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Prostate-Specific Antigen fluctuation: what does it mean in diagnosis of prostate cancer?

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ABSTRACT

Objective: To investigate whether prostate-specific antigen (PSA) fluctuation correlates with a prostate cancer and to assess whether PSA fluctuation could be used for diagnosis of prostate cancer.
Materials and Methods: Our study included 229 patients who were performed a prostate biopsy (non-cancer group, 177; prostate cancer group, 52). Enrolled patients were provided twice PSA tests within 6 months. PSA fluctuation (%/month) was defined as a change rate of PSA per a month. Independent t test was used to compare between two groups. Receiver operator characteristic curve was used to assess the availability as a differential diagnostic tool and the correlation. Simple linear regression was performed to analyze a correlation between PSA fluctuation and other factors such as age, PSA, PSA density, and prostate volume.
Results: There were significant differences in PSA, PSA density, percentage of free PSA, and PSA fluctuation between two groups. PSA fluctuation was significantly greater in non-cancer group than prostate cancer group (19.95±23.34%/month vs 9.63±8.57%/month, P=0.004). The most optimal cut-off value of PSA fluctuation was defined as 8.48%/month (sensitivity, 61.6%; specificity, 59.6%; AUC, 0.633; P=0.004). In a simple linear regression model, only PSA level was significantly correlated with PSA fluctuation.
Conclusion: Patients with wide PSA fluctuations, although baseline PSA levels are high, might have a low risk of diagnosis with prostate cancer. Thus, serial PSA measurements could be an option in patients with an elevated PSA level.

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INTRODUCTION

Prostate-specific antigen (PSA) measurement in patients with serum PSA level above 4.0 ng/mL has a sensitivity of about 20%, and the specificity of PSA measurements is approximately 60% to 70% at this cut-off (1). If patients with PSA levels below 10 ng/mL were submitted to prostate biopsy, 20–40% would be diagnosed with prostate cancer and 60–80% should undergo unnecessary biopsy without detecting prostate cancer (2). Benign prostatic hyperplasia, urethral or prostatic trauma, and prostatitis, as well as prostate cancer, can all be associated with elevated serum PSA levels. Ejaculation and digital rectal examinations have been reported to increase PSA levels but studies have shown the effects to be variable or insignificant (3). These non-malignant conditions which were associated with elevation of a serum PSA would decrease the accuracy of a serum PSA. To improve low sensitivity of PSA, age-adjusted PSA, PSA density (PSAD), PSA velocity (PSAV),

or percentage of free PSA (%Free-PSA) has been introduced and used (4-8). In the last two decades, individual fluctuation in serial PSA measurements has been reported to characterize the normal biological variability in PSA among men without prostate cancer (9-13). The aims of this study were to investigate whether PSA fluctuation correlates with a prostate cancer and to assess Whether PSA fluctuation could be used for diagnosis of a prostate cancer.

MATERIALS AND METHODS

Patients and Study design

This was a retrospective cohort study in the department of urology of Chonnam National University Hospital (Gwangju, Korea) between January, 2012 and March, 2013. This study included 229 patients who were submitted to a transrectal ultrasonography (TRUS) guided prostate biopsy (177 in non-cancer group, 52 in prostate cancer group). TRUS-guided prostate biopsy was performed in at least 8 cores or more of tissue targeting the peripheral zone at the apex, mid gland, and base on each side of the prostate. Enrolled patients were provided twice PSA measurements within 6 months (baseline PSA, PSA_1; secondary PSA, PSA_2), and PSA_2 was measured at the day before prostate biopsy. Patients with urinary tract infection and who were receiving a 5-alpha reductase inhibitor were excluded from the study. The research attained ethical approval from the institutional review board of Connam National University Hospital (IRB No. 210-05-082). The recommendations of the Declaration of Helsinki for biomedical research involving human subjects were followed.

Definition and Measurements

PSA fluctuation (%/mo) was defined as a change rate of PSA ((PSA_2-PSA_1)/PSA1) per a month. PSAD (ng/mL/g) was defined as a PSA_2 divided by prostate volume. Prostate volume (g) was measured according to the prostate ellipsoid formula, multiplying the largest anteroposterior (height, H), transverse (width, W), and cephalocaudal (length, L) prostate diameters by 0.524 ($H \times W \times L \times \pi/6$) by using TRUS. An automated immunoassay analyzer (ARCHITECT i2000SR®, Abbott Diagnostics, Abbott Park, IL, USA) was used for all PSA measurements, and TRUS-guided prostate biopsy was recommended for a PSA level > 3.0 ng/mL or suspicious digital rectal examination.

Statistical analysis

Whitney U test was used to compare between two groups. Receiver operator characteristic (ROC) curve was used to assess the availability as a differential diagnostic tool and the correlation. Simple linear regression was performed to analyze a correlation between PSA fluctuation and other factors such as age, PSA, PSAD, and prostate volume. Statistical significance was set at $P<0.05$. All statistical analyses were performed with SPSS software version 20.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Baseline Characteristics

The patients' baseline characteristics are shown in Table-1. Mean PSA_1 and PSA_2 levels were 5.93 ng/mL and 4.90 ng/mL. PSA fluctuation ranged from 0.12%/month to 122.6%/month, PSAD

Table 1 - Baseline characteristics of patients.

Variables	Mean (range)
Age (year)	66.91 (41-85)
PSA_1 (ng/mL)	5.93 (0.23-24.62)
PSA_2 (ng/mL)	4.90 (0.20-9.96)
Interval of PSA tests (month)	1.93 (1-6)
PSA fluctuation (%/month)	17.61 (0.12-122.60)
PSAD (ng/mL/g)	0.15 (0.01-0.58)
Prostate volume (g)	37.61 (8.90-160)
%Free-PSA (%)	20.22 (3.79-61.50)
No. biopsy results (%)	
Non-cancer	177 (77.3)
Prostate cancer	52 (22.7)

PSA = prostate-specific antigen, **PSA^1** = baseline PSA, **PSA^2 =** secondary PSA, **PSAD =** PSA density, **%Free-PSA =** percentage of free PSA.

from 0.01 ng/mL/g to 0.58 ng/mL/g, and prostate volume from 8.9 g to 160 g. Patients diagnosed with prostate cancer were 52 (22.7%), and patients with non-cancer were 177 (77.3%). Patients with non-cancer presented benign prostatic hyperplasia (155, 67.7%), chronic prostatitis (16, 7.0%), and atypical small acinar proliferation (6, 2.6%).

Comparison between Non-cancer group and Prostate cancer group

PSA_2 and PSAD were significantly lower in non-cancer group than prostate cancer group (4.68±2.18 vs 5.61±1.76 ng/mL, P=0.002; 0.132±0.796 vs 0.227±0.124 ng/mL/g, P<0.001). PSA fluctuation and %Free-PSA was significantly greater in non-cancer group than prostate cancer group (19.95±23.34 vs 9.63±8.57%/month, P=0.004; 21.53±9.74 vs 15.75±7.96%, P<0.001). There was significant difference in prostate volume between the two groups (40.12±19.93 vs 29.05±12.05 g, P<0.001) (Table-2).

ROC curve analyses of PSA, PSAD, %Free-PSA, and PSA fluctuation

PSA_2, PSAD, % Free-PSA, and PSA fluctuation was statistically significant as a differential diagnostic tool. The optimal cut-off values for detecting prostate cancer of PSA and PSAD were defined as 4.92 ng/mL (sensitivity, 65.4%; specificity, 56.5%; area under curve (AUC), 0.64; P=0.002) and 0.155 ng/mL/g (sensitivity, 73.1%; specificity, 71.2%; AUC, 0.762; P<0.001). The appropriate cut-off values of %Free-PSA and PSA fluctuation were defined as 17.31% (sensitivity, 63.3%; specificity, 63.5%; AUC, 0.688; P<0.001) and 8.48%/month (sensitivity, 61.6%; specificity, 59.6%; AUC, 0.633; P=0.004), respectively (Figure-1).

Correlation Analysis between PSA fluctuation and other variables

Simple linear regression was performed to analyze a correlation between PSA fluctuation and other factors such as age, PSA, PSAD, and prostate volume. PSA_1 and PSA_2 levels were significantly correlated with PSA fluctuation in a simple linear regression model (coefficient B, 3.404, P<0.001 in PSA_1; coefficient B, -3.978, P<0.001 in PSA_2). Age, %Free-PSA, PSAD, and prostate volume did not affect on PSA fluctuation (Table-3).

DISCUSSION

After the recent reports of highly anticipated data from the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) and the European Randomized Study of Screening for Prostate Cancer (ERSPC), the benefit of PSA screening remains controversial (14, 15). Twenty--five percent of men with PSA levels from 4 to

Table 2 - Comparison between non-cancer and prostate cancer group.

	Non-cancer group (n=177)	Prostate cancer group (n=52)	P value
Age (year)	66.36±8.45	68.78±7.61	0.103
PSA_1 (ng/mL)	6.00±3.75	5.70±1.70	0.300
PSA_2 (ng/mL)	4.68±2.18	5.61±1.76	0.002
Interval of PSA tests (month)	1.88±1.19	2.07±1.36	0.330
PSA fluctuation (%/month)	19.95±23.34	9.63±8.57	0.004
%Free-PSA (%)	21.53±9.74	15.75±7.96	<0.001
PSAD (ng/mL/g)	0.132±0.796	0.227±0.124	<0.001
Prostate volume (g)	40.12±19.93	29.05±12.05	<0.001

PSA = prostate-specific antigen, **PSA_1 =** baseline PSA, **PSA_2 =** secondary PSA, **%Free-PSA =** percentage of free PSA, **PSAD =** PSA density.

Figure 1 - Receiver operator characteristic curves analyses of secondary prostate-specific antigen (PSA_2), prostate-specific antigen density (PSAD), percentage of free prostate-specific antigen (%Free-PSA), and prostate-specific antigen (PSA) fluctuation. The optimal cut-off values for detecting prostate cancer were defined as 4.92 ng/mL in PSA_2 (sensitivity, 65.4%; specificity, 56.5%; area under curve (AUC), 0.64; P=0.002), 0.155 ng/mL/g in PSAD (sensitivity, 73.1%; specificity, 71.2%; AUC, 0.762; P<0.001), 17.31% in %Free-PSA (sensitivity, 63.3%; specificity, 63.5%; AUC, 0.688; P<0.001), and 8.48 %/month in PSA fluctuation (sensitivity, 61.6%; specificity, 59.6%; AUC, 0.633; P=0.004), respectively.

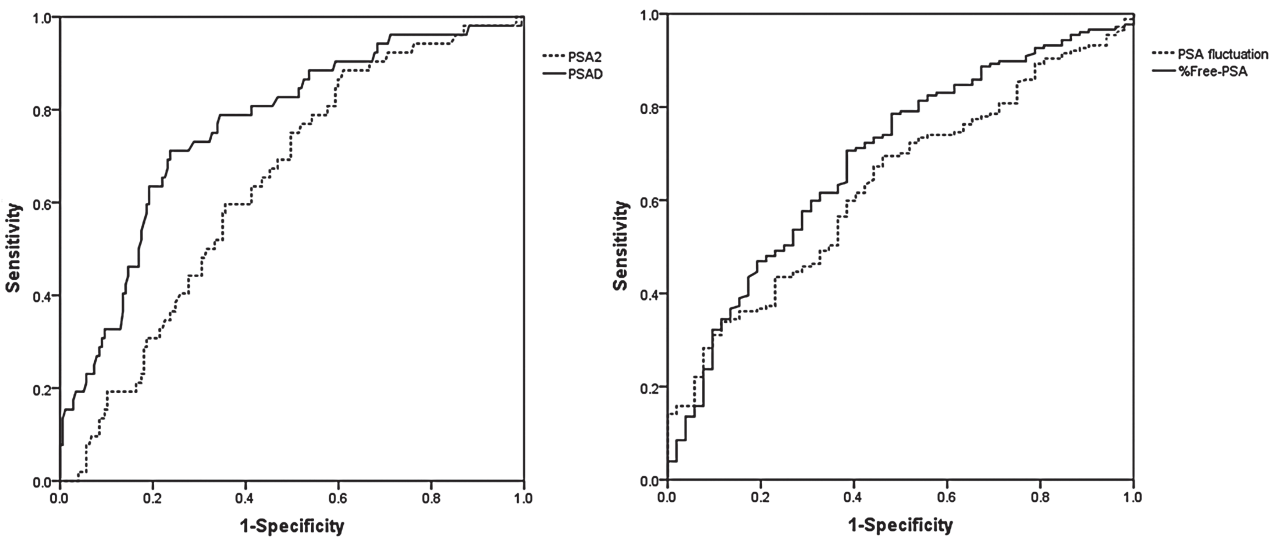

Table 3 - Simple linear regression analyses of prostate-specific antigen fluctuation and clinical parameters.

Variables	Coefficient B	SE	P value
Age (year)	-0.059	0.170	0.728
PSA_1 (ng/mL)	3.404	0.392	<0.001
PSA_2 (ng/mL)	-3.978	0.625	<0.001
%Free-PSA (%)	0.163	0.165	0.325
PSAD (ng/mL/g)	-20.061	16.029	0.212
Prostate volume (g)	-0.029	0.075	0.696

PSA = prostate-specific antigen, **PSA_1 =** baseline PSA, **PSA_2** = secondary PSA, **%Free-PSA =** percentage of free PSA, **PSAD =** PSA density.

10 ng/mL have a biopsy-proven prostate cancer, but 75% undergo unnecessary prostate biopsies, potentially leading to anxiety, discomfort, and significant additional health care cost (16). To improve the low sensitivity of PSA, age-adjusted PSA, PSAD, PSAV, and %Free-PSA have been introduced and used (4-8). In our study, the sensitivity and specificity of PSA was not high (65.4%; 56.5%; AUC, 0.64; P=0.002) in a ROC curve. Similarly with previous reports, both PSAD and %Free-PSA were the available parameters to improve the low sensitivity of PSA (sensitivity, 73.1%, 63.3%; specificity, 71.2%, 63.5%; AUC, 0.762, 0.688). In addition to PSAD and %Free-PSA, we found that PSA fluctuation is associated with the presence of a prostate cancer. Although low sensitivity and specificity, PSA fluctuation could be valuable by using with other PSA indices such as PSAD and %Free-PSA.

In several studies, biological fluctuations in PSA levels have been previously reported to cha-

racterize the normal biological variability in PSA levels among men without prostate cancer (9-13). These reports suggest that PSA fluctuation was unrelated to age (9,10). Roehrborn et al. reported a significant fluctuation between two serum PSA measurements obtained within a short-time interval of less than 90 days, and authors suggested not a single PSA measurement but repeated PSA tests (9). In our study, mean interval of twice PSA measurements was 1.93 months (approximately 57.9 days), and there was no difference in PSA_1 but significant difference in PSA_2 between two groups within a more shorter-time interval. John et al. studied to assess the relationship between prostate volume and PSA fluctuation, and found that PSA fluctuation was not correlated with PSA volume but correlated with baseline PSA levels (11). In our study, PSA fluctuation was correlated with baseline PSA levels, and not correlated with age, PSAD, %Free-PSA, and prostate volume. Thus, we suggest that PSA fluctuation could be used for the differential diagnosis regardless with age and prostate volume. Nixon et al. evaluated daily biological variations of PSA levels by obtaining 10 serum samples from 24 patients during a 2-week (12). They concluded that the degree of biological fluctuation differs among patients, and the difference between serial PSA measurements that is less than 20% to 46% may be due to biological and analytical variation alone. The reports mentioned above targeted to patients without prostate cancer, and focused on the biologic fluctuation itself. The hypothesis of our study was that degree of PSA fluctuation might differ according to the presence or absence of prostate cancer, and we found the characteristic of PSA fluctuation that patients with prostate cancer had a narrow range of fluctuation in serial PSA measurements. In addition, these results are as practically useful as other indices related to PSA such as a PSAD or %Free-PSA.

It is important to clarify that the PSA fluctuation should not be confused with PSAV as described by Carter et al. (17, 18). PSAV represent the rate of change of PSA over time that optimally requires three consecutive PSA measurements over a 2-year period, as described by Carter et al. (17, 18). PSA fluctuation is simply a mathematical estimate of the absolute monthly changes in PSA (ng/mL per a month) between two measurements that can be separated by less than 1 year. In our study, the mechanism of PSA fluctuation could not be investigated; however, PSA fluctuation might include the possibility of physiologic changes in serial PSA measurements, in contrast with the PSAV to consider a disease-progression.

In our study, when patients with prostate cancer (n = 52) were divided by a Gleason score, PSA fluctuation was greater in patients with Gleason score ≤6 (n=22) than Gleason score ≥7 (n=30), although not significantly (10.50±9.45 vs 8.99±7.97 %/month, P=0.535; data are not shown in tables). However, this result might not have sufficient statistical power, due to small sample size. We carefully suppose that there might be differences in the PSA fluctuation between low--risk and high-risk prostate cancer. A study based on larger population is necessary for further conclusive data.

The present study has several limitations. The major limitation is its retrospective design, and thus the present results may be vulnerable to confounding errors and bias. Second, intervals of PSA measurements were not regular. We enrolled patients that measured two times PSA levels within 6 months to minimize the confounding by irregular intervals. Third, there was significant difference in the prostate volume between two groups. However, we could have concluded about the difference of PSA fluctuation between two groups, because PSA fluctuation was not correlated with prostate volume in a simple linear regression model. Finally, this study may not have had sufficient statistical power, due to the relatively small sample size. Future research should include increased sample size to increase the statistical power. A prospective study based on a larger population is necessary for further conclusive data.

CONCLUSIONS

PSA fluctuation is significantly greater in patients without cancer than patients with prostate cancer, and is positively correlated with baseline PSA level. Thus, clinicians should consider that patients with wide PSA fluctuations, although ba-

seline PSA levels are high, might have a low risk of diagnosis with prostate cancer, and that serial PSA measurements could be an option in patients with an elevated PSA level.

ABBREVIATIONS

PSA = prostate-specific antigen
PSA_1 = baseline prostate-specific antigen
PSA_2 = secondary prostate-specific antigen
PSAD = prostate-specific antigen density
PSAV = prostate-specific antigen velocity
%Free-PSA = percentage of free prostate-specific antigen
TRUS = transrectal ultrasonography
ROC = receiver operator characteristic

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CONFLICT OF INTEREST

None declared.

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