

## The Prostate Gland and PSA (Prostate Specific Antigen)

**Serfa Faja**

PhD Candidate

**Amir Shoshi**

General Practitioner

### Abstract

The PSA test is used primarily to screen for prostate cancer. A PSA test measures the amount of prostate-specific antigen (PSA) in your blood. PSA is a protein produced in the prostate, a small gland that sits below a man's bladder. PSA is mostly found in semen, which also is produced in the prostate. Small amounts of PSA ordinarily circulate in the blood. The PSA test can detect high levels of PSA that may indicate the presence of prostate cancer. However, many other conditions, such as an enlarged or inflamed prostate, can also increase PSA levels. We use ImmunoAssay for Quantitative Measurement of PSA in Human Blood / Serum / Plasma with i-CHROMA™ Reader System with high sensitivity and specificity. We have analysed 120 patients and only 2 of them had very high value of PSA so we can determine for a prostate cancer. Additional factors increase the accuracy of PSA testing and it is not sufficient only the PSA to determine a prostate cancer so we need a rectal examination and transrectal ultrasound.

**Keywords:** PSA, prostate, prostate cancer, immunoassay

### Introduction

All men are at some risk for developing prostate cancer, yet there are many men who do not possess correct knowledge about the location and function of this organ that contributes significantly to male development, health, sexual function, and general quality of life <sup>1</sup>. The prostate gland is a secondary sex, exocrine organ that is an integral part of the human male reproductive system <sup>2</sup>. Prostate development begins before birth but rapid growth occurs during puberty in preparation for the production of semen.

<sup>1</sup> Winterich, J. A., Grzywacz, J. G., Quandt, S. A., Clark, P. E., Miller, D. P., Acuña, J., & ...Arcury, T. A. (2009). Men's knowledge and beliefs about prostate cancer: Education, race, and screening status. *Ethnicity & Disease*, 19(2), 199-203

<sup>2</sup> Lang, S., Frame, F., & Collins, A. (2009), Prostate cancer stem cells. *Journal of Pathology*, 217,299–306. doi:10.1002/path.2478

The prostate gland secretes a low alkaline fluid that forms approximately 70% of the volume of the seminal fluid that nourishes and protects sperm during ejaculation<sup>1</sup>. Within the lobes of the prostate there are four zones, the peripheral, transitional, central zones, and anterior fibromuscular stroma<sup>3</sup>. The peripheral zone, which is the largest area, contains about 75% of the glands in the prostate. The peripheral zone is in the outer most part of the prostate, and the lower peripheral zone is fairly close to the rectal wall. The majority of prostate adenocarcinomas originate in this area accounting for 70%-80% of all prostate cancers<sup>3</sup>. The transition zone surrounds the urethra and is anterior 23 to the central zone. It is mostly made up of smooth muscle and occupies about one third of the prostate. Approximately 15% of prostate cancers originate in this region. The central zone is in the center of the prostate and holds most of the remaining glands and surrounds the ejaculatory ducts. Infrequently cancer would originate in this central zone. However, some research has shown that carcinomas originating in this zone tend to be more aggressive and have poor prognoses<sup>2</sup>. The anterior fibromuscular zone is nonglandular and consists of a band of smooth muscle fibers and connective tissue that adjoins the smooth muscle of the bladder and the external sphincter and that prevents the back flow of semen into the bladder <sup>3</sup>.

### **Pathology of the Prostate**

The prostate remains functional and at adult size as long as androgens are present. As men age they have an increasing chance of developing diseases of the prostate. There are three main diseases of the prostate: prostatitis, benign prostatic hyperplasia, and prostate cancer.

Prostatitis is inflammation of the prostate gland caused by infection and is most often characterized by swelling, various urinary problems such as hesitancy, discomfort when passing urine (dysuria), and increased frequency at night (nocturia). Other symptoms include pain in the groin, pelvic, or genital area and painful ejaculation, and may sometimes be accompanied by fever. The peripheral zone of the prostate is the most common site for chronic prostatitis <sup>3</sup>.

Benign prostatic hyperplasia (BPH) is a common occurrence in older men and mainly occurs in the transition zone of the prostate gland. BPH is a nonmalignant enlargement of the prostate gland. Sometimes the inner section of the prostate that is located around the urethra continues to grow and can lead to this common condition that is serious prostate problem, but it is not cancer. When the prostate gland becomes enlarged, it can easily restrict the flow of urine due to compression of the urethra leading to some of the same symptoms described above (dysuria, nocturia, hesitancy, incomplete emptying of the bladder). BPH is a common problem that

---

<sup>1</sup> Zelefsky, M. J., Eastham, J. A., & Sartor, A. O. (2011). Cancer of the prostate. In DeVita, Hellman, and Rosenberg's *Cancer: principles & practice of oncology*, 9th ed. Philadelphia, PA. Lippincott, Williams & Wilkins.

<sup>2</sup> Cohen, R. J., Shannon, B. A., Phillips, M., Moorin, R. E., Wheeler, T. M., & Garrett, K. L. (2008). Central zone carcinoma of the prostate gland: A distinct tumor type with poor prognostic features. *The Journal of Urology*, 179(5), 1762-1767.

affects the quality of life in approximately one third of men older than 50 years and is histologically noticeable in approximately 90% of all men 80 years and older. As many as 14 million men in the United States have symptoms of BPH<sup>1</sup>. These two prostate conditions are important to note because often these are problems that get men to the doctor for prostate examinations and prostate cancer screening because some of the symptoms of these nonmalignant conditions are similar to those of prostate cancer<sup>2</sup>.

## Prostate Cancer Development and Symptoms

Prostate cancer develops as a result of uncontrolled tumor growth in the prostate gland.

Most prostate cancers occur within the peripheral zone of the prostate gland as noted previously, and it is from this area that most needle biopsies are taken. Prostate cancer develops after an initial transformation event, followed by mutations of various genes, including the genes for tumor protein p53 that can lead to tumor progression and metastasis. The enzyme 5-alpha reductase has been implicated in the development of prostate cancer<sup>3</sup>. ). Approximately 95% all prostate cancers develop from the gland cells and are therefore termed prostate adenocarcinomas (the term for cancer that develops in glandular cells). The other 5% of prostate cancers are typically rare and may include transitional cell carcinomas, small cell carcinomas, and squamous cell sarcomas<sup>4</sup>.

## Grading and Staging of Prostate Cancer

The Gleason grading system was developed by Donald Gleason as a method for categorizing prostate cancer based on the microscopic appearance of cancer cells<sup>5</sup>.

Higher Gleason scores are associated with increased levels of PSA in the blood serum and several studies have confirmed that PSA levels were directly proportional to clinically advancing prostate cancer and cancer volume<sup>6</sup>.

## Relationship between PSA Levels and Prostate Cancer Progression

---

<sup>1</sup> Cunningham, G. R., & Kadmon, D. (2013) Epidemiology and pathogenesis of benign prostatic hyperplasia. *UpToDate*. Retrieved from <http://www.uptodate.com/contents/epidemiologyand-pathogenesis-of-benign-prostatic-hyperplasia>

<sup>2</sup> Hale, S., Grogan, S., & Willott, S. (2007). Patterns of self-referral in men with symptoms of prostate disease. *British Journal of Health Psychology*, 12(Pt 3), 403-419.

<sup>3</sup> Hamilton, R. J., & Freedland, S. J. (2011). 5- $\alpha$  reductase inhibitors and prostate cancer prevention: Where do we turn now? *BMC Medicine*, 9(105). doi:10.1186/1741-7015-9-105

<sup>4</sup> National Cancer Institute (2013a). *Health Information National Trends Survey 4 (HINTS 4) Cycle 2 Analytic Recommendations 2013*. Retrieved from [http://hints.cancer.gov/docs/HINTS\\_IDA\\_Report.pdf](http://hints.cancer.gov/docs/HINTS_IDA_Report.pdf)

<sup>5</sup> Gleason, D. F., & Mellinger, G. T. (1974). Prediction of prognosis for prostatic adenocarcinomas by combined histological grading and clinical staging. *Journal of Urology*, 111(1), 58-64.

<sup>6</sup> Stamey, T. A., & Kabalin, J. N. (1989). Prostate specific antigen in the diagnosis and treatment of adenocarcinoma of the prostate. I. Untreated patients. *Journal of Urology*, 141(5), 1070-1083

Both normal healthy and neoplastic prostate cells secrete PSA<sup>1</sup> and an increase in the PSA level can at times be attributed to other benign conditions such as acute prostatitis, benign prostatic hyperplasia, and other conditions. Even though the level of PSA expressed on a per cell basis varies, there is no debate on the fact that PSA is consistently expressed in nearly all prostate carcinomas<sup>11</sup>. The absolute value of serum PSA is useful for determining the extent of prostate cancer and assessing the response to prostate cancer treatment; its use as a screening method to detect prostate cancer is common but controversial. In normal healthy males PSA is secreted into prostatic alveoli. It is then pumped into the prostatic urethra during ejaculation by means of fibromuscular tissue contractions of the prostate and expelled into seminal fluid. Because PSA is primarily released in prostatic secretions, only very small amounts of PSA are expected to be found circulating in the blood serum of a healthy individual. However, in the presence of prostate cancer, the concentration of PSA in the blood increases significantly<sup>2</sup>.

PSA blood serum levels are generally measured in nanograms per milliliter (ng/mL). The American Cancer Society reports that the risk of prostate cancer increases as the PSA level increases, from about 8% with a PSA level of 1 ng/mL to about 25% with a PSA level of 4-10 ng/mL<sup>3</sup>. PSA levels that are greater than 10 ng/mL suggest a more than 67% increased risk of the presence of disease<sup>4</sup>. As indicated in Figure 4, increase in clinical stage leads to an increase in blood PSA levels. Typically healthy men with no pathological prostate problems display blood serum PSA levels in the range 0.5-2 ng/mL.

These minimal levels of PSA enter the circulation by the process of diffusion through a number of anatomic barriers. In early development of prostate cancer these PSA levels may increase to 4-10 ng/mL as a result of destruction of the prostatic tissue. As prostate cancer advances and becomes invasive, significant amounts of PSA escape into the bloodstream. With advanced staged cancer these PSA levels may range from 10 ng/mL to 1,000 ng/mL<sup>13</sup>

### **The Prostate Specific Antigen (PSA) Test**

The PSA test is used primarily to screen for prostate cancer. A PSA test measures the amount of prostate-specific antigen (PSA) in your blood. PSA is a protein produced in

<sup>1</sup> Vickers, A. J., Ulmert, D., Serio, A. M., Björk, T., Scardino, P. T., Eastham, J. A., ... Lilja, H. (2007). The predictive value of prostate cancer biomarkers depends on age and time to diagnosis: towards a biologically-based screening strategy. *International Journal of Cancer*, 121(10), 2212-2217

<sup>2</sup> Kulasingam, V., Diamandis, E. P., Vega, C. P. (2008). Strategies for discovering novel cancer biomarkers through utilization of emerging technologies. *Nature Clinical Practice Oncology*. Retrieved from <http://www.medscape.org/viewarticle/578950>  
<http://img.medscape.com/fullsize/migrated/editorial/journalcme/2008/17049/kulasingam.fig1.gif>

<sup>3</sup> National Cancer Institute. (2013d). Prostate specific antigen (PSA) test. Retrieved from <http://www.cancer.gov/cancertopics/factsheet/detection/PSA>

<sup>4</sup> Ross, M. H., & Pawlina, W. (2011). *Histology a text and Atlas*. (6th ed). Baltimore, MD. Lippincott Williams & Wilkins.

the prostate. PSA is mostly found in semen, which also is produced in the prostate. Small amounts of PSA ordinarily circulate in the blood.

There was and continues to be concern about the large number of false positive test results and the widespread attempts to treat prostate cancers that may have not been life threatening that lead to significant negative side effects and poor quality of life for men<sup>1</sup>.

Because of the controversy regarding the accuracy and efficacy of the use of the PSA, additional factors are being studied to attempt to increase the accuracy of PSA testing<sup>2</sup>. These include:

1. Age-associated reference ranges – As men age the PSA level will naturally increase so that a recorded PSA should be compared to the what is considered normal for men in that age range or age group. However, one important drawback is that most of these studies have been conducted among predominantly Caucasian men and do not necessarily account for possible variations based on ethnicity and other factors<sup>17</sup>.
2. PSA density – PSA levels also increase with increasing prostate size as the benign cells make PSA. PSA density is the calculated ratio of PSA levels and prostate volume measured by transrectal ultrasound (TRUS) <sup>3</sup>.
3. Free PSA to Total PSA ratio – PSA can be measured in two serum types, either total conjugated (which is bound to other proteins) or free PSA. The percentage of free PSA tends to increase in benign prostatic hypertrophy compared with prostate cancer, and increasing size of the prostate correlates with an increase in the percentage of free PSA. However, a lower percentage of free PSA is associated with increased prostate cancer risk. Research studies suggest that measuring the conjugated or free PSA increases the accuracy of diagnosis<sup>4</sup>. The percentage of free PSA relative to the total PSA can be informative as a high ratio is considered favorable while a low percentage PSA is more commonly associated with more aggressive prostate cancer<sup>18</sup>.
4. PSA velocity – This refers to changes in PSA level over time. Sometimes studies consider PSA doubling time. Although some increase with age is expected, a substantial change in PSA velocity has been used to predict prostate cancer and to prompt prostate biopsy. However, some recent research on PSA

---

<sup>1</sup> Barry, M. J. (2009). Screening for prostate cancer – The controversy that refuses to die. *New England Journal of Medicine*. 360(13), 1351-1354.

<sup>2</sup> National Cancer Institute. (2013c). Prostate cancer treatment (PDQ®) – General information about prostate cancer. Retrieved from <http://www.cancer.gov/cancertopics/pdq/treatment/prostate/HealthProfessional>

<sup>3</sup> Catalona, W. J., Southwick, P. C., Slawin K. M., Partin, A. W., Brawer, M. K., Flanigan, R. C.,... Bray, K. R. (2000). Comparison of percent free PSA, PSA density, and age-specific PSA cutoffs for prostate cancer detection and staging. *Urology*, 56(2), 255–260

<sup>4</sup> El Melegy, N. T., Aboulella, H. A., Abul-Fadi, A. M., & Mohamed, N.A. (2010). Potential biomarkers for differentiation of benign prostatic hyperplasia and prostate cancer. *British Journal of Biomedical Science*, 67(3), 109-112.

velocity indicates that biopsy should not be prompted in the absence of other symptoms<sup>12</sup>.

### **Methodology of PSA testing.**

We use ImmunoAssay for Quantitative Measurement of PSA in Human Blood / Serum / Plasma with i-CHROMA™ Reader System.

### **Principle<sup>1</sup>**

The test uses a sandwich immunodetection method, such that the detector antibody in buffer binds to PSA/PSA complex in blood sample and antigen-antibody complexes are captured to antibody that has been immobilized on test strip as sample mixture migrates nitrocellulose matrix. Thus the more PSA antigen in blood, the more antigen-antibody complexes accumulated on test strip. Signal intensity of fluorescence on detector antibody reflects amount of antigen captured and is processed from i-CHROMATM Reader to show PSA concentration in specimen. The working range and the detection limit of i-CHROMATM PSA test are 2-50 ng/ml and 2 ng/ml, respectively.

### **Procedure<sup>2</sup>**

1. Set a Test Device on a dust-free clean place.
2. Check/insert ID Chip onto the instrument. Make sure that the Test Device lot # matches with ID Chip #.
3. Take out one tube of Detection Buffer from refrigerator and leave it at room temperature for a couple of minutes.
4. Draw 30 µL of whole blood (15 µL of serum, plasma) with a transfer pipette and add it to the tube containing Detector Buffer.
5. Mix well the specimen with Detector Buffer by tapping or inverting the tube.
6. Take 75 µL of sample mixture and load it onto the well of disposable Test Device.
7. Insert Test Device onto the holder of i-CHROMA™ Reader. Make sure direction of Test Device and push the device back all the way. Instrument will automatically scan the Test Device after 15 min.
8. Read the results on the display screen of i-CHROMA™ Reader.

### **Performance Characteristics<sup>3</sup>**

1. Analytical Sensitivity  
Analytical sensitivity means the lowest concentration of PSA that the test system can detect with CV<10%. Analytical sensitivity of i-CHROMA™ PSA Test was determined by testing 10 times each using 3 lots of reagents. Analytical sensitivity of i-CHROMATM PSA was 2 ng/ml.
2. Specificity

---

<sup>1</sup> The i-Chroma leaflets, page 1.

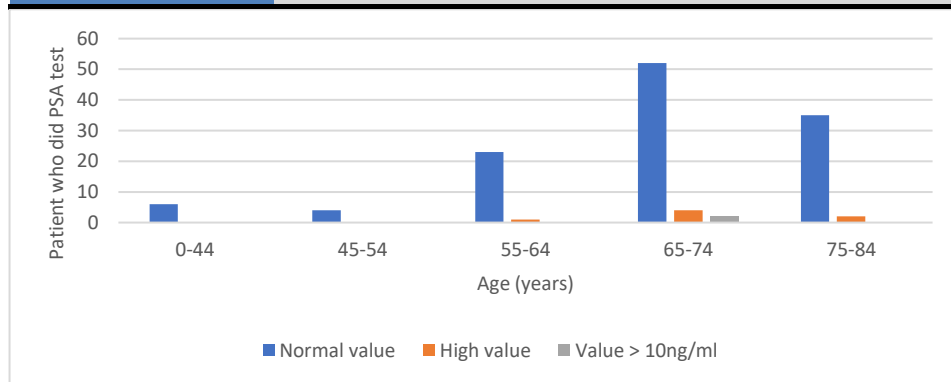
<sup>2</sup> The i-Chroma leaflets, page 2

<sup>3</sup> The i-Chroma leaflets, page 3

Other bio-molecules, such as Hb, CEA, AFP, ALP, CRP, Troponin I, CK-MB-Myoglobin, and Albumin were added to test specimen with much higher level than their physiological level in normal blood. There was no significant interference with the PSA measurement, nor was their any significant assay cross-reactivity with those bio-molecules tested.

Were analysed 120 patients for 2 years and they were grouped according to the age: 0-44 years old, 45-54 years old, 55-64 years old, 65-74 years old and 75-84 years old.

| Age (years) | Normal value | High value | Value > 10ng/ml |
|-------------|--------------|------------|-----------------|
| 0-44        | 6            | -          |                 |
| 45-54       | 4            | -          |                 |
| 55-64       | 23           | 1          |                 |
| 65-74       | 52           | 4          | 2               |
| 75-84       | 35           | 2          |                 |



## Discussion of results

As we see from the chart above there were a small amount of patient who had PSA value greater than normal range according to age that can determine a prostate cancer. This makes us think that PSA measurement is not sufficient in determining prostate cancer.

## Conclusion

For determining a prostate cancer it is not sufficient only a total PSA but is necessary to make digital rectal exam, transrectal ultrasound and totalPSA. Only 2 of the people involved in the study had very high value that determin more than 67 % for prostate cancer, the other group need to do more exams to determin if they have prostatitis or benigne prostate hiperplasia.



## References

- [1] Barry, M. J. (2009). Screening for prostate cancer – The controversy that refuses to die. *New England Journal of Medicine*. 360(13), 1351-1354.
- [2] Catalona, W. J. , Southwick, P. C. , Slawin K. M. , Partin, A. W. , Brawer, M. K. , Flanigan, R. C. , ... Bray, K. R. (2000). Comparison of percent free PSA, PSA density, and age-specific PSA cutoffs for prostate cancer detection and staging. *Urology*, 56(2), 255–260
- [3] Cohen, R. J. , Shannon, B. A. , Phillips, M. , Moorin, R. E. , Wheeler, T. M. , & Garrett, K. L. (2008). Central zone carcinoma of the prostate gland: A distinct tumor type with poor prognostic features. *The Journal of Urology*, 179(5), 1762-1767.
- [4] Cunningham, G. R. , & Kadmon, D. (2013) Epidemiology and pathogenesis of benign prostatic hyperplasia. UpToDate. Retrieved from <http://www.uptodate.com/contents/epidemiologyand->
- [5] El Melegy, N. T. , Aboulella, H. A. , Abul-Fadl, A. M. , & Mohamed, N. A. (2010). Potential biomarkers for differentiation of benign prostatic hyperplasia and prostate cancer. *British Journal of Biomedical Science*, 67(3), 109-112.
- [6] Epstein, R. M. , Alper, B. S. , & Quill, T. E. (2004). Communicating evidence for participatory decision making. *Journal of the American Medical Association*, 291(19), 2359-2366. doi:10. 1001/jama. 291. 19. 2359
- [7] Gleason, D. F. , & Mellinger, G. T. (1974). Prediction of prognosis for prostatic adenocarcinomas by combined histological grading and clinical staging. *Journal of Urology*, 111(1), 58-64.
- [8] Hale, S. , Grogan, S. , & Willott, S. (2007). Patterns of self-referral in men with symptoms of prostate disease. *British Journal of Health Psychology*, 12(Pt 3), 403-419.
- [9] Hamilton, R. J. , & Freedland, S. J. (2011). 5- $\alpha$  reductase inhibitors and prostate cancer prevention: Where do we turn now? *BMC Medicine*, 9(105). doi:10. 1186/1741-7015-9-105
- [10] Kulasingam, V. , Diamandis, E. P. , Vega, C. P. (2008). Strategies for discovering novel cancer biomarkers through utilization of emerging technologies. *Nature Clinical PracticeOncology*. Retrieved from <http://www.medscape.org/viewarticle/578950>
- [11] Lang, S. , Frame, F. , & Collins, A. (2009), Prostate cancer stem cells. *Journal of Pathology*, 217, 299–306. doi:10. 1002/path. 2478
- [12] National Cancer Institute (2013a). Health Information National Trends Survey 4 (HINTS 4)Cycle 2 Analytic Recommendations 2013. Retrieved from



- [13] National Cancer Institute. (2013c). Prostate cancer treatment (PDQ®) – General information about prostate cancer. Retrieved from
- [14] National Cancer Institute. (2013d). Prostate specific antigen (PSA) test. Retrieved from
- [15] pathogenesis-of-benign-prostatic-hyperplasia
- [16] Philadelphia, PA. Lippincott, Williams & Wilkins.
- [17] Ross, M. H. , & Pawlina, W. (2011). Histology a text and Atlas. (6th ed). Baltimore, MD. Lippincott Williams & Wilkins.
- [18] Stamey, T. A. , & Kabalin, J. N. (1989). Prostate specific antigen in the diagnosis and treatment of adenocarcinoma of the prostate. I. Untreated patients. Journal of Urology, 141(5), 1070-1083
- [19] The i-Chroma leaflets, 1-3.
- [20] Vickers, A. J. , Ulmert, D. , Serio, A. M. , Björk, T. , Scardino, P. T. , Eastham, J. A. , ... Lilja, H. (2007). The predictive value of prostate cancer biomarkers depends on age and time to diagnosis: towards a biologically-based screening strategy. International Journal of Cancer, 121(10), 2212-2217
- [21] Winterich, J. A. , Grzywacz, J. G. , Quandt, S. A. , Clark, P. E. , Miller, D. P. , Acuña, J. , & . . Arcury, T. A. (2009). Men's knowledge and beliefs about prostate cancer: Education, race, and screening status. Ethnicity & Disease, 19(2), 199-203
- [22] Zelefsky, M. J. , Eastham, J. A. , & Sartor, A. O. (2011). Cancer of the prostate. In DeVita, Hellman, and Rosenberg's Cancer: principles & practice of oncology, 9th ed.