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# Association of serum total PSA level and free-to-total PSA ratio with grade of prostate cancer in biopsy specimens

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## Abstract

**Introduction:** Prostate cancer is the fourth most common cancer in the men older than 50 years. It is in second place after lung cancer. Although the cause of prostate carcinoma has remained unknown, but clinical and experimental observations suggested the effective role of hormonal, genetic and environmental factors.
**Objectives:** This study aimed to determine the relationship between total serum prostate-specific antigen (PSA) levels and free PSA to total PSA ratio with prostate cancer malignancy grade in biopsy specimens, and was performed according to Gleeson criteria.
**Materials and Methods:** This study is a descriptive-analytical study. In patients with prostatic carcinoma the serum level of total PSA and free PSA were measured and according to the Gleason scoring system degree of malignancy was investigated. All data were analyzed by SPSS software.
**Results:** A significant and direct relationship between free PSA/total PSA and Gleason score was found. Also, a significant correlation was observed between serum PSA level and the grade of the disease.
**Conclusion:** Considering that prostatic carcinoma is one of cancers usually diagnosed late and since biopsy is hardly accepted by patients, with regard to the relationship between serum levels of free PSA and free PSA/total PSA ratio we can use serum level of free PSA and total PSA for diagnosis. Consequently, not only rapid and timely diagnosis of all types of cancer can have a positive impact on the healing process but also have particular effect in the treatment and reducing mortality established by this disease.

## Introduction

Prostate cancer is the fourth most common cancer in the world and the most common visceral cancer in men and in terms of cancer-related deaths in the men older than 50 years, it is in second place after lung cancer (1). The incidence of this disease in different parts of the world, depending on race, age, geographic region is variant (2). This disease is also related to genetics and hormonal factors (2). Although the cause of prostate carcinoma has remained unknown, but clinical and experimental observations suggested the effective role of hormonal, genetic and environmental factors (3). Among hormonal factors, the possible role of androgen is emphasized on. Since the first-degree relatives of affected person are in greater risk, the role of genetic factors has also been

**Key point**

Considering that prostatic carcinoma is one of cancers usually diagnosed late and since biopsy is hardly accepted by patients, with regard to the relationship between serum levels of free prostate-specific antigen (PSA) and free PSA/total PSA ratio we can use serum level of free PSA and total PSA for diagnosis. Consequently, not only rapid and timely diagnosis of all types of cancer can have a positive impact on the healing process but also have particular effect in the treatment and reducing mortality established by this disease.

demonstrated. Also, with regard to the prevalence of prostate carcinoma in the workers of some industries, and the significant geographic differences in prevalence of this disease, the role of environmental factors can be realized (4). Rapid and timely diagnosis and screening of this disease can have a positive impact on patient survival, and may improve the morbidity and mortality (5). The highest incidence of prostate cancer is at ages 65-75. The measurement of serum total prostate-specific antigen (PSA) level and the ratio of free PSA to total PSA are of early detection methods and screening this disease (6,7). So that, measuring PSA serum level is widely used to detect prostate carcinoma at an early stage (8). PSA is a 33 kDa proteolytic enzyme which is produced by normal and neoplastic epithelium prostate (6,7) and its duty is maintaining the succulence of seminal liquid and increasing sperm motility. PSA equal to 4 ng/ml is regarded as the maximum limit of normal values. Although cancer cells produce more PSA but any disorder which affects the normal prostate, such as adenocarcinoma, nodular hyperplasia and prostatitis, can cause an increase in serum level. On the other hand there is a considerable overlap between the serum PSA levels in patients affected with prostate cancer and those with nodular hyperplasia (4). In addition, a small percentage of those who are affected by prostate cancer, especially in lesions confined to the prostate gland, PSA levels do not increase (6-8). Therefore, various methods have been introduced, in order to increase the diagnostic value of total PSA values, that one of them is measuring PSA free form (free PSA) and determining its relation to total PSA. The ratio of serum PSA levels between 4-10 ng/ml mostly can be very useful and helpful. Free-to-total PSA ratio less than 14% , strongly suggests a prostatic carcinoma (7,8).
From microscopic point of view, most of prostate carcinomas are adenocarcinoma, which show varying degrees of differentiation and anaplasia. Since 70%-80% of prostate carcinomas are located in gland's environment, therefore it may be palpable on rectal examination by finger. Therefore, prostate biopsy would be done in case of positive rectal examination or observing high serum level of total PSA, while as mentioned above, the malignant prostate will produce more PSA in compare to normal or hyperplastic prostate.
Some methods have been suggested for histological grading of prostatic carcinoma that the Gleason grading system is the most famous method. This method is categorized based on the degree of glandular differentiation, the gland neoplasm structure, nuclear anaplasia and mitotic activity. According to Gleason grading criteria, the patients affected by prostate cancer are divided into five groups. Considering the high incidence of prostate cancer in Iranian men, and since PSA test is a simple and inexpensive test to screen prostate cancer has been, and free PSA and total PSA tests can be performed in most laboratories.

## Objectives

This study aimed to determine the relationship between total serum PSA levels and free PSA to total PSA ratio with prostate cancer malignancy grade in biopsy specimens, and was performed according to Gleeson criteria.

## Materials and Methods

This study is a descriptive-analytical study, which was done in 2012, in Al-Zahra hospital, Isfahan. Patients who were affected by prostate cancer and referred to this hospital in 2012 were included to the study. The criteria for entering into this study were being affected by prostate cancer, patients' satisfaction for taking part in the study and performing medical tests. The sample size was estimated 82 people using sample size determination formula for correlation studies and considering confidence level of 95%, 80% test power and the correlation between serum PSA and prostate cancer grade which was calculated about 0.3. The mentioned samples were selected through convenience sampling of the patients with desired criteria. In this method 82 individuals of the patients affected by prostate cancer that their disease was confirmed by biopsy were selected and their serum total PSA and free PSA were determined by laboratory. The unit for measuring PSA has been ng/ml in all cases. The malignancy grade of prostate cancer is determined by pathologist according to the analysis of sections stained by hematoxylin and eosin method (8) and based on the Gleason grading criteria which are specified in Table 1.
The information related to disease grade and PSA results as well as patients' demographic data was registered in a form which was prepared for this end. Finally, the obtained information was entered into computer and was analyzed through SPSS software (version 20) and chi-square, *t* test and Spearman correlation test.

## Results

Eighty-five patients were surveyed in this study. The average age of the mentioned patients was 70.1 ± 9.5 years in 28-95 years range. Eight people (9.4%) were under 60 years old, 34 patients (40%) aged 60-69 years, 33 people (38.8%) aged 79-70 years, and 10 patients (11.8%) were aged 80 years and older. The average of serum total PSA level in these patients was 44.8 ± 37 ng/ml with a range of 4.7-221 ng/ml. Also, according to the results of this study all patients had abnormal PSA level (PSA >4 ng/ml).
The average serum total PSA level in people under 60, 69-60, 79-70 and 80 years and older respectively are shown in Table 2, the distribution of serum total PSA level, according to patients' age group. According to one-way analysis of variance (ANOVA), the results were 43.1 ± 15.1, 24.7 ± 4.3, 71.4 ± 24.9 and 71.4 ± 24.9 ng/ml. And based on one-way ANOVA, the differences of serum total PSA levels according to age groups were significant ($P = 0.033$). The correction of age and serum total PSA level was not significant ($P > 0.05$).
The average of free PSA to total PSA ratio in studied patients was 14.4 ± 6.6 in a range of 1 to 29. The average of free to total PSA ratio, in people under 60, 69-60, 79-70 and 80 years and older, was 12.6 ± 8.5, 15.4 ± 6.2, 14.5 ± 4.6 and 12.2 ± 8.2 respectively, and according to one-way

**Table 1.** Gleason grading criteria for prostatic carcinoma

| |
|---|
| Group 1: Plain, separated, uniform with distinct and rounded edges |
| Group 2: Plain, separated, reduced uniformity and the decrease in distinction of the margins of the lesion |
| Group 3a: plain, separated, with various shapes and almost faded lesion margins |
| Group 3b: same as 3a but with smaller glandular part and narrow cellular clusters |
| Group 3c: round and sieve- like lesions which are smooth and sharp, and are related to the papillary lesion |
| Group 4a: fuzzy and scattered lesion with intertwined glandular part |
| Group 4b: same as 4a, with large pale cells (hypernephroid) |
| Group 5a: hard sieve-like, round and sharp lesion with necrotic center (comedocarcinoma) |
| Group 5b: an anaplastic, fuzzy lesion with some glandular and vacuole form, which is indicative of adenocarcinoma. |

**Table 2.** Mean and standard deviation of the PSA levels, the ratio of free PSA/total PSA and age according to the grade of disease

| Age | Free PSA/Total PSA | Total PSA (ng/ml) | Frequency | Gleason score |
|---|---|---|---|---|
| 73.7±3.8 | 22±2.6 | 8.4±1.4 | 3 | 2 |
| 47.7±19.1 | 9±1 | 52.6±10.7 | 24 | 4 |
| 69.2±9 | 15.6±5.5 | 50.9±21 | 9 | 5 |
| 71.3±8.2 | 14.6±7.2 | 9 | 1 | 6 |
| 65 | 17 | 43.5±7.4 | 24 | 7 |
| 68.5±10.5 | 13.7±7.3 | 36.1±8.7 | 14 | 8 |
| 70.2±11.1 | 14.6±7.4 | 64.6±20.3 | 10 | 10 |
| 0.021 | 0.27 | 0.39 | 85 | *P* |

Abbreviation: PSA, prostate-specific antigen.

ANOVA there was no significant difference among these four age groups ($P=0.5$).

In Table 1, the mean and the standard deviation of serum total PSA levels, the ratio of free PSA/ total PSA and patients' age according to Gleason score are shown.

According to the results of this study, there is a reverse correlation between Gleason score and free PSA/total PSA ratio, that was statistically significant ($P=0.037$). Furthermore, correlation of Gleason score and serum PSA levels ($r=0.73$, $P=0.001$) was significant.

## Discussion

The overall objective of this study was to determine the relationship between serum total PSA level and the ratio of free PSA to total PSA with malignity grade of the prostate cancer in the biopsy specimen.

In this study, 82 patients affected to prostate cancer and with average age of 70.1 ± 9.5 were studied. The average total PSA level in these patients was 37 ± 34.8, and all these patients had an abnormal PSA level (more than 4). We found that the level of the PSA had significant difference according to the age group of the patients. Also, the average of free PSA to total PSA in these patients was 14.4 ± 6.6. However, the ratio had no significant difference depending on the age group. On the other hand, a significant and direct relationship between free PSA/total PSA and Gleason score was detected. Accordingly, a significant correlation between serum PSA level and the grade of the disease was observed. Although from theoretical point of view, the border of catching or not catching prostate cancer in PSA test, which is a screening test, is 4 ng/ml (4). On the other hand, free to total PSA ratio is regarded as an index in order to detect the grade of the disease, and it is supposed that with progress of the disease this ratio will increase too. Although, according to the findings of this study, such relationship was not observed between this ratio and the grade of the disease.

The specific antigen of prostate is a glycoprotein made of protease which is expressed in normal and neoplastic prostate tissues (3). Although its expression level in neoplastic is less than prostate normal epithelium, but in gram by gram comparison of normal and malignant tissues, it showed that malignant tissues produces more PSA about 10 times and enters into blood easier (4). In a study Beyer et al investigated the role of Gleason grade in predicting the survival of prostate cancer after its treatment. Their findings showed that both the Gleason grade more than 7 and PSA more than or equal to 10 ng/ml have been associated with increased risk of death from prostate cancer after 10 years (7,9). In two other studies conducted by Xiao et al (10) and Lakhtakia et al (11) in 2004 and 2007, a direct and significant relationship between the grade of disease and the PSA level is observed. Likewise in, the study by Farajian Abbasi et al, an inverse relationship between staining intensity and serum PSA levels was observed (12). Additionally Vickers et al, found a direct relationship between the amount of serum PSA and the Gleason score, and also an inverse relationship between the intensity of staining tissue by PSA marker and Gleason grade was detected (13).

## Limitations of the study

This study was conducted on a small group of patients. We suggest, larger studies on this subject.

## Conclusion

Considering that prostatic carcinoma is one of cancers usually diagnosed late and since biopsy is hardly accepted by patients, with regard to the relationship between serum levels of free PSA and free PSA/total PSA ratio we can use

serum level of free PSA and total PSA for diagnosis. Consequently, not only rapid and timely diagnosis of all types of cancer can have a positive impact on the healing process but also have particular effect in the treatment and reducing mortality established by this disease.

### Authors' contribution
All authors wrote the manuscript equally.

### Conflicts of interest
The authors declared no competing interests.

### Ethical considerations
Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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