

Prostate-Specific Antigen, Digital Rectal Examination and Transrectal Ultrasonography: A Meta-Analysis for This Diagnostic Triad of Prostate Cancer in Symptomatic Korean Men

Jae Mann Song¹, Chun-Bae Kim^{2,3}, Hyun Chul Chung¹, and Robert L. Kane³

Departments of ¹Urology and ²Preventive Medicine, Yonsei University Wonju College of Medicine, Wonju, Korea;

³Clinical Outcomes Research Center, University of Minnesota School of Public Health, Minneapolis, USA.

We conducted a meta-analysis using results from the Korean literature to determine whether prostate-specific antigen (PSA) or digital rectal examination (DRE) or transrectal ultrasonography (TRUS) provides a better diagnostic outcome for possible prostate cancer patients. An extensive literature search of MedRIC database et al. (1980 to 2003) was performed using the medical subject headings "PSA", "DRE", "TRUS" and "prostate cancer". Of the 108 articles that we retrieved, 13 studies (2,029 subjects) were selected for this meta-analysis. The criteria for quality evaluation were as follows: the study subjects must have been compared clinically for suspected prostate cancer, and the articles must have included individual data about sensitivity and specificity for this diagnostic triad based on the biopsy results as a reference standard. For the quantitative meta-analysis process the Hasselblad method was utilized. The pooled sensitivity and specificity for a PSA level greater than 4 ng/mL were 91.3% and 35.9%, respectively; and those for a PSA level greater than 10 ng/mL were 77.3% and 67.5%, respectively; and those for DRE were 68.4% and 71.5%, respectively; and those for TRUS were 73.6% and 61.3%, respectively. According to the results in a fixed effect model for PSA criteria, the estimates of \bar{d} for PSA4 and PSA10 were 0.8517 [95% confidence interval (CI): 0.6694, 1.0340] and 1.0996 (95% CI: 0.9459, 1.2534), respectively. Also, according to the results using a random effect model for both DRE and TRUS criteria, the estimates of \bar{d} for DRE and TRUS were 0.8398 (95% CI: 0.7169, 0.9627) and 0.8002 (95% CI: 0.6714, 0.9289), respec-

tively. The detection rate for combination testing of PSA, DRE and TRUS for the diagnosis of prostate cancer jumped further to 68.3% or to 76.8%. In conclusion, this study suggests that this diagnostic triad for prostate cancer was noneffective when they were used separately. Therefore, we recommend that the urologists should use PSA together with DRE and TRUS for the primary diagnosis of prostate cancer in men with lower urological symptoms.

Key Words: Prostate-specific antigen, digital rectal examination, transrectal ultrasonography, prostate cancer, meta-analysis

INTRODUCTION

Prostate cancer among adult males is the most common neoplasm after skin cancer in most developed countries. Over 200,000 men in the United States are diagnosed annually with prostate cancer and 30,000 men still die from this disease each year.¹ The age-standardized incidence of prostate cancer in the European Union is 65/100,000 and the EU's mortality rate is 26/100,000 per year.² In South Korea the incidence rate of this disease increased from 0.41 per 100,000 during 1985-1989 to 3.38 per 100,000 during 1995-1999. The crude incidence rate of prostate cancer among Korean men estimated to be 10.09 per 100,000. After 50 years old, the age-specific incidence rate increases three or four-fold for every 10-year increase in age.³ These trends have been shown to be related to diet (i.e. the high consumption of meat, dairy products and fats) by Whittemore et al.⁴ and Kolonel et al.,⁵ and also to the improved diagnostic techniques^{6,7} [including prostate-spe-

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Reprint address: requests to Dr. Chun-Bae Kim, Department of Preventive Medicine, Yonsei University Wonju College of Medicine, Wonju 220-701, Korea. Tel: 82-33-741-0344, Fax: 82-33-747-0409, E-mail: kimcb@wonju.yonsei.ac.kr

cific antigen (PSA), transrectal ultrasonography (TRUS), prostatic acid phosphatase, bone scan, computed tomography, magnetic resonance imaging and etc]. Proteomics (surface-enhanced laser desorption/ionization mass spectrometry⁸) and cDNA microarray analysis⁹ have recently been used as sensitive and specific diagnostic serum and tissues tests for prostate cancer.

Among these diagnostic methods of prostate cancer, the digital rectal examination (DRE) is the oldest and least invasive test modality. Although false negative and positive exams on DRE may occur, DRE does detect some prostate cancers that are missed by PSA screening. PSA (i.e., 33-kd glycoprotein consisting of 240 amino acids) is a serine protease that is secreted by the prostate into the semen where it causes lysis of the seminal coagulum. The determination of serum PSA has become the most commonly used tumor marker for prostate cancer¹⁰ since the earliest investigation of tissue-specific antigens of the human prostate by Ablin et al. in 1970¹¹ and the application of an immunoassay method for PSA by Wang et al. in 1979.¹² This diagnostic procedure was introduced to Korea by Dr. Kang J. H. in the early 1980s.¹³ After 1990, there has been an even more dramatic surge in the incidence of prostate cancer following the widespread adoption of serum PSA testing. Moreover, since the introduction of a clinical diagnostic method of prostatic diseases by Watanabe et al. in 1971, the TRUS test has been the diagnosis of choice for prostate cancer.¹⁴ A research result on this diagnostic test was published in Korea by Dr. Kim N.D. in 1982.¹⁵ Therefore, urologists commonly perform clinical assessment by using DRE and serum PSA for patients presenting with urinary symptoms. Additionally, radiological examinations including TRUS may also be employed for assessing the size, form and glandular structure of the prostate and any possible capsular or seminal vesicle involvement.

Numerous retrospective series have been performed and published to date on this diagnostic triad (PSA, DRE and TRUS). In addition, meta-analyses have been conducted to evaluate the effectiveness of this diagnostic triad or on two of these methods that are related to prostate cancer.¹⁶⁻²² Two of these studies have indicated that if all three tests were abnormal, the risk of cancer

on meta-analysis was 68%,¹⁸ and when an examinee has abnormal findings using PSA and DRE, the chance of cancer was from 20-25%.²² However, after 1990, various individual studies on combined PSA, DRE and TRUS for the diagnosis of prostate cancer also have been reported in Korea, but no meta-analysis has been conducted.

Therefore, the aim of this study was to examine the Korean literature with a focus on sensitivity and specificity for comparing the major diagnostic methods of prostate cancer, i.e., PSA, DRE and TRUS, by employing quantitative meta-analysis, and we wanted to determine the relative merits of this diagnostic triad for symptomatic Korean men.

MATERIALS AND METHODS

Searching of data

The first step of our study involved searching the medical journal database sites, i.e., the Medical Research Information Center (MedRIC) (<http://www.medric.or.kr/>) and the National Assembly Library of the Republic of Korea (<http://www.nanet.go.kr/>) from 1980 to 2003. In addition, we searched other potential sources and gave priority to the Korean Journal of Urology (<http://www.urology.or.kr/>) and the Korean Journal of Andrology (<http://www.andrology.or.kr/>). The second step involved a manual search of the contents and bibliographies of each of the retrieved studies. This search was restricted to the Korean-language studies that were conducted on men with lower urinary symptoms. The medical subject headings used for this search were prostate cancer and diagnosis, prostate-specific antigen, digital rectal examination and transrectal ultrasonography.

Meta-analysis

A total of 108 Korean articles were selected that contained information on the comparative results of using PSA, DRE and TRUS for the diagnosis of prostate cancer. Two observers who were both urologist and meta-analyst independently placed the results of the individual articles onto a data sheet; any disagreements were resolved by discus-

sion. The inclusion criteria for this meta-analysis were as follows. 1) Patients who had lower urinary symptoms of prostate cancer or benign prostate hyperplasia. These symptoms were mainly disturbances of urination, hematuria, etc. 2) The diagnostic PSA, DRE and TRUS tests for the clinical diagnosis of prostate cancer must have been simultaneously compared in the each article. 3) The studies included biopsy results as a reference standard to confirm prostate cancer. 4) The articles must have contained sufficient or available numeric information such as a 2×2 contingency data table or the patients' outcome data, e.g., data in terms of sensitivity (S_n), specificity (S_p), and percent agreement of the PSA, DRE, and TRUS testing. Of the 44 articles that were evaluated at the final stage, only 13 of the studies that compared PSA, DRE and TRUS met these inclusion criteria, and so these were selected for the meta-analysis.

For the quantitative meta-analysis process, the Hasselblad method^{23,24} was utilized with the SAS systemTM by Song H.H.²⁵ To integrate results, the sensitivity and specificity on each study's outcome data were used as effect sizes, and the \bar{d} value and 95% confidence interval (CI) of \bar{d} were estimated. Concerning the fixed effects model, additional homogeneity tests were conducted.

Each the estimates of \bar{d} , the variance of \bar{d} , 95% CI of \bar{d} and homogeneity test were produced as follows.

Estimate of

$$d : d = \sqrt{3} [\log_e(S_n / (1 - S_n)) + \log_e(S_p / (1 - S_p))] / \pi$$

(S_n ; sensitivity, S_p ; specificity)

$$d = \sqrt{3} [\log_e(A + 1/2) + \log_e(D + 1/2) - \log_e(B + 1/2) - \log_e(C + 1/2)] / \pi$$

(A; true positive, B; false positive, C; false negative, D; true negative in the 2×2 contingency table)

Variance of d :

$$\text{var}(d) \approx 3 [1 / (A + 1/2) + 1 / (B + 1/2) + 1 / (C + 1/2) + 1 / (D + 1/2)] / \pi^2$$

The combining estimates of effectiveness (\bar{d}) in m studies are usually given by the weighted mean:

$$\bar{d} = (\sum \omega_j d_j) / (\sum \omega_j), \quad (j = 1, 2, 3, \dots, m)$$

where $\omega_j = 1 / \text{var}(d_j)$

Variance of the combined estimate:

$$\text{Var}(\bar{d}) = 1 / (\sum \omega_j)$$

95% CI for the average effect size: $\bar{d} \pm 1.96 \sqrt{\text{Var}(\bar{d})}$

$$\text{Homogeneity test: } Q = \sum \omega_j (d_j - \bar{d})^2 \sim \chi^2_{(m-1)}$$

RESULTS

The general characteristics of the 13 studies²⁶⁻³⁸ are summarized in Table 1. All the studies were published after 1991. A total of 2,029 men with lower urinary symptoms had PSA and DRE performed. Among those men, TRUS were performed on 1,947 of them. All the subjects had TRUS guided transurethral biopsy or transurethral prostatectomy^{27,36} for the pathological diagnosis of prostate cancer. Of the 2,029 symptomatic men, 516 of them (25.4%) were pathologically diagnosed as having prostate cancer, with each study having a wide range (13.5-41.5%). The others were diagnosed with benign prostate hyperplasia (72.9%) and chronic prostatitis etc. (1.7%). The mean age of the patients was 67.8 years and the age of these patients ranged from 30 to 93 years old. The authors of all 13 studies were mostly urologists and only two studies^{35,37} were cooperatively conducted by urologists and a diagnostic radiologist or pathologist.

The sensitivity, specificity and percent agreement of prostate-specific antigens as the diagnostic parameters of prostate cancer in all 13 studies are listed in Table 2. When the PSA criteria were greater than 4 ng/mL (PSA4), the overall sensitivity was 91.3% with a range of 73.3% to 100.0%, and the overall specificity was 35.9% with a range of 13.1% to 88.9%, and each of the values were scattered widely among the studies. In addition, the overall percent agreement of PSA4 with the diagnosis was 50.1% with a range of 32.1% to 84.3%. With a PSA > 10 ng/mL (PSA10), the overall sensitivity was 77.3% with a range of 53.3% to 100.0%, and the overall specificity was 67.5% with a range of 37.7% to 100.0%. In addition, the overall percent agreement of PSA10 with the diagnosis was 69.9% with a range of 50.6% to 86.3%.

The data on sensitivity, specificity and percent agreement for the digital rectal examination and transrectal ultrasonography for detecting prostate cancer are shown in Table 3 and Table 4. The overall sensitivity, specificity and percent agreement (range) for DRE were 68.4% (56.7% to 88.9%),

Table 1. General Characteristics of Studies for the Diagnosis of Prostate Cancer in this Meta-Analysis (N=13)

No. of Ref.	Authors (Year)	Specialty of author(s)	Sample size	Diagnosis by pathological results			Age (years)	
				Cancer	BPH	Others*	Mean	Range
26	Kang SG (1991)	U	51	15 (29.4)	36 (70.6)	-	-	>50
27	Kim TH et al. (1994)	U	133 [†]	18 (13.5)	110 (82.7)	5 (3.8)	67.9	50-85
28	Park HK et al. (1994)	U	93	19 (20.4)	68 (73.1)	6 (6.5)	70.1	50-89
29	Byun HS (1995)	U	81	20 (24.7)	61 (75.3)	-	69.8	52-87
30	Park SW et al. (1995)	U	78	15 (19.2)	60 (76.9)	3 (3.9)	70.3	47-87
31	Choi JH et al. (1996)	U	64	11 (17.2)	53 (82.8)	-	68.0	40-90
32	Seo WK et al. (1996)	U	201	40 (19.9)	155 (77.1)	6 (3.0)	71.0	51-87
33	Kim JH et al. (1998)	U	162	26 (16.0)	136 (84.0)	-	62.7	50-84
34	Jung JY et al. (1998)	U	130	54 (41.5)	76 (58.5)	-	66.0	42-86
35	Yoon JH et al. (1998)	DR+U	210	53 (25.2)	157 (74.8)	-	67.0	41-96
36	Chang HJ et al. (1999)	U	215 [‡]	36 (16.7)	179 (83.3) [§]	-	69.2	54-89
			TRUS:133	35 (26.3)	98 (73.7) [§]	-	-	-
37	Kim JH et al. (2000)	U+P	265	90 (33.9)	169 (63.8)	6 (2.3)	68.6	47-89
38	Jung BC et al. (2002)	U	346	119 (34.4)	219 (63.3)	8 (2.3)	66.0	30-93
Total			2,029	516 (25.4)	1,479 (72.9)	34 (1.7)	67.8	30-93

No. of Ref., Number of Reference; U, Urologist; DR, Diagnostic Radiologist; P, Pathologist.

BPH, Benign Prostate Hyperplasia; TRUS, Transrectal Ultrasonography.

*Others include inflammation (chronic prostatitis), tuberculosis, infarct etc.

[†]All patients took prostatectomy.

[‡]82 patients were diagnosed by transurethral prostatectomy.

[§]The number of patients was recalculated by the data according to the evidence of its study.

71.5% (55.9% to 90.4%), and 70.7% (57.8% to 90.2%), respectively. Also, the overall sensitivity, specificity and percent agreement (range) for TRUS were 73.6% (60.0% to 93.3%), 61.3% (26.5% to 91.7%), and 64.6% (37.0% to 92.2%), respectively.

In order to check the possibility that the differences in the study results may have occurred by chance, a homogeneity test was performed on the all diagnostic tests (Table 5). According to the outcomes of the homogeneity tests for both PSA criteria (PSA4 and PSA10), these studies were homogeneous ($Q=16.11$, $p\text{-value}>0.05$; $Q=13.43$, $p\text{-value}>0.05$), so we used the results in a fixed effect model. Because both the DRE and TRUS tests proved to be significant and heterogeneous ($Q=50.12$, $p\text{-value}<0.001$; $Q=49.70$, $p\text{-value}<0.001$), a fixed effect model was rejected and we then used the results in a random effect model.

In a quantitative meta-analysis using the Haselblad method, the estimate of \bar{d} for PSA4, PSA10, DRE and TRUS were 0.8517 [95% confi-

dence interval (CI): 0.6694, 1.0340], 1.0996 (95% CI: 0.9459, 1.2534), 0.8398 (95% CI: 0.7169, 0.9627), and 0.8002 (95% CI: 0.6714, 0.9289), respectively. Among these diagnostic tools, the estimate of \bar{d} for PSA10 was the largest. Also, the estimate of \bar{d} for PSA (PSA4 and PSA10) was larger than that for DRE and TRUS. However, this diagnostic triad of prostate cancer is judged by the authors of this study to be noneffective.

Among the 13 studies, the results of patients tested by this diagnostic triad were done in only 6 studies.^{27,28,30-32,36} The outcomes of combination testing with PSA, DRE, and TRUS for detecting prostate cancer are shown in Table 6-1 and Table 6-2. If the PSA4 was negative and only the DRE or the TRUS was positive, the detection rate (DR) of prostate cancer was only 6 out of 150 patients (4.0%). Once two tests were positive, even if the PSA4 was negative, the DR of prostate cancer increased from 16.8% to 34.3%. If all results of this diagnostic triad were positive, the DR of prostate

Table 2. Outcomes of Prostate Specific Antigen for Diagnosis of Prostate Cancer by the Study (N=13)

Authors (Year)	Diagnostic Criteria	TP	FP	FN	TN	Sn	Sp	PA
Kang SG (1991)	4 ng/mL	(11	4	4	32)	73.3	88.9	84.3
	10 ng/mL	8	0	7	36	53.3	100.0	86.3
Kim TH et al. (1994)	4 ng/mL	16	63	2	52	88.9	45.2	51.1
	10 ng/mL	15	29	3	86	83.3	74.8	75.9
Park HK et al. (1994)	4 ng/mL	17	47	2	27	89.5	36.5	47.3
	10 ng/mL	15	23	4	51	78.9	68.9	71.0
Byun HS (1995)	4 ng/mL	18	53	2	8	90.0	13.1	32.1
	10 ng/mL	18	38	2	23	90.0	37.7	50.6
Park SW et al. (1995)	4 ng/mL	15	53	0	10	100.0	15.9	32.1
	10 ng/mL	15	29	0	34	100.0	54.0	62.8
Choi JH et al. (1996)	10 ng/mL	10	25	1	28	90.9	52.8	59.4
Seo WK et al. (1996)	4 ng/mL	36	105	4	56	90.0	34.8	45.8
	10 ng/mL	32	56	8	105	80.0	65.2	68.2
Kim JH et al. (1998)	4 ng/mL	26	73	0	63	100.0	46.3	54.9
Jung JY et al. (1998)	4 ng/mL	50	61	4	15	92.6	19.7	50.0
	10 ng/mL	41	21	13	55	75.9	72.4	73.8
Yoon JH et al. (1998)	4 ng/mL	51	126	2	31	96.2	19.7	39.0
	10 ng/mL	43	78	10	79	81.1	50.3	58.1
Chang HJ et al. (1999)	4 ng/mL	33	77	3	102	91.7	57.0	62.8
	10 ng/mL	29	28	7	151	80.6	84.4	83.7
Kim JH et al. (2000)	4 ng/mL	74	106	16	69	82.2	39.4	54.0
Jung BC et al. (2002)	4 ng/mL	114	168	5	59	95.8	26.0	50.0
	10 ng/mL	83	64	36	163	69.7	71.8	71.1
Pooled results	4 ng/mL	461	936	44	524	91.3	35.9	50.1
	10 ng/mL	309	391	91	811	77.3	67.5	69.9

TP, True Positive; FP, False Positive; FN, False Negative; TN, True Negative.

Sn, Sensitivity; Sp, Specificity; PA, Percent Agreement.

All bold numbers were directly calculated in this study using each formula.

cancer jumped further to 68.3%. Also, if the PSA10 was normal and only the DRE or the TRUS was positive, the DR of prostate cancer was only 14 out of 313 patients (4.5%). Once two of tests were abnormal, even if the PSA10 was normal, then the DR of prostate cancer jumped to 18.8-50.0%. If all three diagnostic tests were abnormal, the DR of prostate cancer increased further to 76.8%.

DISCUSSION

Because the estimates of \bar{d} were not large (not close to 3.0) in the results of quantitative meta-

analysis, we concluded that prostate-specific antigen testing, digital rectal examination and transrectal ultrasonography for the diagnosis of prostate cancer were not very effective when used separately. This estimate (\bar{d}) is analogous to the effect-size described for the continuous-outcome measures. Thus, this value (0.8-1.1) as the estimate of \bar{d} would suggest poor separation or discrimination²⁴ by each of this diagnostic triad for the detection of prostate cancer. In general, the measure \bar{d} appears to be more consistent across the studies than is either the sensitivity or specificity, but if either (normality or equal variances) of the assumptions is not met, then the effectiveness

measure will not be independent of the cutoff point.²³ Caution is recommended in using and interpreting this measure of effectiveness, unlike

the receiver operating characteristic (ROC) curve, when assumptions are substantially violated (see Moses et al.).³⁹

Table 3. Outcomes of Digital Rectal Examination for Diagnosis of Prostate Cancer by the Study (N=13)

Authors	Year	TP	FP	FN	TN	Sn	Sp	PA
Kang SG	1991	9	5	6	31	60.0	86.1	78.4
Kim TH et al.	1994	16	11	2	104	88.9	90.4	90.2
Park HK et al.	1994	14	17	5	57	73.7	77.0	76.3
Byun HS	1995	17	24	3	37	85.0	60.7	66.7
Park SW et al.	1995	12	13	3	50	80.0	79.4	79.5
Choi JH et al.	1996	7	19	4	34	63.6	64.2	64.1
Seo WK et al.	1996	27	24	13	137	67.5	(85.1)	81.6
Kim JH et al.	1998	20	22	6	114	76.9	83.8	82.7
Jung JY et al.	1998	39	32	15	44	72.2	57.9	63.8
Yoon JH et al.	1998	38	58	15	99	71.7	63.1	65.2
Chang HJ et al.	1999	30	51	6	128	83.3	71.5	73.5
Kim JH et al.	2000	51	56	39	119	56.7	68.0	64.2
Jung BC et al.	2002	73	100	46	127	61.3	55.9	57.8
Pooled results		353	432	163	1,081	68.4	71.5	70.7

TP, True Positive; FP, False Positive; FN, False Negative; TN, True Negative.

Sn, Sensitivity; Sp, Specificity; PA, Percent Agreement.

All bold numbers were directly calculated in this study using each formula.

Table 4. Outcomes of Transrectal Ultrasonography for Diagnosis of Prostate Cancer by the Study (N=13)

Authors	Year	TP	FP	FN	TN	Sn	Sp	PA
Kang SG	1991	14	3	1	33	93.3	91.7	92.2
Kim TH et al.	1994	15	11	3	104	83.3	90.4	89.5
Park HK et al.	1994	14	20	5	54	73.7	73.0	73.1
Byun HS	1995	16	23	4	38	80.0	62.3	66.7
Park SW et al.	1995	13	23	2	40	86.7	63.5	67.9
Choi JH et al.	1996	9	30	2	23	81.8	43.4	50.0
Seo WK et al.	1996	27	40	13	121	67.5	75.2	73.6
Kim JH et al.	1998	24	100	2	36	92.3	26.5	37.0
Jung JY et al.	1998	34	22	20	54	63.0	71.1	67.7
Yoon JH et al.	1998	47	51	6	106	88.7	67.5	72.9
Chang HJ et al.	1999 (133)*	21	56	14	42	60.0	42.9	47.4
Kim JH et al.	2000	66	99	24	76	73.3	43.4	53.6
Jung BC et al.	2002	79	76	40	151	66.4	66.5	66.5
Pooled results		379	554	136	878	73.6	61.3	64.6

TP, True Positive; FP, False Positive; FN, False Negative; TN, True Negative.

Sn, Sensitivity; Sp, Specificity; PA, Percent Agreement.

All bold numbers were directly calculated in this study using each formula.

*Among the total subjects (215), these patients were taken transrectal ultrasonography.

Table 5. Summary of Meta-Analysis Results by Diagnostic Method for Prostate Cancer

Diagnosis Method	DF	Estimate of \bar{d}	Variance of \bar{d}	95% Confidence Interval of \bar{d}	Q Statistics	p value
PSA4	11	0.8517	0.0087	0.6694 - 1.0340	16.1136	0.1370
PSA10	10	1.0996	0.0062	0.9459 - 1.2534	13.4319	0.2005
DRE	12	0.8398	0.0039	0.7169 - 0.9627	50.1208	<0.001
TRUS	12	0.8002	0.0043	0.6714 - 0.9289	49.7032	<0.001

PSA4, Prostate Specific Antigen (greater than 4 ng/mL)

PSA10, Prostate Specific Antigen (greater than 10 ng/mL)

DRE, Digital Rectal Examination; TRUS, Transrectal Ultrasonography.

DF, Degree of Freedom.

Table 6-1. Outcomes of Combination Testing of PSA4, DRE and TRUS for Detection of Prostate Cancer by the Study (N=5)

Study	Test	PSA4	-	+	-	-	+	+	-	+	Total
	DRE	-	-	+	-	+	-	+	+	+	
	TRUS	-	-	-	+	-	+	+	+	+	
Kim TH et al. (1994)		0/42	2/55	0/4	0/6	1/6	0/3	3/3	12/14	18/133	
Park HK et al. (1994)		2/15	1/33	0/3	0/7	2/7	2/6	0/4	12/18	19/93	
Park SW et al. (1995)		0/1	0/31	0/2	0/6	2/8	3/15	0/1	10/14	15/78	
Seo WK et al. (1996)		3/42	4/66	0/6	0/8	6/15	6/33	1/3	20/28	40/201	
Chang HJ et al. (1999)		0/0	0/14	1/8	0/0	12/31	5/38	2/15	15/27	35/133	
Total		5/100 (5.0)	7/199 (3.5)	1/23 (4.3)	0/27 (0.0)	23/67 (34.3)	16/95 (16.8)	6/26 (23.1)	69/101 (68.3)	127/638 (19.9)	

Data: No. of cancer patients in biopsy result/No. of patients tested by diagnostic triad (%).

PSA4, Prostate Specific Antigen (greater than 4 ng/mL)

DRE, Digital Rectal Examination; TRUS, Transrectal Ultrasonography.

-: Negative result (normal) in the diagnostic test, +: Positive result (abnormal) in the diagnostic test.

Table 6-2. Outcomes of Combination Testing of PSA10, DRE and TRUS for Detection of Prostate Cancer by the Study (N=5)

Study	Test	PSA10	-	+	-	-	+	+	-	+	Total
	DRE	-	-	+	-	+	-	+	+	+	
	TRUS	-	-	-	+	-	+	+	+	+	
Kim TH et al. (1994)		0/71	2/26	0/7	0/6	1/3	0/3	3/5	12/12	18/133	
Park HK et al. (1994)		3/28	0/20	0/6	0/10	2/4	2/3	1/11	11/11	19/93	
Choi JH et al. (1996)		1/12	1/5	0/4	0/8	0/4	2/13	0/5	7/13	11/64	
Seo WK et al. (1996)		5/69	2/39	0/9	2/28	6/12	4/13	1/6	20/25	40/201	
Chang HJ et al. (1999)		0/10	0/4	2/22	1/23	11/17	4/15	4/21	13/21	35/133	
Total		9/190 (4.7)	5/94 (5.3)	2/48 (4.2)	3/75 (4.0)	20/40 (50.0)	12/47 (25.5)	9/48 (18.8)	63/82 (76.8)	123/624 (19.7)	

Data: No. of cancer patients in biopsy result/No. of patients tested by diagnostic triad (%).

PSA10, Prostate Specific Antigen (greater than 10 ng/mL)

DRE, Digital Rectal Examination; TRUS, Transrectal Ultrasonography.

-: Negative result (normal) in the diagnostic test, +: Positive result (abnormal) in the diagnostic test.

According to the rapid advances in diagnostic technology, new diagnostic procedures like PSA and TRUS were introduced to the Korean Medical Association (KMA) in the early 1980s, and many Korean studies on this diagnostic triad of PSA, DRE and TRUS for the diagnosis of prostate cancer have been undertaken since the early 1990s. The widespread application of diagnostic techniques, and especially PSA and systematic biopsies, have played an important role in the increased incidence of prostate cancer.^{3,40} Also, the issues concerning clinical practice guidelines (CPGs) have also established after 1990 by the KMA,⁴¹ and the Korean Urological Association began developing the CPGs for prostate cancer a couple of years ago. Therefore, in this study, we conducted a meta-analysis of PSA, DRE, and TRUS for diagnosing prostate cancer among those subjects with lower urinary symptom, and we particularly focused on sensitivity and specificity according to the eligibility of some databases, like Medline, when searching for Korean articles published since the mid-1990s.

Because the outcome data used in this study were based on retrospective observational studies, there would be considerable variation for the results of primary studies of this diagnostic triad. Furthermore, it was proved that 13 studies were heterogeneous with a statistical significance for both DRE and TRUS criteria, unlike the PSA criteria (PSA4 and PSA10). This variation may have been caused by chance alone (the small sample sizes), but it can also reflect true heterogeneity. Possible clinical sources of such heterogeneity are the between-study differences for the type of test that was used, the selected positivity cutoff point of each test, the patient selection and clinical setting, deficiencies in study design (methodological heterogeneity), or any combination of these factors.^{42,43} To minimize variations of study quality in the meta-analysis for the diagnostic tests, the Cochrane Methods Working Group on Screening and Diagnostic Tests have suggested that the comprehensive validity checklist for primary studies include the study population's recruitment, the patient selection method (selection bias), the verification method (differential reference standard bias), the interpretation of tests method, and the method to avoid residual con-

founding.^{44,45} Therefore, this meta-analysis used only those studies that met the inclusion criteria (including using biopsy results as a reference standard and excluding screening tests on general population^{46,47}) for quality evaluation. Also, because the search was restricted to Korean-language studies, there may be a considerable (English) language bias. In addition, to eliminate any multiple publication bias when there were several articles (including any masters thesis) written by the same authors, clinical data from the most recent publication were used.⁴⁸

Among the several major outcomes of this meta-analysis, the most important outcome was the comparison of PSA, DRE and TRUS as diagnostic tests to detect prostate cancer. The overall sensitivity and overall specificity for PSA4 were 91.3% and 35.9%, respectively; and those for PSA10 were 77.3% and 67.5%, respectively. Also, those for DRE were 68.4% and 71.5%, respectively; and those for TRUS were 73.6% and 61.3%, respectively. If a Korean man with lower urinary symptoms has abnormal PSA levels or DRE or TRUS findings, the chances of him having cancer are about 2 in 5; conversely, when the PSA levels or findings on DRE or TRUS are normal, the chance of missing the cancer is about 10%. Also, the detection rate (50.0%) of combination testing of PSA10 and DRE were larger than that (44.1% or 45.0%) of PSA10 or DRE alone. Further, the detection rate of combination testing of PSA4 or PSA10 with DRE and TRUS jumped to 68.3% or 76.8%. Thus, when this diagnostic triad was abnormal, our result (the probability of prostate cancer) is same or is larger than that (68%) of the Haid et al. study.¹⁸ What exactly does all this mean to the clinician? It means that diagnostic triad for the detection of prostate cancer in men with lower urologic symptoms is a useful tool. Once the PSA is elevated more than 10 ng/mL or the DRE and TRUS are abnormal, then an invasive procedure with close follow-up appears to be necessary.

However, a PSA of greater than 4.0 ng/mL has limited specificity because such elevations also occur in men with benign disease (e.g., prostatic hyperplasia and prostatitis). It is well known that PSA values for prostate cancer and benign prostate hyperplasia have considerable overlap.

Reducing the PSA cutoff point from 10 ng/mL to 4 ng/mL can increase the sensitivity, but doing so will further reduce the specificity. Also, the DRE as a time-honored method of diagnosis may show false negative and positive results.⁴⁹ TRUS is not highly accurate for staging prostate cancer, and it has an overall reported accuracy of only 58%.⁵⁰

The American College of Preventive Medicine (ACPM),⁵¹ the American Urological Association (AUA),⁵² the Singapore Ministry of Health (MOH),⁵³ the American Cancer Society (ACS),⁵⁴ and the U.S. Preventive Services Task Force (USPSTF)⁵⁵ have recently presented their recommendations for screening men for prostate cancer along with the explicit reasoning behind their judgment. Among these five groups, the guidelines from the Singapore MOH and AUA provided recommendations for the diagnosis, treatment and management of prostate cancer in addition to their screening recommendations for this disease. Men aged 50 or older with a life expectancy of greater than 10 years should be given information about the potential benefits and harms of screening for prostate cancer. Although there is agreement among all the groups on the use of PSA and DRE as the primary screening tests for prostate cancer, the AUA, Singapore MOH and ACS explicitly recommend combining the two tests to improve accuracy. Further, the use of TRUS as a screening test for prostate cancer is no longer considered valid by the ACPM or USPSTF, and the AUA recommends against it. Similarly, the Singapore MOH does not address TRUS as a screening test, but rather, it is considered in combination with biopsy for diagnostic purposes.⁵⁶

In conclusion, urologists should take the characteristics of the diagnostic triad (PSA, DRE and TRUS) and the outcomes of meta-analysis (pooled sensitivity and specificity, the estimates of \bar{d}) into consideration. They should use these methods as a combination rather than separately implementing these methods for the primary diagnosis of prostate cancer in men with lower urological symptoms.

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