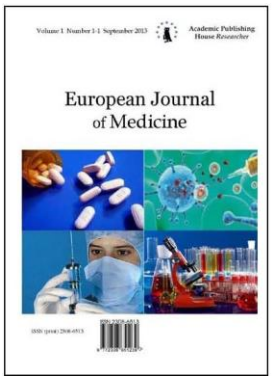
Published in the Russian Federation
European Journal of Medicine
Has been issued since 2013.
ISSN: 2308-6513
E-ISSN: 2310-3434
Vol. 5, No. 3, pp. 124-131, 2014

DOI: 10.13187/ejm.2014.5.124
www.ejournal5.com



UDC 616

Utility of Combination of Diagnostic Tests in Early Detection of Prostate Tumors in West Algerian Hospital

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Abstract

In West of Algeria, incidence of prostate cancer (PCa) is growing and epidemiological data on benign prostatic hyperplasia (BPH) are contradictory. The prostate specific antigen (PSA) joins other tests, as digital rectal examination (DRE) and ultrasound, for better management of patient. This study aimed to assess the association of previously tests with PSA-assay in diagnosis of PCa and BPH, in West Algeria. A retrospective study was performed on two groups of 234 BPH and 56 PCa diagnosed between 2010–2012 at the urology department of the hospital in Saida. Patients underwent various diagnostic tests; DRE, ultrasound, PSA and pathological examination. BPH is more common than PCa and the most dominant age group was from 70 to 79 years. DRE was positive in 67 % of BPH and 63.3 % Pca. Ultrasound examination revealed that the prostatic structure was heterogeneous in 25.5 % of BPH and 92 % PCa. Total PSA (TPSA) was higher than the cut-off value of 4 ng / ml in 37% of BPH and 75 % PCa. Histological forms of Prostatic adenomyofibroma and prostatic adenocarcinoma were the most represented. This study shows that the combination of different tests is more efficient than using a test alone for a definitive diagnosis of PCa or BPH.

Keywords: Prostate cancer; benign prostatic hyperplasia; prostate specific antigen; urology; digital rectal examination; pathological examination.

Introduction

Prostatic diseases are common in elderly men. Prostate cancer (PCa), the most feared of these diseases, has a high incidence in the USA and Europe where it is the second cause of cancer death after lung cancer [1]. For the benign prostate hyperplasia (BPH), it is a universal natural disease occuring from the fifties. It is mainly due to the increase in the volume and weight of the prostate gland, process which is normally natural. Currently, the incidence of PCa in Algeria is not very high, but its evolution draws attention because it is the most increasing form of malignant male tumor [1]. PCa is steadily increasing from 10 new cases in year of 1999 to 746 new cases in 2008 [2]. According to the International Agency for Research on Cancer (IARC), the PCa incidence, adjusted to the age, is estimated at 7.1 cases per 100,000 men and the mortality rate by PCa is 5.3 /

100000 [2]. The statistics of IARC indicate that more than 1,000 new cases of PCa will be identified for the coming years in Algeria (figure 1). BPH and PCa are diagnosed late in Algeria; they were revealed most often by a complication of acute urinary retention in BPH, whereas PCa was detected in advanced tumor stage [2]. In Algeria, means of diagnosis of these diseases once reduced to digital rectal examination (DRE), determination of acid phosphatase and histology, are now complemented by the prostatic ultrasound and serum prostate-specific antigen (PSA) assay. Aims of the present study consist to assess the performance of the combination of previously tests (DRE and histology) with tha later tests (ultrasound and PSA assay) at patients recruited in West Algerian hospitals.

Materials and methods

Patients. This was a descriptive retrospective study. Between January 2010 and December 2012, a total of 385 patients were hospitalized in urology department of Saida hospital, came consulting for urological disorders. Among them, 290 patients older more than 50 years, were included in our study for suspicion of BPH and PCa. All selected patients have a histological diagnosis confirmed. They are divided in two groups; 234 patients with BPH and 56 patients with PCa. Inclusion criteria were: patients older than 50 years, patients with complete medical records, they have undergone the same PSA assay technique (VIDAS-TPSA test), and they reside in the region of Saida located in the West of Algeria.

Clinical data. That's made from the survey forms that contain different parts; number of patients, socio demographic data (age, profession, familial forms, and residence) and DRE. About this clinical test, Only 160 patients (130 BPH and 30 PCa) were enrolled and underwent a DRE but 130 patients (104 BPH and 26 PCa) declined to participate. DRE was performed by physicians service. Assessment takes into account: the volume of the gland, the sharp or soft characters of its outlines, regularity or otherwise of its surface that can be smooth, granular or nodular, elastic consistency, firm, hard or woody, the presence or absence of pain and the state of bulb rectal.

Para clinical data. Three additional tests, frequently performed, were abdomino-pelvic ultrasound, serum-PSA assay and pathological study of prostate biopsy samples.

Abdomino-pelvic ultrasound. In addition to the routine history and physical examination, only 157 patients (132 BPH and 25 PCa) were underwent an abdomino-pelvic ultrasound while 133 patients (102 BPH and 31 PCa) declined to participate in the interview. This examination is requested to assess the weight of the prostate gland and study its structure and contours.

PSA serum-assay. All patients were evaluated by determination of the serum PSA level. Blood samples were collected at the urology department of the Saida hospital and taken directly to the laboratory of biological analysis in the same hospital. Approximately 10 ml of blood were collected intravenously in a dry tube. The blood was centrifuged and serum was frozen at -20 ° C until to be used in the assay. The sera were frozen for a period not exceeding three months and then thawed for achieving total PSA (TPSA) and free PSA (FPSA) assays knowing that for short periods of freezing, TPSA and FPSA assays are little changed. TPSA and FPSA assays are undergone in mini VIDAS analyzer (Bio-Merieux, France). The used method was the technique of enzyme-linked fluorescent assay (ELFA): it is an enzyme immunoassay ELISA "sandwich" in heterogeneous phase where the molecules of PSA are caught between two monoclonal antibodies of murine nature. Reading results of the PSA assay is done in two stages to a final detection by fluorimetry. A quality control was performed for each used kit VIDAS-TPSA to validate the results. The cut-off of PSA is 4 ng / ml, prescribed by the kit supplier. The detection limit of this method is 0.07 ng / ml and the range of the VIDAS-TPSA kit extends to 100 ng / ml. Samples, with concentrations of TPSA over 100 ng / ml, were retested after dilution in sample diluent TPSA (calf serum + sodium azide 0.9 g/l). The PSA density (PSAD) was calculated by dividing the serum PSA level by the prostatic volume.

Histology. Among the 290 patients recruited in our study, only 127 (90 BPH and 37 PCa) agreed to participate fully in the development of the results of histological examination. The samples consisted of prostate biopsies and surgical specimens of prostatectomy and fixed in 10 % formalin, and came from the urology department of the Saida hospital that were sent to the pathology department of the University Hospital of Sidi-Bel-Abbes (area located in

Western Algeria) where taking place the macroscopic and microscopic histological examinations. These samples were processed according to the conventional histological techniques. Surgical specimens, fixed in formalin, were cut into thin slices about 3 mm. The paraffin embedding technique was the method of treatment of these fragments, the slides are stained with hematoxylin and eosin and observed under optical microscope from a low to high magnification.

Statistical analysis. Statistical analysis was performed using the SPSS (*version 11.5*) software. Groups of BPH and PCa patients were described by their numbers, average of means and standard deviation (SD). Comparison of all results was based on using Student's *t*-test for parametric data and Mann- Whitney test for non-parametric data. A two-tailed *p*-value < 0.05 was accepted as statistically significant. Ethical approval was provided by the health research ethics committee of the University of Sidi-Bel-Abbes, in West of Algeria.

Results

The distribution of benign and malignant prostate tumors, at the hospital in Saida, shows BPH and PCa were found in high significative different proportions ($p < 0.001$). The number of patients with BPH (80.6 %) is 4.2 times greater than that of patients with PCa (23,9 %) during the period from 2010 to 2012 (**Table 1)**. The average age of diagnosis in patients BPH and PCa is not significantly different (respectively 68.5 versus 71.3) ($p > 0.05$), the most important numbers are recorded in the age group of 70-79 years, with frequencies of 38.8 and 9 % respectively for BPH and PCa (**Table 1**). No hereditary or genetic predisposition was found in the group of BPH. Although the hereditary form is poorly represented in the group of PCa (2.1 %), patients had a family history of PCa including related history of 1st and 2nd degrees (father, uncle and brother in family with PCa) (**Table 1**). Other demographic characteristics are presented in **table 1**. BPH and PCa are more frequent among pensioners with high percentages, respectively of the order of 26.3 and 10.4 %, the majority of patients BPH and PCa living in urban areas in the area of Saida (respectively 62.5 % versus 66.2 %).

Table 1: Socio demographic data of BPH and PCa patients

Characteristics	BPH (n=234)	PCa (n=56)	*p-value*
Age (years)			
Mean age (±SD)	68.5 (± 1)	71.3 (±2.5)	*0.38*
Dominant age range n, (%)			
60-69	80 (27.7)	12 (4.1)	*P** < 0.01*
70-79	112 (38.8)	26 (9)	*P** < 0.01*
Familial forms n, (%)			
Hereditary	-	6 (2.1)	
Non-hereditary	-	50 (16.6)	
Dominant profession n, (%)			
Pensioners	76 (26.3)	30 (10.4)	*P** < 0.01*
Farmers	44 (15.2)	8 (2.7)	*P** < 0.01*
Civil servant	20 (6.9)	4 (1.3)	*P = 0.02*
Residence n, (%)			
Urban	160 (62.5)	37 (66.2)	*P***< 0.001*
Rural	65 (28)	15 (26.7)	*P**< 0.01*
Unspecified	9 (9.5)	4 (7.1)	*P = 0.03*

BPH: benign prostate hyperplasia
PCa: prostate cancer

The results of DRE and abdomino-pelvic ultrasound in patients with BPH and PCa are showed in **table 2**. Results show extremely significant differences ($p^{***} < 0.001$). In 106 of 160 patients BPH and PCa, DRE was positive, index of suspicion for the presence of prostate pathology, associated mainly with urinary clinical symptoms. DRE showed abnormal findings, characterized

by the presence of prostate abnormalities suggesting BPH in 67 % of all patients and suspicious lesions of PCa in 63.3 % of patients. DRE was not suspicious for prostate tumors in 23 % of BHP and 36.7 % of PCa, even in the presence of serum TPSA higher than the cutoff value of 4 ng/ml (**Table 2**). The results of abdomino-pelvic ultrasound in all patients showed that prostate gland had a homogeneous structure in 55.1 % of BPH and 8.1 % of PCa and heterogeneous structure in 25.5 % of BPH and 91.9 % of PCa (**Table 2**). Unlike the prostatic structure, gland contours seem to be a decisive parameter for distinguishing between BPH and PCa. This study showed that the contours of the prostate were regular in 41.8 % of BPH and only 4 % of PCa (**Table 2**). The regular aspect of the prostate is common sometimes even in the presence of abnormal DRE and elevated PSA.

Table 2: Results of DRE and ultrasound in BPH and PCa patients

Profil and aspect of prostate	BPH (n=234)	PCa (n=56)	*p-value*
DRE n, (%)	**130 (55.5)**	**30 (53.5)**	
Positive DRE	87 (67)	19 (63.3)	*P***<0.001*
Negative DRE	43 (23)	11 (36.7)	*P** <0.01*
Ultrasound n, (%)	**132 (56.4)**	**25 (44.6)**	
Prostate structure			
Homogeneous	78 (55.1)	2 (8.1)	*P < 0.001*
Heterogeneous	54 (25.5)	23 (91.9)	*P < 0.1*
Contours of prostate			
Regular	55 (41.8)	1 (4)	*P < 0.001*
Irregular	19 (13.9)	16 (64)	*P = 0.048*
Unspecified	52 (44.3)	8 (32)	*P < 0.1*

DRE: digital rectal examination

Table 3 summarizes the respective value of TPSA, FPSA, free ratio (FPSA / TPSA) and DPSA. Mean serum TPSA concentrations in the BPH and Pca patients were statistically different in both groups (6.14 and 59.3 ng/ml for the means TPSA for BPH and Pca). There was an overlap in the serum TPSA concentrations between these two groups, the range being 1.61-20.1 and 0.9-1071.4 ng/ml for BPH and PCa respectively (**Table 3**). About 55.5 % of 290 patients (147 BPH and 14 PCa) had a normal serum TPSA (≤ 4 ng/ml) while 44.5 % (87 BPH and 42 PCa) with abnormal TPSA (> 4 ng/ml). A moderate number of BPH patients (37.1 % or 87 / 234) had a serum TPSA concentration above the cut-off of 4 ng/ml, whose 27 % being in the diagnostic gray zone range (4-10 ng/ml) (**Table 3**). In contrast, only 13 % of PCa patients had serum TPSA concentrations in this range. But there has been a high incidence of PCa (37 %) for serum TPSA concentration higher than 20 ng / ml, whereas this frequency was lower in BPH (2.5 %) for the same range of TPSA (**Table 3**). Mean serum FPSA concentration in BPH (1.31 ng/ml) and PCa (0.78 ng/ml) widely different and the difference is significant. The free to total PSA ratio (or FPSA / TPSA) differed significantly between two groups, and this difference remained statistically significant even for TPSA below 4 ng/ml; median values were 40 % in BPH and 11.4 % in PCa, respectively (**Table 3**). PSAD was measured for the high values of TPSA concentrations (TPSA > 10 ng/ml). The serum TPSA concentration to volume of prostate gland is of great importance which is more indicative of the nature of disease. Mean PSAD of BPH was 0.11 (± 0.03 ng/ml/ml), ie below the defined critical threshold value (0.15 ng/ml/ml), while it was greater in PCa (0.17 ng/ml/ml) (**Table 3**).

Table 3: Biological data in BPH and PCa patients

Serum PSA-assay	BPH (n=234)	PCa (n=56)	*p-value*
TPSA (ng/ml)			
Mean (±SD)	6.14 (± 0.56)	59.3 (±10.2)	*P*** < 0.001*
Min-Max	1.61-20.1	0.9 -1071.4	
n, (%)			
≤ 4	147 (63)	14 (25)	*P<0.001*
4 < TPSA ≤ 10	63 (27)	7 (13)	*P<0.001*
10 < TPSA ≤ 20	17 (7.5)	14 (25)	*P<0.05*
> 20	7 (2.5)	21 (37)	*P**<0.01*
FPSA (ng/ml)			
n, (%)	30 (11.7)	12 (21.4)	*P = 0.032*
Mean (±SD)	1.31 (0.6)	0.78 (0.3)	
Free ratio (FPSA / TPSA)			
n, (%)	30 (11.7)	12 (21.4)	*P < 0.001*
Mean (±SD) (%)	40 (13.2)	11.4 (5.1)	
PSA density (PSAD)			
n, (%)	24 (10.2)	21 (37.5)	*P = 0.04*
Mean (±SD)	0.11 (±0.03)	0.17 (± 0.07)	

TPSA: total prostate specific antigen
FPSA: free prostate specific antigen

Results are highly significant with regard to the histological study (*p*** < 0.001*).

Pathological examination of biopsies and surgical specimens have revealed that the benign prostatic hypertrophy were mainly Prostatic adenomyofibroma (56.2 %) followed by small frequencies of other types of BPH represented especially by 3.3 % of adenoma and 2.2 % of nodular hyperplasia (**Table 4**). Prostate cancers were mainly dominated by adenocarcinoma observed in 86.4 % of cases, followed by in situ carcinoma (4 cases; 10.8 %) and a case of PIN (prostatic intra epithelial neoplasia) (**Table 4**). Distribution of adenocarcinoma, as Gleason score, is presented in **Table 4**.

Table 4: Anatomo-pathological data in BPH and PCa patients

Histological types	Patients (n=290)	Frequencies (%)	*p-value*
BPH (n = 234)			
n, (%)	90	38.4 (90/234)	*P*** < 0.001*
PAMF	51	56.2 (51/90)	
Adenoma	3	3.3 (3/90)	
Nodular hyperplasia	2	2.2 (2/90)	
PCa (n = 56)			
n, (%)	37	66 (37/56)	
Prostate adenocarcinoma	32	86.4 (32/37)	*P*** < 0.001*
Carcinoma in situ	4	10.8 (4/37)	
PIN	1	2.7 (1/37)	
Gleason score			
4	3	8.1 (3/37)	
5	5	13.5 (5/37)	*P** < 0.01*
6	12	32.4 (12/37)	
7	10	27 (10/37)	
8	4	10.8 (4/37)	
9	2	5.4 (2/37)	
10	1	2.7 (1/37)	

PAMF: Prostatic adeno-myo-fibroma

The combination of different tests was very effective in early detection of BPH and PCa and the results were highly significant ($p^{**} < 0.01$). More combined tests is used, more the probability of detection is great. The use of several tests, in combination, was very effective because the detection rate of PCa was 22.2 and 18.8 %, in our study, respectively for the association of the tests (Anatomopathology, ultrasound, PSA) and (anatomopathology, DRE, ultrasound) (**Table 5**). Similarly, the detection rate of BPH was high when we combined three tests together, for example the association (Anatomopathology, ultrasound, PSA) has allowed a detection rate of 21.4 % in the group of BPH patients (**Table 5**).

Table 5: Combination of diagnostic tests in early detection of BPH and PCa

Combination of tests	BPH (234) n, (%)	PCa (56) n, (%)	*p-value*
Ultrasound	6 (2.5)	3 (5.3)	$P < 0.05$
DRE	-	1 (1.7)	
Ultrasound + DRE	14 (5.9)	3 (5.3)	$P^{**} < 0.01$
PSA + DRE	10 (4.2)	4 (7.1)	
PSA + Ultrasound	12 (5.1)	4 (7.1)	
PSA + DRE + Ultrasound	16 (6.8)	2 (3.5)	
Anatomopathology	20 (8.5)	4 (7.1)	
Anatomopathology + DRE	26 (11.1)	6 (10.7)	
PSA + DRE + Anatomopathology	34 (14.5)	7 (12.5)	
DRE + Ultrasound + Anatomopathology	44 (18.8)	10 (17.8)	
PSA + Ultrasound + Anatomopathology	52 (22.2)	12 (21.4)	

Discussion

This study shows that benign tumors, especially BPH, is the most common prostate tumors in a western Algeria. PCa is a disease less diagnosed in Western Algeria. The frequency of PCa has shown lower in our study. Tunisian study carried out by Khouaja *et al*, in 1998, showed that 7.3 % of PCa were detected at 642 patients [3]**.** Age represents the main factor in BPH and PCa etiology. We find the results more or less close of those found in studies underwent by Dongazok *et al* [4]. A risk of PCa may be multiplied by five in family antecedents [5]. In addition, lack of physical activity has an influence on the PCa evolution mainly at pensioners. Patients BPH and PCa, in urban areas, are the most affected and it seems to be related to lifestyle and environmental factors such as occidental dietary behavior common in the western Algerian cities. DRE is a valuable opportunity and allowed diagnosis of BPH and PCa. DRE can be considered as a performance test if one applies. Abdomino-pelvic ultrasound plays a significant role in the diagnosis of PCa otherwise highlight the heterogeneous character of the internal structure of prostate disease or highlighting the homogeneity of BPH. But it is not so, because we obtained in our study, 25.5 % of BPH with heterogeneous structure against 55.1 % with homogeneous structure. For Utzmann *et al*, there's only 16 % of BPH with heterogeneous structure against 84 % BPH with homogeneous structure [6]. Many studies have recommended the serum-TPSA assay in the detection of prostate diseases. High serum-TPSA concentration was related to the age difference and the increase in the volume and weight of the prostate gland. Mean serum TPSA concentration, in PCa of our series, was 59.3 ng/ml. This value is much closer to that reported by Aboukoua-Kouassi *et al* [7] who found 64.9 ng / ml, but it is further away from the value advanced by Konan *et al* [8] that's 115.8 ng / ml. Studies have shown that levels of TPSA greater than 15 ng/ml increase the metastatic risk of PCa [9]. Stamey *et al*, in their studies, showed that majority of PCa patients with serum TPSA higher than 15 ng/ml had microscopic capsular penetration, and at TPSA more than 40 ng/ml, most had pelvic node metastases [9]. Several groups have developed algorithmic methods for clinical decision (PSA velocity, free ratio of PSA and PSA density...). This present study showed that the use of the free ratio (FPSA / TPSA) is an aid in the differential diagnosis. Christenson *et al* showed that the free ratio was of 16 % for PCa and of 28 % for BPH [10]. A recent study by Catalona established a median free ratio of 9.2 % for PCa, compared to 18.8% for BPH [10]**.** Our study showed that,

in 37.5 % of PCa patients, PSAD was of 0.17 (higher than 0.15) while PSAD in BPH patients was of 0.11 (lower than 0.15). It should be noted that the possibility to identify patients with PCa is minimal when PSAD is less than 0.15. Several authors have stated that PSAD could be useful marker helping to distinguish patients with BPH from patients with PCa more accurately than PSA alone [11]. Pathological examinations of surgical specimens, in our study, revealed a large percentage of prostatic adenomyfibroma which are benign prostatic tumors. The high frequency of adenocarcinoma in our PCa group, is in agreement with literature data [3]. Carcinoma in situ are, however, less prevalent in the prostate. We found, in our work, a case of PIN that had suspicious lesions in pathological examination. It was unexpected to get a case of PIN in our population because this histo-pathological type is very rare in Western Algeria. On the other hand, it is argued that high-grade PINoccur rather a decade in the black population of the USA and Brazil compared to Caucasian populations [12]. In our study, nearly half PCa patients had a low-grade carcinoma as in the study of Prost et al., in France [13]. To make this study more credible and very successful, we used several strategies combining different tests (DRE, ultrasound, PSA assay and pathological examinations). The combination of three tests yielded a high rate of detection of prostate tumors better than the use of a single diagnostic test that can evoke a low detection rate. In Japan, Shimizu et al. conducted mass screening for PCa using PSA and DRE as indices without age limit and reported that the detection rate for PCa was 1 % when these parameters were combined [14]**.** However, they indicated that the detection rate was 0.56 % when PSA alone was examined. Further more, Imai et al [15], conducted mass screening using PSA, DRE and ultrasound in males older more than 50 years and reported that the detection rate was 1.56 %.

Conclusion

Benign and malignant prostatic tumors are in a marked increase in Algeria. We must work to combine the previously diagnostic tests to the later tests in order to make a definitive diagnosis especially for PCa that will allows us to control the incidence and mortality of this disease in our country.

Acknowledgement

The authors thank all members of pathology laboratory of Sidi-Bel-Abbes UHC and doctors, of Urology Department in Saida Hospital, for their great contribution during interviews with patients, as the medical staff who helped in identifying and contacting patients and finally all men who agreed to participate in this study.

Conflict of interest statement. The authors declare that they do not have any conflict of interest.

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