatie?

In **hoofdstuk 2** wordt in een review vroege opsporing van prostaatkanker met behulp van de PSA-test besproken, evenals de problemen rondom overdiagnose en welke mogelijkheden er bestaan om de overdiagnose te verminderen. Data beschikbaar in de wetenschappelijke literatuur tonen dat bepaalde mannen voordeel kunnen hebben van vroege opsporing van prostaatkanker. Langetermijn data van de grootste gerandomiseerde studie naar vroege opsporing van prostaatkanker (ERSPC) laat zien dat het aantal mannen wat moet worden gescreend om één prostaatkankerdode te voorkomen nog altijd daalt. Dat geldt ook voor het aantal mannen wat moet worden behandeld om één prostaatkankerdode te voorkomen. Deze getallen komen nu in de buurt van de getallen die bij vroege opsporing van borstkanker als acceptabel werden beschouwd voor de invoering van een landelijk screeningprogramma. Het toepassen van risicostratificatiemiddelen zoals een risicowijzer, merkstoffen uit het bloed of de urine, en het toepassen van de MRI kan het mogelijk maken om nog selectiever te screenen op prostaatkanker, zodat alleen de mannen die er echt voordeel van zullen ondervinden gediagnosticeerd en (mogelijk) behandeld zullen worden.

De toepassing van één zo'n risicostratificatiemiddel, de PSA-density, wordt beschreven in **hoofdstuk 3**. Door naast PSA ook naar het volume van de prostaat (PSA-density = PSA/volume van de prostaat) te kijken, kan binnen de Aziatische populatie prostaatkanker beter worden gediagnosticeerd. Dit effect bleek nog groter in obese Aziatische mannen. Obese Aziatische mannen met een PSA-density >0.15 hadden een vier keer zo hoge kans op prostaatkanker bij vergelijkbare PSA-waarden.

Een ander risicostratificatiehulpmiddel, de Prostaatwijzer, heeft laten zien dat door variabelen te combineren tot een formule, deze beter in staat is het risico op prostaatkanker en het risico op hooggradig prostaatkanker te voorspellen dan wanneer alleen PSA zou worden gebruikt. De Prostaatwijzer werd meermaals gevalideerd in andere cohorten van

Westerse mannen. In **hoofdstuk 4** wordt juist gekeken of de Prostaatwijzer ook kan worden toegepast in een Aziatische setting. In eerste instantie presteerde de Prostaatwijzer voldoende bij toepassing in een Aziatische setting, maar bestond er wel het risico dat de kans op prostaatkanker te hoog werd ingeschat. Daarop werd de formule achter de Prostaatwijzer voor Aziatische mannen aangepast, waarna de Prostaatwijzer veel beter presteerde. Als proef op de som werd dit gecontroleerd in een ander cohort Aziatische mannen. Daaruit bleek dat na de aanpassing de kans op prostaatkanker voor Aziatische mannen accuraat werd voorspeld.

In **hoofdstuk 5** blijkt vervolgens dat door de toepassing van de Prostaatwijzer, 36% van de onnodige biopten had kunnen worden voorkomen, net als 39% van de gevallen waarbij koorts optreedt na het nemen van een biopt, of 42% van het aantal ziekenhuisopnames na een biopt. Dit is met name van belang met betrekking tot het stijgende percentage sepsis dat optreedt na het nemen van prostaatbiopten.

Deel 2: Het gebruik van de Prostate Health Index bij het diagnosticeren van prostaatkanker in Aziatische mannen.

Bij Kaukasische mannen is gebleken dat de PHI bloedtest toegevoegde waarde heeft voor het diagnosticeren van prostaatkanker. In de introductie werd de lagere prevalentie van prostaatkanker onder Aziatische mannen reeds beschreven en in hoofdstuk 4 lieten we zien dat de formule achter de Prostaatwijzer moest worden aangepast voordat de Prostaatwijzer kon worden toegepast in een Aziatische populatie. Het was nog niet bekend of de PHI één-op-één kon worden toegepast bij Aziatische mannen.

Hoofdstuk 6 beschrijft een studie waarin de PHI voor het eerst wordt toegepast bij Aziatische mannen met een PSA 4-10 ng/mL en een normaal DRE. PHI bleek een drie keer hogere specificiteit te hebben dan PSA, waardoor 45% van de biopten – waarvan met 90% zekerheid kan worden gezegd dat het geen hooggradig prostaatkanker betrof – kon worden voorkomen. In hoofdstuk 7 werd de PHI bloedtest ook toegepast bij Aziatische mannen met een PSA 10-20 ng/mL en een normaal DRE. Ook hier liet de toepassing van PHI veel betere resultaten zien, dan wanneer alleen voor de toepassing van de PSA was gekozen. Hoofdstuk 6 en 7 laten dus zien dat er een verband bestaat tussen de PHI en het risico op prostaatkanker bij Aziatische mannen. In hoofdstuk 8 laten we vervolgens zien dat PHI ook kan voorspellen welke kankers een agressievere pathologie vertonen. In mannen met een PHI score >35, had 60.8% een risico op pT3 of Gleason ≥ 7 prostaatkanker. Voor mannen met een PHI score <35 was dit risico 16.1%. Naast dat de uitkomst van de PHI bloedtest de beslissing om wel of geen biopt te nemen zou kunnen beïnvloeden, zou de score ook kunnen worden meegenomen bij het maken van een behandelbeslissing als prostaatkanker eenmaal is gediagnosticeerd.

De PHI referentiewaarde laat het risico op prostaatkanker zien binnen verschillende PHI ranges. Deze zijn gebaseerd op data van Kaukasische mannen. In **hoofdstuk 9** wordt de rol van PHI onderzocht in verschillende regio's waar de prevalentie van prostaatkanker van elkaar verschilt. Zo worden er mannen geïncludeerd uit vier Europese steden en mannen uit vier Aziatische steden. In mannen met een PSA <10 ng/mL werd er een vier keer zo groot verschil gezien in het risico op prostaatkanker tussen Europese en Aziatische mannen. Ook werden er verschillen gezien in het aantal kankers bij verschillende PHI ranges tussen Europese en Aziatische mannen. Het is daarom aan te raden om een aangepaste referentiewaarde te gebruiken wanneer het Aziatische mannen betreft om zo te voorkomen dat het risico op prostaatkanker wordt overschat en er nog meer onnodige biopten worden genomen. Bij een sensitiviteit van 90% van hooggradige prostaatkanker kan bij Aziatische mannen 56% onnodige biopten worden voorkomen en 33% Gleason 6 tumoren, in vergelijking met 40% en 31%, respectievelijk, bij Europese mannen.

Bij de Prostaatwijzer zagen we al dat het toevoegen van variabelen aan de achterliggende formule de inschatting van het risico verbeterd. Dit geldt ook het toevoegen van variabelen aan de formule wanneer deze in een Aziatische populatie wordt toegepast. Zo blijkt in **hoofdstuk 10** dat het opnemen van DRE, de grootte van de prostaat en leeftijd, naast de uitslag van de PHI bloedtest, het mogelijk maakt om met nog meer zekerheid te voorspellen wie een verhoogt risico heeft op het krijgen van prostaatkanker. Voor hooggradig prostaatkanker zagen we zo'n effect niet. Maar in hoofdstuk 7 zagen we dat voor Aziatische mannen met een relatief hogere PSA-waarde tussen de 10-20 ng/mL verdere risicostratificatie op basis van leeftijd, PSA, en eerdere negatieve biopten wel mogelijk was.

In de meeste wetenschappelijke artikelen wordt er geschreven over hoe de toepassing van nieuwe bloedtesten (zoals PHI) in theorie biopten zou kunnen besparen. In **hoofdstuk 11** wordt een studie beschreven waarin de daadwerkelijke impact van PHI in de dagelijkse klinische praktijk wordt gerapporteerd. Van de Hong Kong-Chinese mannen met een PSA-waarde tussen 2-10 ng/mL besloot 82% van de mannen nadat ze hun PHI-score hadden gehoord om niet direct een biopt te ondergaan. Door met behulp van PHI alleen die mannen met een hoger-risico ook daadwerkelijk te biopteren steeg het aantal Gleason 3+3=6 en Gleason 3+4=7 (Gleason Grade groep ≥2) kankers van 2.8% (wanneer alleen een PSA-strategie zou worden toegepast) naar 14.7%. Van de mannen met meer dan twee jaar follow-up die een PHI bloedtest ondergingen, werden 9.8% met een PHI-score <35 en 26.4% met een PHI-score >35 alsnog gebiopteerd, wat resulteerde in 11% en 28.6% Gleason ≥3+4=7 diagnoses. Door PHI in de klinische praktijk toe te passen, konden meer dan 80% van de biopten worden voorkomen. Ook het aantal hooggradige prostaatkankers dat werd gediagnosticeerd verbeterde ten opzichte van het aantal diagnosis wanneer een strategie met alleen PSA zou worden toegepast. Een hogere PHI waarde bij het eerste meetmoment was gecorreleerd aan de gevonden bioptuitkomsten naderhand en kan daarom worden ingezet om het aantal vervolgbezoeken per patiënt te optimaliseren.

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PHD PORTFOLIO DRS. PETER KA-FUNG CHIU

Name PhD student: drs. Peter Ka-Fung Chiu	**PhD period: January 2015-August 2019**
Erasmus MC Department: Urology	**Promotor: Prof. dr. M.J. Roobol-Bouts & Prof. dr. C.H. Bangma**
Research School: Nihes	**Copromotor: dr. L.D.F. Venderbos**

1. PhD training	**Year**	**Workload**	
		Hours	**ECTS**
General courses			
Scientific integrity	2017		0.5
Specific courses			
Epworth Robotic Prostatectomy masterclass	2015	9	
Prostate MRI Imaging & biopsy masterclass	2015	9	
EAU 2016 – ESU/ESUT/ESUI Hands-on training in MRI Fusion Biopsy	2016	9	
EAU 2016 – ESU course Metastatic prostate cancer	2016	3	
UAA 2017 – Masterclass on Robotic prostatectomy	2017	3	
Men's health cadaveric workshop	2017	14	
SIU 2017 – Prostate MRI masterclass	2017	3	
SIU 2017 – Innovators MRI-TRUS Fusion hands-on course	2017	5	
EAU 2018 – Focal therapy for prostate cancer	2018	3	
Seminars and workshops			
Department of Urology, Erasmus MC journal club	2016		1
Department of Urology, Erasmus MC journal club	2017		1
ERSPC Meeting at Erasmus MC, presentation	2017		1
Division of Urology, Department of Surgery, Prince of Wales Hospital, Journal club & Research meeting	2016		1
Division of Urology, Department of Surgery, Prince of Wales Hospital, Journal club & Research meeting	2017		2
Division of Urology, Department of Surgery, Prince of Wales Hospital, Journal club & Research meeting	2018		2
Division of Urology, Department of Surgery, Prince of Wales Hospital, Journal club & Research meeting	2019		1
Presentations			
15th Urological Association of Asia Congress, Hong Kong – abstract	2017		1
Annual SIU Meeting, Lisbon, Portugal – abstract	2017		1
Annual EAU meeting, - abstract	2018		1
16h Urological Association of Asia Congress, Japan – abstract	2018		1
EMUC meeting, Amsterdam, The Netherlands - abstract	2018		1
Annual EAU meeting, - abstract	2019		1
International conferences			

Annual EAU meeting, Munich, Germany	2016		1
Annual EAU meeting, London, UK	2017		1
Urological Association of Asia, Hong Kong	2017		1
Annual SIU meeting, Lisbon, Portugal	2017		1
Annual EAU meeting, Copenhagen, Denmark	2018		1
Urological Association of Asia, Kyoto, Japan	2018		1
EMUC meeting, Amsterdam, The Netherlands	2018		1
Annual EAU meeting, Barcelona, Spain	2019		1
2. Teaching	**Year**	**Workload**	
		Hours	**ECTS**
Lectures to fellow Urologists			
1. Male reproductive system and their function (CNS, pituitary, testis, epididymis, prostate, seminal vesicles, scrotum, penis) Master of Science in Reproductive Medicine and Clinical Embryology, Dept of O&G, The Chinese University of Hong Kong, 10 Sept 2016	2016		1
2. Lecture: Testosterone - synthesis and regulation Master of Science in Reproductive Medicine and Clinical Embryology, Dept of O&G, The Chinese University of Hong Kong, 10 Sept 2016	2016		1
3. Lecture: Late onset hypogonadism Urology symposium 2016, Nov 2016, Prince of Wales Hospital	2017		1
4. PSA and its persisting ambiguities European Association of Urology Nursing Course, Multi-professional Management of Prostate cancer, April 2017, Pamela Youde Nethersole Eastern Hospital, Hong Kong	2017		1
5. Masterclass in Image Fusion Prostate Biopsy 5th August 2017, 15th Urological Association of Asia Congress, Hong Kong	2017		1
6. Take home message in Andrology 6th August 2017, 15th Urological Association of Asia Congress, Hong Kong	2017		1
7. Experience sharing of Prostate Health Index in Hong Kong Macao Laboratory Medicine Association (MLMA) dinner symposium, 1st Dec 2017, Macau, China	2017		1
8. Principles of green light prostatectomy In Laser applications in Urology symposium, 26th Jan 2018, Prince of Wales Hospital, Hong Kong	2018		1
9. The Challenges in PVP and Local Experience Sharing 20180327 Boston Scientific BPH symposium, 27th Mar 2018, Hong Kong	2018		1
10. Prostatic Artery Embolization for BPH European Association of Urology Nursing Course, Multi-professional Management of Prostate cancer, 7th April 2018, Pamela Youde Nethersole Eastern Hospital, Hong Kong	2018		1

11. The use of Prostate Health Index in prostate cancer diagnosis - an Asian perspective Macau Urological Association Annual Scientific Meeting, 22nd Sept, 2018, Macau	2018	1
12. Indocyanide Green (ICG) angiography and varicocelectomy Scientific Meeting, Andrology section of Greater Bay Area Doctors' Association, 20th Oct, 2018, Guangzhou, China	2018	1
13. Update on Transperineal MRI-Ultrasound fusion prostate biopsy – CUHK experience Pre-congress transperineal biopsy workshop, North District Hospital, 10th Urology Symposium, 25 Oct, 2018, Hong Kong	2018	1
14. The use of Indocyanide green (ICG) in varicocelectomy 10th Urology Symposium, 25-27 Oct, 2018 Hong Kong	2018	1
15. MRI Ultrasound fusion prostate biopsy – tips and tricks Taiwan Urological Association mid year meeting, 26 Jan 2019, Tainan, Taiwan	2019	1
Tutorials to surgical trainees, Hong Kong	2016-2018	3
Tutorials to medical students	2017-2019	5
TOTAL	**58**	**46.5**