

## ORIGINAL ARTICLES

### PROSTATE SPECIFIC ANTIGEN: 25 YEARS OF CLINICAL USE IN KUWAIT

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Since the late 1980s, prostate specific antigen (PSA) has established itself as the most important tumor marker in all solid tumor oncology and has become indispensable in the management of prostate cancer. Since the introduction of PSA-based screening, there has been a marked increase in the incidence of clinically, and pathologically, organ-confined disease, and the majority of prostate cancers diagnosed today in most countries in the West are non palpable PSA-detected tumors (T1C). However, controversy surrounds the use of PSA as a routine screening tool, and for this reason, great efforts have been devoted to understanding the relationship between PSA and tumor biology. A central issue in this controversy is the fact that PSA is organ-specific, not cancer-specific, such that changes in serum PSA are not always a manifestation of cancer, but rather may be due to inflammation, trauma, or most commonly, simple benign prostatic hyperplasia (BPH). Furthermore, considerable overlap exists in PSA levels among men with prostate cancer and BPH. This is in the so called "diagnostic gray zone" of serum PSA levels between 4.0 and 10.0 ng/mL. Due to questions surrounding the specificity of PSA in the diagnosis of prostate cancer a number of modifications have been proposed to increase the value of this analyte, namely PSA-derivatives such as age specific PSA, PSA density, PSA volume and PSA isoforms. In this review we will first present the practical applications of PSA and PSA derivatives in the diagnosis and management of prostate cancer. We also emphasize, the importance of establishing local reference ranges and the need for knowledge of other factors affecting PSA levels.

**Key Words:** prostate specific antigen, prostate cancer, diagnosis, treatment.

#### INTRODUCTION

Prostate specific antigen (PSA) was introduced into clinical practice in 1980<sup>1</sup>. Originally used for monitoring patients with prostate cancer in the early 1980s, by mid 1980 onwards, the usefulness of serum PSA as a screening tool for prostate cancer had been established<sup>2</sup>. It is therefore appropriate for urologists worldwide to celebrate the 25<sup>th</sup> birthday of the clinical use of this molecule. In doing so, it is pertinent to look at the lessons learnt over the past 25 years, about the clinical utility of this marker. In these 25 years, PSA has established itself as a classical tumor marker for prostate cancer: for detection,

diagnosis, screening, predicting prognosis, monitoring response to therapy and detection of disease recurrence<sup>2</sup>. Currently requests for serum PSA around the world exceed 50 million per year. In the USA, annual expenditure on serum PSA is said to be in excess of US \$ 50 million.<sup>2</sup> Determination of serum PSA in asymptomatic men, i.e. screening for prostate cancer, remains controversial. The correct interpretation of serum PSA results is far more complicated than most physicians realize as many factors, some of them benign, can cause elevation of serum PSA. It is not surprising therefore that a new syndrome called "PSA-itis" has emerged in urological practice. Thus, PSA

has been used as an acronym for "promoters of stress and anxiety" or even "providentially sent antigen!". These stem from the anxiety induced in patients with high PSA but no underlying prostate cancer.

### History of PSA

The PSA molecule was discovered by Hara et al.<sup>3</sup>, and given the name seminoprotein. In 1978 Sensabaugh<sup>4</sup> purified the protein from seminal plasma. He thought it would be a potential semen marker that would be useful in forensic medicine, specifically in cases of rape. Wang et al.<sup>5</sup> purified the protein from the prostate tissue and gave it the name Prostate Specific Antigen - as it was believed to be found exclusively in prostatic tissue. PSA was subsequently demonstrated in serum in 1980 by Kuriyama et al.<sup>1</sup>. It has also been demonstrated in other organs namely breast, salivary gland and kidney, but in much smaller concentrations compared to the prostate. Thus from its humble beginning in the 1970s and 1980s PSA has become, currently, the most important tumor marker for prostate cancer.

### PSA - Physiology

PSA is a single chain serine protease with MW 33 - 34 KD which exists in the form of 5 isomers. The PSA molecule is composed of 92% peptide and 8% carbohydrate. PSA in serum consists mostly of complexes with inhibitors; the predominant complex is with  $\alpha$ 1 antichymotrypsin (ACT). Complexed PSA is more stable, while the free form, which is minor in amount, is very labile. Total serum PSA is the sum of free PSA + PSA complexed with ACT. Most assay kits for PSA can detect the 2 forms of PSA in serum. Table 1 shows the molecules to which PSA is complexed.

### PSA - Functions

PSA is an important part of prostatic secretions. Its functions are as follows: to liquefy the seminal coagulum, thus releasing the spermatozoa, to catalyze the hydrolysis of other substrates, e.g. IGF BP-3, to

catalyze the degradation of extracellular matrix proteins (fibronectin and laminin) and being a protease, it may play a role in cancer invasion and metastasis. Fig. 1 shows a simplified network of PSA physiology. Basically, PSA exists in the form of pro-PSA which requires activation by human kallikrein<sup>2</sup> before the active PSA is released into the circulation. There is an equilibrium with other physiological substrates.

PSA as a molecule may have harmful or beneficial effects. The possible beneficial effects of PSA include: lower tissue PSA is associated with more aggressive forms of prostate cancer, and patients with PSA positive tumors have earlier disease stage, live longer and relapse less frequently. On the other hand, evidence that PSA may have deleterious effects includes the fact that breast tumors with a high tissue PSA content do not respond well to tamoxifen therapy, PSA may activate latent TGF- $\beta$ , stimulate cell detachment and facilitate tumor spread. PSA may also proteolyse the basement membrane and mediate invasion and metastases.

### Sources of PSA

The major sources of PSA include the prostatic epithelium and epithelial lining of periurethral glands. The minor sources are: benign (from sweat, endometrium, milk) and malignant (from breast, salivary glands).

### PSA in Non - Prostatic Illness

Some studies have shown that renal function has no significant effect on PSA level. Other studies showed higher free PSA but normal total PSA in patients on dialysis. Liver disease has no significant effect on serum PSA levels. Some tumors like breast cancer and renal cell cancer (RCC) produce small amounts of PSA.

### In Vitro Stability of PSA

In whole blood, there is a significant decrease of 3.5% in free PSA after 5 to 6 hours of storage at room temperature. When fresh serum is stored at room temperature,

**Table 1:** Molecules to which PSA is Complexed.

Formal Name	Common Name	Description
Total PSA	t-PSA	All immunodetectable forms in serum, primarily f-PSA and complexed PSA
Free PSA	f-PSA	Noncomplexed PSA May be proteolytically active or inactive in seminal fluid. Only inactive in serum
PSA complexes	PSA-ACT	PSA covalently bound to alpha 1 antichymotrypsin inhibitor. Major immunodetectable form in serum
	PSA-AMG	PSA covalently linked and encapsulated by alpha 2 macroglobulin. Not detected by any available immunoassay.
	PSA-PC	PSA covalently bound to protein C inhibitor. Not detected in serum
	PSA-AT	PSA covalently bound to alpha 1 antitrypsin. Trace amount in serum

there is a 2 – 5 % loss in free PSA per day, while total PSA remains stable after 7 days. When fresh serum is stored at -40 C, there is a significant decrease in free PSA after 7 days while there is a slight decrease in total PSA<sup>6</sup>. When serum is stored at -200 to -700C, PSA remains stable for up to 2 years. PSA is remarkably stable with repeated freezing and thawing<sup>6</sup>.

### PSA in Clinical Practice

The most important use of serum PSA estimation remains the diagnosis of prostate cancer. However several factors affect PSA levels. Serum PSA levels depend on the age and ethnic / racial origin of the patient, as shown in Table 2. It increases with age. The normal values are 0 - 4 ng/ml for men aged < 50, and 0 - 6 ng/ml for men aged > 50. As a rule of thumb, higher values are found in "Western" countries, while lower values are found in "Eastern" countries. For the diagnosis of prostate cancer, PSA is reputed to have a sensitivity of 71%, specificity of 75% and a positive predictive value of 37%.<sup>7,8</sup>

The PSA level may be elevated in the following conditions: increasing age, BPH,

clinical and occult prostatitis (commonest cause of elevated PSA in Kuwait as shown in Fig. 1<sup>8</sup>), prostatic abscess, prostatic infarction, prostate cancer (commonest cause in Western countries), after urethral manipulation, e.g cystoscopy, after TURP (within 6 weeks), after prostate biopsy, following bicycle or horse riding, post-ejaculation, urinary retention etc.

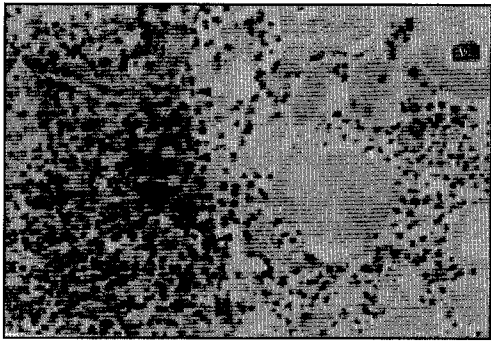
On the other hand, abnormally low levels may be drug-induced, e.g. 5- $\alpha$ -reductase inhibitor (finasteride), or may be found in patients undergoing treatment for prostate cancer (i.e. hormone manipulation) or following TURP.

PSA per gram of tissue is higher in malignant (3 ng/ml) compared to benign prostate tissue (0.75 ng/ml) (Fig. 2). However BPH is still the most common cause of elevated serum PSA in most countries of the world. In addition to producing more PSA per gram of tissue, invasive prostate cancer disrupts the prostate blood barrier, further increasing the entry of PSA into the serum. In men with prior negative prostate biopsies, acute or chronic inflammation of the prostate has been found to be more

**Table 2:** The Effect of Age and Race on Serum PSA Levels (ng/ml).

Age (Years)	Caucasians	Africans	Arabs*
40-49	0.0 – 2.5	0.0 – 2.0	0 - 0.9
50-59	0.0 – 3.5	0.0 – 4.0	0 – 1.6
60-69	0.0 – 3.5	0.0 – 4.5	0 – 2.9
70-79	0.0 – 3.5	0.0 – 5.5	0 – 5.5

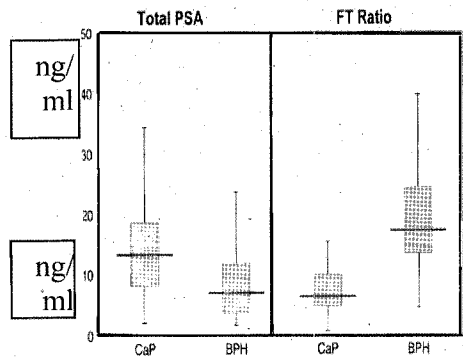
\* Kehinde et al BJU Int 2005.<sup>7</sup>



**Fig. 1:** Photomicrograph of prostate gland showing acute inflammatory changes. The epithelium is disrupted (arrow heads) and infiltrated by mixed inflammatory cells which merge with the heavy periglandular infiltrate consisting of macrophages, lymphocytes and some neutrophils. Lumen contains fragments of corpora amylacea, neutrophils and other debris (H and E). PSA at presentation 93 ng/ ml. A breach (by infection, prostate cancer or trauma) of the basement membrane of the prostate epithelium will lead to release of PSA into the circulation.

prevalent in patients with a serum PSA >4 ng/ml compared with those with lower levels<sup>8</sup>. Acute or chronic prostatic inflammation, with or without prostatic infarction, has been found to be responsible for PSA levels above 300 ng/ ml<sup>8,9</sup> and in one reported case above 900 ng/ml<sup>10</sup> indicating the need for histological confirmation before patients are told that they have prostate cancer. DRE has been shown to cause a transient and minimal rise in PSA, the PSA changes having been reported in multiple settings to have little clinical significance. Thus, the current recommendation is that serum PSA levels are accurate and reliable after DRE<sup>11</sup>.

In situations where the PSA level is elevated / lowered for any reason indicated



**Fig. 2:** Total PSA and % free PSA (FT ratio) in prostate cancer (CaP) and BPH.

above, it tends to return to normal 4 -6 weeks after removal of the stimulus, for example after prostate biopsy or TURP. In cases where high levels are due to the presence of urinary tract infection (UTI) or prostatitis, the PSA values tend to return to normal after successful treatment of the infection<sup>8,12</sup>. Failure of PSA to return to 0-4 ng/ml after successful treatment of infection is an indication for prostate re-biopsy to exclude prostate cancer<sup>8</sup>.

For patients with PSA in the gray zone of diagnosis of prostate cancer, i.e. 4-10 ng/ml, the determination of % free PSA is often helpful to reduce the need for unnecessary prostatic biopsies (Fig. 2). The % free PSA is derived as follows:

$$\% \text{ Free PSA} = \text{Free PSA (ng/ml)} / \text{Total PSA (ng/ml)} \times 100$$

% Free PSA < 12 % suggests the presence of prostate cancer, while

**Table 3:** Age-Specific Mean Values for Serum Total PSA, Free, PSA and % Free PSA in Normal Arab Males.

Patient Group / Age in years		Mean $\pm$ S.D		
Age	No.	Total PSA (ng/ml)	Free PSA (ng/ml)	%Free PSA
15-19	52	0.32 $\pm$ 0.25	0.07 $\pm$ 0.05	25 $\pm$ 6.12
20-29	68	0.56 $\pm$ 0.32	0.12 $\pm$ 0.11	21.1 $\pm$ 3.11
30-39	64	0.49 $\pm$ 0.33	0.11 $\pm$ 0.08	21.2 $\pm$ 4.22
40-49	62	0.55 $\pm$ 0.68	0.13 $\pm$ 0.25	23.2 $\pm$ 5.22
50-59	78	1.12 $\pm$ 2.09	0.18 $\pm$ 0.17	14.2 $\pm$ 2.67
60-69	60	2.76 $\pm$ 4.26	0.43 $\pm$ 0.43	14.8 $\pm$ 3.11
70-79	12	4.14 $\pm$ 3.49	0.68 $\pm$ 0.58	14.2 $\pm$ 2.31

**Table 4:** Reference Intervals for Male Kuwaiti Population Compared to Values Used by Ministry of Health, Kuwait Laboratories (MOHKL) and as Suggested by Kit Manufacturers (DSL, USA).<sup>13\*</sup>

Institution	TT (nmol/L)	DHEAS (nmol/L)	ADT (nmol/L)	LH (miu/L)	FSH (miu/L)	Prolactin (nmol/L)	IGF-1 (ng/ml)	IGFBP-3 (ng/ml)	PSA (ng/ml)
MOHKL	8-35	1.0-7.3	0.8-2.8	0.4-5.7	1.1-13.5	80-230	71-261	900-4000	0 - 4
DSL, USA*	9-60	2.2-15.2	2-9.2	0.8-7.6	0.7-11.1	53-360	78-956	900-4000	0 - 4
Present study*	3-31	0.9-11	0.5-4.3	1-11	0.5-11	42 - 397	41-542	88-2098	0 - 3.1**
p*	<0.001	<0.01	<0.01	NS	NS	NS	<0.01	NS	NS

\*p-values for differences between reference intervals as suggested by kit manufacturers and those obtained in male Kuwaitis

NS = not significant

% Free PSA > 18 % indicates BPH or other benign causes of elevated PSA.

Prostate cancer can be detected using either digital rectal examination (DRE), PSA or transrectal ultrasound (TRUS) of the prostate gland. DRE and TRUS are invasive. DRE is cheap, fast but subjective and lacks sensitivity. On the other hand, PSA as a screening test for prostate cancer is superior to DRE and TRUS, because it is objective, cost effective (US \$ 10.00 per test), widely acceptable and can detect prostate cancer before any abnormalities can be detected by DRE or TRUS.

Many clinicians advocate annual PSA tests on men aged between 50 and 75 years. However, due to the slow rate of growth of early prostate cancer longer intervals between tests might be more appropriate.

Recent decision analyses have supported the use of screening every two years. In Africans, Whites or anyone with a family history of prostate cancer it is advisable to start testing at an earlier age of 40 or 45 years, as these racial groups have a higher incidence of prostate cancer. Testing may be discontinued at the age of 75, or at 65 years in men with persistently low levels of PSA (<1.0 ng/ml).

From the foregoing, it is obvious that there is a need to improve the sensitivity and / or specificity of PSA as a screening tool. This can be achieved by utilizing PSA density and serial measurement of PSA to determine PSA velocity. The use of age - related reference values and measurement of both free and complexed PSA in addition to total PSA, e.g. determining the % free PSA, all may aid in the correct diagnosis of prostate cancer.

**Table 5:** Comparison of Serum PSA and Prostate Volume as a Function of Age in Healthy USA Whites\*, Japanese\*, Chinese\*\* and Arabs\*

Age Range (Years)	Serum PSA Range (ng/ml)				Prostate Volume Range (cc)		
	USA Whites*	Japanese*	Arabs*	Chinese**	USA Whites*	Japanese*	Arabs*
40-49	0-2.5	0-2	0-0.9	0-1.2	13-51	9-33	8-22
50-59	0-3.5	0-3	0-1.6	0-2.4	15-60	9-35	9-27
60-69	0-4.5	0-4	0-2.9	0-3.2	17-70 <sup>1</sup>	10-37 <sup>2</sup>	9-30 <sup>1,2</sup>
70-79	0-6.5	0-5	0-5.5	0-3.4	20-82	11-40	10-33

\*Data from Oesterling et al 1995<sup>14</sup>

\*\* Data from He et al 2004<sup>15</sup>

\*Data from Kehinde et al 2005<sup>7</sup>

<sup>1</sup>p< 0.001 (Arabs versus USA whites) <sup>2</sup>p<0.06 (Arabs versus Japanese) (p calculated using Student's t-test.)

In a study between 1999 and 2003, we established the age-specific reference range for PSA in the Kuwaiti population<sup>7,13</sup>. A summary of the results is shown in Fig. 3 and 4 and Tables 3<sup>13</sup>,4<sup>13</sup>,5<sup>7,14,15</sup>. These results show that the PSA reference range for Kuwaitis is 1.0 – 3.1 ng/ml, and the free PSA range is 0.1- 1.22 ng/ml<sup>7,13</sup>. As pointed out by Oesterling et al.<sup>14,16</sup> and shown by our data from Kuwait<sup>7,13</sup>, there is a need for urologists to establish PSA reference ranges in their areas of practice, so that patients can be treated appropriately.

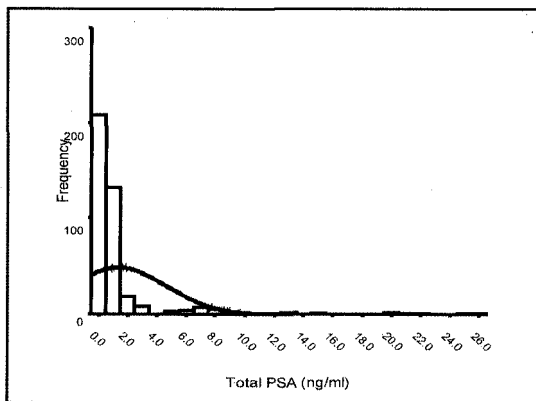
Table 5 shows the reason why the PSA is lower in the Arab population compared to USA Whites: the Arabs have a smaller prostate volume compared to USA Whites<sup>7,14</sup>.

The question whether screening for prostate cancer is worthwhile remains a controversial topic for the following reasons: decreased mortality due to early detection of prostate cancer by screening is negated by the morbidity of cancer treatment. The other issue is whether screening could detect cancers that would remain quiescent with the patient dying from other disease, i.e. "tigers" versus "pussy-cats". That this may be the case in some instances is borne out by the fact that second generations of familial prostate cancer patients are often detected at age 50 or earlier. In most cases the first generations were diagnosed with prostate cancer at the

age of 70 or 80 years. Currently there is no accurate way of predicting which cancers will behave like "tigers" and which would behave like "pussy-cats". Hence, research efforts must be directed at "identifying" PSA arising from potentially aggressive clones of cells that may metastasize.

The other issue is the cost of PSA estimation. Is it cost-effective to screen 2000 people and detect only 3 new cases of prostate cancer? A recent review of data from the Rotterdam Section of the European Randomized Study of Screening for Prostate Cancer concluded that prostate cancer screening leads not only to the diagnosis in men with smaller volume, lower grade, earlier stage prostate cancers, but it also results in over-diagnosis and over-treatment<sup>17</sup>.

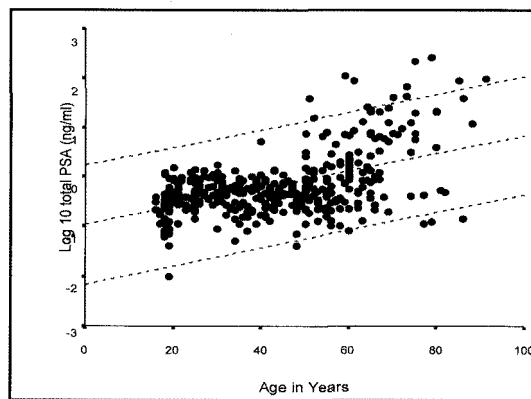
Because of these controversies surrounding screening for prostate cancer, targeted screening for prostate cancer has been advocated. This means screening men at a greater risk of developing prostate cancer, such as those with a family history of prostate cancer, men from certain ethnic groups (e.g. African Americans or Africans), men from a certain country of origin (e.g. African - Americans living anywhere) and country of residence (e.g. Japanese living in the USA, but there may be no need to screen Japanese living in Japan).<sup>14</sup>



**Fig. 3:** Frequency distribution of total PSA profile in normal Arab males.

Apart from the diagnosis of and screening for prostate cancer, other major uses of serum PSA estimation are as follows:

1. **Staging prostate cancer:** The serum PSA level is used in staging prostate cancer, because it tends to increase with increasing prostate cancer stage, although considerable overlap exists depending on the degree of differentiation of the tumor. Men with prostate cancer and PSA < 10 ng/ml are less likely to have skeletal metastases which may obviate the need for a bone scan in their overall evaluation. On the other hand, most prostate cancer patients with PSA >30 ng/ml have lymph node metastases and are therefore not ideal candidates for radical prostatectomy.
2. **Response to hormonal manipulation in stage-D disease:** The PSA level is inversely proportional to survival. The disease progression-free survival has been estimated to be 36, 12.7 and 7.4 months for PSA 0-99, 100-499 and >500 ng/ml respectively.<sup>18</sup>
3. **Use of PSA in monitoring patient's response to treatment of prostate cancer:** PSA is the marker of choice in the follow-up of patients with prostate cancer. Serial PSA levels can be used to assess the success of radical prostatectomy indicated by PSA <0.01 ng/ml within 72 hours of surgery. A PSA greater



**Fig. 4:** Serum PSA as a function of age in healthy Arab men.

than 0.4 ng/ml, six months after radical prostatectomy, is indicative of residual disease. Following local radiotherapy, the PSA level may take up to 6 months to reach a nadir level.

The nadir PSA is the lowest PSA level obtained before it starts to rise again following hormone manipulation, radiotherapy or radical surgery. The nadir PSA is directly proportional to total pre-treatment PSA. A lower nadir PSA is associated with prolonged progression-free survival.

4. **Prognosis :** The lower the total PSA at the time of diagnosis, the better the overall survival. Thus, men with higher pre-operative PSA values are at a significantly higher risk of advanced disease and biochemical progression<sup>18,19</sup>.

However, the primary reason for estimating serum PSA level remains the diagnosis and management of patients with prostate cancer.

### PSA Derivatives

Although the sensitivity of PSA is quite impressive, the positive predictive value (PPV) of PSA has been questioned.<sup>20</sup> When PSA is 4.0 to 10.0 ng/ml, the PPV is 18% to 25% (mean 21%), and when PSA is greater than 10 ng/ml, the PPV is 58% to 64% (mean 61%)<sup>21,22</sup>. As a result, methods to enhance

the performance of PSA have evolved<sup>23</sup>.

### PSA Density (PSAD)

PSAD, the serum PSA divided by gland volume in cc, has been suggested to improve PSA specificity. A PSAD of greater than 0.15 ng/ml has been shown to increase the specificity of detection of prostate cancer when compared with total serum PSA<sup>24-26</sup>, however, the optimal cutoff is controversial. Early studies by Benson et al. evaluated the efficacy of PSAD for prostate cancer detection<sup>27</sup>. The mean PSAD in those with prostate cancer and BPH was 0.581 and 0.044, respectively. No patient with BPH had a PSAD greater than 0.117, and only one had a density of 0.1 or greater. Among patients with a PSAD of 0.1 or greater, 97% had prostate cancer. Despite these promising results, this PSA modification involves multiple sources of potential error, such as ultrasound operator variability, assay variability, interindividual heterogeneous stromal/epithelial ratios, and sampling bias.<sup>28</sup> One large multicenter study that compared PSA and PSAD for early detection of prostate cancer found that, in men with PSA of 4 to 10 ng/ml, if a PSAD cutoff of 0.15 was used, then 47% of the cancers would be missed.<sup>29</sup> Others have promoted the use of transition zone PSAD (TZ-PSAD), defined as the serum PSA divided by the volume of the transition zone<sup>30</sup>. Although initial reports were encouraging, this parameter is subject to the same sources of error as PSAD<sup>28,31</sup>. In summary, while PSAD and TZ-PSAD may boast an increased specificity and avoidance of up to 37% of biopsies, they risk missing an unacceptable number of clinically significant cancers.

### PSA Velocity (PSAV)

PSAV has been proposed to improve the PPV of PSA. Carter et al.<sup>32</sup> first reported that an annual increase of 0.75 ng/ml per year in serum PSA identified men who would develop prostate carcinoma. Using this cutoff, specificity reportedly increased to over 90% with 72% sensitivity in predicting prostate cancer in men with PSA less than 10.0 ng/ml. Importantly, the recommended interval

between PSA measurements is 1.7 to 2.0 years, and at least three PSA measurements are recommended to obtain maximal benefit from using PSAV measurements<sup>32</sup>.

Other studies debate the utility of PSAV owing to the significant intra-individual (biologic) variability and inter-assay (analytic) variability, particularly in the setting of relatively short time intervals between PSA tests and PSA in the low ranges<sup>33,34</sup>. Additionally, PSAV requires longitudinal samples over many years, during which disease progression may occur. Furthermore, men harboring prostate cancer often have a PSAV of less than 0.75 ng/ml per year, especially those with PSA levels less than 4.0 ng/ml<sup>35</sup>. Still, the rate of change of PSA over time may prove to be a significant indicator of malignant or premalignant change in prostate histology for patients with borderline elevations in serum PSA.

A corollary to PSAV is the rate at which PSA doubles, or PSA doubling time (PSADT).<sup>36</sup> This has been the subject of numerous recent investigations and will be discussed later, as it relates to prognostic predictions in newly diagnosed and recurrent prostate cancer.

The role of the free to total PSA ratio in increasing the PPV of total PSA estimation has been discussed above. The role of other isoforms of PSA in the overall management of patients with prostatic diseases, in particular prostate cancer, is currently under intense investigation<sup>37-39</sup>.

### PSA Kinetics before and after Primary Treatment

The PSA doubling time (PSADT), both before primary treatment and at the time of disease recurrence after primary therapy for prostate cancer, has been shown to independently predict disease outcome<sup>40,41</sup>. After radical prostatectomy or radiotherapy, various cut-points for PSADT have been examined for their ability to predict disease progression and survival. For example, Pound et al.<sup>42</sup> examined 315 men with biochemical



recurrence after radical prostatectomy and followed them for clinical evidence of progression. They found that men with a PSADT of less than 10 months experienced significantly lower metastasis-free survival than men with PSADT more than 10 months. Other well-established clinicopathologic parameters such as Gleason score and time from prostatectomy to biochemical failure also contributed to the nomogram for post-radical prostatectomy metastasis-free survival; however, PSADT was an independent factor in multivariate analysis. Other investigators have reported similar findings, although the cut-points for PSADT have been variable.

A more recent report that examines PSA velocity (PSAV) in the year preceding prostate cancer diagnosis significantly adds to the efforts to improve our ability to predict disease aggressivity and to better counsel patients about primary therapy<sup>43</sup>. A study of 1095 patients with newly diagnosed prostate cancer who underwent prostatectomy showed that the PSAV in the year preceding prostate cancer diagnosis not only predicted adverse pathologic parameters and disease-free survival, but also cancer-specific and overall survival following prostatectomy. A man with a PSAV of greater than 2 ng/ml/year was nearly 10 times more likely to die of prostate cancer than a man with a PSAV of less than 2 ng/ml/year.

Still, the analysis of the subset of patients with PSAV greater than 2 ng/ml/year showed that grade, stage and PSA remained important stratifying factors of both cancer-specific and overall survival, suggesting that although PSAV is an independent variable on multivariate analysis, the impact of these well-established factors cannot be overlooked.

A significant consideration in evaluating this study is that PSAV was only calculated by using the PSA measurement closest in time to diagnosis and all PSA values within one year before diagnosis. Most men who are diagnosed by PSA in the USA have only a yearly PSA before a PSA is obtained that precipitates biopsy and a cancer diagnosis. If these findings correlate with the PSA velocities calculated over several years

before a diagnosis of prostate cancer, and if these findings are confirmed by other large trials, then it certainly may affect the way we stratify for clinical trials, counsel patients for primary treatments, or screen with PSA.

The definition of PSA failure after radiation therapy or surgery has been controversial<sup>44,45</sup>. Similarly, the rate of relative decline in PSA after treatment with androgen ablation, cytotoxics or other investigational agents has been the subject of numerous reports<sup>46,47</sup>. To date, PSA has not been accepted as a surrogate marker for survival after various treatments in advanced prostate cancer<sup>48</sup>. However, the kinetics of PSA, whether by PSADT or PSAV, are gaining greater momentum and likely will be used in the future for entry into clinical trials, risk stratification, and prediction modeling<sup>49</sup>.

### The Future of PSA

Further research is required to make PSA more sensitive and specific than it is at present. The role of the other derivatives of PSA such as free PSA fraction,  $\alpha 2$  - macroglobulin fraction,  $\alpha 1$  - antichymotrypsin fraction in the management of prostatic diseases needs to be further determined. Research should be directed at defining the role of other markers of prostate diseases, e.g. human glandular kallikrein-2, prostate specific membrane antigen, and P27. The role of reverse transcriptase polymerase chain reaction (RT-PCR) for further study of PSA needs to be defined in detecting circulating prostate cancer cells to aid in staging prostate cancer. Much work needs to be done, as at present the use of RT-PCR is associated with high rates of false positive and false negative results, and also lack of reproducibility. Within the past decade, advances in proteomics have stimulated a search for new biomarkers of prostate cancer with increased specificity. A recent report described the initial assessment of early prostate cancer antigen C (EPCA-2) as a serum marker for the detection of prostate cancer and examined its sensitivity and specificity<sup>50</sup>. The preliminary report showed that EPCA-2 may be a novel biomarker associated with prostate cancer

that has a high sensitivity and specificity and accurately differentiates between men with organ confined and non-organ confined disease<sup>50</sup>. The discovery of other markers of early prostate cancer other than PSA is eagerly awaited in the not too distant future.

In conclusion: all factors considered, at present PSA is the best tumor marker available for prostate cancer. It remains one of the most useful tumor markers in oncology today. PSA can detect prostate cancer at an early curable stage in about 90% of cases. It can aid in the diagnosis, staging and monitoring of disease progression in prostate cancer.

It is anticipated that future studies will provide further insight into prostate cancer biology and the identification of newer and perhaps better biomarkers to either replace or complement PSA. Although it is clear that limitations to the PSA test exist, including the inability to completely separate men with life-threatening cancer from those without cancer, it remains the best prostate cancer marker available for both detection and prognostication, particularly when coupled with assessment of changes in the PSA level over time. Because of the aforementioned uses of PSA, it seems that the announcement of "the death of PSA" has been rather premature! It appears that there is still more life in the PSA story<sup>18,20</sup>. Finally, the correct interpretation of PSA is an art as well as a science requiring careful consideration of all the clinical details.

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## RESUME

### ANTIGENE SPECIFIQUE DE PROSTATE : 25 ANS D'UTILITE CLINIQUE A KUWAIT

Depuis la fin des années 1980, l'antigène spécifique de prostate (PSA) s'est établi comme marqueur de tumeur le plus important de toute l'oncologie et est devenu indispensable dans la gestion du cancer de prostate. Depuis l'introduction du dépistage par le PSA, il y a eu une augmentation marquée de l'incidence clinique et pathologique du cancer prostatique confiné, et la majorité des cancers de prostate diagnostiqués aujourd'hui dans la plupart des pays dans l'ouest sont des tumeurs détectées par PSA et non palpables (T1C). Cependant, la polémique entoure l'utilisation de PSA comme outil courant de dépistage, et, pour cette raison, de grands efforts ont été consacrés à étudier le rapport entre PSA et la biologie de la tumeur. Une issue centrale dans cette polémique est le fait que le PSA est spécifique de l'organe, non spécifique du cancer, tel que les variations du PSA ne sont pas toujours une manifestation de cancer, mais plutôt peut être dues à l'inflammation, trauma, ou le plus généralement, l'hyperplasie prostatique bénigne simple (BPH). En outre, le chevauchement considérable existe dans des niveaux de PSA parmi les hommes avec cancer de prostate et BPH. C'est dans la prétendue « zone diagnostique grise » des niveaux du sérum PSA entre 4.0 et 10.0 ng/ml. En raison des questions entourant la spécificité de PSA dans le diagnostic du cancer de la prostate on a proposé un certain nombre de modifications pour augmenter la valeur de cette analyse, à savoir PSA-dérivés tels que la PSA spécifique de l'âge, la densité de PSA, le volume de PSA et les isoformes de PSA. Dans cette revue nous présenterons d'abord les applications pratiques de la PSA et des dérivés de PSA dans le diagnostic et la gestion du cancer de prostate. Nous soulignons également l'importance d'établir les gammes de référence locales et

le besoin de connaissance d'autres facteurs affectant des niveaux de PSA. Mots Clés: antigène spécifique de prostate, cancer de prostate, diagnostic, traitement.

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