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Relationship between Prostatic Specific Antigen (PSA) and volume of the prostate in the Benign Prostatic Hyperplasia in the elderly

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Abstract

Increase of the Prostatic Specific Antigen (PSA) is a non-invasive, sensitive and specific markers for prostatic diseases, including prostatic cancer. However, age-related Benign Prostatic Hyperplasia (BPH), as well as prostatitis, may at the same time alter PSA values. The aim of this study was to evaluate the relationship between ageing and PSA, and whether age-specific upper normal limits of PSA should be considered for elderly patients. We evaluated 569 consecutive subjects aged 60 years or more (mean age 74.2 years) who were free from malignant prostatic disease, without clinical evidence of prostatic phlogosis and who were not receiving PSA levels affecting drugs. All patients underwent Digital Rectal Examination (DRE) and Trans-Rectal Ultrasonography (TRU), with determination of the three prostatic diameters, the Maximum Adenoma Diameter (MAD) and calculation of the prostatic volume (PV) by the ellipsoid formula. PSA was determined in all patients before DRE and TRU, and the PSA free ratio was determined in those with total PSA values > 4 ng/ml. The PSA density was calculated according to the formula PSA/PV. One hundred and seventy-nine subjects (31.6%) were found to have PSA values > 4 ng/ml: among them, 26 (14.5%) had values exceeding 10 ng/ml. Age was slightly correlated with PV ($P < 0.05$), but not with PSA values. On the contrary, PSA values were strongly related with PV and MAD ($P < 0.01$ both). Mean PSA-free ratio was $16.3 \pm 6.0\%$ and most of patients had values in the so-called 'grey zone' of discrimination between benignity and malignity.

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Elevated PSA levels are common in older subjects without evidence of prostatic malignancy; PSA values are poorly affected by age itself and strongly correlated with increasing PV. These results suggest the possibility to consider as indicative of benignity PSA values between 4 and 10 ng/ml, when these values are associated with relevant increase of PV and with PSA-free ratio greater than 10%.

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1. Introduction

Most of prostatic diseases occur in advanced age. The Prostatic Specific Antigen (PSA), synthesized only by prostatic gland cells, is currently regarded as a sensitive and specific markers for prostatic diseases, including Benign Prostatic Hypertrophy (BPH), prostatitis and cancer. Although very sensitive, it is not at all specific for a special prostatic disease. Currently total PSA values >4 ng/ml are considered pathologic, and when exceeding 10 ng/ml are strongly suggestive of malignancy. However, ageing is associated with physiological hypertrophic modifications of the prostate and BPH is extremely common among older subjects [1,2]. It is widely demonstrated that BPH may be associated with slight increases in PSA values [3,4]. Oesterling [5] found a positive correlation between PSA and prostatic volume (PV), whereas Dalkin et al. [6] and Crawford [7] proposed age-specific PSA ranges.

There remain important areas of uncertainty about the relationship between ageing, BPH and 'normal' PSA values. The aim of this study was to evaluate primarily the relationship between ageing, increasing PV and PSA values, and, secondary, whether these relationships might justify the adoption of age-specific PSA values.

2. Subjects and methods

In the period between March 1999 and May 2000, 569 consecutive patients were enrolled among those admitted to the Geriatric Acute Ward and to the Urology Department of Molinette, a university-teaching hospital in Turin, according to the following inclusion criteria: age >60 and ≤ 90 years, Digital Rectal Examination (DRE) negative for suspected malignancy, absence of prostatic malignancy on the basis of postoperative histological specimens and/or negative bioptic response in patients with PSA values exceeding 4 ng/ml, absence of clinical and histological evidences of prostatic phlogosis [8] and absence of current or previous medical treatment with drugs which could affect PSA values (5- α reductase inhibitors, GnRH agonists, antiandrogens, progestative agents and α -channel blockers) [9,10].

In all patients serum total PSA was determined using immunoenzymatic assay (Immulite 2000); in patients whose total PSA values were greater than 4 ng/ml, the

PSA free ratio was also determined. Blood sample for PSA determination were obtained before DRE and Trans-Rectal Ultrasonography (TRU) to avoid false positive results due to the compression of the gland. DRE was performed in all patients by qualified urologist, aimed to exclude objective evidence suggestive of malignancy or phlogosis, and to evaluate volume and consistence of the prostate. TRU was performed by radiologist qualified in this investigation using a 5 MHz probe and the following measures were determined: anteroposterior (*A*), transversal (*B*) and longitudinal (*C*) diameters of the whole prostate and the Maximum Adenoma Diameter (MAD). The PV was calculated according to the ellipsoid formula [11]: $PV = 4/3\pi \times A/2 \times B/2 \times C/2$. The TRU examination was completed by obtaining multiple bioptic specimens to rule out the presence of malignancy in those patients who were suspected for cancer in reason of high PSA values and/or abnormal DRE.

The PSA density (PSAD) was calculated by dividing the total PSA value for the volume of the prostate ($PSAD = PSA/PV$).

Statistical analysis was performed by Student *t*-test, ANOVA and evaluation of the Pearson's index of linear correlation '*r*', for continuous variables, using SPSS/PC+ packaging.

3. Results

Five hundred and sixty-nine subjects (mean age 74.2 ± 6.8 years, range 60–90 years) participated at the study. The following mean values (\pm standard deviation) were observed: PSA 3.71 ± 3.07 ng/ml; PV 55.5 ± 29.9 ml (upper normal limit: 15 ml [12]; MAD 3.6 ± 1.2 cm; and PSAD 0.067 ± 0.055 ng/ml.

Three hundred and ninety subjects (68.4%) had total PSA values within the upper normal limit (≤ 4 ng/ml), while 179 patients (31.6%) had PSA values exceeding this limit. Among these latter subjects, 153 (85.5%) had PSA values >4 and ≤ 10 ng/ml and 26 (14.5%) had total PSA values >10 ng/ml.

Only 16 subjects (2.8%) had PV within the upper normal limit (15 ml); moderate and severe increases of the PV were observed, respectively in 449 (80%) and in 104 (17.2%) patients.

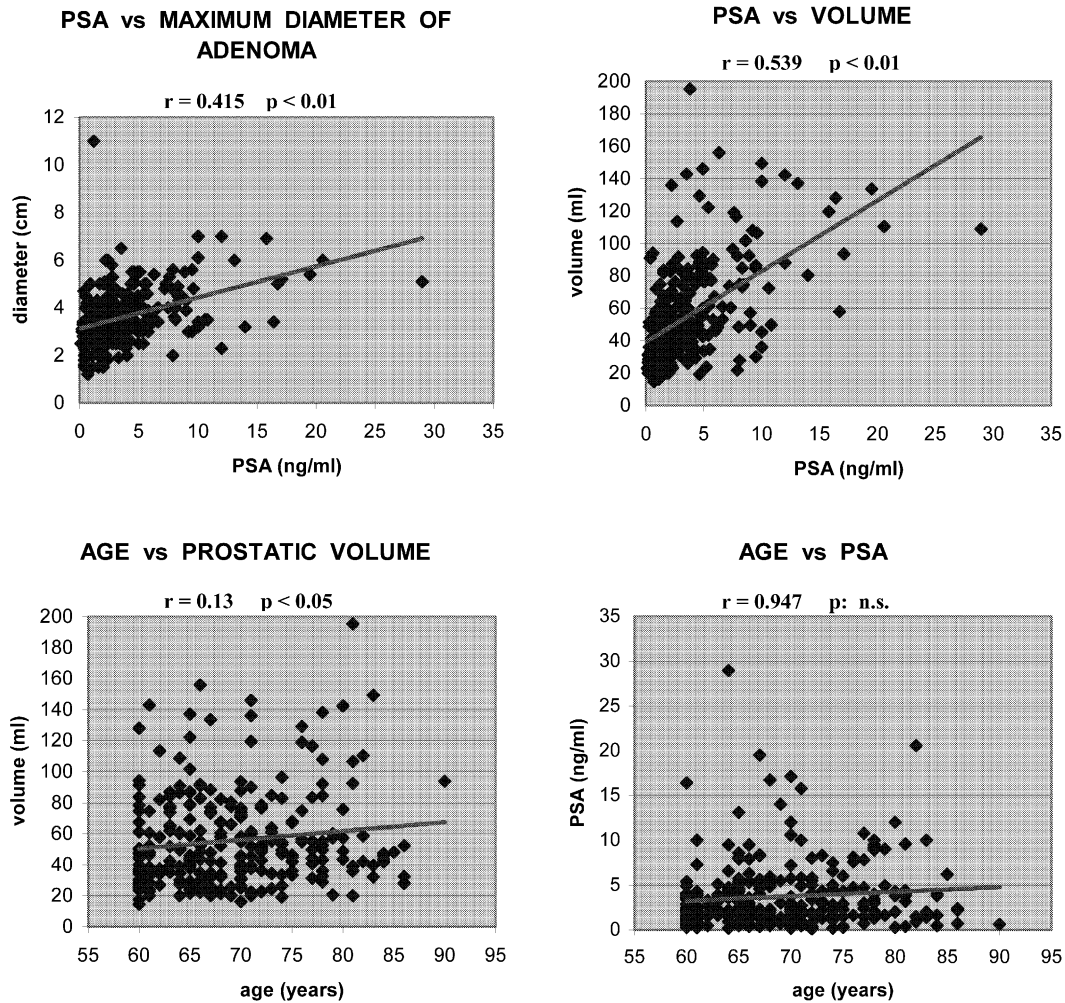


Fig. 1. Pearson's correlation between the variables (PSA, age, PV, maximum diameter of adenoma).

Age was found to be weakly but significantly correlated with increasing PV ($P < 0.05$), but not with total PSA values, whereas PSA values were strongly correlated either with PV and with MAD ($P < 0.01$ both) (Fig. 1). Table 1 shows mean PV and MAD values according to PSA ranges commonly used in clinical settings (≤ 4 , > 4 and ≤ 10 , > 10 ng/ml): either PV and MAD values increased significantly ($P < 0.0001$ both) according to the increasing values of PSA considered.

The mean PSA free ratio in the 179 subjects with total PSA > 4 ng/ml was $16.3 \pm 6.0\%$; most of these subjects had PSA free ratio values between the 25th and the 75th percentile, (respectively 12.3 and 20.2%). No significant correlations were observed between PSA free values and

other variables investigated (PV, age, PSA and MAD) with the exception of a slight inverse correlation with PSAD.

4. Discussion

In this study we observed that roughly a third of subjects over 60 years had PSA values exceeding the upper normal limit. Despite the high prevalence of this alteration, results of the present study indicate that this finding should not be considered ageing-related but rather age-associated disease related. In fact, accordingly with previous studies [3,4,13], we found strong

Table 1

Values (media \pm standard deviation) of PV and maximum diameter of adenoma in relation with PSA expressed for groups

	PSA ≤ 4 ng/ml ($n = 390$)	4 > PSA ≤ 10 ng/ml ($n = 153$)	PSA > 10 ng/ml ($n = 26$)	F	P
Volume (ml)	45.94 \pm 23.35	72.10 \pm 30.44	101.72 \pm 4.81	53.38	< 0.0001
Diameter of adenoma (cm)	3.29 \pm 1.08	4.19 \pm 0.97	4.81 \pm 1.50	28.03	< 0.0001

correlations of PSA values with PV and MAD values, but not with age itself [14,15]. Moreover, the absence of a correlation between age and PSAD (which is a volume-corrected PSA) strongly reinforces this conclusion. Therefore, as suggested in previous papers [3,4,13,16], it is likely the increased amount of secreting tissue, as it occurs in BPH, is the main responsible for these slight to moderate increases in PSA values. Although the increase of PSA values may be considered slight to moderate (≤ 10 ng/ml) in most of patients, a small group of subjects (4.5%) may have more severe increases (> 10 ng/ml). The PSA free ratio is of limited utility in these patients: in fact in most subjects with PSA values exceeding the upper normal limit; the PSA free ratio values were within the so-called grey zone. These data indicate that in older subjects values of PSA exceeding the upper normal limit are commonly observed in absence of malignant disease, thereby increasing the likelihood of false positive results. In our view, these results provide further arguments against 'abuse' of PSA as diagnostic or screening tool in elderly subjects. Whether routine screening of all men is cost-effective remains controversial, especially for men age 75 and older [17]. If early detection of prostatic cancer improves health outcomes, the population most likely to benefit from screening will be men 50–70 years of age who were at higher risk. Older men and men with other significant medical problems who have limited life-expectancy are unlikely to benefit from screening [18].

Some limitations of this study should be discussed. The cross sectional design of this study and the absence of prospective observation do not allow to verify the true absence of malignancy. In fact, even the negativity of multiple bioptic specimens does not rule out, particularly in severe BPH, the possibility of a carcinoma in situ. The adoption of a hospital-derived sample might have facilitated the selection of subjects with more severe diseases. Finally, the absence of a comparison with a group of consecutive patients with prostate cancer does not seem to limit the validity of the results observed.

With these limits, this study showed that slight to moderate increases of PSA values are common in older subjects without evidence of malignancy and that they are mainly accounted for by a greater PV. On these basis, the adoption of age-specific range for PSA values is not recommended. This possibility of false positive results further reduces the indications to use PSA as a diagnostic screening tool in elderly subjects.

Reviewers

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Biographies

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He promoted the creation of the University Post-graduating Course of Psychogeriatrics. Main research fields: Atherosclerosis and ageing; Geriatric therapy; Public Health Organization (services for the elderly). He has devoted himself to the problems of gerontology and geriatrics for over 30 years, with particular regard to the matters connected with the life quality of the elderly. He has proposed intervention models aimed at preserving their physical, psychological and social autonomy and maintaining them in the family as long as possible. He was one of the first to realize the day hospital for the elderly and has proposed an original model of home care.

He is currently involved in the development of a department for high risk disabling pathologies.