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VALUE OF VARIOUS PSA PARAMETERS FOR DIAGNOSING PROSTATE CANCER IN MEN WITH NORMAL DIGITAL RECTAL EXAMINATION

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ABSTRACT

Objectives**:** The risks of identifying prostate cancer (PCa) in patients with serum total PSA (tPSA) between 4 and 10 ng/dl are between 25 and 35%. There are no data in Brazil showing the incidence of disease when all variables for PSA assessment are considered altogether, specifically tPSA, free fraction, PSA velocity and PSA stratified by age. The objective in this work was to define the incidence of disease in a population of men with abnormal values of PSA variables and normal digital rectal examination.

Materials and Methods**:** Between 1998 and 2003, 273 prostate biopsies were performed by the same radiologist and analyzed by the same pathologist. All patients had a normal digital rectal examination and biopsy had been indicated due to tPSA above 4 ng/dl or free-to-total PSA ratio (F/T PSA) below 15% or PSA velocity higher than 25% per year or a PSA level regarded as high for the age range. The relationship between these parameters and the positivity for prostate caner was determined.

Results**:** Patients' mean age was 63.8 years, and PCa was identified in 135 cases (49.5%). The incidence of PCa, related to unitary variations in tPSA, ranged from the limits of 33 to 80%, respectively, in tPSA < 3 and PSA between 15.1 to 20. When the other PSA parameters were assessed (free PSA, PSA according to age, rise velocity) PCa was detected in more than 25.3% of cases.

Conclusion: When patients with normal digital rectal examination are selected for prostate biopsy due to tPSA levels above 4 or F/T PSA ratio lower than 15% or PSA velocity higher than 25% per year or high PSA for the age range, the incidence of PCa is quite higher than that observed in a population selected exclusively with basis on total PSA value.

Key words: prostatic neoplasms; diagnosis; prostate-specific antigen; biopsy
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INTRODUCTION

Prostate cancer (PCa) is the fourth cause of death in men worldwide (9.2%) being surpassed only by lung (18%), stomach (11.9%) and colon/rectum cancer (9.4%) (1). According to data from the Brazilian National Cancer Institute (INCA) and the Health Ministry, prostate cancer is the second cause of death for men in Brazil, being surpassed only by lung cancer. For 2003, it is estimated the occurrence of 32,240 new cases and 8,230 deaths dues to this cancer.

Due to the magnitude of the impact over public health, strong efforts have been made aiming the prevention, early diagnosis and treatment of this disease. Strategies for increasing the early detection are focused on the determination of prostate specific antigen (PSA) in serum, digital rectal examination and transrectal ultrasonography (TRUS) with prostate biopsy (2).

PSA measurement, considered as an isolated method for screening PCa, offers some advantages in relation to digital rectal examination of prostate or TRUS. Result is quantitative, does not depend on the examiner and blood drawing is better accepted by patients (3).

In patients with benign prostate hyperplasia (BPH) its concentration rises in 30 to 50% of cases. Such increase is more pronounced in prostate cancer, occurring in 25 to 92%, and is dependant on tumor volume (4). It must be stressed that PSA is not prostate cancer-specific, but tissue-specific, and several benign conditions can affect its serum concentration (5). Moreover, a number of studies indicate that not every case of PCa cause an increase in PSA (6,7).

Despite these inconveniences, the use of PSA for detecting PCa is a worldwide practice. Recently, epidemiological studies showed a decrease in mortality resulting from this disease of up to 20% in some series where PSA was routinely dosed for screening this neoplasia (8,9).

Data are favorable, but unarguably there are limitations in the use of serum PSA for assessing potential PCa cases. For this reason, new measurements have appeared concerning the measurement of this marker, including PSA discrimination by age, PSA L/T ratio and PSA velocity, all three promote a higher detection of this neoplasia (10).

Aiming to study the significance of PSA serum levels in a population of men with normal digital rectal examination of the prostate, the PSA parameters were assessed in association with the positivity for prostate cancer in TRUS-guided prostate biopsies.

MATERIALS AND METHODS

We conducted a retrospective study of 273 transrectal ultrasonography-guided prostate biopsies, performed by a single radiologist and analyzed by the same pathologist, in the period from January 1998 to January 2003, in a single hospital.

The ultrasonography-guided prostate biopsy was indicated according to criteria previously established: cases with tPSA above 4 ng/dl, free/total PSA ratio (F/T PSA) below 15%, PSA velocity higher than 25% per year and high PSA value for age as described by Oesterling et al. in 1993 (11). The serum tPSA concentration was measured by immunometric method with results in ng/ml, using various kits, according to the laboratory where the test was performed.

The digital rectal examination was considered normal when no alterations were identified or, if present, they were characteristic of BPH (prostate with increased volume with fibroelastic consistency, smooth surface, without nodules or hardening areas).

Patients with tPSA above 20 ng/ml, altered digital rectal examination, cases of repeated prostate biopsy and those submitted to previous treatment (PCa and BPH) were excluded from the analysis.

Dada obtained were tabulated, evaluating the incidence of prostate cancer, in men with normal digital rectal examination, in the following unitary variations for tPSA: lower than 3.0; from 3.1 to 4.0; from 4.1 to 5.0; from 5.1 to 6.0; from 6.1 to 7.0; from 7.1 to 8.0; from 8.1 to 9.0; from 9.1 to 10.0; from 10.1 to 15.0 and from 15.1 to 20; and in other PSA parameters: tPSA > 4; tPSA / age; tPSA 4 -10 and F/T PSA < 15%; tPSA > 4 and PSA velocity > 25%/year; tPSA 2.6 - 4 and F/T PSA < 15%; tPSA < 4 and PSA velocity > 25%/year.

RESULTS

In the group under analysis of 273 patients the mean age was 63.8 years (42 to 82 years) and 135 (49.5%) presented prostate cancer.

tPSA values and the number of prostate fragments removed in the biopsy are represented in Table-1.

The prevalence of PCa in relation to tPSA categories ranged between the extremes of 33 to 78.6%, respectively, in tPSA < 3 and PSA between 15.1 and 20 (Table-2).

The criteria for indication of biopsy assessing the various PSA parameters in relation to the incidence of PCa are showed in Table-3.

DISCUSSION

The present work retrospectively assessed 273 prostate biopsies in men without abnormalities

Table 1 *– Age, total PSA (tPSA) and number of fragments in biopsies from 273 patients.*

PCa in Biopsy	Mean Age (years) (mean) (min/max)	Mean tPSA (ng/dl) (mean) (min/max)	No. of Fragments (mean) (min/max)
Positive = 135 cases	65.3 (46/82)	8.4 (1.4/20)	9.9 (5/25)
Negatives = 138 cases	62.4 (42/81)	8.3 (0.5/20)	12.7 (5/32)
Total = 273 cases	63.8	8.35	11.3

PCa = prostate cancer

on the digital rectal examination of the prostate that presented tPSA levels between 0.5 and 20 ng/dl. Biopsy was indicated in cases of abnormal tPSA values or F/T PSA ratio or PSA velocity/year or PSA for age. The results obtained show that the incidence of prostate cancer was superior to that observed when campaigns for detecting the disease are performed using tPSA levels only.

The present work the incidence of PCa was 49.5%, superior to that observed by Candas et al. (12), who performed an investigational population study without assessing PSA parameters. The results are presented in Table-4. However, the values obtained find a parallel in literature in large series where several PSA measures were assessed, such as those by Han et al. with 2404 patients, by Guillonneau et al. with 1000 cases and by Catalona et al. with 1870 patients, where the frequency of cases with localized prostate cancer and normal digital rectal examination (stages T1a, T1b and T1c) was, respectively, 44%, 67% and 39% (13-15).

In another study, with 1280 prostate biopsies, the authors reported 34% OF prostate neoplasia when there was any alteration in PSA associated to normal digital rectal examination (16). Cooner et al. (3) found lower figures, ranging between 9% when tPSA was lower than 4 ng/dl and 31% in patients with tPSA >10.

Table 2 *– Prevalence of prostate cancer in patients with normal digital rectal examination.*

Total PSA (ng/dl)	No. of Cases	Cancer No.	Cancer %
< 3	9	3	33.3
3.1 a 4	15	7	46.7
4.1 a 5	27	13	48.1
5.1 a 6	30	14	46.7
6.1 a 7	40	21	52.5
7.1 a 8	27	14	51.8
8.1 a 9	31	15	48.4
9.1 a 10	21	11	52.4
10.1 a 15	59	28	47.5
15.1 a 20	14	11	78.6

Table 3 – *Incidence of prostate cancer in relation to various PSA parameters for indicating biopsy.*

PSA Parameters (ng/ml)	No. of Cases	Cancer No.	Cancer %
tPSA > 4	131	66	24.2
tPSA 4 – 10 + F/T PSA < 15%	71	35	12.8
tPSA /Age	41	20	7.3
tPSA > 4 + PSA Velocity > 25%/year	12	6	2.2
tPSA < 4 + PSA Velocity > 25%/year	12	5	1.9
tPSA 2.6 - 4 + F/T PSA < 15%	6	3	1.1
Total	273	135	49.5

Table 4 *– Prevalence of prostate cancer according to stratified values of total PSA (tPSA).*

tPSA (ng/dl)	* Present Study		** Candas et al. (ref. 17)	
	No.	%	No.	%
< 3	3	33.3	37	2.0
3.1 a 4	7	46.7	41	6.0
4.1 a 5	13	48.1	31	8.3
5.1 a 7	35	50.0	56	13.9
7.1 a 10	40	50.6	52	22.5
10.1 a 20	39	53.4	59	31.4

** = Population whose biopsy was indicated by change in any parameter for PSA assessment; ** = Screening work for detection of PCa without considering PSA levels.*

The results presented surpass the values of incidence of PCa found in investigational population works for research on prostate neoplasia, which often do not consider the various PSA parameters. The present study shows that the prostate biopsy in men with normal digital rectal examination, when other PSA measurements are considered, promotes an increase in the diagnosis of neoplasia as demonstrated in Table-3, and that maybe theses cases would be undiagnosed if we assessed only by isolated PSA measurement. Gann et al. obtained a higher detection of PCa (15 to 25%), when they associated the assessment of free PSA values (10). Another factor that may be associated with these results is the higher number of fragments obtained in the prostate biopsy which showed an average above 11 in this work (Table-1).

Ravery et al. (17) reported a series with 303 patients where the increase of fragments in prostate biopsy (12 fragments) promoted the diagnosis in additional 17% of cases. In a study with 2299 consecutive biopsies, Presti et al. (18) demonstrated that a higher number of fragments increases the detection of this neoplasia, with such indication being more relevant in men under 60 years-old or in those with tPSA < 7 ng/ml.

The results demonstrate that PSA dosage has certain limitations, however when all parameters of PSA measurements are used, such as stratification by age, fractioning or rise velocity, the disease can be diagnosed in a higher number of patients.

CONCLUSION

When patients with normal digital rectal examination are selected for prostate biopsy due to tPSA levels above 4 or F/T PSA ratio lower than 15% or PSA velocity higher than 25%/year or high PSA value for age, the incidence of PCa is largely superior to that observed in a selected population assessed exclusively through serum tPSA levels.

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