

Prostatic Specific Antigen (PSA) Relationship to Patients Age, Prostate Volume and Prostate Histology at St Mary's Hospital Lacor.

T.R. Okello¹, N.O. Alema², D.M. Ogwang³

¹Head of Department of Surgery at St Mary's Hospital Lacor and Senior Honorary Lecturer, Dept of Surgery of Gulu University Medical School.

²Head of Accidents and Emergencies, St Mary's Hospital Lacor, Honorary Lecturer, Dept of Surgery of Gulu University Medical School.

³Institutional Director, St Mary's Hospital Lacor, Senior Honorary Lecturer, Dept of Surgery of Gulu University Medical School.

Correspondence to: Dr. Okello Tom Richard, Email: okellotomrich@yahoo.co.uk

Background: *The use of PSA for the diagnosis of cancer prostate has remained controversial as well as unreliable because many factors affect PSA levels. Included amongst the many factors that can increase PSA level are riding bicycle, rectal exam, sex, age, serum calcium, prostate inflammation, increased prostate volume. This study was aimed at determining the clinic-patho-radiological finding of patients presenting with enlarged prostate and to determine the PSA profile of all patients presenting with enlarged prostate in St. Mary's Hospital Lacor.*

Results: *Approximate 135 patients were evaluated in the study and significantly, elderly persons constituted 64.5%, compared with Adult (34.5%) and youth 1%, (P=0.00). Most patients presented with retention of urine (30%), dribbling of urine (23%), hesitancy (16%) and dysuria (13%). When the serum PSA was classified into Low (0.1-2.4ng/ml), Moderate (2.5-3.9ng/ml) and High 4ng/ml and above, we found that 60.7% of the patients had high PSA while 9.6% had moderate and low was 29.6%. PSA correlates positively with patients age (r= 0.24, P=0.005). Prostates volume also correlates positively with serum PSA, (Pearson's Correlation r=0.275 and P= 0.002). Age and prostate volume also had a significant relation P=0.054 but there was only a very weak relationship between PSA level and Histological diagnosis, (Pearson's correlation r=0.1).*

Conclusion: *Age and prostate volume significantly correlate with serum PSA, just as age and prostate volume also correlates significantly.*

Key words: Prostatic specific antigen (PSA), volume, age, histology.

Introduction

The incidence of prostate cancer varies widely between countries and ethnic groups. Whereas native Japanese have the lowest incidence, Black-Americans have the highest rates worldwide¹. Indeed, prostate cancer is the most commonly diagnosed non-skin cancer and the second leading cause of cancer death in the USA with approximately 241,740 American men diagnosed with the disease in 2012 alone of which 28,170 of them died². Furthermore, the incidence of prostate cancer in the United States and certain western countries has risen sharply during the last decade and the increase is more pronounced in the United States, Canada, Australia, France and the Asian countries³.

However, the reported incidence of cancer prostate in Asia is much lower than that in African Americans and European Caucasians, and there is somewhat better prognosis in Asian immigrants who develop prostate cancer in the United States⁴. It is postulated that Soy food consumption is associated with a 25% to 30% reduced risk of prostate cancer in Asian⁴. In their study, Bjarne, Synnøve, Knutsen, and Gary⁵ in 1998 also reported that men with high consumption of soy beans had reduced risk of prostate cancer.

In developing countries prostate cancer may be less common, however its incidence and mortality has been on the rise². This may be attributed to lack of dedicated efforts to search for the cancer. In fact cancer prostate incidence is influenced by the intensity of diagnostic efforts, mortality reports and active prostate specific antigen (PSA) screening⁴. Even when treated with radical prostatectomy the high PSA relapse rate signifies early metastasis even at low tumor volume⁶. Prostate-specific antigen (PSA) is the only established and routinely implemented clinical biomarker for prostate cancer detection and disease status². The introduction of total prostate specific antigen (total PSA) testing in blood has revolutionized the detection and management of men with prostate cancer because Men who will eventually develop Prostate cancer have increased total PSA levels years or decades before the cancer is diagnosed. However, PSA has limited value for Prostate Cancer screening and prognostication⁷.

Prostate cancer screening using PSA has been controversial, as no studies have proven that this strategy reduces mortality from prostate cancer. There is also no cutoff point of PSA with simultaneous high sensitivity and high specificity for detecting prostate cancer, hence PSA may be unreliable⁸. Serum PSA measurements show variable reliability when it comes to diagnosis of Prostate cancer, given the dynamics of PSA physiology⁹. In general, prostate biopsy has not been recommended unless PSA levels exceed a threshold value of 4.0 ng/mL, with slightly lower values recommended recently by some authors. Indeed 15% of men with a PSA value less than 4.0 ng/mL have prostate cancer and 15% of these cancers are high grade⁸. Even when changes in prostate-specific antigen (PSA) over time (PSA velocity) aid prostate cancer detection, there is little justification for formal calculation of PSA velocity if PSA level is ≥ 3 ng/ml for cut points to determine biopsy in men¹⁰.

The use Prostate-specific antigen (PSA) level typically results in over diagnosis of cancer prostate for a substantial number of men¹¹. This is because many factors affect PSA levels. Cycling causes an average 9.5% increase in PSA, when measured within 5 minutes post cycling¹¹. In addition in men over 40years a positive PSA screening result is significantly associated with increased age, marital status (married), higher socioeconomic status like higher educational attainment, and health care access^{12,18}. Serum calcium and serum parathyroid hormone (PTH) stimulate prostate growth in men without clinical prostate cancer and have implications of increasing PSA level¹³. There is also a tendency of correlation between the presence of inflammatory prostatitis with an elevation of PSA¹⁴ and according to Dong et al¹⁵, significant relationship also exists between PSA and Prostate volume. Hence use of PSA as a screening tool for prostate cancer leaves a lot to be desired.

There remain gross disparities between the prostate cancer risk and a given PSA level thus posing challenges to the use of PSA-driven algorithms to determine whether biopsy to rule out prostate cancer is indicated or not¹⁶. Prostate-specific antigen (PSA) lacks both sensitivity and specificity as a serum tumor marker in diagnosis and screening of prostate adenocarcinoma⁸. Its role in diagnosis of active prostate cancer has also remained controversial, yet it is the most prevalently used marker for prostate cancer, hence the need to evaluate other factors that affect serum PSA beside cancer prostate. The main objectives of this study were To determine the clinic-patho-radiological findings and the PSA profile of all patients present with enlarged prostate at St. Mary's Hospital Lacor in Uganda

Patients and Methods

A descriptive study was done on all males patients presenting at the St Mary' hospital Lacor surgical unit between Jan 2012 to Dec 2013 with enlargement of the prostate. St. Mary's hospital Lacor is a rural based 483 bed hospital located in Northern Uganda and is also a teaching hospital for Gulu University medical school. In the 2 years (2012-2013), all patients

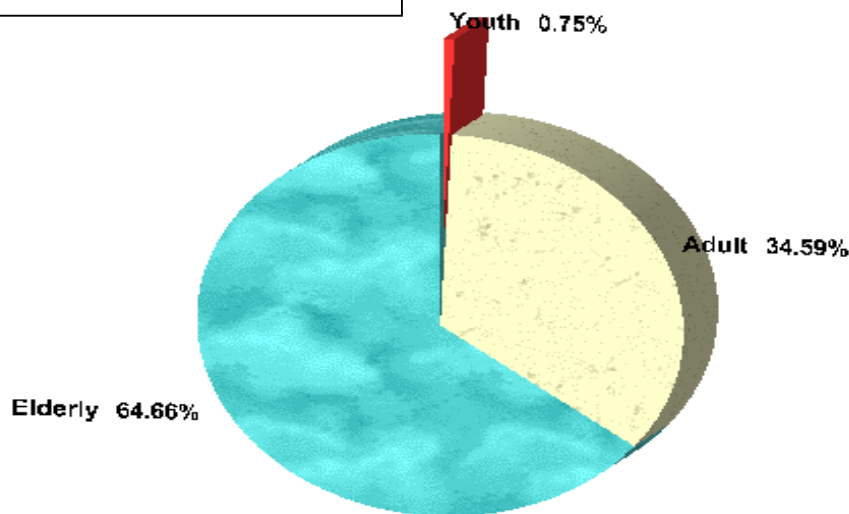
with suspected prostatic enlargement had their main clinical presentation appraised and Digital Rectal Exam done. They also had ultrasonography of the pelvis to assess their prostate volume and they were sent to the laboratory to remove sample for Prostatic specific Antigen (PSA) test prior to being sent for a side room procedure of tru-cut biopsy prostate. No cut off PSA was used; hence every one with enlarged prostate had a biopsy. At least 3 cylindrical samples were obtained at biopsy with a 16 gauge tru-cut gun. The histology samples were analyzed by a pathologist who was blinded but had to diagnose Adenocarcinoma (cancer prostate), Benign Prostatic Hypertrophy (BPH), Prostatitis or Normal tissue. Patient whose sample was insufficient to make histological diagnosis had a repeat tru-cut and those who never did PSA were expunged from the data set for analysis.

The patient’s biographic data, main presenting symptom, clinical diagnosis, prostate volume, serum PSA level and histological findings were collected, coded, entered and analyzed using SPSS.

Results

Approximate 135 patients were evaluated in the study. The youngest person was 33years and the oldest was 98 years, Mean age 68.5year (SD+/- 13years). Significantly, elderly persons constituted 64.5%, compared with Adult who made up to 34.5% and approximately 1% was a youth (P=0.00) (Figure 1). The high proportion of elderly persons in this study is because as one ages, the prostate also tend to enlarge as a result of decrease in androgen hormone level. Prostate volume often increases with age¹⁷.

Figure 1. Age Distribution



Presenting symptoms

Most patients presented with retention of urine (30%), dribbling of urine (23%), hesitancy (16%) and dysuria (13%) and this observed difference was significant P=0.00 (Table 1). On examination, 80% of the patients had clinical evidence of BPH and cancer prostate was 13%.

(P=0.00). However, of the patient who were clinically diagnosed with BPH, 46% correlated well with the histological finding While for those diagnosed with clinical caner prostate, 72% were found to have a positive histology findings, (P= 0.04). Therefore clinical evaluation is emphasized and complementary to PSA marker.

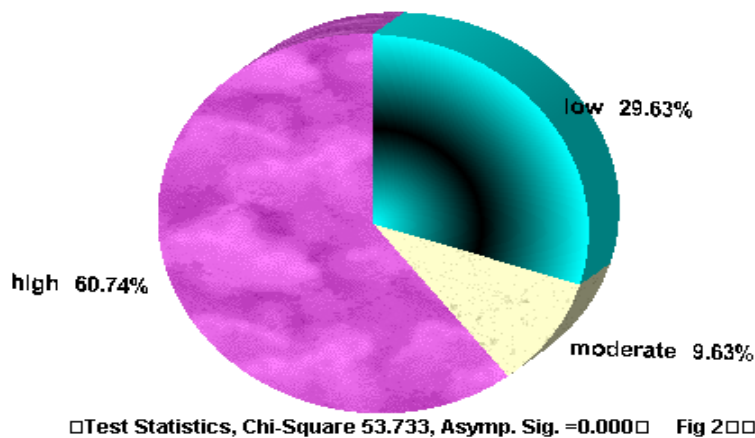
Table 1 Presenting Main symptom

Symptom	Frequency	Percent (%)
Urinary retention	40	29.6
Dysuria	18	13.3
Dribbling of urine	31	23.0
straining to pass urine	9	6.7
Difficulty passing urine	22	16.3
Frequency	6	4.4
Others	6	4.4
Hematuria	2	1.5
Metastasis	1	.7
Total	135	100.0

PSA Analysis.

Of the 135 patients enrolled in the study, the serum PSA ranged from 0.1ng/ml to 88.7ng/ml with average of 15.6ng/ml. When the serum PSA was classified into Low (0.1-2.4ng/ml), Moderate (2.5-3.9ng/ml) and High 4ng/ml and above, we found the 60.7% of the patients had high PSA while 9.6% had moderate and low was 29.6%, (P value=0.00). Therefore when PSA is taken for all patients with enlarged prostate, a significant proportion of patients tend to have a high PSA P=0.000 (Fig 2).

Figure 2. Serum PSA



Prostate Histology

Histological examination of prostate biopsy revealed BPH (39%), Cancer prostate (33%), inflamed prostate (15%) and intraepithelial neoplasms (12%). These observed difference in histology finding is significant ($P=0.00$), (Table 2 below). Therefore a great proportion of those patients who presented with enlargement of the prostate had cancer prostate, hence the need to biopsy all the enlarged prostates.

Table 2 Histology findings

		<i>Frequency</i>	<i>%</i>
Valid	BPH	53	39.3
	Adenocarcinoma	44	32.6
	Prostatitis	20	14.8
	PIN 1	11	8.1
	PIN 2	1	.7
	PIN 3	3	2.2
	Normal	1	.7
	Total	133	98.5
Missing	Bad sample	2	1.5
Total		135	100.0

Relationship between PSA, Prostate volume, Age, and Histology (Correlations)

As shown in table 3 below and using Figure 2, PSA correlates positively with patients age ($r=0.24$, $P=0.005$). Therefore as age advances, PSA also tends to increase. Hence elderly persons (more than 65years old) presenting with enlarged prostate should have a tru-cut biopsy of prostate irrespective of the PSA level.

In this study, prostate volume ranged from 18 to 236 mls with mean prostate volume was 78.8mls (SD+/-41mls). Prostates volume correlates positively with serum PSA, Pearson's Correlation $r=0.275$ and $P=0.002$. Therefore as prostate volumes increases, PSA also increases. Furthermore prostate volume also correlates positively with increasing age (Pearson's correlation $r=0.176$ and $P=0.054$ (table 3). There is a weak relationship between PSA level and Histological diagnosis, (Pearson's correlation $r=0.1$, Table 3).

As shown in Table 4, of all the patients whose PSA ranged within the low prostate cancer detection levels of 0-2.4ng/dl, 54% had BPH and 15.4% were found to be having cancer prostate. Of those whose PSA was considered high (≥ 4 ng/dl), 32% had BPH and 42% had cancer prostate. This finding was not statistically significant Chi square 13.561, $P=0.33$.

As shown in Table 4, of all the patients whose PSA ranged within the low prostate cancer detection levels of 0-2.4ng/dl, 54% had BPH and 15.4% were found to be having cancer prostate. Of those whose PSA was considered high (≥ 4 ng/dl), 32% had BPH and 42% had cancer prostate. This finding was not statistically significant Chi square 13.561, $P=0.33$.

Table 3. PSA, Prostate Volume and Histological findings

		Cancer Detection rate of PSA	Histology findings	Prostate volume	Age Group
Cancer Detection rate of PSA	Pearson Correlation	1	.097	.275(**)	.240(**)
	Sig. (2-tailed)		.265	.002	.005
	(P value)				
Histology findings	N	135	133	120	133
	Pearson Correlation	.097	1	.074	-.188(*)
	Sig. (2-tailed)	.265		.424	.031
Prostate volume	(P value)				
	N	133	133	118	131
	Pearson Correlation	.275(**)	.074	1	.176
Age Group	Sig. (2-tailed)	.002	.424		.054
	(P value)				
	N	120	118	120	120
Age Group	Pearson Correlation	.240(**)	-.188(*)	.176	1
	Sig. (2-tailed)	.005	.031	.054	
	(P value)				
	N	133	131	120	133

** Correlation is significant at the 0.01 level (2-tailed). * Correlation is significant at the 0.05 level (2-tailed).

Table 4 Cancer Detection rate of PSA and Histology findings

Cancer Detection rate of PSA	Histology findings							Total
	BPH	Adeno-carcinoma	Prostatitis	PIN 1	PIN 2	PIN 3	Normal	
Low (N)/%	21 53.8%	6 15.4%	8 20.5%	4 10.3%	0 .0%	0 .0%	0 .0%	39 100.0%
Moderate (N)/%	6 46.2%	4 30.8%	2 15.4%	1 7.7%	0 .0%	0 .0%	0 .0%	13 100.0%
High (N)/%	26 32.1%	34 42.0%	10 12.3%	6 7.4%	1 1.2%	3 3.7%	1 1.2%	81 100.0%
Total	53 39.8%	44 33.1%	20 15.0%	11 8.3%	1 .8%	3 2.3%	1 .8%	133 100.0%

Discussion

In this study, Approximate 135 patients were evaluated in the study. The youngest person was 33years and the oldest was 98years, Mean age 68.5year (SD+/- 13years) Fig 1. Significantly, elderly persons constituted 64.5%, compared with Adult who made up to 34.5% and approximately 1% was a youth (P=0.00). Other authors have reported similar mean age, and that prostate volume increase with age¹⁷. This is because as one ages, the prostate also tend to enlarge as a result of decrease in their androgen hormone level. Older Age at biopsy can be predictive of the disease⁸. PSA measurements before age 50years has been reported to help risk-stratify men for intensity of Prostate Cancer screening¹⁹.

Most patients presented with retention of urine (30%), dribbling of urine (23%), hesitancy (16%) and dysuria (13%) and this observed difference was significant $P=0.00$ (Table 1). On examination, 80% of the patients had clinical evidence of BPH and cancer prostate was 13%. ($P=0.00$). However, of the patient who were clinically diagnosed with BPH, 46% correlated well with the histological finding While for those diagnosed with clinical cancer prostate, 72% were found to have a positive histology findings, ($P= 0.04$). Therefore clinical evaluation is emphasized besides PSA because when taken together with a man's age, family history, ethnicity, and digital rectal exam results, PSA levels add to the overall estimate of the risk of cancer¹⁹ and abnormal DRE result and older age at biopsy are often predictive for high-grade prostate cancer⁸.

According to Figure 2, of the 135 patients, the serum total PSA ranged from 0.1ng/ml to 88.7ng/ml with average of 15.6ng/ml. When the serum PSA was classified into Low (0.1-2.4ng/ml), Moderate (2.5-3.9ng/ml) and High 4ng/ml and above, we found the 60.7% of the patients had high PSA while 9.6% had moderate and low was 29.6%, (P value=0.00). Young *et al*⁶ (2011) had earlier classified the cancer detection level of PSA as below 2.5ng/ml, from 2.5 to 4.0ng/ml, and above 4.0ng/ml, as 13.3%, 13.6% and 26.5%, respectively⁶. Therefore when PSA is taken for all patients with enlarged prostate, a significant proportion of patients tend to have a high PSA $P=0.000$ (Fig 2). Most other studies on PSA analysis have used a cut-off level of 4ng/ml, and they have reported high cancer detection rate if PSA is more than 4ng/ml^{6,20,21}.

As shown in Table 2, Histological examination of prostate biopsy revealed BPH (39%), Cancer prostate (33%), inflammation of prostate (15%) and intraepithelial neoplasms (12%). These observed difference in histology finding significant is ($P=0.00$). These finding contrast with the findings of those who biopsied the prostate only if the PSA was more than 4ng/ml. For example the finding of prostate cancer prevalence of 20.9%, benign prostatic hypertrophy of 4.7%, prostatitis of 74.4% by Young *et al*⁶ (2011) suggest a low cancer detection rate by limiting biopsy to a PSA cut-off of 4ng/ml yet that is an unreliable cut off^{8,9}. This finding suggests that we should biopsy all clinically symptomatic enlarged prostate.

Table 3 shows a positive correlation ship between PSA and patients age ($r= 0.24$, $P=0.005$). Therefore as age advances, PSA also tends to increase and most of the elderly persons have PSA ≥ 4 ng/ml. This finding in our study is also similar to the report of [Ornstein et al](#)⁷ (1998) that PSA levels correlated significantly with age⁷. Collins *et al*¹⁷ (2008) also found an independent association between PSA and age when controlled for volume¹⁷. [Liu, Wang, Su, et al](#)²⁰ (2013) found that males with a baseline PSA 3–3.99 ng ml⁻¹ have a 57.81% chance, that their PSA would increase above 4.0 ng ml⁻¹ over the following 4 years ($P<0.0001$)²⁰, thus emphasizing how advancing age correlate with PSA increase. Furthermore it was established that Serum PSA levels show an exponential increase with advancing age²¹. However PSA value of ≥ 4 ng/ml is suspicious and must be biopsied⁸. Other authors independently reported that PSA concentration in men with a prostate volume <25 cc also showed a continuous increase with aging²².

Although our study found a mean prostate volume 78.8mls and others reported a lower value 32 mls¹⁷ which may be attributable to our poor health seeking behavior, the study found that Prostates volume correlates positively with serum PSA, Pearson's Correlation $r=0.275$ and $P= 0.002$. In 1998, Ornstein *et al*⁷, reported prostate volume as being significant predictors PSA. The positive relation between PSA and prostate volume was also reported independently by many other authors^{15,19,22,23}. Furthermore the study also found that prostate volume also correlates with increasing age (Pearson's correlation $r= 0.176$ and $P= 0.054$. Collins, Lee, Mckelvie *et al*²¹ 2008 got a similar finding just as Berges, and Oelke²² in 2011 and Mettlin, Littrup, Kane *et al*²⁴ (2006) also got a similar findings

There is a weak relationship between PSA level and Histological diagnosis, (Pearson's correlation $r=0.1$, table 3 and table 4 (Chi square 13.561, $P= 0.33$). This can be attributed to the fact the PSA is unreliable and controversial when used in diagnosis of cancer prostate and can be misleading if entirely relied upon^{8,9,10,11,12,14,19, 23, 25,26}.

Conclusion

Age and prostate volume significantly correlate with serum PSA and age and prostate volume also correlates significantly. Since PSA correlates weakly with histological findings, it should therefore be used in in-conjunction with other clinico-biographic parameters to diagnose cancer prostate.

Acknowledgement

The following doctors: Achidri, Ojara, Alanyo, Laker, and Lukode who participated in the biopsy and collection of data as well as surgery one staffs who provided a conducive environment for the procedure are hereby sincerely thanked for their participation. The radiology and Laboratory are also highly appreciated for measuring prostate volume and PSA respective and thank you.

Reference

1. R.K. Ross, L. Bernstein, M.C. Pike, B.E. Henderson, R.A. Lobo, F.Z. Stanczyk, H. Shimizu, "5-alpha-reductase activity and risk of prostate cancer among Japanese and US white and black" males. *The Lancet*, Volume 339, Issue 8798, 11 April 1992, Pages 887-889
2. Otis W. Brawley "Trends in Prostate Cancer in the United States" *J Natl Cancer Inst Monogr*. 2012 September; 2012(45): 152-156. doi: 10.1093/jncimonographs/lgs035
3. Potosky *et al*, 1995; Mercer *et al*, 1997; Majeed and Burgess, 1994; Weller *et al*, 1998, Quoted in Ann W. Hsing*, Lilian Tsao, Susan S. Devesa "International trends and patterns of prostate cancer incidence and mortality" *International Journal of Cancer*, Volume 85, Issue 1, pages 60-67, 1 January 2000
4. Tomomi Kimura "East meets West: ethnic differences in prostate cancer epidemiology between East Asians and Caucasians" *Chin J Cancer*. 2012 September; 31(9): 421-429. doi: 10.5732/cjc.011.10324
5. Bjarne K. Jacobsen, Synnøve F. Knutsen, Gary E. Fraser "Does high soy milk intake reduce prostate cancer incidence? The Adventist Health Study (United States)" *Cancer Causes & Control* December 1998, Volume 9, Issue 6, pp 553-557
6. Young Jung Kim, Sun-Ouck Kim, Kwang Ho Ryu, In Sang Hwang, Eu Chang Hwang, Kyung Jin Oh, Seung Il Jung, Taek Won Kang, Dong Deuk Kwon, Kwangsung Park, and Soo Bang Ryu "Prostate Cancer Can Be Detected Even in Patients with Decreased PSA Less than 2.5 ng/ml after Treatment of Chronic Prostatitis" *Korean J Urol*. 2011 July; 52(7): 457-460. doi: 10.4111/kju.2011.52.7.457
7. Ornstein David K. Deborah S. Smith Peter A. Humphrey William J. Catalona. "The Effect Of Prostate Volume, Age, Total Prostate Specific Antigen Level And Acute Inflammation on The Percentage of Free Serum Prostate Specific Antigen Levels In Men Without Clinically Detectable Prostate Cancer" *The Journal of Urology* Volume 159, Issue 4, Pages 1234-1237, April 1998
8. Ian M. Thompson, MD; Donna Pauler Ankerst, PhD; Chen Chi, MS; M. Scott Lucia, MD; Phyllis J. Goodman, MS; John J. Crowley, PhD; Howard L. Parnes, MD; Charles A. Coltman, MD "Operating Characteristics of Prostate-Specific Antigen in Men With an Initial PSA Level of 3.0 ng/mL or Lower FREE" *JAMA*. 2005; 294(1): 66-70. doi: 10.1001/jama.294.1.66
9. Affonso Celso Piovesan, Geraldo de Campos Freire, Fabio César Miranda Torricelli, Paulo Cordeiro, Renato Yamada, and Miguel Srougi "Incidence of Histological Prostatitis and Its

- Correlation with PSA Density” Clinics (Sao Paulo). 2009 November; 64(11): 1049–1051. doi: 10.1590/S1807-59322009001100003
10. Andrew J. Vickers, Tineke Wolters, Caroline J. Savage, Angel M. Cronin, M. Frank O'Brien, Kim Pettersson, Monique J. Roobol, Gunnar Aus Peter T. Scardino, Jonas Hugosson, Fritz H. Schröder, and Hans Lilja “Prostate-Specific Antigen Velocity for Early Detection of Prostate Cancer” *Eur Urol*. 2009 November; 56(5): 753–760.
 11. Ballentine H Carter, Luigi Ferrucci, Anna Kettermann, Patricia Landis, E. James Wright, Jonathan I. Epstein, Bruce J. Trock, and E. Jeffrey Metter “Detection of Life-Threatening Prostate Cancer With Prostate-Specific Antigen Velocity During a Window of Curability” *J Natl Cancer Inst*. 2006 November 1; 98(21): 1521–1527. doi: 10.1093/jnci/djj410
 12. Sandra L. Mejak, Julianne Bayliss, and Shayne D. Hanks³ “Long Distance Bicycle Riding Causes Prostate-Specific Antigen to Increase in Men Aged 50 Years and Over” *PLoS One*. 2013; 8(2): e56030. doi: 10.1371/journal.pone.0056030
 13. Halcyon G. Skinner and Gary G. Schwartz “The Relation of Serum Parathyroid Hormone and Serum Calcium to Serum Levels of Prostate-Specific Antigen: A Population-Based Study” *Cancer Epidemiol Biomarkers Prev*. 2009 November; 18(11): 2869–2873. doi: 10.1158/1055-9965.EPI-09-0730
 14. Ulmert David, Angel M Cronin, Thomas Björk, Matthew F O'Brien, Peter T Scardino, James Eastham, Charlotte Becker, Göran Berglund, Andrew J Vickers, and Hans Lilja “Prostate-specific antigen at or before age 50 as a predictor of advanced prostate cancer diagnosed up to 25 years later: A case-control study” *BMC Med*. 2008; 6: 6. Published online 2008 February 15. doi: 10.1186/1741-7015-6-6
 15. Shahrokh F. Shariat, Axel Semjonow, Hans Lilja, Caroline Savage, Andrew J. Vickers, and Anders Bjartell “Tumor markers in prostate cancer I: blood-based markers” *Acta Oncol*. 2011 June; 50(Suppl 1): 61–75. doi: 10.3109/0284186X.2010.542174
 16. Andrew J. Vickers, Angel M. Cronin, Monique J. Roobol, Jonas Hugosson, J. Stephen Jones, Michael W. Kattan, Eric Klein, Freddie Hamdy, David Neal, Jenny Donovan, Dipen J. Parekh, Donna Ankerst, George Bartsch, Helmut Klocker, Wolfgang Horninger, Amine Benchikh, Gilles Salama, Arnauld Villers, Steve J. Freedland, Daniel M. Moreira, Fritz H. Schröder, and Hans Lilja “The relationship between prostate-specific antigen and prostate cancer risk: the Prostate Biopsy Collaborative Group” *Clin Cancer Res*. 2010 September 1; 16(17): 4374–4381. doi: 10.1158/1078-0432.CCR-10-1328
 17. Collins G.C, R. J. Lee, G. B. Mckelvie, A. C. N. Rogers, M. Hehir “Relationship between Prostate Specific Antigen, Prostate Volume and Age in the Benign Prostate” *British Journal of Urology* Volume 71, Issue 4, pages 445–450, April 1993 DOI: 10.1111/j.1464-410X.1993.tb15990.x published online: 26 NOV 2008
 18. Hyung Seok Seo and Nam Kyu Lee “Predictors of PSA Screening Among Men Over 40 Years of Age Who Had Ever Heard about PSA” *Korean J Urol*. 2010 June; 51(6): 391–397. doi: 10.4111/kju.2010.51.6.391
 19. Shahrokh F. Shariat, Peter T. Scardino, and Hans Lilja “Screening for Prostate Cancer: An Update” *Can J Urol*. 2008 December; 15(6): 4363–4374.
 20. Ming Liu, Jian-Ye Wang, Hong-Xue Su, Gang Wan, Ling Zhu, and Xiao-Ming Wang “A longitudinal study of PSA and its influential factors in a cohort of Chinese men with initial PSA levels less than 4 ng ml⁻¹” *Asian J Androl*. 2013 July; 15(4): 483–486. doi: 10.1038/aja.2013.41
 21. Mohan Adhyamand Anish Kumar Gupta “A Review on the Clinical Utility of PSA in Cancer Prostate” *Indian J Surg Oncol*. 2012 June; 3(2): 120–129. doi: 10.1007/s13193-012-0142-6
 22. Berges R, Oelke M. “Age-stratified normal values for prostate volume, PSA, maximum urinary flow rate, IPSS, and other LUTS/BPH indicators in the German male community-dwelling population aged 50 years or older” *World J Urol*. 2011 Apr; 29(2): 171–8. Doi: 10.1007/s00345-010-0638-z. Epub 2011 Jan 8.

23. Al Baha Barqawi, Brian K. Golden, Michael K. Brawer, Colin O'Donnell, E. David Crawford
"Observed effect of age and body mass index on total and complexed PSA: Analysis from a national screening program"**Urology**Volume 65, Issue 4 , Pages 708-712, April 2005
24. Curtis Mettlin, Peter J. Littrup, Robert A. Kane,Gerald P. Murphy M.D.Fred Lee, Arthur Chesley, Robert Badalament, Fatollah K. Mostofi, Relative sensitivity and specificity of serum prostate specific antigen (PSA) level compared with age-referenced PSA, PSA density, and PSA change, Article first published online: 28 JUN 2006, DOI: 10.1002/1097-0142(19940901)74:5<1615::AID-CNCR2820740520>3.0.CO;2-6
25. Gabriel P. Haas, Nicolas Delongchamps,Otis W. Brawley, Ching Y. Wang, DVM, and Gustavo de la Roza, "The Worldwide Epidemiology of Prostate Cancer: Perspectives from Autopsy Studies" Can J Urol. 2008 February; 15(1): 3866–3871.
26. Robert B. NadlerPeter A. HumphreyDeborah S. SmithWilliam J. CatalonaTimothy L. Ratliff
"Effect of Inflammation and Benign Prostatic Hyperplasia on Elevated Serum Prostate Specific Antigen Levels" The Journal of Urology
Volume 154, Issue 2 , Pages 407-413, August 1995