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Serum level of follicle-stimulating hormone is associated with extraprostatic extension of prostate cancer

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Purpose: To determine whether serum follicle-stimulating hormone (FSH) can be used to predict the aggressiveness of prostate cancer prior to radical prostatectomy.
Methods: Ninety-six patients who underwent radical prostatectomy for biopsy proved cT1c-T2N0M0 prostate cancer between 2003 and 2008 were identified for retrospective analysis. Using univariate regression analysis, potential variables of extraprostatic tumor extension were identified, including prostate-specific antigen (PSA), luteinizing hormone, FSH, testosterone, biopsy findings, and age. These variables of interest were analyzed by logistic and linear regression analysis to determine if serum FSH is predictive of extraprostatic extension.
Results: Extraprostatic extension was pathologically confirmed in 18 of 96 patients (18.8%). Statistical analysis confirmed that serum FSH was significantly associated with extraprostatic extension ($P=0.04$). However, age, PSA level, Gleason score, number of tumors, and serum testosterone level were not found to be independent predictors of extraprostatic extension.
Conclusions: Selective expression of FSH receptor on the surface of blood vessels of prostate cancers has recently been reported. Measuring serum FSH preoperatively in patients with prostate cancer may provide clinically relevant information about extraprostatic spread of tumor.

Keywords: Prostate neoplasms, FSH, FSH receptors

INTRODUCTION

In patients with prostate cancer, low testosterone level has been shown to be associated with advanced tumor stage at presentation, positive surgical margins, high Gleason score, and worse overall survival [1-5]. We have previously reported that low serum testosterone level is a significant predictor of high-grade prostate cancer among patients referred for prostate biopsy [6]. Multivariate logistic regression analysis also revealed statistically significant differences in serum levels of follicle-stimulating hormone (FSH) in patients with and without prostate cancer [6].

The hypothalamo-pituitary-gonadal axis regulates the production of testosterone through luteinizing hormone (LH) and FSH secretion. FSH is a key hormone in reproduction. It stimulates sertoli cell proliferation in immature testes and maintains normal spermatogenesis in adults [7]. FSH binds to FSH receptor, which is expressed in both testicular sertoli cells and ovarian granulosa cells. FSH receptor is a member of the superfamily of receptors, which is characterized by

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the presence of seven transmembrane structures coupled to G-proteins. Although FSH receptor expression has been detected in prostate tissues, including prostate cancer, the direct biological function of FSH in prostate carcinogenesis and prostate cancer progression has not been well characterized [8].

Recently, FSH receptor has been detected on the surface of blood vessels in a wide range of tumors, including prostate [9]. Although signal transduction through G-protein-coupled receptors is a major biochemical pathway involved in the regulation of cell proliferation by growth factors, the exact biological function of FSH signaling in tumor vessels remains unknown. FSH receptor expression by endothelial cells may be associated with the proliferation and invasiveness of cancerous cells. In this study, we investigated the association between serum FSH levels and extraprostatic extension, based on the hypothesis that FSH/FSH receptor signaling may play a role in regulating the growth and invasiveness of prostate cancers.

MATERIALS AND METHODS

We reviewed, retrospectively, the medical records of all prostate cancer patients who underwent radical prostatectomy at Teikyo University School of Medicine Hospital from January 2003 through November 2008. Patients eligible for this study were unselected and accrued consecutively. This review identified 96 patients with biopsy and imaging proved cT1c-T2N0M0 prostate cancer who underwent radical prostatectomy. All patients gave written informed consent, and approval was obtained from the hospital Research Ethics Board. The histopathological evaluation was performed by a single pathologist (Y.T.), and none of the patients had prostate cancer-specific treatment before this study.

Serum prostate-specific antigen (PSA) levels were measured by chemiluminescence enzyme immunoassay with a Lumipulse kit (Fujirebio, Tokyo, Japan). Serum testosterone levels were measured using the Architect testosterone kit (Abbott Japan, Tokyo, Japan). LH and FSH levels were measured using electrochemiluminescence immunoassay with the ECLusys kit (Roche Diagnostics, Basel, Switzerland).

We performed univariate logistic regression analysis to screen for prognostic variables of extraprostatic extension. The following potential factors were analyzed: age, tumor size (maximal length of tumor of radical prostatectomy specimen), number of tumors of radical prostatectomy specimen, serum PSA, LH, FSH, and testosterone levels. Using important prognostic factors and variables found to be statistically significant on univariate logistic regression analyses, we then performed multivariate logistic regression analysis to investigate the association between serum level of FSH and extraprostatic extension.

LH and FSH were evaluated separately to avoid potential confounding due to multicollinearity because of the high correlation between LH and FSH. We used log-transformed values of serum PSA, LH, FSH, testosterone levels, and tumor size because of their nonnormal distribution. Similar analyses were performed with linear regression analysis to assess the association between serum FSH levels and tumor size. Since using either untransformed or log-transformed tumor size did not affect the statistical significance on linear regression analysis, we reported the result of using untransformed tumor size, as are more clinically meaningful.

A P-value of <0.05 was considered to be statistically significant. Analyses were performed using SAS 9.1.3 (SAS Institute Inc., Cary, NC, USA).

RESULTS

The characteristics of the study population with radical prostatectomy are shown in Table 1. A single pathologist (Y.T.) analyzed the cohorts with respect to pathologic stage, tumor numbers and tumor size (maximum length of tumor). Univariate logistic regression analysis revealed statistically significant differences in PSA ($P=0.01$), tumor size ($P<0.001$), LH ($P=0.004$), FSH ($P=0.01$), and Gleason score ($P=0.01$) in patients with and without extraprostatic extension (Table 2). On the other hand, there were no statistically significant differences in testosterone levels between these groups ($P=0.22$). According to the multivariate logistic regression analysis, there were statistically significant differences in selected variables, such as tumor size ($P=0.04$) and FSH ($P=0.04$) (Table 3). In

Table 1. Comparison between the group with and without extraprostatic extension

Variable	Total patients	Patients with capsule invasion	Patients without capsule invasion
No.	96	18	78
Age (yr), median (range)	64.3 (43.0–80.0)	65.2 (43.0–75.0)	64.1 (48.0–80.0)
No. of tumors	2.28	1.94	2.36
Tumor size (mm)	9.95	18.88	7.75
PSA	9.83	13.49	8.99
LH	8.22	12.90	7.17
FSH	13.74	23.67	11.57
TST	449.18	412.78	456.71
Gleason score	6.88	7.50	6.73

PSA, prostate-specific antigen; LH, luteinizing hormone; FSH, follicle-stimulating hormone; TST, testosterone.

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Table 2. Logistic regression analysis evaluating risk of extraprostatic extension (single regression)

Variable	OR (95% CI)	*P*-value
Age	1.03 (0.95–1.14)	0.540
No. of tumors	0.89 (0.66–1.20)	0.450
Gleason score	1.815 (1.14–2.88)	0.010
Log PSA	2.78 (1.23–6.3)	0.010
Log LH	6.41 (1.8–22.9)	0.004
Log FSH	4.04 (1.5–10.84)	0.010
Log TST	0.37 (0.07–1.84)	0.220
Log tumor size	17.85 (3.75–84.85)	<0.001

OR, odds ratio; CI, confidence interval; PSA, prostate-specific antigen; LH, luteinizing hormone; FSH, follicle-stimulating hormone; TST, testosterone.

addition, we analyzed each factor associated with tumor size. On multivariate linear regression analysis using the variables to be statistically significant on the univariate linear regression analysis, there were statistically significant differences in FSH ($P=0.01$) and PSA ($P<0.001$) for tumor size (Table 4). On the basis of these results, we determined that FSH was the independent variable with predictive value for extraprostatic extension and tumor size.

Table 3. Logistic regression analysis evaluating FSH and risk of extraprostatic extension (multiple regression)

Variable	OR (95% CI)	*P*-value
Gleason score	2.04 (0.75–5.54)	0.16
Log PSA	0.65 (0.13–3.29)	0.60
Log tumor size	23.93 (1.10–521.36)	0.04
Log FSH	4.47 (1.09–18.31)	0.04

Luteinizing hormone and FSH were evaluated separately to avoid potential confounding due to multicollinearity.
FSH, follicle-stimulating hormone; OR, odds ratio; CI, confidence interval; PSA, prostate-specific antigen.

Table 4. Linear regression analysis evaluating association of tumor size (multiple regression)

Variable	Parameter (95% CI)	*P*-value
Gleason score	1.51 (0.02–3.00)	0.050
No. of tumors	–0.17 (–0.91–0.58)	0.660
Log FSH	2.82 (0.72–4.92)	0.010
Log PSA	5.72 (3.40–8.02)	<0.001

Luteinizing hormone and FSH were evaluated separately to avoid potential confounding due to multicollinearity.
CI, confidence interval; FSH, follicle-stimulating hormone; PSA, prostate-specific antigen.

DISCUSSION

Previous studies have demonstrated the presence of FSH receptor expression in tumor cells of prostate cancer by immunohistochemical analysis [10,11] and in some cell lines by reverse transcription-polymerase chain reaction [12]. Recently, FSH receptor has also been detected in vessels adjacent to the tumor cells of prostate cancer [9]. These results suggest that FSH receptor is activated, or signaled, by its ligand FSH, and that this signaling may have an important role in prostate carcinogenesis and prostate cancer progression. In the present study, we showed that FSH is a significant marker of extraprostatic extension in human prostate cancer. The finding of increased serum FSH in prostate cancer patients who have invasive tumors allows us to hypothesize that FSH signaling is involved in prostate cancer progression and in the development of extraprostatic spread of tumor. It was previously shown that binding of FSH and FSH receptor in ovarian granulosa cells induces an increase in hypoxia inducible factor 1 protein levels, which leads to up-regulation of vascular endothelial growth factor [13]. This result suggests that FSH signaling in prostate cancer cells may promote angiogenesis surrounding prostate tumors.

To determine the precise role of FSH/FSH receptor signaling in prostate cancer, it is necessary to investigate the invasive potential of human prostate cancer cell lines that express FSH receptor. Our own preliminary data demonstrate that prostate cancer cell lines 22Rv1, LNCaP, and PC-3 express FSH receptor (unpublished data). It had been previously reported that FSH stimulates the growth of prostate cancer in the PC-3 cell line [11]. Further study has the potential to elucidate the biological role of FSH signaling in prostate cancer cells.

The next question one has to ask is what is the source of elevated serum FSH in patients with prostate cancer? One possibility for the observed increase in FSH production is stimulation of the anterior pituitary gland through the hypothalamo-pituitary-gonadal axis. Testosterone reduces FSH production by decreasing the hypothalamic secretion of gonadotropin-releasing hormone, which, in turn, inhibits pituitary production of FSH [8]. In other words, when testosterone is decreased during the progression of prostate cancer, the negative feedback regulatory pathway increases the secretion of FSH in the pituitary gland. In this study, however, we did not see any statistically significant differences in testosterone levels between patients with and without extraprostatic extension. The other possibility is that the observed increase in FSH is produced by the prostatic epithelial cells. In a previous study, the expression of FSH in human prostate cancer tissues was detected by immunohistochemistry, but the cancerous glands stained heterogeneously [14]. The most interesting finding was that prostate cancer cells in metastatic lymph nodes stained for FSH but adjacent normal tissues were negative [14].

In conclusion, in this study, we demonstrate that measuring serum FSH in prostate cancer patients might provide clinically relevant information about extraprostatic extension of tumor. Finding a more sensitive biomarker for the early detection of prostate cancer remains a priority. Information about the potential for extraprostatic extension of tumor would be particularly useful in weighing the option of radical prostatectomy. The question remains, how precisely does FSH contribute to prostate cancer progression? Although further study is required, we postulate that blocking FSH and/or FSH receptor signaling may be a new strategy in the treatment of prostate cancer patients.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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