Current Science International 1(1): 1-6, 2011
ISSN: 2077-4435

Igf-1 And Psa In Prostate Cancer Detection

[1]Ahmed M. Domaa and [2]Omar S. Abd El-Fattah

[1]Department of Pharmacology, Faculty of Pharmacy, Al-Margrb University, Al-Khoms, Libya
[2]Department of Biochemistry, National Cancer Institute, Cairo, Egypt

ABSTRACT

Introduction : Prostate cancer (PCa) is the second most frequent malignancy diagnosed in adult men. Androgens are considered the primary growth factors for prostate normal and cancer cells. However, other non-androgenic growth factors are involved in the growth regulation of PCa cells. Insulin-like Growth Factor (IGF-1) modulates cell growth and survival, and is thought to be important in tumor development. The association between IGF-1 and PCa risk is well established. However, there is no evidence that the measurement of IGF-1 enhances the specificity of PCa detection beyond that achievable by serum PSA levels. **Objective:** The aim of this work was to examine the biochemical relationship between serum IGF-1 and prostatic enlargement (either malignant or benign). Also, to determine if measuring serum IGF-1 level can improve the detection of PCa. **Subjects and Methods:** A consecutive series of 27 men with newly diagnosed untreated PCa, 30 men with newly diagnosed untreated Benign Prostatic Hyperplasia (BPH), and 24 healthy men controls were recruited. The diagnosis of PCa and BPH was made by transrectal ultrasound (TRUS) guided prostate biopsies followed by histopathological investigation. Serum total and free PSA and IGF-1 levels were measured by using chemiluminescence's technique. Serum levels of IGF-1, total and free PSA were compared between cases and controls. **Results:** Serum IGF-1 levels were significantly higher in both PCa (231 ± 7.62 ng/ml, mean ± SEM, $p < 0.001$) and BPH patients (215 ± 9.20 ng/ml, $p < 0.01$) than in controls (176 ± 5.60 ng/ml). The median of both free and total PSA was significantly higher in both PCa and BPH patients as compared to control group ($p < 0.001$). Only total PSA was significantly higher in PCa than BPH patients ($p < 0.05$). The area under the curve (AUC) for total PSA, free PSA, and IGF-1 were 0.89, 0.81, and 0.72,respectively. **Conclusions:** The present results suggest that serum IGF-1 levels provide no useful information in the diagnosis of PCa or BPH. In addition, the measurement of IGF-1 does not enhance the specificity of PCa detection beyond that achievable by serum PSA alone, but rather that IGF-1 may be predictive of later cancer development

Key words: Prostate cancer- IGF-1- PSA

Introduction

Prostate cancer is one of the most commonly diagnosed malignancies in men and is the second leading cause of cancer-related death worldwide (Jemal *et al.,* 2009).

Serum PSA is a sensitive marker of PCa, but its positive predictive value is low. Studies have shown that a PSA threshold of 4 ng/ml allows a closer approximation to optimal sensitivity and specificity. At this cut-off, PSA has impressive sensitivity rates vary from 78% (Espana *et al.,* 1998) to 100% (Unal *et al.,* 2000) and specificity rates vary from 15% (Aragona *et al.,* 2005) to 66% (Unal *et al.,* 2000).

Unfortunately, the specificity of PSA is not high enough. This is due to several factors not related to PCa that can affect the concentration of PSA in the serum. These factors include pre-analytical conditions of PSA measurement, type of PSA immunoassay, intra-individual fluctuations of PSA, prostate volume, and prostatic inflammation (Semjonow *et al.,* 2000).

Due to the lack of specificity, many modifications of PSA have been proposed in an attempt to improve the performance of this analyte. These modifications include PSA density (Ohori *et al.,* 1995), age-specific PSA ranges (Oesterling *et al.,* 1993), percentage of free PSA (% fPSA) (Catalona *et al.,* 1998), PSA density of transition zone (Zlotta *et al.,* 1997), PSA velocity (Carter *et al.,* 1992), and other PSA isoforms (Huber *et al.,* 1995). Although the cancer specificity of PSA can be improved by these modifications, further improvement is needed.

The IGF system is a complex molecular network that has two ligands (IGF-1 and IGF-2), two receptors (IGF-1R and IGF-2R), six high-affinity-binding proteins (IGFBP-1 to IGFBP-6) and several binding-protein proteases (LeRoith & Roberts, 2003). IGFs are mitogenic peptides that have an important role in regulating cell proliferation, differentiation and apoptosis (Pollak, 2001) and they have been related to the pathogenesis of PCa (Mantzoros *et al.,* 1997) and BPH (Cohen, 1998).

The effects of IGFs are mediated through type-1 IGF receptor, a tyrosine kinase that shares certain structural similarities with insulin receptor. The availability of free IGFs for interaction with IGF receptor-1 is modulated by IGFBPs (Pollak, 2001). In the plasma greater than 90% of circulating IGF-1 is bound to IGFBP-3.

Corresponding Author: Ahmed M. Domaa, Department of Pharmacology, Faculty of Pharmacy, Al-Margrb University, Al-Khoms, Libya

The affinity of IGFBP-3 for IGF-1 is decreased by proteases that cleave binding proteins and may cause growth by increasing the availability of free IGF-1. PSA is a serine protease that may modulate the activity of IGF-1 (Cohen, 1998).

Subjects And Methods:

Controls:

Twenty four healthy volunteers, the mean age ± standard deviation (61.8 ± 6.38 years) referred to the central laboratory, Tripoli Teaching Hospital for blood sampling. Subjects were included if they were men older than 50 years of age, apparently healthy, not having a history of drug or alcohol abuse and not taking medications known to influence prostate functions and to be fasting overnight. Subjects were excluded if they were smokers, subjected to a constipation or digital rectal examination within the past month, suffering from any urological disorder or any other cancer.

Patients:

The study included 67 consecutive patients who presented to Tripoli Teaching Hospital, between September 2009 and March 2010. These patients were referred to outpatient clinic exclusively by urologists due to elevated total serum PSA or suspicious digital rectal examination.

After patients provided informed consent, blood samples were obtained before any prostatic manipulation, followed by TRUS guided prostate biopsy. Of the patients, 27 men (age 62.9 ± 7.21 years) were diagnosed with PCa, and 30 men (age 64.6 ± 6.86 years) were diagnosed with BPH.

Patients were included if they were older than 50 years of age, not having a history of drug or alcohol abuse and to be fasting overnight. Patient's exclusion criteria included any biopsy, digital rectal examination, or prostatic massage antedating blood collection by 6 weeks, prior prostate surgery, concurrent medical treatment for prostate disease, suffering from any other urological disorder or any other cancer.

Blood Sampling and Laboratory Methods:

Overnight fasting venous blood samples were withdrawn at morning after 10 minutes rest in the sitting position. Samples were allowed to clot for about 30 minutes, and then centrifuged at 4000 rpm for about 10 minutes. The yielded serum was aliquoted and stored at -70□C until the time of analysis. Serum total and free PSA (Correale *et al.,* 1996) and IGF-1 (Elmlinger *et al.,* 2005) levels were measured by using chemiluminescence's technique (IMMULITE 1000®, Siemens, Germany).

Statistical Analyses:

All analyses and graphics were performed using GraphPad Prism version 5 (GraphPad Software, San Diego).

Mann-Whitney *U* test was used to compare the median of free and total PSA between PCa, BPH, and controls. One way Analysis of Variance (ANOVA) followed by Tukey's procedure was used to compare mean of IGF-1 between PCa, BPH, and controls. Differences between means or medians were considered statistically significant at *P*□ *0.05.*

To evaluate the specificity versus sensitivity of IGF-1, total PSA, and free PSA receiver-operating characteristic (ROC) curves were drawn and the AUC was calculated.

Results:

Table 1 and Fig. 1 show the analysis of various parameters. Serum IGF-1 levels were significantly higher in both PCa (231 ± 7.62 ng/ml, $p < 0.001$) and BPH patients (215 ± 9.20 ng/ml, ($p < 0.01$)) than in controls (176 ± 5.60 ng/ml).

The median of both free and total PSA was significantly higher in both PCa and BPH patients as compared to control group ($p < 0.001$). Only total PSA was significantly higher in PCa than BPH patients ($p < 0.05$).

The accuracy of IGF-1 for PCa detection was evaluated by ROC analysis. The AUC was 0.72 for IGF-1, 0.81 for free PSA, and 0.89 for total PSA Fig. 2).

Table 1: Age and serum markers of the participants

	Control	BPH	PCa	*P value	#P value
No. of cases	24	30	27		
Mean age ± SD	61.8 ± 6.38	64.6 ± 6.86	62.9 ± 7.21		
Total PSA (ng/ml)					
Mean ± SEM	1.22 ± 0.08	12.2 ± 1.38	37.5 ± 5.90		
Median	1.30	10.3*	23.2*#	< 0.001	< 0.05
Free PSA (ng/ml)					
Mean ± SEM	0.27 ± 0.02	2.14 ± 0.25	3.91 ± 0.60		
Median	0.27	2.00*	2.60*	< 0.001	ns
IGF-1 (ng/ml)					
Mean ± SEM	176 ± 5.60	215 ± 9.20*	231 ± 7.62*	< 0.01	ns

* Significant from control # Significant from BPH

PCa: Prostate cancer BPH: Benign Prostatic Hyperplasia PSA: Prostatic Specific Antigen IGF-1:Insulin like Growth Factor1

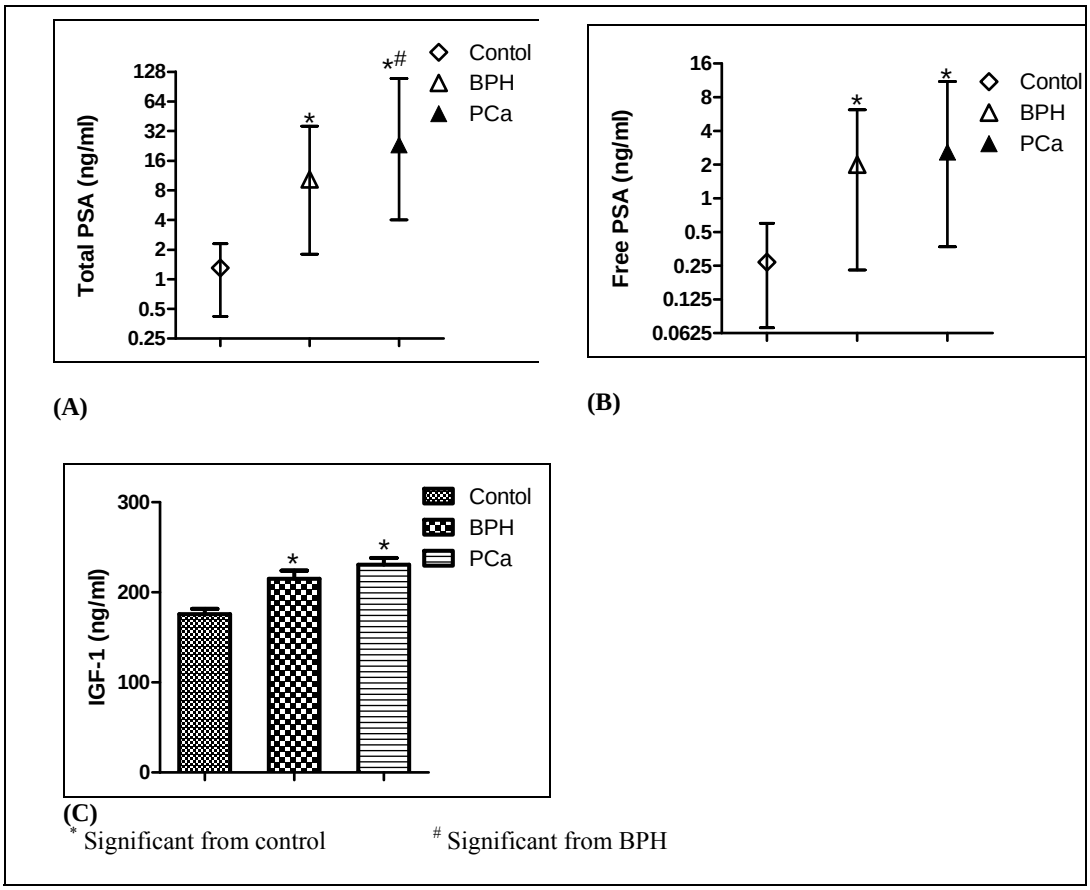

Fig. 1: Serum levels of (A) total PSA, (B) free PSA, and (C) IGF-1 (ng/ml) in control, BPH, and PCa groups

Discussion:

The introduction and use of PSA for PCa screening and detection has changed the face of PCa, in particular as it relates to the well-recognized stage migration of disease (Loeb & Catalona, 2007). PSA is now the most widely used noninvasive screening tool in solid tumors, although its routine use has been the subject of continued controversy owing to its limited specificity (Lin, 2009).

The usefulness of PSA as a marker for PCa emerged in 1980 by Papsidero *et al.*, which was the first report of increased PSA levels in the serum of patients with PCa. In 1981, Kuriyama *et al.* suggested PSA as a marker for the disease. Since that time, PSA has gained an indispensable place in the early detection, staging, and follow-up of PCa, and is considered the first line test in PCa screening.

The present results are in line with all previous studies that have used the total PSA to detect the prostatic diseases. The serum total PSA was significantly higher in both PCa and BPH patients than normal subjects were.

Curr. Sci. Int. 1(1): 1-6, 2011

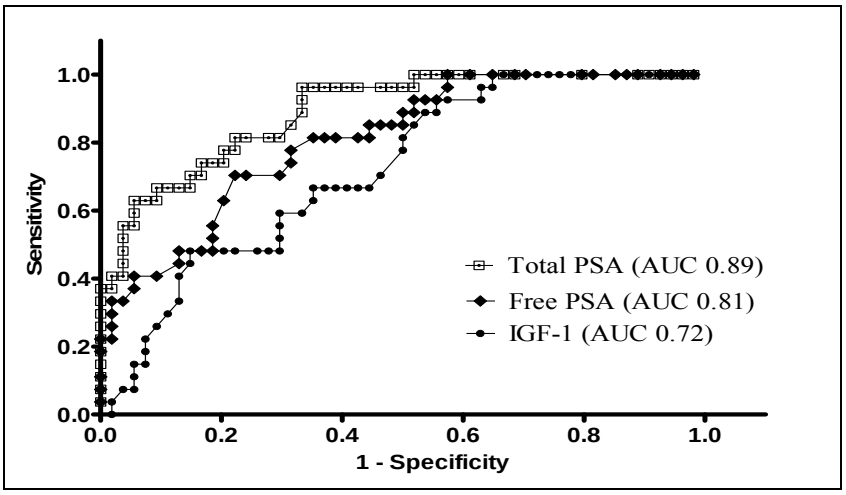

Fig. 2: ROC curves for sensitivity versus 1-specificity for total PSA, free PSA, and IGF-1.

Unfortunately, the specificity of PSA is not high enough. Due to the lack of specificity, many modifications of PSA have been proposed in an attempt to improve the performance of this analyte (Semjonow *et al.,* 2000).

The evidence that low androgen levels do not exclude PCa suggests that other growth factors, such as IGFs family, also have a role in the prostate carcinogenesis (Morgentaler *et al.,* 1996). In the present study, patients with PCa or BPH showed significantly elevated levels of IGF-1 when compared to control.

These findings are in line with Chan *et al.* (1998) who showed a 2.4-fold increased risk of PCa in the highest IGF-1 quartiles. In addition, two case-control studies of newly diagnosed patients showed that serum IGF-1 was higher in men with PCa than in controls (Mantzoros *et al.,* 1997) and (Wolk *et al.,* 1998).

In addition, Oliver *et al.* (2004) investigated 176 cases and 324 matched controls selected out of a cohort of 7,383 men and observed that the risk of PCa increased across quartiles of IGF-1 and IGF-2.

A meta-analysis done by Shi *et al.* (2001) evaluated 14 case-control studies for the association between IGF-1 level, IGFBP-3 level and PCa, the combined data showed that circulating levels of IGF-1 were significantly higher in PCa patients. Another meta-analysis of 9 prospective studies, that included 1,512 men with PCa, found a similar result (Morris *et al.,* 2006).

Roddam *et al.* (2008) reanalyzed the individual data from 12 prospective studies (3,700 PCa cases and 5,200 control participants) on the relationships between circulating levels of IGFs and subsequent PCa risk. A 38% increased odds of PCa risk, comparing highest versus lowest quartiles of IGF-1.

Recently, Rowlands *et al.* (2009) conducted the largest systematic review of studies reporting on the association of IGF-1 with the risk of PCa. Unlike previous metaanalyses, this one included both retrospective and prospective studies (42 studies) and demonstrated that the published literature is consistent with an average 21% increase risk of PCa per standard deviation increase in IGF-1. They also showed a stronger association of IGF-1 with more aggressive and advanced cancers, compared to non-aggressive and localized ones.

Nevertheless the majority of studies that support the role of IGF-1 as a predictor for PCa development, Cutting *et al.* (1999) observed no statistical significant difference of serum IGF-1 levels between PCa patients and controls. Moreover, Finne *et al.* (2000) concluded that there is a negative association between serum IGF-1 and PCa risk and it is not a useful diagnostic test for PCa.

In the present study, the AUC for IGF-1 (0.72) was lower than that for both serum total (0.89) and free PSA (0.81) indicating that serum IGF-1 levels do not improve the accuracy of PSA alone for distinguishing cancer.

These findings are in line with (Chan *et al.,* 1998), (Stattin *et al.,* 2000) and (Harman *et al.,* 2000) who did not suggest that serum IGF-1 is a marker for PCa detection, but rather that IGF-1 may be predictive of later cancer development.

Finally, Chan *et al.* (2002) concluded that circulating levels of IGF-1 and IGFBP-3 may predict the risk of developing advanced-stage PCa, but their utility for screening patients with early stage disease may be limited. Additionally, Ismail *et al.* (2003) concluded that serum IGF-1 and IGFBP-3 do not predict the results of prostate biopsy.

Conclusions:

The present results suggest that serum IGF-1 levels provide no useful information in the diagnosis of PCa or BPH. In addition, the measurement of IGF-1 does not enhance the specificity of PCa detection beyond that achievable by serum PSA alone, but rather that IGF-1 may be predictive of later cancer development

References

Aragona, F., P. Pepe, M. Motta, A. Saita, G. Raciti, P. La Rosa, D. Nicolosi, A. Dammino, G. Minaldi, G. Rizza, G. Azzarello and C. Aragona, 2005. Incidence of prostate cancer in sicily: results of a multicenter case-findings protocol. Eur Urol., 47: 569-74.

Carter, H., C. Morrell, J. Pearson, L. Brant, C. Plato, E. Metter, D. Chan, J. Fozard and P. Walsh, 1992. Estimation of prostate specific growth using serial PSA measurements in men with and without prostate disease. Cancer Res., 52: 3323-8.

Catalona, W., A. Partin, K. Slawin, M. Brawer, R. Flanigan, A. Patel, J. Richie, J. deKernion, P. Walsh, P. Scardino, P. Lange, E. Subong, R. Parson, G. Gasior, K. Loveland and P. Southwick, 1998. Use of the percentage free prostate-specific antigen to enhance differentiation of prostate cancer from benign prostatic disease: a prospective multicenter trial. JAMA 279: 1542-7.

Chan, J., M. Stampfer, E. Gionannucci, P. Gann, J. Ma, P. Wilkinson, C. Hennekens and M. Pollak, 1998. Plasma insulin-like growth factor-I and prostate cancer risk: a prospective study. Science, 279: 563-6.

Chan, J., M. Stampfer, J. Ma, P. Gann, J. Gaziano, M. Pollak and E. Giovannucci, 2002. Insulin-like growth factor I (IGF-1) and IGF binding protein-3 as predictors of advanced-stage prostate cancer. J Natl Cancer Inst 94: 1099-106.

Cohen, P., 1998. Serum insulin-like growth factor-1 levels and prostate cancer risk–interpreting the evidence. J Natl Cancer Inst., 90: 876-9.

Correale, M., A. Pagliarulo, G. Donatuti, F. Sturdà, A. Capobianco, V. Stigliani, M. Rizzello, S. Circhietta, F. Pignatelli, L. Leone, V. Frusciante, S. Modoni, and F. Schittulli, 1996. Preliminary clinical evaluation of free/total PSA ratio by the IMMULITE system. Int J Biol Markers., 11(1): 24-8.

Cutting, C., C. Hunt, J. Bland, A. Dalgleish and R. Kirby, 1999. Serum insulin-like growth factor-1 is not a useful marker of prostate cancer. BJU Int., 83: 996-9.

Elmlinger, M., M. Zwirner and W. Kuhnel, 2005. Stability of IGF-1 and IGFBP-3 measured by the immulite automated chemiluminescence assay system in different blood specimens. Clin lab., 51: 145-52.

Espana, F., M. Royo, M. Martínez, M. Enguídanos, C. Vera, A. Estellés, J. Aznar, J. Jiménez-Cruz and M. Heeb, 1998. Free and complexed prostate specific antigen in the differentiation of benign prostatic hyperplasia and prostate cancer: studies in serum and plasma samples. J Urol., 160: 2081-8.

Finne, P., A. Auvinen, H. Koistinen, W. Zhang, L. Maattanen, S. Rannikko, T. Teuvo Tammela, M. Seppala, M. Hakama and U. Stenman, 2000. Insulin-like growth factor-1 is not a useful marker of prostate cancer in men with elevated levels of prostate-specific antigen. J Clin Endocrinol Metab., 85: 2744-7.

Harman, S., E. Metter, M. Blackman, P. Landis and H. Carter, 2000. Serum levels of IGF-1, IGF-2, IGF-binding protein-3, and prostate-specific antigen as predictors of clinical prostate cancer. J Clin Endocrinol Metab., 85: 4258-85.

Huber, P., H. Schmid, G. Mattarelli, B. Strittmatter, G. van Steenbrugge and A. Maurer, 1995. Serum free PSA: isoenzymes in benign hyperplasia and cancer of the prostate. Prostate, 27: 212-9.

Ismail, H., M. Pollak, H. Behlouli, S. Tanguay, L. Begin and A. Aprikian, 2003. Serum insulin-like growth factor (IGF)-1 and IGF-binding protein-3 do not correlate with Gleason score or quantity of prostate cancer in biopsy samples. BJU Int., 92: 699-702.

Janssen, J., M. Wildhagen, K. Ito, B. Blijenberg, Van R. Schaik, M. Roobol, H. Pols, S. Lamberts and F. Schröder, 2004. Circulating free IGF-1, total IGF-1, and IGF binding protein-3 levels do not predict the future risk to develop prostate cancer: results of a case-control study involving 201 patients within a population-based screening with a 4-year interval. J Clin Endocrinol Metab., 89: 4391-6.

Jemal, A., R. Siegel, E. Ward, Y. Hao, J. Xu and M. Thun, 2009. Cancer Statistics, 2009. CA Cancer J Clin., 59: 225-49.

Kuriyama, M., M. Wang, C. Lee, L. Papsidero, C. Lillian, H. Inaji, N. Slack, T. Nishiura, G. Murphy and T. Chu, 1981. Use of human prostate-specific antigen in monitoring of prostate cancer. Cancer Res., 41: 3874-6.

LeRoith, D. and C. Roberts, 2003. The insulin-like growth factor system and cancer. Cancer Lett., 195: 127-37.

Lin, D., 2009. Beyond PSA: Utility of novel tumor markers in the setting of elevated PSA. Urologic Oncology, 27: 315-321.

Loeb, S. and W. Catalona, 2007. Prostate-specific antigen in clinical practice. Cancer Lett., 249: 30-9.

Mantzoros, C., A. Tzonou, L. Signorello, M. Stampfer, D. Trichopoulos and H. Adami, 1997. Insulin-like growth factor 1 in relation to prostate cancer and benign prostatic hyperplasia. Br J Cancer., 76: 1115-8.

Marszalek, M., J. Wachtera, A. Ponholzer, T. Leithac, M. Rauchenwald, and S. Madersbachera, 2005. Insulin-like growth factor 1, chromogranin A and PSA serum levels in prostate cancer patients and controls. Eur Urol., 48: 34-39.

Morgentaler, A., C. Bruning and W. DeWolf, 1996. Occult prostate cancer in men with low serum testosterone levels. JAMA 276(23): 1904-6.

Morris, J., L. George, T. Wu and N. Wald, 2006. IGFs and cancer: no role in screening. Evidence from the BUPA study and meta-analysis of prospective epidemiological studies. Br J Cancer., 95(1): 112-7.

Oesterling, J., S. Jacobsen, C. Chute, H. Guess, C. Girman, L. Panser and M. Lieber, 1993. Serum prostate-specific antigen in a community-based population of healthy men. Establishment of age specific reference ranges. JAMA 270: 860-4.

Ohori, M., J. Dunn and P. Scardino, 1995. Is prostate-specific antigen density more useful than PSA levels in the diagnosis of prostate cancer?. Urology, 46: 666-71.

Oliver, S., D. Gunnell, J. Donovan, T. Peters, R. Persad, D. Gillatt, A. Pearce, D. Neal, F. Hamdy and J. Holly, 2004. Screen-detected prostate cancer and the insulin-like growth factor axis: results of a population-based case-control study. Int J Cancer., 108: 887-92.

Papsidero, L., M. Wang, L. Valenzuela, G. Murphy and T. Chu, 1980. A prostate antigen in sera of prostate cancer patients. Cancer Res., 40: 2428-32.

Pollak, M., 2001. Insulin-like growth factor and prostate cancer. Epidemiol Rev, 23: 59-66.

Roddam, A., N. Allen, P. Appleby, T. Key, L. Ferrucci and H. Carter, 2008. Insulin-like growth factors, their binding proteins and prostate cancer risk: analysis of individual patient data from 12 prospective studies. Ann Intern Med., 149(7): 461-71.

Rowlands, M., D. Gunnell, R. Harris, L. Vatten, J. Holly and R. Matin, 2009. Circulating insulin-like growth factor peptides and PCa risk: a systematic review and meta-analysis. Int J Cancer., 124(10): 2416-29.

Semjonow, A., G. De Angeles, F. Oberpenning, H. Schmidt, B. Brandt and L. Hertle, 2000. The clinical impact of different assays for prostate specific antigen. BJU Int., 86: 590-7.

Shi, R., H. Berkel and H. Yu, 2001. Insulin-like growth factor-I and prostate cancer: a meta-analysis. Br J Cancer., 85(7): 991-6.

Stattin, P., A. Bylund, S. Rinaldi, C. Biessy, H. Dechaud, U. Stenma, L. Egevad, E. Riboli, G. Hallmans and Kaaks, R., 2000. Plasma insulin-like growth factor-I, insulin-like growth factor-binding proteins, and prostate cancer risk: a prospective study. J Natl Cancer Inst., 92: 1910-7.

Unal, D., J. Sedelaar, R. Aarnink, van G. Leenders, H. Wijkstra, F. Debruyne and de la J. Rosette, 2000. Three-dimensional contrast-enhanced power Doppler ultrasono-graphy and conventional examination methods: the value of diagnostic predictors of prostate cancer. BJU Int., 86(1): 58-64.

Wolk, A., C. Mantzoros, S. Andersson, R. Bergstrom, L. Signorello, P. Lagiou, H. Adami and D. Trichopoulos, 1998. Insulin-like growth factor 1 and prostate cancer risk: a population-based, case-control study. J Natl Cancer Inst., 90: 911-5.

Zlotta, A., B. Djavan, M. Marberger and C. Schulman, 1997. Prostate-specific antigen density of the transition zone: a new effective parameter for prostate cancer prediction. J Urol., 157: 1315-21.