



European Association of Urology



Prostate Cancer

The Clinical Potential of Pretreatment Serum Testosterone Level to Improve the Efficiency of Prostate Cancer Screening

Masashi Yano, Takashi Imamoto*, Hiroyoshi Suzuki, Satoshi Fukasawa, Satoko Kojima, Akira Komiya, Yukio Naya, Tomohiko Ichikawa

Department of Urology, Graduate School of Medicine, Chiba University, Chiba, Japan

Article info

Article history:

Accepted August 20, 2006

Published online ahead of print on September 12, 2006

Keywords:

Prostate cancer
 Testosterone
 Prostate biopsy
 Gleason score



www.eu-acme.org/europeanurology

Please visit

www.eu-acme.org/europeanurology to read and answer questions on-line. The EU-ACME credits will then be attributed automatically.

Abstract

Objectives: The aim of the present study was to evaluate the clinical value of the pretreatment serum testosterone (T) level as a potential predictor of prostate cancer risk in screening for prostate cancer.

Materials and methods: The subjects were 420 patients suspected of having prostate cancer who underwent prostate biopsy, and whose pretreatment T levels were recorded. We checked for association between the presence of prostate cancer and the following clinical factors: pretreatment serum T level, age, pretreatment prostate-specific antigen (PSA) level, digital rectal examination findings, ratio of free to total PSA, prostate volume, and PSA density (PSAD).

Results: Overall, there was no significant difference in mean pretreatment T level between patients diagnosed with cancer (3.9 ± 2.4 ng/ml) and patients diagnosed with benign prostate disease (BPD; 3.7 ± 1.7 ng/ml); diagnosis was based on prostate biopsy. However, among patients with PSA <10 ng/ml, the pretreatment T level was significantly higher in patients diagnosed with prostate cancer (4.2 ± 2.6 ng/ml) than in patients diagnosed with BPD (3.6 ± 1.4 ng/ml) ($p = 0.007$); a similar trend was observed among patients with PSAD <0.15 ng/ml/cc. Multivariate analysis indicated that pretreatment T level was an independent significant predictor of positive prostate biopsy ($p = 0.020$). Additionally, the serum T level was significantly lower in patients with a Gleason score ≥ 7 (3.7 ± 2.1 ng/ml) versus a score <7 (4.2 ± 1.7 ng/ml) ($p = 0.030$). Also, serum T levels were significantly higher in well-differentiated prostate cancer (4.8 ± 2.1 ng/ml) versus moderately differentiated (3.8 ± 1.3 ng/ml) or poorly differentiated (3.7 ± 1.4 ng/ml) ($p < 0.01$).

Conclusions: Among relatively low-risk patients, serum T level was an independent significant predictor of positive prostate biopsy, suggesting that the efficiency of prostate cancer screening can be improved by including measurement of serum T level.

© 2006 European Association of Urology. Published by Elsevier B.V. All rights reserved.

* Corresponding author. Department of Urology, Chiba University Graduate School of Medicine, 1-8-1 Inohana, Chuo-ku, Chiba 260-8670, Japan. Tel. +81 43 226 2134; Fax: +81 43 226 2136. E-mail address: t-imamo@pg7.so-net.ne.jp (T. Imamoto).

1. Introduction

Prostate cancer is the result of a complex and unclear interaction between ageing, genetic factors, hormones, growth factors, and environment. Hormones, particularly androgens, are believed to play a key role in the etiology of prostate cancer because they are necessary for growth and maintenance of the prostate gland [1,2].

Studies comparing circulating male sex hormone levels between subjects with and without prostate cancer have produced widely varying results. Gann et al. [3] found a statistically significant increasing risk of prostate carcinoma with increasing levels of testosterone and an inverse trend in this risk with increasing levels of sex hormone-binding globulin (SHBG). On the other hand, Ritva et al. [4] reported that there was no association between serum testosterone, SHBG, or androstenedione concentrations and the occurrence of subsequent prostate carcinoma.

In prostate cancer, prostate-specific antigen (PSA) measurement has become the most valuable tool for the diagnosis and treatment of patients with prostate cancer. However, discriminating between prostate cancer and benign prostate disease (BPD) is difficult, particularly in patients with intermediate PSA levels between 4.1 and 10 ng/ml. PSA protein is expressed in the normal and malignant prostate gland; thus, it is not a prostate cancer-specific protein. Therefore, a more sensitive and specific diagnostic test is necessary to detect prostate cancer. Several PSA derivatives, such as the ratio of free to total PSA (F/T ratio) and PSA density (PSAD), have been examined in an attempt to improve the efficiency of prostate biopsy [5–8].

The usefulness of the pretreatment serum level of testosterone (T) as a predictor of prostate cancer in Japanese patients has not previously been determined. In the present study of 420 Japanese patients suspected of having prostate cancer who underwent prostate biopsy, we investigated the value of the T level for predicting the presence of prostate cancer. In addition, we checked for relationships between the pretreatment serum T level and several clinical and pathologic factors.

2. Materials and methods

The subjects were 420 patients (mean age: 68.3 ± 7.7 yr; range: 42–89) suspected of having prostate cancer who underwent prostate biopsy at Chiba University Hospital between January 2001 and May 2005, and whose pretreatment T levels were recorded. Patients who received any

hormonal treatment before biopsy were excluded from the study.

Blood samples were taken in the morning. Serum T level was measured by radioimmunoassay with the use of the DPC total testosterone kit (Nippon DPC Corp, Tokyo, Japan). Serum-free and total PSA levels were measured with the use of the Architect PSA kit (Abbott Laboratories, Chicago, IL, USA).

Transrectal ultrasound (TRUS)-guided systematic biopsy of the prostate was performed with the use of a scanner and a 7-MHz transducer. The prostate was scanned in the transverse and sagittal planes with the patient in the lithotomy position. Prostate volume was determined by using the formula for a prolate ellipsoid ($\text{width} \times \text{length} \times \text{height} \times 0.523$).

Random systematic biopsies were performed with the use of an automatic biopsy gun and an 18-gauge needle with TRUS guidance. Basically, biopsies comprised six peripheral zones and two transition zones; additional biopsies were obtained if the ultrasound images or digital rectal examination (DRE) findings indicated suspect areas. The histologic grade was determined by using the World Health Organization classification and Gleason grading system.

Statistical significance was assessed by using the Student *t* test and one-way analysis of variance. Univariate or multivariate analysis of predictors of prostate cancer was

Table 1 – Overall pretreatment characteristics of the 420 patients

Variable	No. of patients (%)
Total testosterone (ng/ml)	
<2.0	24 (6.0)
2.0–2.9	94 (23.3)
3.0–3.9	136 (33.9)
4.0–4.9	89 (22.0)
>4.9	59 (14.7)
Mean/median	
3.786/3.69	
Age (yr)	
<60	49 (11.6)
60–64	75 (17.8)
65–69	112 (26.6)
70–74	100 (23.8)
>74	84 (20)
Mean/median	
68.3/69	
PSA (ng/ml)	
0–4	19 (4.5)
4.1–10	188 (28.2)
10.1–20	92 (22.0)
>20	119 (28.4)
Unknown	1 (0.002)
Mean/median	
10.18/10.3	
DRE	
Positive	139 (33.1)
Negative	100 (23.8)
Unclear	181 (43.1)

DRE: digital rectal examination; PSA: prostate-specific antigen.

Table 2 – Pathologic factors of the 216 patients diagnosed with prostate cancer

Variable	No. of patients (%)
Pathologic Gleason score	
≤6	77 (35.8)
7	66 (31.8)
8–10	64 (29.6)
Pathologic differentiation	
Well differentiated	32 (15.9)
Moderately differentiated	92 (45.8)
Poorly differentiated	77 (38.3)

performed by using a logistic regression model. A *p* value <0.05 was considered to indicate significance.

3. Results

The general characteristics of all 420 patients are summarized in Table 1. The pathologic Gleason score and pathologic differentiation of patients diagnosed with prostate cancer are shown in Table 2. The mean Gleason score was 7, and 77 patients (35.8%) had a Gleason score <7. Table 3 shows univariate analysis of the relationship of pretreatment T to clinical and pathologic factors. There was no significant difference in mean pretreatment T level between patients diagnosed with cancer (3.9 ng/ml) and patients diagnosed with BPD (3.7 ng/ml); diagnosis was based on prostate biopsy. Similarly, there was no significant association of pretreatment T level with age, pretreatment PSA, DRE findings, or ratio of free to total PSA (F/T ratio). However, results of the analysis using Pearson correlation coefficient showed that pretreatment T level was significantly associated with PSAD (*p* = 0.010, *r* = 0.099) and prostate volume (*p* = 0.002, *r* = −0.101). There was a significant association between low pretreatment T levels and large prostate volume (*p* = 0.0145, serum T level = −0.007 × prostate volume + 4.151).

Among patients with a PSA <10 ng/ml, the pretreatment T level was significantly higher in patients diagnosed with prostate cancer (4.2 ng/ml) than in patients diagnosed with BPD (3.6 ng/ml); a similar trend was observed among patients with a PSAD <0.15 ng/ml/cc (Table 3).

In addition, pretreatment T levels were significantly associated with pathologic Gleason score and tumour grade. The serum T level was significantly lower in patients with a Gleason score ≥7 than in patients with a Gleason score <7. Also, serum T levels were significantly higher in patients with well-differentiated prostate cancer than in other patients (Table 4).

Univariate analysis using a logistic regression model of relationships between selected factors and prostate cancer risk in all patients indicated that all selected factors other than serum T level (pretreatment serum level of PSA, age, presence of nodule, F/T ratio, prostate volume, and PSAD) were significant predictors of positive prostate biopsy (not shown). On the other hand, among patients with a PSA <10 ng/ml, only serum T level (*p* = 0.007) and F/T ratio (*p* = 0.050) were significant predictors of positive prostate biopsy (Table 5).

Table 6 shows a multivariate analysis of the relationship of positive prostate biopsy to serum T level and F/T ratio, according to the logistic regression analysis of patients with a PSA <10 ng/ml. This analysis indicates that pretreatment T level was an independent significant predictor of positive prostate biopsy (*p* = 0.020).

In addition, we analysed the positive rate of prostate biopsy at various cutoff values. As a result, in patients with a PSA <10 ng/ml, the positive rate of prostate biopsy in patients with serum T levels ≥5.5 ng/ml was significantly higher than that in patients with serum T levels <5.5 ng/ml (*p* = 0.040, 57.8% vs. 32.3%). This serum T level was threshold

Table 3 – Univariate analysis of relationship of pretreatment testosterone levels with pathologic diagnosis in 2 patient subgroups

Subgroups	Diagnosis	Testosterone (ng/ml)			<i>p</i> value
		Mean	Median	Range	
PSA (ng/ml) <10	Cancer	4.2	3.855	0.90–9.35	0.008
	Not cancer	3.63	3.650	0.10–8.56	
PSAD (ng/ml/cc) <0.15	Cancer	4.42	4.12	1.83–6.91	0.028
	Not cancer	3.67	3.74	1.89–6.81	

PSA: prostate-specific antigen; PSAD: prostate-specific antigen density.

Table 4 – Univariate analysis of relationship of pretreatment testosterone levels with clinical and pathologic factors

Variable	Testosterone (ng/ml)			p value
	Mean	Median	Range	
Diagnosis				0.090
Cancer	3.90	3.725	0.90–12.7	
Not cancer	3.66	3.650	0.10–8.56	
DRE				0.806
Positive	3.89	3.670	0.09–8.56	
Negative	3.75	3.735	0.16–12.7	
Pathologic Gleason score				0.030
≤6	4.21	3.95	0.90–12.7	
7–10	3.73	3.62	0.09–9.35	
Pathologic differentiation				<0.010*
Well differentiated	4.85	4.355	1.39–12.7	
Moderately differentiated	3.80	3.68	0.90–9.35	
Poorly differentiated	3.71	3.54	0.09–7.74	

DRE: digital rectal examination.
* Well differentiated versus moderately, poorly differentiated, or both.

Table 5 – Univariate analysis of relationship between selected factors and positive prostate biopsy in patients with PSA <10 ng/ml, according to the logistic regression model

Variable	Relative HR	95%CI	p value
PSA (ng/ml)	1.150	0.967–1.263	0.136
F/T ratio (%)	0.964	0.928–1.001	0.050
DRE	1.679	0.768–3.674	0.197
Age	1.022	0.983–1.063	0.277
Total testosterone (ng/ml)	1.310	1.068–1.605	0.007

CI: confidence interval; DRE: digital rectal examination; F/T: ratio of free to total PSA; HR: hazard ratio; PSA: prostate-specific antigen.

with 90% diagnostic specificity in patients with a PSA <10 ng/ml.

4. Discussion

Prostate cancer is one of the most common cancers among Western populations, and its incidence is increasing in Asia. Prostatic development and growth depend on androgenic stimulation. In 1941, Huggins et al. [9] published the first report of a relationship between serum T and prostate cancer. They reported that appreciable clinical improvement occurred in 15 of 21 patients who were

diagnosed with advanced or metastatic prostate carcinoma and were treated with castration, and that, in 3 patients who were injected with testosterone propionate, serum acid phosphatase level and patients' pain increased. Currently, the association between serum T and prostate cancer is incompletely understood.

Some studies suggest that high testosterone levels are associated with increased risk of prostate cancer. A study by Gann et al. [3] suggests that high levels of circulating testosterone and low levels of SHBG are associated with increased risk of prostate cancer. Terrence et al. [10] performed a meta-analysis of all previously published studies of

Table 6 – Multivariate analysis of significant predictors of positive prostate biopsy in patients with PSA <10 ng/ml, according to the logistic regression model

Variable	Relative HR	95%CI	p value
F/T ratio (%)	0.964	0.928–1.002	0.558
Total testosterone (ng/ml)	1.311	1.038–1.656	0.020

CI: confidence interval; F/T: ratio of free to total PSA; HR: hazard ratio.

hormonal predictors of risk for prostate cancer. When their meta-analysis was restricted to studies in which mutual adjustment was performed for all measured serum hormones, age, and body mass index, the results indicated that men with total testosterone levels in the highest quartile are 2.34 times more likely to develop prostate cancer than other men.

On the other hand, several studies indicate that testosterone levels are associated with clinical prognosis, pathologic Gleason score, and pathologic tumour stage. Ishikawa et al. [11] and Ribeiro et al. [12] reported that patients with pretreatment testosterone levels <3 ng/ml had shorter intervals free of progression than patients with pretreatment testosterone levels >3 ng/ml. Hoffman et al. [13] observed that prostate cancer patients with low free serum testosterone levels (≤ 1.5 ng/dl) had more extensive cancer and higher Gleason scores. Massengill et al. [14] and Imamoto et al. [15] found that the mean pretreatment T level was significantly lower in patients with non-organ-confined prostate cancer (pT3–T4, N1) than in patients with organ-confined cancer (pT2). They also suggested that a lower pretreatment T level appears to be predictive of extraprostatic disease in patients with localized prostate cancer.

There have been many attempts to characterize the influence of the prostate on serum hormone levels. Schatzl et al. [16,17] reported that men with prostate cancer had lower serum levels of human luteinizing hormone, human follicle-stimulating hormone, estradiol, and testosterone than patients with benign prostatic hyperplasia.

What are the mechanisms that lead to the endocrine changes observed in men with prostate cancer? A study by Miller et al. [18] indicates that the prostate (and particularly prostate cancer cells) secretes proteins that exert negative feedback on the hypothalamic-pituitary-gonadal hormone axis. There have been several studies of serum total and free T levels before and after radical prostatectomy [19]. In those studies, serum total and free T levels were significantly elevated after surgery, and patients with high-grade prostate cancer had significantly lower levels of both total and free T than patients with moderate-grade prostate cancer. Those results suggest that any inhibitory factors produced in the prostate are mainly produced by prostate cancer cells. Similarly, in the present study, we found that pretreatment T levels were significantly lower in patients with a Gleason score ≥ 7 than in patients with a Gleason score <7 .

It has been suggested that inhibin may play a role in reducing testosterone levels. Inhibin produced in

the testes and prostate inhibits production and/or secretion of pituitary gonadotropins [20–22]. Studies of inhibin in the prostate have been limited to animal prostates; consequently, the role of inhibin in human prostate tissue is not well defined.

In the present study, there was no significant difference in mean pretreatment T level between the patients diagnosed with cancer (by prostate biopsy) and the patients diagnosed with BPD. However, among patients with a PSA <10 ng/ml, the pretreatment T level was significantly higher in patients diagnosed with prostate cancer than in patients diagnosed with BPD; a similar trend was observed among patients with a PSAD <0.15 ng/ml/cc.

The present results suggest the following sequence of events. The serum T level is higher during the early stages of prostate cancer than in the time before the development of prostate cancer. However, as the malignancy and stage of prostate cancer progress, prostate cancer cells produce one or more factors (e.g., inhibin) that exert negative feedback on the hypothalamic-pituitary-gonadal hormone axis. This sequence of events would explain the present finding that among patients with a PSA <10 ng/ml (i.e., excluding patients in advanced stages of prostate cancer), the pretreatment T level was significantly higher in patients diagnosed with prostate cancer than in patients diagnosed with BPD, and that among all 420 patients (i.e., including patients with progressive cancer), there was no significant difference in the pretreatment T level between patients diagnosed with prostate cancer and patients diagnosed with BPD.

The present results suggest that among patients with a PSA <10 ng/ml (i.e., patients who are either cancer-free or are in the early stages of prostate cancer), the pretreatment T level is a useful predictor of prostate cancer. They also suggest that the pretreatment T level has a potential for predicting pathologic features such as the Gleason score and differentiation of the prostate cancer.

This study has the limitations of its retrospective nature and small population size. Further study with large clinical trials is needed to construct the predicting model composed by the pretreatment T level and other factors.

5. Conclusions

In the present study, there was no significant difference in the mean pretreatment T level between all patients diagnosed with cancer and all patients diagnosed with BPD by prostate biopsy. However,

among patients with a PSA <10 ng/ml or a PSAD <0.15 ng/ml/cc, the pretreatment T level was significantly higher in patients diagnosed with prostate cancer than in patients diagnosed with BPD. The results of multivariable analysis using a logistic regression model for patients with a PSA <10 ng/ml indicated that serum T level was an independent significant predictor of positive prostate biopsy, suggesting that the efficiency of prostate cancer screening of relatively low-risk patients can be improved by including measurement of serum T level.

Acknowledgements

This work was supported by a Grant-in-Aid from the Ministry of Education, Culture, Sports, Science and Technology (Contract grant numbers: 14207061, 16591582, 16689026 and 17791006), the Japanese Foundation for Prostate Research (2004), and the Japanese Urological Association (2006).

References

- [1] Chan JM, Stampfer MJ, Giovannucci EL. What causes prostate cancer? A brief summary of the epidemiology. *Semin Cancer Biol* 1998;8:263–73.
- [2] Ekman P. Genetic and environmental factors in prostate cancer genesis: identifying high-risk cohorts. *Eur Urol* 1999;35:362–9.
- [3] Gann PH, Hennekens CH, Ma J, Longcope C, Stampfer MJ. Prospective study of sex hormone levels and risk of prostate cancer. *J Natl Cancer Inst* 1998;88:1118–26.
- [4] Ritva H, Kimmo A, Markku HV, et al. Serum testosterone and sex hormone-binding globulin concentrations and the risk of prostate carcinoma. *Cancer* 1999;86:312–5.
- [5] Catalona WJ, Southwick PC, Slawin KM, et al. Comparison of percent free PSA, PSA density, and age-specific PSA cutoffs for prostate cancer detection and staging. *Urology* 2000;56:255–60.
- [6] Kikuchi E, Nakashima J, Ishibashi M, et al. Prostate specific antigen adjusted for transition zone volume: the most powerful method for detecting prostate carcinoma. *Cancer* 2000;89:842–9.
- [7] Brawer MK, Cheli CD, Neaman IE, et al. Complexed prostate specific antigen provides significant enhancement of specificity compared with total prostate specific antigen for detecting prostate cancer. *J Urol* 2000;164:1671–2.
- [8] Ito K, Yamamoto T, Kubota Y, et al. Usefulness of age-specific reference range of prostate-specific antigen for Japanese men older than 60 years in mass screening for prostate cancer. *Urology* 2000;56:278–82.
- [9] Huggins C, Stevens RE, Hodges CV. Studies on prostatic cancer: II. The effect of castration on advanced carcinoma of the prostate gland. *Arch Surg* 1941;43:209–12.
- [10] Shaneyfelt T, Husein R, Bublely G, Mantzoros CS. Hormonal predictors of prostate cancer: a meta-analysis [related articles]. *J Clin Oncol* 2000;18:847–53.
- [11] Ishikawa S, Soloway MS, Van der Zwaag R, Todd B. Prognostic factors in survival free progression after androgen deprivation therapy for treatment of prostate cancer. *J Urol* 1989;141:1139–42.
- [12] Ribeiro M, Ruff P, Falkson G. Low testosterone and a younger age predict a poor outcome in metastatic prostate cancer. *Am J Clin Oncol* 1997;20:605–8.
- [13] Hoffmann M, De Wolf W, Morgenthaler A. Is low serum free testosterone a marker for high grade prostate cancer? *J Urol* 2000;163:824–7.
- [14] Massengill JC, Sun L, Moul JW, et al. Pretreatment total testosterone level predicts pathological stage in patients with localized prostate cancer treated with radical prostatectomy. *J Urol* 2003;169:1670–5.
- [15] Imamoto T, Suzuki H, Fukasawa S, et al. Pretreatment serum testosterone level as a predictive factor of pathological stage in localized prostate cancer patients treated with radical prostatectomy. *Eur Urol* 2005;47:308–12.
- [16] Schatzl G, Reiter WJ, Thürridl T, et al. Endocrine patterns in patients with benign and malignant prostatic disease. *Prostate* 2000;44:219–24.
- [17] Schatzl G, Madersbacher S, Thürridl T, Waldmüller J, Kramer G, Haitel A, et al. High-grade prostate cancer is associated with low serum testosterone levels. *Prostate* 2001;47:52–8.
- [18] Miller LR, Partin AW, Chan DW, et al. Influence of radical prostatectomy on serum hormone levels. *J Urol* 1988;160:449–53.
- [19] Zhang PL, Rosen S, Veeramachaneni R, Kao J, DeWolf WC, Bublely G. Association between prostate cancer and serum testosterone levels. *Prostate* 2002;53:179–82.
- [20] Lokeshwar BL, Hurkadli KS, Sheth AR, Block NL. Human prostatic inhibin suppresses tumor growth and inhibits clonogenic cell survival of a model prostatic adenocarcinoma, the Dunning R3327G rat tumor. *Cancer Res* 1993;53:4855–9.
- [21] Risbridger G, Thomas T, Gurusingham CJ, McFarlane JR. Inhibin-related proteins in rat prostate. *J Endocrinol* 1996;149:93–9.
- [22] Ying SY, Zhang Z, Huang G. Expression and localization of inhibin/activin subunits and activin receptors in the normal rat prostate. *Life Sci* 1997;60:397–401.