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THE USEFULNESS OF SERUM FREE/TOTAL PSA RATIO FOR DIAGNOSIS OF PROSTATE CANCER IN ABNORMAL TOTAL PSA SCREENING THAI PATIENTS

Mrs. Sansnee Senawong

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By	:	Sansnee Senawong, M.D.
Field of Study	:	Health Development
Thesis Advisor	:	Associate Professor Kriangsak Prasopsanti, M.D., M.sc.
Thesis Co-Advisor	:	Professor Nalinee Aswapokee, M.D., M.Sc.

Accepted by Faculty of Medicine, Chulalongkorn University in partial fulfillment of the requirements for Master's Degree

……..…….…… Dean of the Faculty of Medicine
(Professor Pirom Kamolratanakul, M.D, M.Sc.)

Thesis Committee

……..…….…… Chairman
(Associate Professor Somjai Wangsuphachart, M.D., M.Sc.)

……..…….…… Thesis Advisor
(Associate Professor Kriangsak Prasopsanti, M.D., M.Sc.)

……..…….…… Thesis Co-Advisor
(Professor Nalinee Aswapokee, M.D., M.Sc.)

……..…….…… Member
(Associate Professor Anupan Tantiwong, M.D., M.Sc.)

……..…….…… Member
(Doctor Chulaluk Komoltri, DrPH)

ศันสนีย์ เสนะวงษ์ : ประโยชน์ของการตรวจหาอัตราส่วน พีเอสเออิสระ ต่อ พีเอสเอรวม ในเลือดเพื่อการวินิจฉัยมะเร็งต่อมลูกหมากในชายไทย (THE USEFULNESS OF SERUM FREE/TOTAL PSA RATIO FOR DIAGNOSIS OF PROSTATE CANCER IN ABNORMAL TOTAL PSA SCREENING THAI PATIENTS) **อาจารย์ที่ปรึกษา : รศ.นพ.เกรียงศักดิ์ ประสพสันติ, พ.บ., ว.ว. (ศัลยศาสตร์) อาจารย์ที่ปรึกษาร่วม : ศ.พญ.นลินี อัศวโภคี, พ.บ. ว.ว. (อายุรศาสตร์), 48 หน้า** ISBN : 974-17-5491-4

เป็นการศึกษาเพื่อประเมินประสิทธิภาพในการวินิจฉัยโรคมะเร็งต่อมลูกหมาก และความคุ้มค่าคุ้มทุนของการตรวจหาอัตราส่วนพีเอสเออิสระต่อพีเอสเอรวมในเลือด เพื่อการวินิจฉัยมะเร็งต่อมลูกหมากในชายไทยที่มีระดับสารบ่งชี้มะเร็งพีเอสเอรวมในเลือดผิดปกติ โดยทำการศึกษาในชายไทย 233 ราย ทุกรายจะได้รับการวินิจฉัยโรคมะเร็งต่อมลูกหมากโดยการตัดชิ้นเนื้อจากต่อมลูกหมากเพื่อตรวจทางพยาธิวิทยา และประเมินประสิทธิภาพการวินิจฉัยโรคมะเร็งต่อมลูกหมากของการตรวจดังกล่าวเมื่อใช้ค่าตัดสินผลการตรวจ (cut-off) ที่แตกต่างกัน โดยศึกษาจากความไว ความจำเพาะ ความแม่นยำ และตัวแปรอื่นๆ รวมทั้งทำการวิเคราะห์ความคุ้มค่าคุ้มทุนของการตรวจดังกล่าวเพื่อการวินิจฉัยโรคมะเร็งต่อมลูกหมากด้วย

ผลการศึกษาพบว่า ไม่สามารถสรุปค่าตัดสินผลการตรวจที่เหมาะสมที่สุดได้ แต่ค่าที่ควรใช้ในการตัดสินผลการตรวจ คือ 0.15, 0.18, 0.20, 0.25 และ 0.28 โดยขึ้นกับกลุ่มผู้ป่วยที่มีระดับพีเอสเอรวมแตกต่างกัน การวิเคราะห์ความคุ้มค่าคุ้มทุนพบว่าการตรวจหาอัตราส่วนพีเอสเออิสระต่อพีเอสเอรวมในเลือดเพื่อช่วยในการตัดสินใจทำการตัดชิ้นเนื้อต่อมลูกหมากในผู้ป่วยที่มีระดับพีเอสเอรวมในเลือดสูงผิดปกตินั้น ไม่สามารถแสดงผลที่คุ้มค่าคุ้มทุนมากกว่าการใช้ผลการตรวจระดับพีเอสเอรวมในเลือดเพียงอย่างเดียวในการตัดสินใจทำการตัดชิ้นเนื้อต่อมลูกหมาก ดังนั้นแพทย์จำเป็นต้องพิจารณาเลือกใช้ค่าตัดสินผลการตรวจอัตราส่วนพีเอสเออิสระต่อพีเอสเอรวมในเลือดตามกลุ่มผู้ป่วย โดยเปรียบเทียบความไว ความจำเพาะ และปัจจัยอื่นๆ ของการใช้ค่าตัดสินผลการตรวจที่แตกต่างกันเพื่อประกอบการพิจารณา

สาขาวิชาการพัฒนาสุขภาพ ลายมือชื่อนิสิต.....

ปีการศึกษา 2543 ลายมือชื่ออาจารย์ที่ปรึกษา.....

ลายมือชื่ออาจารย์ที่ปรึกษาร่วม.....

4375431630 MAJOR HEALTH DEVELOPMENT
KEY WORD : PROSTATE CANCER, FREE/TOTAL PSA RATIO, TOTAL PSA, DIAGNOSIS
SANSNEE SENAWONG : THE USEFULNESS OF SERUM FREE/TOTAL PSA RATIO FOR DIAGNOSIS OF PROSTATE CANCER IN ABNORMAL TOTAL PSA SCREENING THAI PATIENTS. THESIS ADVISOR : ASSOCIATE PROFESSOR KRIANGSAK PRASOPSANTI, M.D., M.Sc. THESIS CO-ADVISOR : PROFESSOR NALINEE ASWAPOKEE, M.D., M.Sc. 48 pp. ISBN : 974-17-5491-14

Two hundreds and thirty three patients were included to evaluate the diagnostic performances and cost-effectiveness of serum free/total PSA ratio for diagnosis of prostate cancer when used in combination with conventional screening tests, serum total PSA and digital rectal examination. The diagnostic performances; sensitivity, specificity, positive predictive value, negative predictive value, accuracy and likelihood ratio, with different cut-off values were evaluated. Decision tree and cost-effectiveness analysis were studied to determine the most appropriate cut-off value of serum free/total PSA ratio that should be used in prostate cancer diagnosis program.

It could not be definitely concluded which was the most appropriate cut-off value of serum free/total PSA ratio as the indication to perform prostate biopsy in Thai patients with abnormal serum total PSA, but the potential cut-off candidates ranged from 0.15 to 0.28 (0.15, 0.18, 0.20, 0.25, 0.28) depending on the patient groups with different serum total PSA. The cost-effectiveness analysis could not show the clear benefit of serum free/total PSA ratio when performed in serial with serum total PSA over serum total PSA alone as indication for prostate biopsy. The urologists should weight between the differences in diagnostic performances, benefits and risks of performing serum free/total PSA ratio with different cut-off values to minimize unnecessary biopsy.

Field of study : Health Development Student's signature……..…..…

Academic year : 2000 Advisor's signature……...…

Co-advisor's signature…….

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LIST OF ABBREVIATIONS

PSA	Prostate specific antigen
BPH	Benign prostatic hypertrophy
DRE	Digital rectal examination
TRUS	Transrectal ultrasound
IPSS	The International Prostate Symptom Score
ROC curve	Receiver Operating Characteristic curve
SD	Standard deviation
CI	Confidence interval
PPV	Positive predictive value
NPV	Negative predictive value
LR	Likelihood Ratio
CE ratio	Cost-Effectiveness ratio
pCA	Prostate cancer

CHAPTER 1

BACKGROUND AND RATIONALE

Prostate cancer is the most common cancer and the major leading cause of death from cancer in Western men[1-4]. The patients at risk are males aged 50 years old or more. It was found that most of the patients in early stage prostate cancer have no specific symptoms and signs. The voiding dysfunction symptoms presented in these patients are usually caused by underlying benign prostatic hyperplasia (BPH)[1-4]. Generally the clinically diagnosed prostate cancer has already spread outside the gland, usually into the bones, before the first diagnosis is made[4]. Cure is impossible in metastatic prostate cancer stage and median survival time is in the range of 18-30 months in spite of endocrine treatment[4]. Thus the only opportunity for a cure of prostate cancer is at an early stage when the cancer is still the organ-confined disease. In this connection, the prostate cancer screening program in general population at risk was recommended in Western countries. The recommended methods used for screening of prostate cancer are digital rectal examination (DRE) and serum prostate specific antigen (PSA) level determination[5]. The recommended gold standard is pathological diagnosis from transrectal ultrasound (TRUS) guided prostate biopsy tissue[5]. At present, although the prostate cancer screening program in general population at risk is recommended in Western countries, but there are many controversial aspects in practice.

In contrast, prostate cancer is less common in Asian countries[3,6-8]. In Thailand, the incidence of prostate cancer is 3.8 per 100,000 population and being the tenth cause of death from cancer in Thai men[7]. The prostate cancer screening program in general population at risk in our country seems to be not appropriate and not

cost-effective. However, it was found that in 1990-1995, when PSA was not widely used in Thailand, 90% of prostate cancer patients at Siriraj Hospital were diagnosed in advanced stage and the mortality rate was high[9-10]. But after the prostate evaluation program for early detection of prostate cancer was introduced and promoted in Siriraj hospital, the early stage cancer and more curable diseases were diagnosed. The prevalence of prostate cancer among the patients who visit the prostate evaluation program at Siriraj Hospital and undergone prostate biopsy during 1998-2000 was 20% (data from an ongoing study about early detection of prostate cancer at Siriraj Hospital). With these evidences, prostate cancer screening program may have some benefit in our country setting.

Are the recommended screening methods and other information studied in western men appropriately used in Thai patients ?

The two major problems about prostate cancer screening policy in Thailand are the risk of invasive gold standard and cost-effectiveness of the program. The gold standard, TRUS-guided prostate biopsy, required 6 times biopsies (six-sextant biopsy) including the representative area of the whole prostate gland[11]. This method is invasive, experience-required and need expensive instruments. The recommended indications to perform this invasive gold standard are abnormal DRE and/or abnormal PSA. But these two methods are not the perfect screening tests. Digital rectal examination (DRE), although it is more specific and much cheaper than PSA, but it is subjective and required experience of the examiner. Prostate specific antigen (PSA), although it is more expensive than DRE, but it is more reliable and was found in many studies that serum PSA could detect more prostate cancer[1,3,12,13], as well as a greater proportion of organ-confined cancer[14] than did DRE.

In this situation, other reliable test with higher specificity is needed in order to minimize the unnecessary TRUS-guided prostate biopsy from the false positive result of the serum PSA. The free/total PSA ratio may be the most potential one. Since it was demonstrated in many studies that, by choosing the appropriate cut-off value, the

free/total PSA ratio could provide a higher specificity with a minimal impairment in test sensitivity when compared to the serum PSA[3,15-18]. However, the efficacy of serum free/total PSA ratio was still controversial. The sensitivity and specificity were varied among studies (65-95% sensitivity and 31-90% specificity) since the different cut-off values were used, ranged from 0.10 to 0.25[2,3,15-27]. Furthermore, it was found racial differences in the serum PSA levels among White, Black and Asian men[3,5,15,16,28,29], but the answer for whether free/total PSA ratio also has racial difference or not is still not clearly concluded.

Thus, in order to answer whether the recommended screening methods and other information studied in western men can be applied to Thai patients, the study to evaluate the efficacy and cost-effectiveness of free/total PSA ratio in diagnosis of prostate cancer in Thai patients should be conducted.

CHAPTER 2

LITERATURE REVIEW

It was found that the prevalence and incidence of prostate cancer increase with age. In USA, less than 1% of prostate cancers are detected in men younger than 50 years old, 16% are discovered in men aged 50-64 years and the remaining 83% are detected in men older than 64 years of age[1]. In Thailand, the age distributions of prostate cancer patients diagnosed at Siriraj Hospital during 1990-1992[9] and 1993-1995[10] were summarized in the Table 2.1.

Table 2.1 : Age distribution of prostate cancer patients diagnosed at Siriraj Hospital during 1990-1992[9] and 1993-1995[10]

Age (year)	Prostate CA (%) , 1990-1992	Prostate CA (%) , 1993-1995
<50	2.0	3.2
50 – 59	14.6	8.4
60 – 69	24.0	27.4
70 – 79	43.8	36.8
≥ 80	15.6	24.2

Voiding dysfunction is common in elderly men. The most common cause of these symptoms is benign prostatic hyperplasia (BPH). The use of the international prostate symptom score (IPSS) is recommended to evaluate the voiding dysfunction in the patients. It includes 7 symptoms ; incomplete emptying, increased frequency, intermittency, urgency, weak stream, hesitancy and nocturia. Each symptom are graded in 0-5 score, so the total score is 35. There are 3 subdivision classes of

symptom : IPSS 0-7 is minor, IPSS 8-19 is moderate and IPSS 20-35 is severe symptom group[30].

Since most of the patients in early stage prostate cancer have no specific symptoms, and the clinically diagnosed prostate cancer usually has already spread outside the gland before the first diagnosis is made[4]. So, the screening program in general population at risk for early detection of prostate cancer is recommended in many western countries by using DRE and serum PSA concentration. It was found that by using DRE alone to detect prostate cancer, less than 50% of them were organ-confined disease[31], and the positive predictive value of the examination are about 26-35%[1]. For PSA, although there are many studies proposed that serum PSA concentration may detect significantly more prostate cancer[1,3,12,13], as well as a greater proportion of organ-confined cancer[14] than does DRE, 20-48% of patients with organ-confined cancer had normal PSA levels (≤ 4 ng/ml)[3,14-16]. The estimated sensitivity, specificity, positive predictive value and cancer detection rate of DRE and serum PSA (> 4 ng/ml) are shown in the Table 2.2.[1,16]

Table 2.2 : The estimated sensitivity, specificity, positive predictive value and cancer detection rate of DRE and serum PSA (> 4 ng/ml) in the evaluation for prostate cancer

Method	Sensitivity (%)	Specificity (%)	PPV (%)	Detection rate (%)
DRE	69-89	84-98	26-35	1.3-1.7
Serum PSA (> 4 ng/ml)	57-79	59-68	25-54	2.2-2.6

In order to improve the clinician's ability to detect more early and potentially curable prostate cancers, many concepts were introduced including PSA density (PSAD), PSA velocity (PSAV), age-specific reference ranges and free/total PSA ratio.

PSA density (PSAD), firstly introduced by Benson and associates[32], is the ratio of the serum PSA concentration and prostate volume as determined by transrectal ultrasonography. PSAD of 0.15 or less was proposed to be normal. Unfortunately, PSAD is limited by several factors including the cost and invasiveness of the technique, the inaccuracy of ultrasound to determine the precise prostate volume[2,3,16,28,33].

PSA velocity (PSAV), firstly introduced by Carter and co-workers[34], is the rate of increasing PSA values in one year. The PSAV of 0.75 ng/ml or greater per year suggests for the presence of prostate cancer[2,3,16,34]. Since there may be variability of PSA levels measured by different assay, so it is important that the same assay and laboratory should be used for each measurement[3,16,33]. Furthermore, in patients treated with endocrine therapy (finasteride), the interpretation of serum PSA results in this group of patients has to be more careful. Because finasteride (or Proscar) is a 5α-reductase inhibitor that competitively inhibits the conversion of testosterone to dihydrotestosterone, which is the essential factor for prostatic growth. It was found that this drug may decrease the level of serum PSA of the treated patient to approximately 50% of the baseline value after 6 to 12 months of treatment[2].

For the concept of age-specific reference ranges, it was found that serum PSA concentration correlates directly with the patient's age and the median serum PSA concentration will increase with each decade of age. Thus, the clinically appropriate reference ranges of serum PSA should depend on patient's age[28]. Many studies claimed that by using age-specific reference ranges as criteria to perform prostate biopsy, the sensitivity of PSA test for early detection of prostate cancer in younger men is increased by decreasing the number of false-negative PSA results. In the other hand, the specificity of the PSA test for cancer detection in older men is improved by decreasing the number of false-positive PSA results[2,3,15,16,28,33,35]. But this concept is still controversial and not widely used. In a large study of 6630 men, it was found that the total cut-point of 4 ng/ml was superior to age-specific reference for early detection of prostate cancer ranges in men older than 60 years of age[36], since the potential

decrease in cancer detection rate if age-specific reference ranges were used in such age group. In addition, the differences of age-specific ranges in different racial population were found. And the recommended age-specific reference ranges for each racial group are summarized in the Table 2.3 below[3,6,15,28,29]. At present, what is the appropriate cut-off value of serum total PSA to perform prostate biopsy is still have no definite answer.

Table 2.3 : Age-specific reference ranges of total PSA levels based on race

	Serum prostate specific antigen (ng/ml)		
Age (year)	White	Black	Asian
40-49	0-2.5	0-2.0	0-2.0
50-59	0-3.5	0-4.0	0-3.0
60-69	0-4.5	0-4.5	0-4.0
70-79	0-6.5	0-5.5	0-5.0

About the free/total PSA ratio, it was found that PSA presented in the serum as many molecular forms, free form and bound forms which complexed to many kinds of serum proteins. The major components of serum PSA bound forms were PSA complexed to the serine protease inhibitors α1-antichymotrypsin (PSA-ACT) and α2-macroglobulin (the latter is undetectable with current immunoassay)[19-21]. The commercially test of total PSA is the combination of all immunodetectable forms in serum, primarily free PSA and PSA-ACT. Since it was found that the PSA-ACT complex was found in greater proportion in prostate cancer patients' sera than in patients with benign prostatic diseases[19-21], and the ratio of free to total PSA was significantly lower in prostate cancers patients compared to non-cancer group. Thus, free/total PSA ratio was proposed to be an useful method to discriminate between benign and malignant prostate diseases[2,3,15,16,19-21]. However, the usefulness of free/total PSA ratio was controversial. The cut-off value of free/total PSA ratio to discriminate between normal

and abnormal results were varied among studies, ranged from 0.10 to 0.25, resulting in wide ranges of the sensitivity (65-95%) and specificity (31-90%)[2,3,15-27]. No standard cut-off value was recommended now. And whether free/total PSA ratio had racial difference or not is still not clearly concluded.

About the tumor marker measuring method, there are many techniques available for quantifying the concentration of total PSA and free PSA in serum, such as enzyme immunoassay (EIA or ELISA), radioimmunoassay (RIA), chemiluminescence or electrochemiluminescence assay. These methods have quite the same level of sensitivity. The method for tumor marker determination at Immunology Laboratory, Siriraj Hospital is EIA technique by using the automated EIA machine : the Cobas Core (Roche Diagnostics, Switzerland). The Cobas Core PSA Total EIA II and Cobas Core PSA Free EIA are solid phase enzyme immunoasssay, sandwich type. Both assays use highly specific mouse monoclonal antibodies to PSA which measure free PSA and PSA-ACT complexed with equal potency (equimolarity). The standardization and calibration of these diagnostic test kits were performed against the PSA standardization samples (Standford University) according to the approved guidelines of the NCCLS (National Committee for Clinical Laboratory Standard, USA). The precision studies were already done for intra-assay precision, inter-assay precision, dilution linearity, detection limit, test for equimolarity, and clinical samples study compared with other widely accepted test kits[37-39].

CHAPTER 3

RESEARCH METHODOLOGY

3.1 Research Questions

3.1.1 Primary research question

3.1.1 What is the most appropriate cut-off value of serum free/total PSA ratio that should be used as the indication to perform prostate biopsy in Thai patients who have abnormal serum total PSA (>4 ng/ml) ?

3.1.2.1 What are the diagnostic performances (sensitivity, specificity, positive predictive value, negative predictive value, accuracy and likelihood ratio) of serum free/total PSA ratio at each cut-off candidates in Thai patients who have abnormal serum total PSA ?

3.1.2 Secondary research questions

What is the cost-effectiveness of performing serum free/total PSA ratio in serial with serum total PSA as the indication for prostate biopsy in Thai patients, comparing to performing serum total PSA alone ?

3.2 Research Objectives

3.2.1 To determine the most appropriate cut-off value of serum free/total PSA ratio and its diagnostic performances that should be used as the indication to perform prostate biopsy for diagnosis of prostate cancer in Thai patients who have abnormal serum total PSA.

3.2.2 To evaluate the cost-effectiveness of serum free/total PSA ratio performing in serial with serum total PSA as an indication to perform prostate biopsy for

diagnosis of prostate cancer in Thai patients who have abnormal serum total PSA as compared to performing serum total PSA alone.

3.3 Conceptual Framework

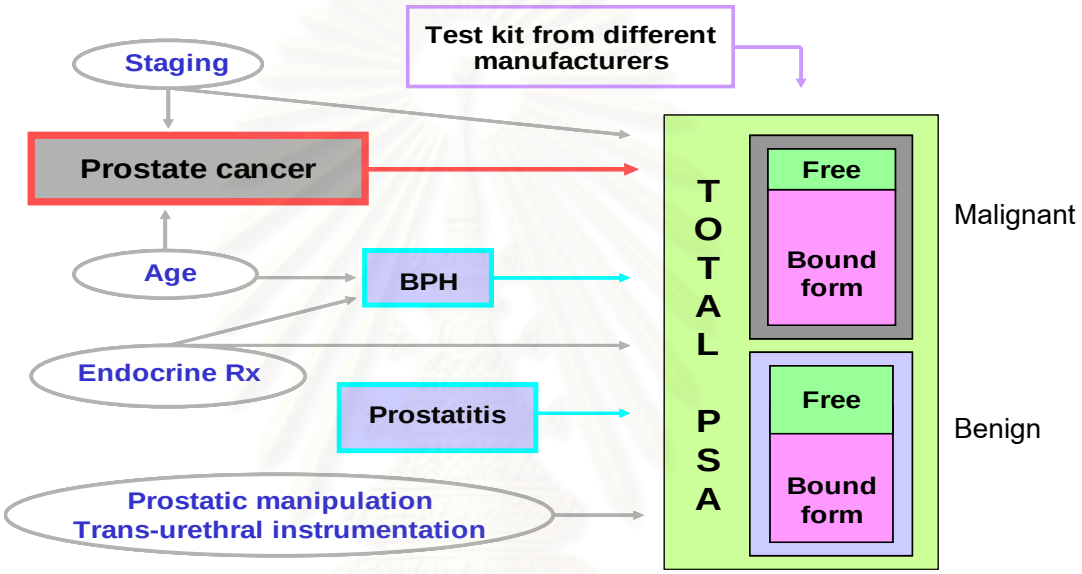


Figure 3.3.1 : Conceptual framework

Prostatic specific antigen (PSA) presented in the serum as many molecular forms, free form and bound (or complexed) forms. The serum total PSA detected was the combination of all immunodetectable forms in serum. Difference in the ratio of free and total PSA was found between malignant and benign prostatic diseases. Since it was found that bound-form PSA was found in greater proportion in prostate cancer patients' sera than in patients with benign prostatic diseases[19-21], so the ratio of free to total PSA was significantly lower in prostate cancers patients compared to non-cancer group.

The factors that might affect the serum level of total PSA were shown in the conceptual framework diagram. Serum levels of any tumor markers, including PSA, varied with cancer staging. The higher the cancer stage, the higher the serum tumor

marker level. However, since all tumor markers were not specific to any cancers, so many benign conditions, such as inflammation, could induce elevated serum tumor marker level. For serum total PSA, both benign prostatic hypertrophy (BPH) condition and prostatitis could induce elevation of serum total PSA level. And since the incidence of BPH increased with increasing age, so it was found that serum total PSA level usually increased with age too.

Any prostatic manipulation, such as digital rectal examination and transurethral instrumentation, could induce transient elevation of serum total PSA level because PSA was manually squeezed from prostate gland by these manipulations. In contrast, endocrine therapy for BPH might decrease the level of serum total PSA of the treated patient.

Another important factor affected the serum total PSA level was the test kit used to determine total PSA level. Since the PSA-specific monoclonal antibody used in different manufacturer test kit might be different, so the serum total PSA level detected by different manufacturer test kit might be different too. This issue is very important for the clinicians who want to use serum tumor marker level as a monitoring tool in cancer treatment.

3.4 Operational Definition

3.4.1 Prostate cancer

Diagnosed by histological examination of prostatic biopsy tissue by using the malignant characteristics in nuclear features, architecture of the gland and Gleason grading system for prostatic adenocarcinoma as diagnostic criteria.

3.4.2 Benign prostatic hyperplasia (BPH)

Diagnosed by histological examination of prostatic biopsy tissue by using the benign characteristics in nuclear features and architecture of the gland as diagnostic criteria.

3.4.3 Voiding dysfunction

It is a group of symptoms in IPSS (International Prostate Symptom Score), recommended by WHO, consisting of 7 symptoms : sense of residual urine, frequent urination, difficulty in urination, intermittency, hesitancy, urgency and nocturia. All symptoms are graded on a scale of 0 to 5, and the total symptom score is 35.

3.4.4 Digital rectal examination (DRE)

DRE is the examination to evaluate the prostate gland for the presence of malignancy by determining the size, consistency, nodularity and asymmetry of the prostate gland.

3.4.5 Trans-rectal ultrasound (TRUS) guided prostate biopsy

It is done in 6 sextant of prostate gland under precaution technique and antibiotic prophylaxis. The malignant suspicious sites are always included as biopsy sites.

3.4.6 Prostate specific antigen (PSA)

PSA is a serine protease enzyme produced by prostatic epithelial cells. There are two groups of serum PSA molecular form ; free form and complexed forms. The serum total PSA and serum free PSA levels can be determined by immunological methods such as EIA, RIA, chemiluminescence/electrochemiluminescence technique. The total PSA is the combination of free PSA and all immunodetectable complexed forms. The free/total PSA ratio is the proportion of free PSA and total PSA level of that sample specimen. The normal range of serum total PSA is 0-4 ng/ml.

3.5 Research Design

The research design is cross-sectional descriptive study. The place of study is the Urology Clinic, Department of Surgery and the Immunology Laboratory, Department of Immunology, Faculty of Medicine Siriraj Hospital.

3.6 Population and Sample

3.6.1 Target population

The target population of the study was Thai males, with or without voiding dysfunction symptoms, who have abnormal serum total PSA level (> 4 ng/ml) and/or abnormal digital rectal examination result, which are the indications to perform prostate biopsy for pathological diagnosis of prostate cancer.

3.6.2 Sampled population

The sampled population was patients, with or without voiding dysfunction symptoms, who attend prostate evaluation program or Urology Clinic at Siriraj Hospital and meet the eligible criteria.

3.6.3 Inclusion criteria

3.6.3.1 Thai male aged 50 years old or older

3.6.3.2 Serum total PSA level > 4 ng/ml and/or Abnormal digital rectal examination result

3.6.3.3 Informed consent for prostate biopsy

3.6.4 Exclusion criteria

3.6.4.1 Unsuitable conditions for prostate biopsy, including bleeding tendency, clinical diagnosis of acute or subacute prostatitis (tender prostate with or without fever)

3.6.4.2 Received endocrine therapy for BPH

3.6.4.3 Previous manipulation of prostate or transurethral instrumentation within 48 hours prior to blood sampling for serum total and free PSA determination

3.6.4.4 Known case of bladder cancer

3.6.4.5 Uncontrolled urinary tract infection

3.6.5 Sample size calculation

The formula used for sample size calculation is $N = \frac{Z^2 PQ}{d^2}$

N = Number of patients diagnosed as pCA (or non-pCA) by gold standard

P = Expected sensitivity (or specificity) of the test

Q = 1 – P

d = Allowable error

Since the objective of performing the test of interest (free/total PSA ratio) is to minimize the unnecessary biopsy, so the high specificity is expected.

If the expected specificity (P) = 0.80 , Q = 0.2 , the acceptable error (d) = 0.1

$$N = \frac{(1.96)^2 (0.8 \times 0.2)}{(0.1)^2} = 61.5 \text{ non-prostate cancer cases}$$

But cancer is very serious disease, so we cannot accept high false negative results.

If the accepted sensitivity (P) = 0.90 , Q = 0.1 , the acceptable error (d) = 0.1

$$N = \frac{(1.96)^2 (0.9 \times 0.1)}{(0.1)^2} = 34.5 \text{ prostate cancer cases}$$

Since the proportion of prostate cancer among patients undergone prostate biopsy at Siriraj Hospital (1998-2003) was 20%, to get 35 prostate cancer cases, a total of 175 patients, aged 50 years old or older with serum total PSA > 4 ng/ml and/or abnormal digital rectal examination, were recruited into the study.

3.7 Outcome Measurement

3.7.1 Main outcome

3.7.1.1 ROC curve of the serum free/total PSA ratio test

3.7.1.2 Diagnostic performances : sensitivity, specificity, positive predictive value, negative predictive value, accuracy and likelihood ratio of the serum free/total PSA test

3.7.2 Secondary outcome

Cost-effectiveness of performing the serum free/total PSA ratio test

3.7.3 Administrative variables and baseline variables

3.7.3.1 Administrative variables

- Name , Address , Identification number

3.7.3.2 Baseline variables

- Age (year)
- Digital rectal examination results

  0 = Normal prostate or Non-suggestive prostate cancer

  1 = Suggestive prostate cancer

  (induration, nodule, whole hard prostate gland)
- Serum total PSA (ng/ml)

3.7.4 Outcome variables

3.7.4.1 Serum free PSA (ng/ml)

3.7.4.2 Serum free/total PSA ratio

3.7.4.3 Pathological diagnosis

3.7.5 Gold standard

The definite histological diagnosis from transrectal ultrasound (TRUS) guided prostate biopsy specimen was the gold standard in this study. The characteristics in nuclear features, architecture of the gland and Gleason grading system for prostatic adenocarcinoma was used as pathological diagnostic criteria. The pathologists who performed the histological diagnosis were blinded from the results of digital rectal examination and tumor marker levels.

The transrectal ultrasound (TRUS) guided prostate biopsy was performed under precaution technique and antibiotic prophylaxis. If the DRE of that patient showed normal or non-suggestive prostate cancer result, the biopsy would be done in the random 6 sextant of prostate gland[11]. The malignant suspicious sites from DRE or transrectal ultrasound results were always included as the biopsy sites.

3.7.6 Tumor marker determination

Serum total PSA and free PSA levels were determined by enzyme immunoassay (EIA) technique, using the Cobas Core PSA Total EIA II and Cobas Core PSA Free EIA test kits and done by the Cobas Core automated EIA analyzer (Roche Diagnostic, Switzerland). All technicians involved in laboratory process were blinded.

The automated analyzer was calibrated as manufacturer recommendations to test the validity of the results. The reliability of the test results was evaluated by randomly determining the test in duplicated specimens. The storage and preparation of all the test reagents and sample specimens were strictly followed the manufacturer recommendations.

3.8 Data Collection

Patients with or without voiding dysfunction symptoms → Attend prostate evaluation program or Urology clinic

↓

Blood sampling (for serum total PSA and free PSA)

Digital rectal examination

↓

Patients fit with eligible criteria

↓

TRUS-guided prostate biopsy (for pathological diagnosis)

3.9 Data Analysis

3.9.1 Analysis of baseline variables

3.9.1.1 The age and serum total PSA in prostate cancer and non-prostate cancer group will be reported in means and standard deviations.

3.9.1.2 The DRE result (suggestive and non-suggestive of cancer) in prostate cancer and non-prostate cancer group will be reported as percentages.

3.9.2 Analysis of outcome variables

3.9.2.1 Serum free PSA and free/total PSA ratio in prostate cancer and non-prostate cancer groups will be reported in means, standard deviations and 95% confidence intervals. The means of free/total PSA ratio in prostate cancer and non-prostate cancer groups will be compared by using unpaired t-test (or Mann-Whitney U test, if not normally distributed)

3.9.2.2 The receiver operating characteristic (ROC) curve of the free/total PSA ratio test will be performed to determine the potential cut-off value candidates.

3.9.2.3 The diagnostic performances (sensitivity, specificity, positive predictive value, negative predictive value, accuracy and likelihood ratio) of serum free/total PSA ratio at each different potential cut-off points will be evaluated.

3.9.2.4 The decision analysis comparing the cost-effectiveness of each potential cut-off value candidates will be performed. The direct medical charges in patient's view point will be used. The criteria for decision making in decision analysis include the highest specificity that provide the lowest acceptable sensitivity and the most cost-effective program

3.9.2.5 The economical analysis comparing the candidate programs used to detect prostate cancer in Thai patients (serum total PSA alone and serum free/total PSA ratio in serial with serum total PSA) will be performed.

3.10 Ethical Consideration

Informed consents were required in all of the patients enrolled to the study. The recommended standard criteria for prostate biopsy (abnormal DRE and/or serum total PSA > 4 ng/ml) were used.

3.11 Limitations

If the results from both criteria for decision making in decision analysis are not concordant, the definite conclusion to answer the primary research question may be not achieved. The clinicians should have to decide by themselves, by using all of the study information such as the sensitivity, specificity and likelihood ratio of the test, what should be the preferred cut-off value of serum free/total PSA ratio in their settings.

3.12 Benefits of the Study

The serum free/total PSA ratio is expected to be used as an additional screening test (or indication) to perform prostate biopsy in order to minimize the unnecessary biopsy.

The study results may be helpful as the preliminary information for the policy makers to decide whether the prostate cancer screening program may have any role in Thailand and the study to identify the appropriate prostate cancer screening program in Thailand should be conducted or not.

3.13 Administration and Time Schedule

	2000				2001				2002	
	Jan-Mar	Apr-Jun	Jul-Sep	Oct-Dec	Jan-Mar	Apr-Jun	Jul-Sep	Oct-Dec	Jan-Mar	Apr
Preparation the proposal and Staff meeting	/		/	/						
Data collection	/	/	/	/	/	/	/			
Data analysis							/	/		
Thesis writing									/	
Thesis defense										/

CHAPTER 4

RESULTS

The study was conducted in Urology clinic, Department of Surgery, Faculty of Medicine Siriraj Hospital from the year 2000 through 2003. The total number of 233 patients were included in the study. Patients' age, digital rectal examination (DRE) results and serum total PSA levels were collected as baseline information. However, the digital rectal examination results could be collected only in 117 patients (50.2%), while the other 116 patients (49.8%) were missing. Serum total PSA and free PSA levels were determined by using Cobas Core automated enzyme immunoassay technique (Roche, Switzerland), and then, the serum free/total PSA ratio was calculated. All of the 233 patients undergone the gold standard, transrectal ultrasound (TRUS) guided prostate biopsy, due to abnormal serum total PSA (> 4 ng/ml) and/or abnormal digital rectal examination results. Among these, 69 patients (29.6%) were pathological diagnosed as prostate cancer, while 164 (70.4%) were negative for prostate cancer.

Table 4.1 : Descriptive statistics of baseline variables (age) in prostate cancer and non-cancer groups

	Prostate Cancer (n = 69)	Non-Cancer (n = 164)
Age (year)		
- mean ± SD	68.3 ± 8.8	67.9 ± 7.3
- minimum , maximum	52 , 86	52 , 89
- 95% CI for mean	66.2 , 70.4	66.8 , 69.1

Table 4.2 : Descriptive statistics of baseline variables (serum total PSA) in prostate cancer and non-cancer groups

	Prostate Cancer (n = 69)	Non-Cancer (n = 164)
Serum total PSA (ng/ml)		
- mean ± SD	33.1 ± 42.9	9.3 ± 11.6
- minimum , maximum	3.5 , 257.2	0.4 , 98.3
- 95% CI for mean	22.8 , 43.4	7.6 , 11.1

Table 4.3 : Percentage of digital rectal examination (DRE) results in prostate cancer and non-cancer groups

DRE result	Prostate Cancer (n = 15)	Non-Cancer (n = 102)	Total (n = 117)
Abnormal	15 (100%)	71 (69.6%)	86 (73.5%)
Normal	0 (0%)	31 (30.4%)	31 (26.5%)

4.1 Descriptive Statistics and Diagnostic Performances of Serum Free/Total PSA Ratio in Patients with Abnormal Serum Total PSA (> 4 ng/ml) and/or Abnormal Digital Rectal Examination

The serum free PSA and free/total PSA ratio of the total 233 patients who had abnormal serum total PSA (>4 ng/ml) and/or abnormal digital rectal examination were determined. The diagnostic performances ; sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy and likelihood ratio (LR), of serum total PSA, digital rectal examination and serum free/total PSA ratio when using different cut-off values for diagnosis of prostate cancer in Thai patients with abnormal total PSA (> 4 ng/ml) were evaluated.

Table 4.1.1 : Descriptive statistics of outcome variables (serum free/total PSA ratio) in prostate cancer and non-cancer groups

	Prostate Cancer (n = 69)	Non-Cancer (n = 164)
Serum free/total PSA ratio		
- mean ± SD	0.12 ± 0.08	0.18 ± 0.10
- minimum , maximum	0.02 , 0.55	0.04 , 0.88
- 95% CI for mean	0.10 , 0.13	0.16 , 0.19

Table 4.1.2 : Diagnostic performances of serum total PSA , cut-off 4 ng/ml

total PSA	pCA	no CA	*total*	Sens.	Spec.	PPV	NPV	Accu.	LR+
suggest pCA	68	125	*193*	98.55	23.78	35.23	97.50	45.92	1.29
not pCA	1	39	*40*						
	69	*164*	*233*						

Table 4.1.3 : Diagnostic performances of digital rectal examination

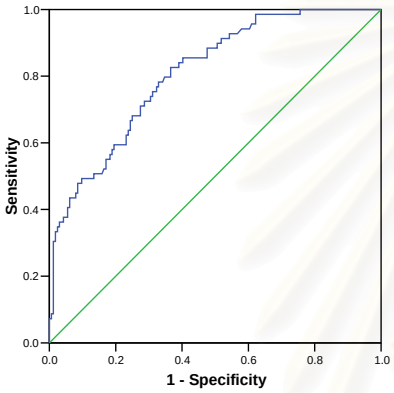
DRE	pCA	no CA	*total*	Sens.	Spec.	PPV	NPV	Accu.	LR+
suggest pCA	15	78	*93*	100	23.53	16.13	100	33.33	1.31
not pCA	0	24	*24*						
	15	*102*	*117*						

Table 4.1.4 : Diagnostic performances of serum free/total PSA ratio in patients with total PSA > 4 ng/ml and/or abnormal DRE

Cut-off 0.10	pCA	no CA	total	Sens.	Spec.	PPV	NPV	Accu.	LR+
suggest pCA	**38**	**28**	66	55.07	82.93	57.58	81.44	74.68	3.23
not pCA	**31**	**136**	167						
total	69	164	233						
Cut-off 0.11	pCA	no CA	total						
suggest pCA	**45**	**37**	82	65.22	77.44	54.88	84.11	73.82	2.89
not pCA	**24**	**127**	151						
total	69	164	233						
Cut-off 0.12	pCA	no CA	total						
suggest pCA	**48**	**48**	96	69.57	70.73	50.00	84.67	70.39	2.38
not pCA	**21**	**116**	137						
total	69	164	233						
Cut-off 0.15	pCA	no CA	total						
suggest pCA	**54**	**75**	129	78.26	54.27	41.86	85.58	61.37	1.71
not pCA	**15**	**89**	104						
total	69	164	233						
Cut-off 0.18	pCA	no CA	total						
suggest pCA	**59**	**98**	157	85.51	40.24	37.58	86.84	53.65	1.43
not pCA	**10**	**66**	76						
total	69	164	233						
Cut-off 0.20	pCA	no CA	total						
suggest pCA	**63**	**116**	179	91.30	29.27	35.20	88.89	47.64	1.29
not pCA	**6**	**48**	54						
total	69	164	233						
Cut-off 0.22	pCA	no CA	total						
suggest pCA	**64**	**128**	192	92.75	21.95	33.33	87.80	42.92	1.19
not pCA	**5**	**36**	41						
total	69	164	233						
Cut-off 0.25	pCA	no CA	total						
suggest pCA	**66**	**141**	207	95.65	14.02	31.88	88.46	38.20	1.11
not pCA	**3**	**23**	26						
total	69	164	233						

4.2 Receiver Operating Characteristic (ROC) Curve

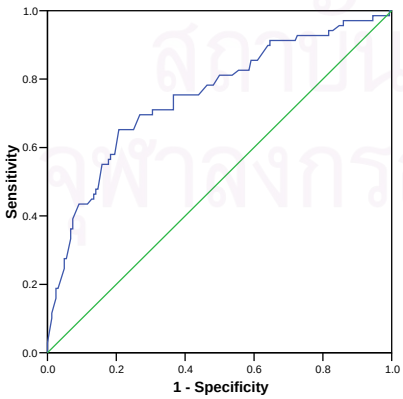
The ROC curve of serum total PSA and serum free/total PSA ratio in patients with abnormal serum total PSA (>4 ng/ml) and/or abnormal DRE results are shown in Figure 4.2.1 and Figure 4.2.2, respectively.



Test Result Variable(s): total PSA

Area Under ROC Curve	Std. Error	Asymptotic Sig.	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
.808	.029	.000	.751	.866

Figure 4.2.1 : ROC curve of serum total PSA in patients with abnormal serum total PSA (>4 ng/ml) and/or abnormal DRE results



Test Result Variable(s): free/total PSA ratio

Area Under ROC Curve	Std. Error	Asymptotic Sig.	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
.751	.036	.000	.680	.822

Figure 4.2.2 : ROC curve of serum free/total PSA ratio in patients with abnormal serum total PSA (>4 ng/ml) and/or abnormal DRE results

4.3 Decision Analysis

4.3.1 Decision tree

The decision analysis comparing the cost-effectiveness of serum free/total PSA ratio with different cut-off value would be performed by using the decision tree shown below. The criteria for decision making were the cut-off value with highest specificity that provided the lowest acceptable sensitivity.

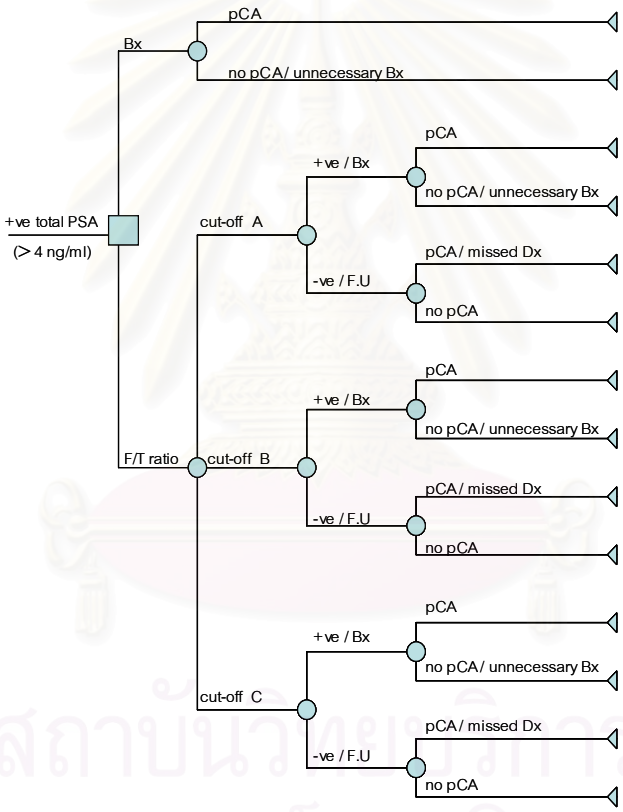


Figure 4.3.1.1 : Decision tree for cost-effectiveness evaluation

From Table 4.1.2, the sensitivity and specificity of serum total PSA when used as an indication for prostate biopsy were 98.6% and 23.8%, respectively. The best scenario needed should be the additional test that provides high specificity with minimal decrease the sensitivity of the conventional test, serum total PSA. So, the examples of potential cut-off value candidate of serum free/total PSA ratio for diagnosis

of prostate cancer in Thai patients with abnormal total PSA (> 4 ng/ml) that provided higher specificity than serum total PSA with lowest acceptable sensitivity, shown in Table 4.1.4, might be 0.20, 0.18 and 0.15. But if we thought that sensitivity was more important because we did not want to miss any cancer patients, in this situation the cut-off that provide high sensitivity, such as the cut-off at 0.25, may be more interesting.

If direct medical charges were used in the study, and estimated charges for prostate biopsy with antibiotics prophylaxis, serum total PSA and serum free PSA were 1100, 450 and 550 Baht, respectively, the results of decision analysis were shown in Figure 4.3.1.2.

4.3.2 Cost-effectiveness ratio (CE ratio)

CE ratio of pCA detection program = Cost / pCA detection rate

From decision analysis results in Figure 4.3.1.2 :

Program A : Abnormal total PSA / Prostate biopsy

CE ratio = 1550 / 0.30 = 5166.67

It means that, by using Program A, the cost to detect one prostate cancer patient is 5166.67 Baht.

Program B : Abnormal total PSA / Free/total PSA ratio, **cut-off 0.15** / Prostate biopsy

CE ratio = 1605 / 0.23 = 6978.26

It means that, by using Program B, the cost to detect one prostate cancer patient is 6978.26 Baht.

Program C : Abnormal total PSA / Free/total PSA ratio, **cut-off 0.20** / Prostate biopsy

CE ratio = 1847 / 0.27 = 6840.74

It means that, by using Program C, the cost to detect one prostate cancer patient is 6840.74 Baht.

Program D : Abnormal total PSA / Free/total PSA ratio, **cut-off 0.25** / Prostate biopsy

CE ratio = 2000 / 0.29 = 6896.55

It means that, by using Program D, the cost to detect one prostate cancer patient is 6896.55 Baht.

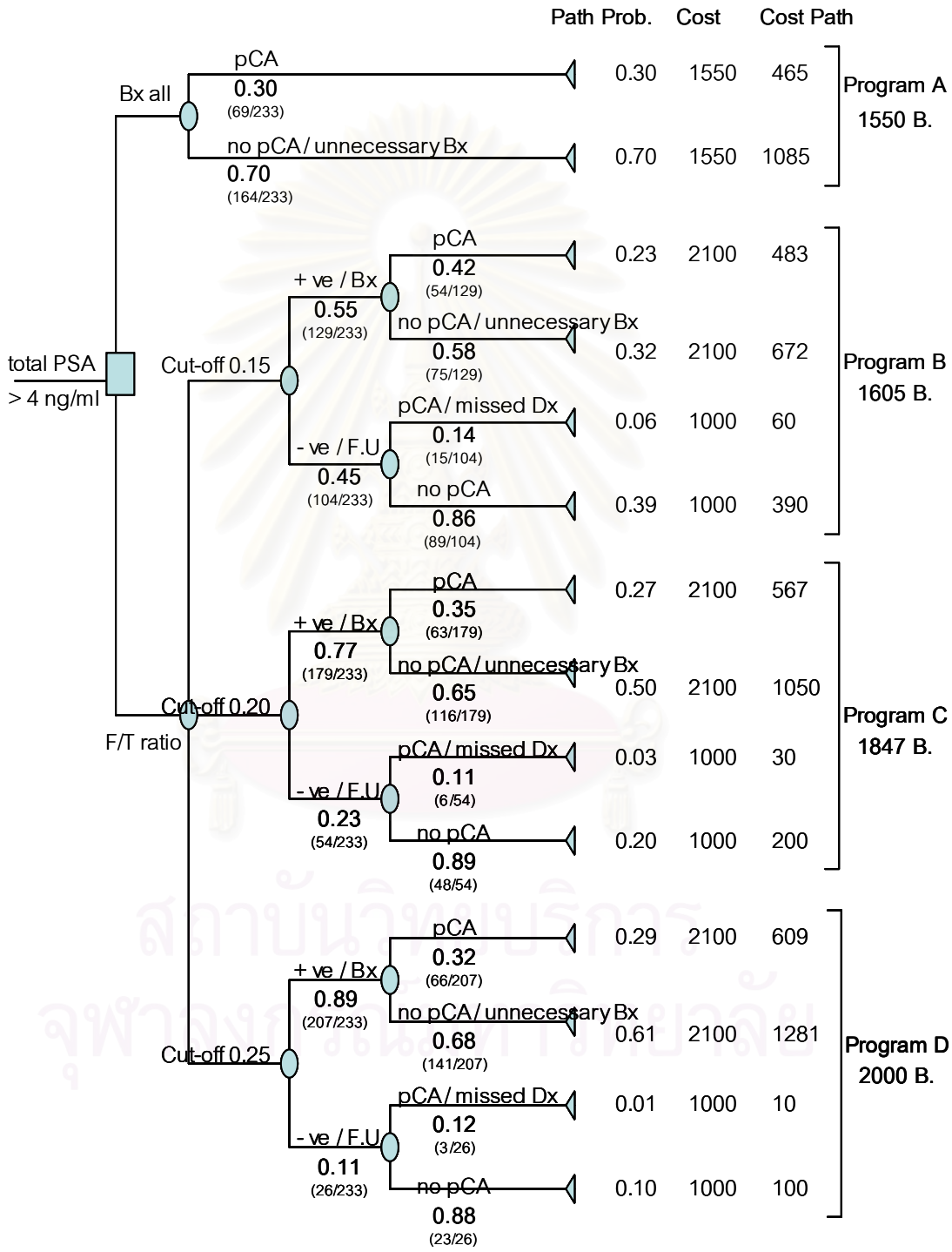


Figure 4.3.1.2 : Decision analysis comparing the cost-effectiveness of serum free/total PSA ratio with different cut-off value

Table 4.3.2.1 : Comparison of prostate cancer screening program candidates

	Total PSA	Total PSA + Free/Total PSA Ratio		
	Program A	Program B	Program C	Program D
Biopsy rate (%)	100	55	77	89
Decrease biopsy (%)	-	45	23	11
Prostate cancer detection (%)	30	23	27	29
Missed diagnosis (%)	0	6	3	1
Average Cost for 1 patient (Baht)	1550	1605	1847	2000
Cost for 1 pCA patient detection (Baht)	5166.67	6978.26	6840.74	6896.55

Program A : Abnormal total PSA and/or Abnormal DRE + Prostate biopsy

Program B : Abnormal total PSA and/or Abnormal DRE + Abnormal Free/Total PSA ratio, at cut-off 0.15 + Prostate biopsy

Program C : Abnormal total PSA and/or Abnormal DRE + Abnormal Free/Total PSA ratio, at cut-off 0.20 + Prostate biopsy

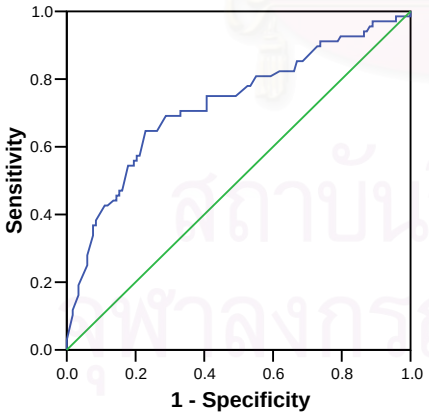
Program D : Abnormal total PSA and/or Abnormal DRE + Abnormal Free/Total PSA ratio, at cut-off 0.25 + Prostate biopsy

4.4 Subgroup Analysis

4.4.1 Diagnostic Performances and ROC Curve of Serum Free/Total PSA Ratio in Patients with Serum Total PSA > 4 ng/ml

Although both abnormal serum total PSA (> 4 ng/ml) and abnormal digital rectal examination results were internationally accepted as indications to performed prostate biopsy, but some used only the abnormal serum total PSA (> 4 ng/ml) result as prostate biopsy indication. Thus, if only the abnormal serum total PSA (> 4 ng/ml) was used as the indication to perform prostate biopsy, the total patients included with this criteria would be 186. Among these, 68 patients (36.6%) were pathological diagnosed as prostate cancer, and 118 (63.4%) were non-cancer patients.

The ROC curve of serum free/total PSA ratio in this subgroup was shown in Figure 4.4.1.1. And the diagnostic performances of serum free/total PSA ratio when using different cut-off values for diagnosis of prostate cancer in Thai patients with abnormal total PSA (> 4 ng/ml) were evaluated and shown in Table 4.4.1.1



Test Result Variable(s): free/total PSA ratio

Area Under ROC Curve	Std. Error	Asymptotic Sig.	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
.724	.040	.000	.646	.803

Figure 4.4.1.1 : ROC curve of serum free/total PSA ratio in patients with abnormal serum total PSA (>4 ng/ml)

Table 4.4.1.1 : Diagnostic performances of serum free/total PSA ratio in patients with total PSA > 4 ng/ml

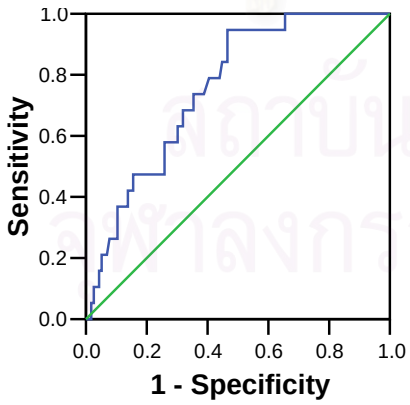
Cut-off 0.10	pCA	no CA	total	Sens.	Spec.	PPV	NPV	Accu.	LR+
suggest pCA	**37**	**23**	60	54.41	80.51	61.67	75.40	70.97	2.79
not pCA	**31**	**95**	126						
total	68	118	186						
Cut-off 0.11	pCA	no CA	total						
suggest pCA	**44**	**28**	72	64.71	76.27	61.11	78.95	72.04	2.73
not pCA	**24**	**90**	114						
total	68	118	186						
Cut-off 0.12	pCA	no CA	total						
suggest pCA	**47**	**38**	85	69.12	67.80	55.29	79.21	68.28	2.15
not pCA	**21**	**80**	101						
total	68	118	186						
Cut-off 0.15	pCA	no CA	total						
suggest pCA	**53**	**61**	114	77.94	48.31	46.49	79.17	59.14	1.51
not pCA	**15**	**57**	72						
total	68	118	186						
Cut-off 0.18	pCA	no CA	total						
suggest pCA	**58**	**80**	138	85.29	32.20	42.03	79.17	51.61	1.26
not pCA	**10**	**38**	48						
total	68	118	186						
Cut-off 0.20	pCA	no CA	total						
suggest pCA	**62**	**92**	154	91.18	22.03	40.26	81.25	47.31	1.17
not pCA	**6**	**26**	32						
total	68	118	186						
Cut-off 0.22	pCA	no CA	total						
suggest pCA	**63**	**99**	162	92.65	16.10	38.89	79.17	44.09	1.10
not pCA	**5**	**19**	24						
total	68	118	186						
Cut-off 0.25	pCA	no CA	total						
suggest pCA	**65**	**106**	171	95.59	10.17	38.01	80.00	41.40	1.06
not pCA	**3**	**12**	15						
total	68	118	186						

4.4.2 Diagnostic Performances and ROC Curves of Serum Total PSA and Serum Free/Total PSA Ratio in Patients with Serum Total PSA ≤ 10 ng/ml and/or Abnormal Digital Rectal Examination Results

Since the expected advantage of using serum free/total PSA ratio in addition with serum total PSA as the indication for prostate biopsy was to minimize unnecessary prostate biopsy. And it was known that the higher the tumor marker level, the higher probability of cancer is expected. So, the most important patient group that needed serum free/total PSA ratio as the additional information for prostate biopsy decision should be the patients with slightly elevated serum total PSA level.

If we wanted to use serum free/total PSA ratio as an additional indication for prostate biopsy in order to minimize unnecessary prostate biopsy only in the patients with serum total PSA ≤ 10 ng/ml, the total patients included with this criteria would be 135. Among these, 19 patients (14.1%) were pathological diagnosed as prostate cancer, and 116 (85.9%) were non-cancer patients.

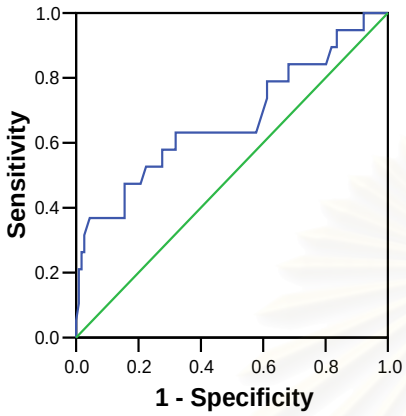
The ROC curve of serum total PSA and serum free/total PSA ratio in this subgroup was shown in Figure 4.4.2.1 and Figure 4.4.2.2, repectively.



Test Result Variable(s): total PSA

Area Under ROC Curve	Std. Error	Asymptotic Sig.	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
.756	.050	.000	.659	.853

Figure 4.4.2.1 : ROC curve of serum total PSA ratio in patients with serum total PSA ≤ 10 ng/ml and/or abnormal DRE



Test Result Variable(s): free/total PSA ratio

Area Under ROC Curve	Std. Error	Asymptotic Sig.	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
.670	.076	.018	.520	.820

Figure 4.4.2.2 : ROC curve of serum free/total PSA ratio in patients with serum total PSA ≤ 10 ng/ml and/or abnormal DRE

The diagnostic performances of serum total PSA and serum free/total PSA ratio when using different cut-off values for diagnosis of prostate cancer in Thai patients with serum total PSA ≤ 10 ng/ml were shown in Table 4.4.2.1 and Table 4.4.2.2 , respectively.

Table 4.4.2.1 : Diagnostic performances of serum total PSA ratio, cut-off 4 ng/ml, in patients with serum total PSA ≤ 10 ng/ml and/or abnormal DRE

total PSA	pCA	no CA	*total*	Sens.	Spec.	PPV	NPV	Accu.	LR+
suggest pCA	18	77	*95*	95	33.62	18.95	98	42.22	1.43
not pCA	1	39	*40*						
	19	*116*	*135*						

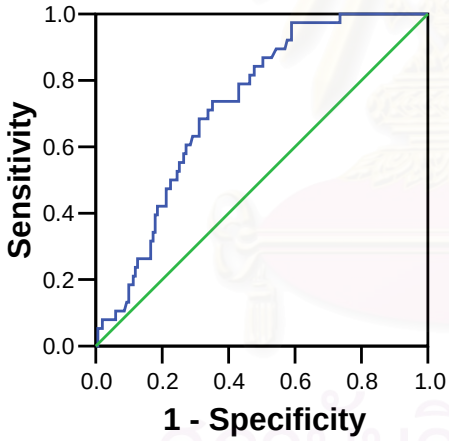
Table 4.4.2.2 : Diagnostic performances of serum free/total PSA ratio in patients with serum total PSA ≤ 10 ng/ml and/or abnormal DRE

Cut-off 0.10	pCA	no CA	total	Sens.	Spec.	PPV	NPV	Accu.	LR+
suggest pCA	7	14	21	36.84	87.93	33.33	89.47	80.74	3.05
not pCA	12	102	114						
total	19	116	135						
Cut-off 0.12	pCA	no CA	total						
suggest pCA	10	30	40	52.63	74.14	25.00	90.53	71.11	2.04
not pCA	9	86	95						
total	19	116	135						
Cut-off 0.15	pCA	no CA	total						
suggest pCA	12	50	62	63.16	56.90	19.35	90.41	57.78	1.47
not pCA	7	66	73						
total	19	116	135						
Cut-off 0.18	pCA	no CA	total						
suggest pCA	12	66	78	63.16	43.10	15.38	87.72	45.93	1.11
not pCA	7	50	57						
total	19	116	135						
Cut-off 0.20	pCA	no CA	total						
suggest pCA	15	78	93	78.95	32.76	16.13	90.48	39.26	1.17
not pCA	4	38	42						
total	19	116	135						
Cut-off 0.22	pCA	no CA							
suggest pCA	16	86	102	84.21	25.86	15.69	90.91	34.07	1.14
not pCA	3	30	33						
total	19	116	135						
Cut-off 0.25	pCA	no CA	total						
suggest pCA	17	97	114	89.47	16.38	14.91	90.48	26.67	1.07
not pCA	2	19	21						
total	19	116	135						
Cut-off 0.28	pCA	no CA	total						
suggest pCA	18	102	120	94.74	12.07	15.00	93.33	23.70	1.08
not pCA	1	14	15						
total	19	116	135						

4.4.3 Diagnostic Performances and ROC Curves of Serum Total PSA and Serum Free/Total PSA Ratio in Patients with Serum Total PSA ≤ 20 ng/ml and/or Abnormal Digital Rectal Examination Results

If we wanted to use serum free/total PSA ratio as an additional indication for prostate biopsy in order to minimize unnecessary prostate biopsy only in the patients with serum total PSA ≤ 20 ng/ml, the total patients included with this criteria would be 189. Among these, 38 patients (20.1%) were pathological diagnosed as prostate cancer, and 151 (79.9%) were non-cancer patients.

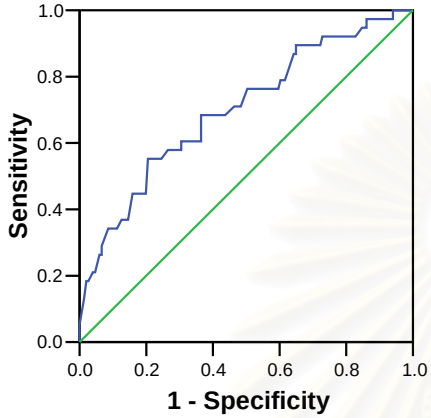
The ROC curve of serum free/total PSA ratio in this subgroup was shown in Figure 4.4.3.1 and Figure 4.4.3.2 , respectively.



Test Result Variable(s): total PSA

Area Under ROC Curve	Std. Error	Asymptotic Sig.	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
.726	.039	.000	.650	.803

Figure 4.4.3.1 : ROC curve of serum total PSA ratio in patients with serum total PSA ≤ 20 ng/ml and/or abnormal DRE



Test Result Variable(s): free/total PSA ratio

Area Under ROC Curve	Std. Error	Asymptotic Sig.	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
.700	.049	.000	.604	.797

Figure 4.4.3.2 : ROC curve of serum free/total PSA ratio in patients with serum total PSA ≤ 20 ng/ml and/or abnormal DRE

The diagnostic performances of serum total PSA and serum free/total PSA ratio when using different cut-off values for diagnosis of prostate cancer in Thai patients with serum total PSA ≤ 20 ng/ml were shown in Table 4.4.2.1 and Table 4.4.2.2 , respectively.

Table 4.4.3.1 : Diagnostic performances of serum total PSA ratio, cut-off 4 ng/ml, in patients with serum total PSA ≤ 20 ng/ml and/or abnormal DRE

total PSA	pCA	no CA	*total*	Sens.	Spec.	PPV	NPV	Accu.	LR+
suggest pCA	37	112	*149*	97.37	25.83	24.83	97.50	40.21	1.31
not pCA	1	39	*40*						
	38	*151*	*189*						

Table 4.4.3.2 : Diagnostic performances of serum free/total PSA ratio in patients with serum total PSA ≤ 20 ng/ml and/or abnormal DRE

Cut-off 0.10	pCA	no CA	total	Sens.	Spec.	PPV	NPV	Accu.	LR+
suggest pCA	17	26	43	44.74	82.78	39.53	85.62	75.13	2.60
not pCA	21	125	146						
total	38	151	189						
Cut-off 0.11	pCA	no CA	total						
suggest pCA	21	34	55	55.26	77.48	38.18	87.31	73.02	2.45
not pCA	17	117	134						
total	38	151	189						
Cut-off 0.12	pCA	no CA	total						
suggest pCA	22	44	66	57.89	70.86	33.33	86.99	68.25	1.99
not pCA	16	107	123						
total	38	151	189						
Cut-off 0.15	pCA	no CA	total						
suggest pCA	27	69	96	71.05	54.30	28.13	88.17	57.67	1.55
not pCA	11	82	93						
total	38	151	189						
Cut-off 0.18	pCA	no CA	total						
suggest pCA	30	92	122	78.95	39.07	24.59	88.06	47.09	1.30
not pCA	8	59	67						
total	38	151	189						
Cut-off 0.20	pCA	no CA	total						
suggest pCA	34	107	141	89.47	29.14	24.11	91.67	41.27	1.26
not pCA	4	44	48						
total	38	151	189						
Cut-off 0.22	pCA	no CA	total						
suggest pCA	35	118	153	92.11	21.85	22.88	91.67	35.98	1.18
not pCA	3	33	36						
total	38	151	189						
Cut-off 0.25	pCA	no CA	total						
suggest pCA	36	130	166	94.74	13.91	21.69	91.30	30.16	1.10
not pCA	2	21	23						
total	38	151	189						

CHAPTER 5

DISCUSSION

Prostate cancer is the most common cancer and the major leading cause of death from cancer in Western men[1-4]. Most of the patients in early stage prostate cancer have no specific symptoms and signs, while almost all the clinically diagnosed prostate cancer has already spread outside the gland before the first diagnosis is made[4]. So the prostate cancer screening program in general population at risk was recommended in Western countries. But in Thailand, the incidence of prostate cancer is lower, so, the prostate cancer screening program in general population at risk in our country seems to be not appropriate and not cost-effective. However, it was found that at the time PSA was not widely used in Thailand, 90% of prostate cancer patients at Siriraj Hospital were diagnosed in advanced stage and the mortality rate was high[9-10]. But after the prostate evaluation program for early detection of prostate cancer was introduced and promoted in Siriraj hospital, the early stage cancer and more curable diseases were diagnosed. So with these evidences, prostate cancer screening program might have some benefit in our country setting.

The data from prostate evaluation program during 1998-2000, conducted by Tantiwong A and colleagues (unpublished data), found that the prevalence of prostate cancer in elderly Thai men in the community around Siriraj Hospital was 0.75%. The prevalence of abnormal digital rectal examination (DRE) and abnormal serum total PSA (>4 ng/ml) were 8.7% and 17.3% respectively. Furthermore, the prevalence of prostate cancer among the patients who visited prostate evaluation program at Siriraj Hospital and undergone prostate biopsy was 20%. The sensitivity and specificity of DRE, total PSA and combined test in that study were shown in Table 5.1

Table 5.1 : Sensitivity and specificity of DRE, total PSA and combined total PSA/DRE test in patients attended prostate evaluation program at Siriraj Hospital, during 1998-2000

Test	Sensitivity	Specificity
Digital rectal examination (DRE)	77.8	57.2
Serum total PSA, cut-off 4 ng/ml	96.3	24.8
Combined DRE + total PSA , parallel testing	99.2	14.2
Combined DRE + total PSA , serial testing	74.9	67.8

In that study, Tantiwong A and colleagues concluded that individuals should be screened for prostate cancer by using both DRE and serum total PSA. The most appropriate and cost-effective prostate evaluation program in Thailand should be started with DRE and followed by serum total PSA and TRUS prostate biopsy (unpublished data).

Since TRUS-guided prostate biopsy is an invasive and painful diagnostic test, furthermore, the patients also have risks of biopsy complications, such as bleeding and infection. So, doctors should give them as much information as possible for decision making. In this situation, more reliable screening program with higher specificity than the conventional screening program may be needed in order to minimize the unnecessary TRUS-guided prostate biopsy.

In this study, we evaluated the diagnostic performances of free/total PSA ratio and its cost-effectiveness as another prostate cancer screening test candidate when performed in serial after abnormal serum total PSA and/or abnormal DRE, which was the prostate cancer screening program recommended by Tantiwong A and colleagues.

After analyzed the diagnostic performances of free/total PSA ratio with different cut-off values performed in patients with abnormal serum total PSA and/or abnormal DRE (Table 4.1.4), it was found that the sensitivity and specificity of the test were not as high as expected when firstly designed the study. Nevertheless, when using the criteria for decision making as cut-off value with highest specificity that provided the lowest acceptable sensitivity, it was found that the potential cut-off value candidates of serum free/total PSA ratio for diagnosis of prostate cancer in Thai patients with abnormal total PSA (> 4 ng/ml) and/or abnormal DRE might be 0.20, 0.18 and 0.15, because these cut-off candidates provided higher specificity than serum total PSA with acceptable sensitivity. But cancer is serious disease, so, if we thought that test sensitivity was more important than specificity because we did not want to miss any cancer patients, in this situation the cut-off value that provided high sensitivity but low specificity, such as the cut-off value at 0.25, might be more interesting. Some representatives of the potential cut-off candidates ; 0.15, 0.20 and 0.25, were further analyzed their cost-effectiveness when used as the additional test with serum total PSA for prostate biopsy, as shown in Figures 4.3.1.2.

In the cost-effectiveness analysis, there were many factors involved in the effectiveness, benefit and risk of the prostate cancer screening program. Some factors, such as pain and missed diagnosis, were difficult to estimate their value in currency. With this limitation, only direct medical charges were used in the study. However, the results of decision analysis comparing between the prostate cancer screening program candidates, by using decision tree and cost-effectiveness ratio were summarized in Table 4.3.2.1. It was found that using serum free/total PSA ratio in serial with conventional prostate screening tests, serum total PSA and DRE, increased cost of the prostate cancer screening program. With different cut-off value selected, serum free/total PSA ratio, when performed in serial after abnormal serum total PSA and/or abnormal DRE, could decrease prostate biopsy with different rates. But in the same time, it provided increased rate of missed diagnosis too. Furthermore, the diagnostic

performances of serum free/total PSA ratio did not show any advantage over serum total PSA and DRE. Thus, whether serum free/total PSA ratio had any role in prostate cancer screening program or not depended on the opinion of both the patients and the urologist who wanted to use this test in order to minimize the unnecessary biopsy. They should weight by themselves between the benefits, risks and cost of performing this new test, serum free/total PSA ratio, as a combined test with conventional prostate screening tests, DRE and serum total PSA.

Furthermore, since it was known that the higher the tumor marker level, the higher the probability of cancer, with this evidence, the most important patient group that needed serum free/total PSA ratio as the additional information for prostate biopsy decision in order to minimize unnecessary prostate biopsy should be the patients with slightly elevated serum total PSA level, such as $\leq$ 10 ng/ml, whose the probability of prostate cancer was low. In subgroup analysis, the diagnostic performances of serum free/total PSA ratio for diagnosis of prostate cancer in Thai patients with serum total PSA $\leq$ 10 ng/ml and $\leq$ 20 ng/ml when using different cut-off values were summarized in Table 4.4.2.2 and Table 4.4.3.2, respectively. It was found that in patients with serum total PSA $\leq$ 10 ng/ml group, the diagnostic performances of the test, at each cut-off values, were much lower than in the patients with total PSA >4 ng/ml (with no higher limit) and/or abnormal DRE group, especially for the sensitivity of the test. So, if the same decision making criteria was used, the potential cut-off candidates of serum free/total PSA ratio for diagnosis of prostate cancer in patients with serum total PSA $\leq$ 10 ng/ml might be the cut-off value that provided acceptable sensitivity with quite low specificity, such as the cut-off at 0.25 or 0.28.

The difference in diagnostic performances of the test at the same cut-off value between different patient groups with different serum total PSA confirmed the comment of this study, which already mentioned, that whether serum free/total PSA ratio

had any role in prostate cancer screening program or not depended on the opinion of both the patients and the urologist who wanted to use this test in order to minimize the unnecessary biopsy. They should weight by themselves between the benefits and risks of performing this test, serum free/total PSA ratio, as a combined test with conventional prostate screening tests, DRE and serum total PSA.

CHAPTER 6

CONCLUSION

This study was a cross-sectional descriptive study which was designed to evaluate the diagnostic performances and cost-effectiveness of a new test, serum free/total PSA ratio, for diagnosis of prostate cancer when used in combination with conventional screening tests, serum total PSA and digital rectal examination (DRE).

The total number of 233 patients were included in the study. The pathological diagnosis from transrectal ultrasound (TRUS) guided prostate biopsy specimen was used as gold standard. The diagnostic performances including sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy and positive likelihood ratio (+ LR) of serum free/total PSA ratio with different cut-off values for diagnosis of prostate cancer in Thai patients with abnormal total PSA (> 4 ng/ml) and/or abnormal DRE were evaluated. The decision analysis by using decision tree and cost-effectiveness ratio were studied to determine the most appropriate cut-off value of serum free/total PSA ratio that should be used in prostate cancer screening program.

From diagnostic performance results and using the criteria for decision making as the cut-off value with highest specificity that provided the lowest acceptable sensitivity, the potential cut-off value candidates of serum free/total PSA ratio for diagnosis of prostate cancer in Thai patients with abnormal total PSA (> 4 ng/ml) and/or abnormal DRE might be 0.20, 0.18 and 0.15, because these cut-off candidates provided higher specificity than did in serum total PSA with acceptable sensitivity. But cancer is serious disease, so, if we thought that test sensitivity was more important than specificity because we did not want to miss any cancer patients, in this situation the cut-off value

that provided high sensitivity but low specificity, such as the cut-off at 0.25, might be more interesting. Furthermore, in patients with slightly elevated serum total PSA level, such as ≤ 10 ng/ml, whose the probability of prostate cancer was low, the potential cut-off candidates might be the cut-off that provided acceptable sensitivity with quite low specificity, such as the cut-off at 0.25 or 0.28.

The cost-effectiveness study, that compared the biopsy rate, prostate cancer detection rate, missed diagnosis rate, average cost for one patient in the program and cost for one prostate cancer detection (CE ratio), could not show the clear benefit of serum free/total PSA ratio when performed in serial with serum total PSA over performing the conventional prostate screening tests, serum total PSA and DRE, as an indication to perform prostate biopsy for diagnosis of prostate cancer.

From all the data analyzed in this study, it could not be definitely concluded which cut-off value was the most appropriate cut-off value of serum free/total PSA ratio as the indication to perform prostate biopsy in Thai patients with abnormal serum total PSA (>4 ng/ml). Because no definite benefit of serum free/total PSA ratio, at any cut-off values, over the conventional prostate cancer screening tests, serum total PSA and DRE, could be identified. The urologists who wanted to use this test in order to minimize unnecessary biopsy should weight by themselves between the differences in diagnostic performances, benefits and risks of performing serum free/total PSA ratio with different cut-off values.

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VITAE

Sansnee Senawong was born on October 14, 1961 in Bangkok, Thailand. She graduated the medical degree from the Faculty of Medicine Siriraj Hospital, Mahidol University in 1985 and started her work as the instructor in Division of Immunology, Department of Microbiology, Faculty of Medicine Siriraj Hospital. After finished the pediatric residency program and received Board of Pediatrics from Thai Medical Council in 1991, she was assigned to take care the clinical immunology activities of the Division. In 1993, after the Department of Immunology was formally established, she was in charge as the Director of Immunology/Serology Laboratory.

She enrolled in the Thai CERTC training program in 2000 as funded by the Faculty of Medicine Siriraj Hospital, Mahidol University. Currently, she is working as Deputy Chairman, Department of Immunology and Assistant Dean of Medical Information Technology, Faculty of Medicine Siriraj Hospital.