THE VALUE OF SCREENING TESTS FOR DETECTION OF PROSTATE CANCER IN 1000 SAUDI MEN

Baher A. Kamal, *FRCS, DrCh (Uro)*
Department of Urology, College of Medicine, King Faisal University, Dammam, Saudi Arabia

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هدف الدارسة : دراسة أهمية اختبارات الكشف عن سرطان البروستاتا لدى الرجال السعوديين.
الطريقة الدارسة: قياس معدلات مؤشر سرطان البروستاتا المركب وغير المركب وكذلك حساب نسب غير المركب إلى المركب. أيضاً إجراء فحص شرجى للبروستاتا. عمل أشعة بالموجات الفوق صوتية من الشرج مع أخذ عينة من البروستاتا فى حالة ارتفاع مؤشر البروستاتا عن 4وحدات أو وجود اشتباه فى سرطان البروستاتا عن طريق الفحص الشرجى. شملت الدراسة 1000 رجل سعودى ابتداءا من سن 45سنة.
نتائج الدارسة : نتج عن الدراسة تقسيم المرضى الى مجموعتين. الأولى تتكون من 849 مريضاً خالين من المرض تبعاً لمعدل مؤشر البروستاتا و الفحص الشرجى و فحص الموجات فوق الصوتية من الشرج. و لقد أوجدت المعدلات الطبيعية لمؤشر البروستاتة من هذه المجموعة. المجموعة الثانية تتكون من 151مريضاً يشتبه بوجود المرض بهم لارتفاع مؤشر البروستاتا. أجرى أخذ عينة من البروستاتا عن طريق الشرج فى 55 مريضاً, أما باقى المرضى (96) فلم تؤخذ منهم عينة لعدم المراجعة. وجد المرض فى 22حالة من 55 مريضاً وأجريت مقارنة بين المجموعتين.
خاتمة: أوجدت الدراسة أهمية مؤشر البروستاتا و الفحص الشرجى و عدم أهمية فحص الموجات الصوتية من الشرج فى اكتشاف المرض.

الكلمات المرجعية : مؤشر البروستاتا - الفحص الشرجى-الموجات الصوتية- سرطان البروستاتا- السعوديين.

Objectives*: Predicting the value of screening tests in the detection of prostate cancer in Saudi men.*
Methods*: The study was conducted in King Fahd Hospital of the University, Al-Khobar. Total, free and percent free serum prostate specific antigen (PSA) were measured in Saudi men above the age of 45 years. Transrectal ultrasonography (TRUS) and needle biopsy were performed on those with suspicious digital rectal examination (DRE) and or PSA >4ng/ml. A group of 849 Saudi men were with normal PSA levels and normal DRE were considered cancer free.. The remaining 151 patients with PSA >4ng/ml were suspicious for prostate cancer. Only 55 patients agreed to have TRUS and needle biopsy*
Results*: PSA testing and DRE had the highest positive predictive value but this value dropped when TRUS was added.*
Conclusion: *PSA and DRE are the main tests for the detection of prostate cancer, while TRUS is valuable when sample are taken of a wide area of prostate tissue in men at high risk of cancer.*

Key Words*: Prostatic specific antigen, Digital rectal examination, Transrectal ultrasonography, Screening tests, Prostate Cance, Saudis.*

Correspondence to:
Dr. Baher A. Kamal*, P.O. Box 40036, Al-Khobar 31952, Saudi Arabia*
E-mail: drbaherkamal@yahoo.com

INTRODUCTION

The incidence of prostate cancer is rising worldwide as a result of an increase in the elderly population. This is attributed to the improvement of health services, and more importantly the increasing number of diagnosis by prostate specific antigen (PSA) testing.[1] The rationale for screening is the detection of early disease (organ confined) which is amenable to cure.[2-4]

PSA remains the best and most widely used tumor marker in urology today.[5] The cutoff value for normal serum PSA is 4 ng/ml. The probability of cancer varies with the degree of PSA elevation. If the initial value is between 4 and 10 ng/ml, 25% of men are expected to have prostate cancer, while about 60% of men with a PSA concentration above 10 ng/ml will have prostate cancer.[6]

Percent free PSA constitutes an important diagnostic tool for differentiating between benign and malignant prostatic disease with increased specificity. The use of free PSA, reduced false positive results in patients with PSA levels between 4 to 10 ng/ml.[7]

Although PSA has the highest positive predictive value for prostate cancer, the use of PSA without digital rectal examination (DRE) is not recommended because 25% of men with prostate cancers have PSA levels less than 4 ng/ml.[8-10]

DRE is an inexpensive and simple test, but lacks sensitivity and specificity.[11] The positive predictive value for DRE ranges from 21% to 53% depending on the degree of suspicion for cancer and whether the population studied are referred or screened.[8,9,12] DRE and serum PSA are the most useful first line tests for assessing the risk of prostate cancer in an individual.[12-14]

Transrectal ultrasonography (TRUS) alone is not accurate and has a low sensitivity and specificity as a screening test for prostate cancer. The limitation of TRUS in prostate cancer detection is that most hypoechoeic lesions of the prostate are not necessarily malignant.[9,10]

Furthermore, due to the presence of isoechoeic cancers, 25% to 50% of cancers can be missed if only hypoechoeic areas are biopsied.[15] Therefore, any patient with a DRE suspicious for prostate cancer or a PSA elevation should undergo prostate biopsy regardless of TRUS findings if an early diagnosis of cancer is to be guaranteed.

This study defines the magnitude of prostatic cancer in a sample of Saudi men above 45 years of age. It also addresses the readiness and willingness of asymptomatic Saudis to be enrolled in screening tests for prostate cancer, and the feasibility for a mass screening study.

PATIENTS AND METHODS

This was a prospective study carried out in a period of 18 months from April 2001 to October 2002 in King Fahd Hospital of King Faisal University, Al-Khobar, Saudi Arabia. One thousand Saudi patients presenting to the outpatient department or admitted to King Fahd Hospital of the University, Al-Khobar, for different reasons were selected at random for this study. Digital rectal examination (DRE), total PSA and free PSA were performed (using microparticle enzyme immunoassay method) on all patients. Patients with a PSA < 4ng/ml and normal DRE were considered cancer free. The means of PSA values for all age groups were compared using the Anova test. Correlation coefficient test was used to test the correlation between age and PSA levels. The 95th percentile was used to define the upper limit of normal values of PSA. Percent free PSA was calculated. Transrectal ultrasonography and needle biopsy of the prostate were carried out if an abnormality was detected by DRE or serum levels of PSA were >4ng/ml. Patients who underwent prostatic biopsy were categorized according to the biopsy as benign or malignant, and their results were compared. All statistical work in this study was performed by the researcher using the medical statistical program SPSS.

RESULTS

Of the 1000 Saudi patients, selected, 849 showed no evidence of malignancy. They were divided into 5 age groups, of 10-year intervals starting from the age of 45. The mean values of total, free and percent free PSA were measured for all age groups (Figure 1). There

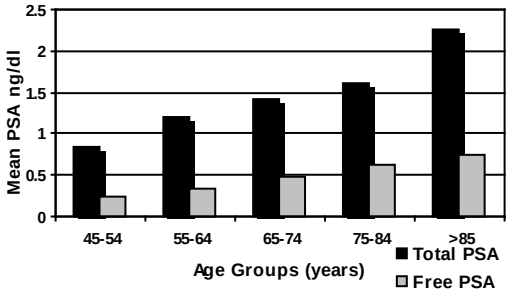

Figure 1: *The means of total PSA and free PSA for all patients*

was a positive correlation between increase in age and increase in total PSA (r=0.263, p<0.01), free PSA (r= 0.356, p<0.01) and percent free PSA (r=0.098, p<0.01). The mean value of total PSA was 0.84 for the age 45-54 years, 1.19 for 55-64 years, 1.42 for 65-74 years, 1.61 for 75-84 years of age, and 2.25 for those more than 85 years of age (Table 1). The mean value of free PSA was 0.24 for the age 45-54 years, 0.34 for 55-64 years, 0.47 for 65-74 years, 0.62 for the age 75-84 years of age, and 0.75 for those more than 85 years old (Table 2). The percent free PSA was between 33.09% and 37.11% for all groups (Table 3). The difference between the mean values of total PSA, free PSA and percent free PSA for all age groups was statistically significant (F=16.208, P<0.05, F=30.158, P<0.05, and F=2.819, P<0.05, respectively) (Tables 1,2,3). The 95th percentile was obtained for all men to define the upper limit of normal total PSA (Tables 1,2,3). The remaining 151 patients had PSA of > 4 ng/ml. TRUS with needle biopsy was performed in 55 patients only. The remaining 96 patients either refused or did not show up for this procedure. Thirty three out of the 55 patients (60%) had negative biopsies for prostatic cancer. Twenty-seven patients had benign proastatic hyperplasia, one had chronic

Table 1*: Total PSA values for 849 patients with PSA <4 ng/ml*

Age	Number	Mean	SD	Average	95% CI	95 percentile
45-54	250	0.84*	0.69	0.07-3.70	0.75-0.93	2.31
55-64	314	1.19*	0.95	0.02-3.96	1.08-1.30	3.01
65-74	204	1.42*	1.09	0.02-3.92	1.26-1.58	3.55
75-84	68	1.61*	1.11	0.02-3.92	1.32-1.89	3.77
>85	13	2.25*	1.17	0.9-3.53	1.35-3.15	-

*Significant difference (F=16.208, p<0.05) SD=Standard deviation, CI=Confidence interval of mean

Table 2*: Free PSA values for all 752 patients*

Age	Number	Mean	SD	Average	95% CI	95 percentile
45-54	233	0.24*	0.22	0.01-2.17	0.21-0.27	0.58
55-64	282	0.34*	0.25	0.01-1.36	0.31-0.37	0.82
65-74	168	0.47*	0.40	0.01-2.08	0.41-0.53	1.32
75-84	60	0.62*	0.48	0.01-1.95	0.49-0.74	1.78
>85	9	0.75*	0.51	0.16-1.55	0.39-1.14	-

*Significant difference (F=30.158, p<0.05) SD=Standard deviation, CI=Confidence interval of mean

Table 3*: Value of Free/Total PSA ratios values for all 752 patients*

Age	Number	Mean	SD	Average	95% CI	95 percentile
45-54	233	33.09*	16.83	4-84	30.9-35.3	67.3
55-64	282	34.45*	15.64	1-89	32.6-36.3	62.9
65-74	168	34.65*	15.42	1-90	32.3-37.0	61.0
75-84	60	38.92*	14.90	12-81	35.1-42.8	66.9
>85	9	37.11*	21.51	5-73	20.9-53.6	-

*Significant difference (F=2.819, p<0.05) SD=Standard deviation, CI=Confidence interval of mean

Table 4: *Comparison of PSA results in relation to the pathology at different PSA levels*

PSA Ng/ml	Benign TPSA	Benign FPSA	Benign Ratio	Malignant TPSA	Malignant FPSA	Malignant Ratio
4-10	22	22	22	3	2	2
	6.67	2.18	31.50	7.03	0.43	6.5*
	(1.7)	(1.1)	(10.7)	(0.9)	(0.2)	(2.1)
4-20	22	22	22	6	5	5
	6.67	2.18	31.50	10.95	1.82	13.80*
	(1.7)	(1.1)	(10.7)	(4.5)	(2.0)	(12.6)
>20	5	5	5	16	15	15
	43.83	5.06	10.80	509.15	83.91	18.47
	(30.4)	(4.5)	(7.1)	(847.4)	(123.1)	(18.4)

*p<0.05, N=number of patients, ( ) = Standard deviation
TPSA=Total PSA, FPSA=Free PSA, Ratio=Free/Total PSA

cystitis and chronic prostatitis, one had carcinoma in situ, and the remaining 4 had invasive transitional cell carcinoma of the bladder with prostatic involvement. Twenty two patients (40%) had positive biopsies for prostatic cancer. The mean percent free PSA was 28.78% and 17.30% (t= 2.544, p<0.01) for those with benign and malignant prostate, respectively. The percent free PSA showed a significant difference between patients with benign and malignant prostate, both at a total PSA level between 4 and 10 and between 4 and 20. The percent free PSA is not valid above PSA level of 20 ng/ml (Table 4). The positive predictive value of PSA test alone was 40%, while the positive predictive value was 75% when combined with DRE. However, if the PSA test was combined with DRE and TRUS, the positive predictive value dropped to 33%.

DISCUSSION

Screening for prostate cancer in this study was attempted on a relatively narrow scale. It was noted that the elderly population in Saudi Arabia lacked health education on prostate cancer. The absence of follow up after first assessment or refusal to have prostatic biopsy done was noticed among a significant number of patients. These pitfalls should be taken into consideration when implementing a wide multicentric screening program.

In this study, normal PSA values for 849 Saudi men aged 45 years to 85+ years were recorded. A correlation exists between advancing age and PSA increase.[16,17-29] Some authors found a correlation between advancing age and total PSA increase only, with no correlation with free PSA and percent free PSA.[22] A significant correlation between increase in age and the increase in total PSA, free PSA and percent free PSA was found in this study.

The mean values of total PSA were lower among the Saudi patients in this survey compared to the international figures.[27-29] Similar values were recorded in only one study.[21] The mean of percent free PSA among the Saudi patients was above 30% in all age groups. Some authors proposed that the percent free PSA is valid only at total PSA range from 4-10ng/ml.[30,31] The optimum value of percent free PSA for screening for prostate cancer still needs to be assessed, especially at the PSA range below 4ng/ml.[32]

As a population-based study, our upper limit of normal PSA (95th percentile) was close to that of Chinese and Korean studies.[33,18,19,26] Our findings agree with those of other studies that propose racial variations of PSA values.[17-20,33-35]

The percent free PSA in our patients was significantly lower when the prostate biopsy was positive for cancer. The percent free PSA was considered valid in patients with PSA 4-10 ng/ml and 4-20 ng/ml. However, it was no more valid with PSA > 20 ng/ml. Some authors state that PSA ratio has its greatest value for men with serum PSA value between 2 and 10 ng/ml,[36] while others believe that it is valid with PSA levels between 4 and 20 ng/ml.[14,16,30,37-44]

PSA has the highest positive predictive value for prostate cancer, and can increase the predictive value of DRE diagnosis.[8,12] The positive predictive value for PSA alone in this study was 40%. This increased to 75% when DRE was added, and dropped to 33% when TRUS was also added. TRUS has the limitation of being operator dependent.

It is known that 25%-50% of prostate cancers can be missed if only hypoechoeic areas were biopsied.[8] Also, 50% of non-palpable cancer, more than 1 cm in greatest dimension, are not visualized by ultrasound.[15] As a means of localizing early prostate cancers TRUS has its limitations.[9,45] In agreement with other investigators,[8] TRUS is best used for wide-area sampling of prostate tissue in men at a higher risk of cancer.

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