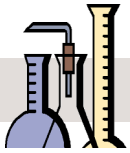

# Relationship between Prostate Size and Percent Free Prostate-Specific Antigen in Patients with Operable Prostate Cancer

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**Key words:** prostate cancer, free prostate-specific antigen, prostate size

## Abstract

**Background:** The free-to-total prostate-specific antigen ratio is the best marker for optimizing prostate cancer detection. The main problem with studies of percent free PSA is the variability of reported cutoff values.

**Objectives:** To evaluate the influence of prostate size on the ratio of free to total PSA.

**Methods:** The study group included 58 patients (mean age 66.4 years) with clinically localized prostate cancer treated surgically at our institution. Total PSA and free PSA levels were measured by a solid phase enzyme immunoassay test (Hoffman-La Roche, Basel, Switzerland). The percent free PSA was compared with prostate size as determined from the surgical specimen.

**Results:** A direct relation was noted between prostate size and the percent free PSA value ($r$=0.49, $P$=0.0001). Mean percentage free PSA was 9%±0.004 in men with normal-sized gland while in men with large prostate (>60 g) the average percent free PSA was 15.9±0.09 ($P$=0.001).

**Conclusions:** In patients with prostate cancer the percent free PSA level is influenced by the gland size. The larger the prostate the higher the proportion of the free PSA. Such information may have influence on the recommendation for prostate biopsy in screening programs for early detection of prostate cancer.

*IMAJ 2000;2:889–891*

The use of serum prostate-specific antigen testing combined with digital rectal examination has resulted in markedly increased detection of organ-confined potentially curable prostate cancers. Increased level of PSA is the main indication for prostate biopsy. However, only 25% of men undergoing prostate biopsy will have cancer [1,2]. New assays that can help to reduce the number of unnecessary biopsies along with morbidity anxiety and costs have been introduced [3–6]. The free-to-total PSA ratio provides the best clinical value for optimizing prostate cancer detection. Nevertheless, despite being a useful marker, the main problem with studies of percent free PSA is the lack of consensus regarding appropriate threshold, and hence the variations in reported results [7–10]. The aim of the present study was to evaluate the impact of prostate size on the ratio of free-to-total PSA in men with clinically localized prostate cancer.

PSA = prostate-specific antigen

## Materials and Methods

We studied retrospectively a group of 58 previously untreated patients with clinically localized prostate cancer. All underwent bilateral pelvic lymphadenectomy and radical retropubic prostatectomy at our institution.

The histological hematoxylin and eosin slides were reviewed by the study pathologist (E.S.) to confirm the diagnosis. Each prostate was weighed and measured in three dimensions before fixation with 10% neutral buffered formalin. In all cases blood samples were taken before the diagnostic procedures within 60 days before prostatectomy. Total PSA and free PSA concentrations were determined by a solid phase enzyme immunoassay test (Hoffman-La Roche, Basel, Switzerland). The assays use two highly specific monoclonal antibodies to PSA, and were monitored on a Cobas Core instrument.

### Statistical analysis

Student's $t$-test was used to determine the significance of differences between the means of two normally distributed subgroups. The equality of variances was tested with the Levene test. Non-parametric subgroups were compared by the Mann-Whitney U test. Possible correlation between the prostate weight and the percent free PSA was assessed using Pearson's test. Two-tailed $P$ values of 0.05 or less were considered to be statistically significant.

## Results

The patients' ages ranged from 50 to 73 years (mean age 66.4). Table 1 summarizes the statistical data on total PSA, free PSA, free-to-total PSA ratio, and prostate weight.

**Table 1.** Prostate size and various forms of PSA levels in 58 patients with localized prostate cancer

| | Prostate size (ml) | PSA level (ng/ml) Total | Free | % Free/PSA |
|---|---|---|---|---|
| Median | 50.0 | 8.7 | 0.9 | 0.095 |
| Mean | 58.0 | 11.45 | 1.05 | 0.11 |
| SD | 24.5 | 11.09 | 0.93 | 0.074 |
| Range | 20–135 | 1.8–79.6 | 0.1–3.2 | 0.04–0.41 |

The volume of the prostate ranged from 20 to 135 ml (median 50 ml, mean 58±24.5). Serum levels of total and free PSA ranged from 1.8 to 79.6 ng/ml and 0.1 to 3.2 ng/ml, respectively with a median of 8.7 ng/ml (mean 11.45±11.09) for total PSA and median of 0.9 ng/ml (mean 1.05±0.93) for free PSA. The median percent free PSA was 9.5% (mean 11±7.4) ranging from 4 to 41%. The relationship between free-to-total PSA ratio and prostate size is shown in Figure 1. Direct and significant correlation was noted between prostate weight and the percent free PSA ($r$=0.49, $P$=0.0001, Pearson test). For relatively small prostates (60 g) the average ratio was significantly higher, being 0.159±0.09 ($P$=0.001, Student $t$-test) [Figure 2]. For maintaining 90% sensitivity we calculated the following cutoff values: 14.7% and 25.35% for small and large size glands respectively.

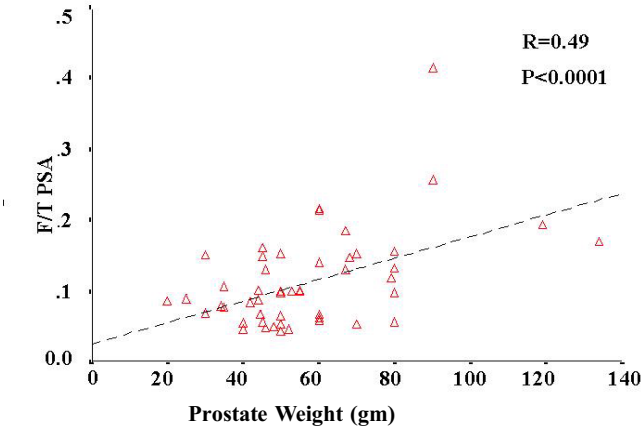


**Figure 1.** Relationship between free to total PSA ratio and prostate weight In 58 patients with clinically localized prostate cancer.

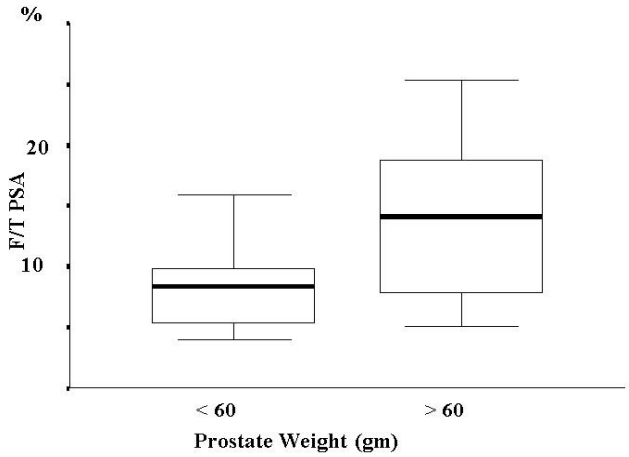


**Figure 2.** Distribution of percent free PSA for small and large prostates in 58 patients with localized prostate cancer.

## Discussion

Since the first report by Stenman et al. in 1991 [11], various studies have shown that the percent free PSA serves to increase the ability of serum PSA to distinguish men with an early prostate cancer from men with benign prostatic hypertrophy [7–10]. Taken together these data suggest that the percentage of free PSA decreases as the probability of having prostate cancer on biopsy increases. In general the results of the above mentioned studies vary greatly, with percent free PSA cutoff points ranging from 14% to 28% [10,12]. Possible causes for the variability in the cutoff value might be differences in the populations studied, the incidence of prostate cancer among the tested populations, storage conditions of archival serum samples, and calibration of the clinical assays [13].

In the present study we have shown that the ratio of free PSA to total PSA in patients with clinically localized prostate cancer is also influenced by prostate size. The larger the prostate the higher the fraction of free PSA. The mean level for prostate weighing up to 60 g was 9% versus 15.9% for glands more than 60 g ($P$=0.001). Almost identical findings were reported by Catalona and colleagues [14], who retrospectively studied 63 men with BPH, 30 men with prostate cancer and enlarged gland, and 20 men with prostate cancer and normal size gland. The median percent free PSA was 19% in men with BPH, 16% in patients with cancer and large gland, and 9% in patients with cancer and a normal size gland [7]. Based on these results a prospective multicenter clinical trial was later conducted. The trial comprised 773 men (379 with cancer and 394 with BPH) enrolled primarily through prostate cancer screening programs. All subjects had undergone ultrasound-guided prostatic biopsy and thus had a histologically confirmed diagnosis. Again, the prostate volume as estimated by trans-rectal ultrasound directly correlated with percent of free PSA ($r$=0.55, $P$=-0.001) [14].

The positive correlation between percent free PSA and prostate volume was also demonstrated by Stephan et al. [15]. Different results however were reported by Egawa and co-workers from Japan [16], who studied 113 patients with prostate cancer and found no association between gland size and free-to-total PSA ratio. Like our study, the prostate size was determined on the basis of surgical specimen measurement and not by ultrasonic evaluation. Lack of correlation between trans-rectal ultrasound-estimated prostate volume and percent free PSA was reported by Douglas and

BPH = benign prostatic hypertrophy

colleagues from the Armed Forces Institute of Pathology [17].

The most important finding of our study was that we were able to show a direct correlation between prostate gland size and the percent free PSA in patients with prostate cancer. The larger the gland the higher the value of the percent free PSA. A possible explanation is the fact that patients with prostate cancer and enlarged gland often also have benign hypertrophy that could reduce the impact of the cancer on the free PSA level. The clinical implication of such a finding is the need to adjust the cutoff value of percent free PSA to the prostate size when making the decision whether or not to recommend biopsy of the prostate. For example, in men with a normal size prostate a threshold level of 14.70% will detect 90% of the neoplasms versus 23.35% for patients having larger glands. We believe that such information can increase the sensitivity in screening programs for early detection of prostate cancer.

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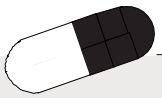
## *Capsule*



### Desperately seeking a diabetes gene

Non-insulin-dependent diabetes mellitus (NIDDM) affects 10–20% of people over age 45 in many developed countries, and it is increasing in incidence. An example of a complex trait, NIDDM is thought to arise from a combination of environmental and genetic factors, and the genetic contribution is likely to arise from several interacting genes, each carrying critical, yet subtle, alterations.

Undaunted by the complexity of their task, Horikawa et al. report progress in the search for genetic variations that influence the propensity to develop NIDDM. Using positional cloning methods, they found that specific polymorphisms in CAPN10, a chromosome 2 gene that encodes a widely expressed calpain-like cysteine protease, are associated with NIDDM in both Mexican-American and Finnish populations. Whether these genetic variations in CAPN10 are causal factors in the disease or merely co-segregating markers is unclear, but this question can now be addressed in clinical and laboratory studies.

*Nat Genet* 2000;26:163