Asian Journal of Andrology (2009) 11: 493–497

www.nature.com/aja

Original Article

Retrospective descriptive analysis of the physiological kinetics of prostate-specific antigen in men older than 75 years

Maria Chiara Sighinolfi[1], Salvatore Micali[1], Stefano De Stefani[1], Arrigo Cicero[2], Filippo Cianci[1], Marco Giacometti[1], Giampaolo Bianchi[1]

[1]*Department of Urology, University of Modena and Reggio Emilia, Modena 41100, Italy*
[2]*Clinical Medicine and Applied Biotechnology Department, Alma Mater Studiorum University of Bologna, Bologna 40100, Italy*

Abstract

Several studies have compared prostate-specific antigen (PSA) kinetics in men with and without cancer, but there has been no adequate analysis of the longitudinal variation in PSA. The aim of this study was to assess the fluctuations in PSA in a cohort of elderly men in an attempt to define a physiological pattern of PSA kinetics. We searched a specific cohort of patients aged > 75 years and with PSA value < 2.0 ng mL^{-1}. A history of all PSA values over the past 10 years was compiled for each patient to create a database of patients fitting the following criteria: (1) minimum of five PSA measurements, (2) over at least 5 years. Exclusion criteria were: (1) PSA < 0.2 ng mL^{-1} at each measurement and (2) having had more than one PSA test per year. In all, 1 327 patients (mean age: 78.52 years) fit the inclusion criteria. The mean variation from the first to the last PSA test was 0.05 ± 0.43, with a mean follow-up of 6.79 ± 1.71 years. Over the same period, the mean fluctuation from the lowest to the highest PSA value was 0.04 ± 0.55 (P = 0.925). The mean annual PSA velocity (PSAV) was calculated by dividing the mean variation from the first to the last PSA test by the number of years of observation for each patient and was set at 0.0104 ± 0.1050. Concluding, in a large-scale cohort of elderly individuals considered healthy and evaluated for a considerable follow-up, the average annual PSAV as well as the average fluctuation from the lowest to the highest PSA value are insignificant.

Asian Journal of Andrology (2009) 11: 493–497. doi: 10.1038/aja.2008.2; published online 18 May 2009.

Keywords: human sperm nucleus, histones, protamine, telomere

1 Introduction

Since its widespread clinical introduction in the late 1980s, prostate-specific antigen (PSA) testing has gained popularity and has revolutionized the diagnosis of prostate cancer [1]. PSA is a kallicrein-like serine protease (33 kDa) produced almost exclusively by the epithelial cells of the prostate. Prostate cancer is commonly associated with serum PSA levels that are higher than those observed in benign prostatic hyperplasia (BPH), and thus has been widely used to screen the malignant condition from the benign one. In fact, PSA level as an independent variable is a better predictor of cancer

Correspondence to: Dr Maria Chiara Sighinolfi, Department of Urology, University of Modena and Reggio Emilia, Via del Pozzo 71, Modena 41100, Italy.
Fax: +39-059-422-2863 E-mail: sighinolfic@yahoo.com
Received: 14 March 2008 Revised: 16 June 2008
Accepted: 3 August 2008 Published online: 18 May 2009

than a suspicious finding on digital rectal examination or trans-rectal ultrasound [2]. As a result, the number of locally advanced or metastatic cases of prostate cancer has progressively decreased. However, for practical and clinical purposes, PSA is organ- but not cancer-specific to the prostate gland. A limitation of PSA as a tumor marker is the substantial overlap in values between men with benign alterations (prostatic hyperplasia, prostatitis, urinary retention) and those with prostate cancer [1]. Furthermore, the PSA threshold that warrants additional evaluation is still a matter of discussion; there is no currently accepted lower cutoff value, although a value of 4.0 ng mL^{-1} has been used in many studies. In addition, the prostate biopsy strategy may change according to the PSA values, and such an approach can be planned individually [3]. In younger men (50–66 years old), the cancer detection rate has been found to be as high as 13.2% in the PSA interval 3–4 ng mL^{-1} [4]. In a recent study of 12 078 men aged under 50 years, a cutoff value of 2.0–2.5 ng mL^{-1} was deemed to be the one most reasonable in contemporary practice [5].

As the PSA value lacks sensitivity and specificity for detection of prostate cancer, alternative PSA derivatives have been evaluated for potential use in testing: free/total PSA (f/t PSA) [6] and PSA velocity (PSAV). PSAV has been identified as a potential clinical marker for this purpose. A PSAV of 0.75 ng mL^{-1} per year, or an annual increase of 20%, is suggestive of prostate cancer [7–11], and this level is accepted as a valid parameter for indicating prostate biopsy. Moreover, PSAV is associated with some characteristics of tumor aggressiveness, such as Gleason score [12], and a PSA increase of > 2.0 ng mL^{-1} in the year before diagnosis has been found to be associated with a higher risk of death due to prostate cancer after radical prostatectomy or radiation therapy [13, 14]. A more recent study suggested that the cutoff for distinguishing the most aggressive forms of prostate cancer could be set at 0.35 ng mL^{-1} per year [15].

However, it is necessary to distinguish the increases in PSA caused by the presence of cancer tissue from the physiological fluctuations of PSA. Several studies have investigated PSAV in the cancer population compared with PSAV in the non-cancer population; however, an adequate analysis of longitudinal fluctuation in the normal population has been lacking. In addition, the majority of studies investigating a PSAV threshold have been done in a selected population, usually composed of relatively young men, and have thus failed to detect the underlying physiological fluctuation that may occur in middle-aged or elderly men.

The aim of our study was to retrospectively assess PSA variations in elderly men who had PSA values < 2.0 ng mL^{-1} for a 5- to 10-year period in an attempt to define physiological fluctuation. The research focuses on PSA kinetics, and the results will contribute to defining the threshold of PSAV as a diagnostic tool for prostate cancer.

2 Materials and methods

Beginning in March 2006, we analyzed retrospective PSA data from the Central Laboratory of the Hospital-University of Modena (Modena, Italy), in search of a specific cohort of male patients aged > 75 years in 2005 and with PSA values < 2.0 ng mL^{-1}. For each subject, a retrospective search for PSA values recorded over the previous 10 years was made for the purpose of creating a database of patients meeting the following criteria: (1) a minimum of five PSA measurements, (2) over at least 5 years. The exclusion criteria were: (1) a PSA level < 0.2 ng mL^{-1} at every test and (2) having had more than one PSA test each year. These criteria were intended to reduce the risk of including subjects with clinical prostatis or of a diagnosis or recurrence of prostate cancer.

Annual PSA measurements were assessed longitudinally and collected in a database. The variation from the first to the last PSA measurement was calculated for each patient, as well as the variation from the lowest to the highest PSA value throughout the course of follow-up, to assess the major sources of individual variation. These two variables were divided by the number of years of follow-up to obtain the mean annual variation in PSA from the first to the last and from the lowest to the highest measurement for each patient.

All data were entered in a statistical database (Statistical Package for Social Sciences for Windows, version 13; SPSS, Chicago, IL, USA). Descriptive analyses of all variables were recorded, and statistical analyses were performed using the paired samples t-test and the Mann-Whitney *U* test. The cutoff for statistical significance (*P*) was fixed at 0.05.

3 Results

Throughout 2005, data from 20 000 patients aged > 75 years and with a PSA < 2.0 ng mL^{-1} were collected. In total, 1 327 subjects fit the inclusion criteria

(more than five PSA measurements for at least 5 years) and were eligible for the study.

The mean age in 2005 was 78.52 ± 3.35 years (range: 75–89 years). The mean variation from the first to the last PSA measurement was 0.05 ± 0.43 (range: –1.46 to 1.49) (variable A) for a mean follow-up of 6.79 ± 1.71 years. During the same period, the mean fluctuation from the lowest to the highest PSA value was 0.04 ± 0.55 (variable B). No statistically significant difference was found ($P = 0.925$) between variables A and B.

Additionally, the mean annual fluctuation (variable C) was calculated by dividing variable A by the number of years of observation for each patient, and the mean variation per year was set at 0.0104 ± 0.1050 (range: –0.5 to 0.6). Similarly, we divided the maximal individual fluctuation (variable B) by the number of years, obtaining a mean of 0.0123 ± 0.1260 (range: –0.5 to 0.6) (variable D). The comparison between variables C and D was not significant ($P = 0.25$).

Figure 1 shows the mean annual fluctuation (variable C) stratified for PSA range (< 1 ng mL^{-1} and 1–2 ng mL^{-1} in the first PSA measurement).

Of the 1 327 subjects, we studied a subgroup of 71 individuals with 7 years of consecutive PSA assessment. The fluctuation across years of observation was not significant ($P = 0.137$ between the 1st and 2nd years, $P = 0.162$ between the 2nd and 3rd years, $P = 0.166$ between the 3rd and 4th years, $P = 0.67$ between the 4th and 5th years, $P = 0.88$ between the 5th and 6th years and $P = 0.694$ between the 6th and 7th years [Figure 2]). For these 71 individuals, we calculated the mean PSA values from the first to the last measurement, fluctuation from the lowest to the highest measurement and PSAV; the results of these calculations were 0.06 ± 0.52 ng mL^{-1} (range: –1.22 to 1.55 ng mL^{-1}), 0.02 ± 0.80 ng mL^{-1} (range: –1.9 to 1.8 ng mL^{-1}) and 0.01 ± 0.07 ng mL^{-1} per year (range: –0.15 to 0.26 ng mL^{-1}), respectively.

4 Discussion

PSA assessment has been widely performed because of its usefulness in the diagnosis of early prostate cancer, with the measurement of PSAV improving the detection of such neoplasm. In the previous study focusing on PSA kinetics, Carter *et al*. [7] found that PSA level as a function of time in patients with localized prostate cancer was significantly higher than that in men without prostate cancer 5 years before diagnosis. Several authors have concluded that the increase in PSA values in patients with prostate cancer is 10-fold greater than in the case of BPH (0.3 ng mL^{-1}) [7, 15, 16]. However, there are physiological and biological fluctuations in PSA level that can occur even in non-cancer conditions. For example, Tchetgen *et al*. [17] reported a statistically significant increase in PSA levels after ejaculation in 87% of men older than 50 years. Rapid increases in PSA values were described even after digital rectal examination or cystoscopy [1], and, as published recently, sexually transmissible infections can induce a 40% increase in PSA [18]. Beyond the fluctuation owing to ejaculation, sexual function or medical problems, Roehrborn *et al*. [19] reported that in

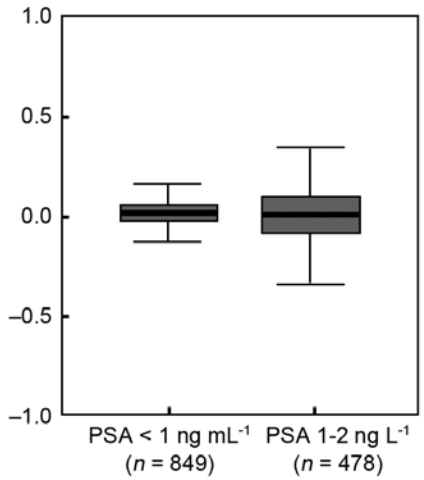

Figure 1. Mean annual fluctuation (variable C) stratified for prostate-specific antigen (PSA) range (< 1 ng mL^{-1} and 1–2 ng mL^{-1} in the first PSA measurement) .

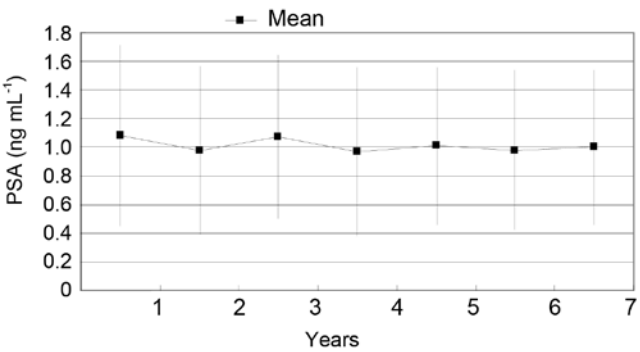

Figure 2. Mean prostate-specific antigen (PSA) values per year in a subgroup of 71 patients with 7 years of consecutive PSA assessment ($P = 0.137$ between the 1st and 2nd years; $P = 0.162$ between the 2nd and 3rd years; $P = 0.166$ between the 3rd and 4th years; $P = 0.67$ between the 4th and 5th years; $P = 0.88$ between the 5th and 6th years; and $P = 0.694$ between the 6th and 7th years).

295 subjects with initial PSA levels < 10 ng mL^{-1}, 33% showed changes of more than ± 1.0 ng mL^{-1} in 90 days. Similarly, Riehmann *et al*. [20] reported a biological fluctuation of 55% in 39 subjects without prostate cancer in whom PSA was measured more than three times, with an average measurement interval of 10.3 months. It is necessary to optimize the calculation method, measurement interval and cutoff values to distinguish the PSAV rise due to prostate cancer from that due to physiological fluctuation.

For the most part, the reported studies consider PSAV with regard to the diagnosis of prostate cancer as follows: a rapid improvement before the cancer diagnosis can suggest the aggressiveness of the pathology, as stated by D'Amico and co-workers [13, 14].

Considering the importance of PSAV and its clinical application in the field of prostate cancer, it is also necessary to measure PSA kinetics in a large healthy population. For this purpose, we entered the Central Laboratory of the Hospital–University of Modena, searching for a specific population aged > 75 years and with PSA value < 2.0 ng mL^{-1}. In those who meet these criteria, the risk of prostate cancer is very low; although a valid PSA threshold does not exist, Ito *et al*. [21] described an age-specific reference range of PSA that can increase the sensitivity, specificity and efficiency of PSA to 92.4%, 91.2% and 84.3%, respectively. According to their finding, the cutoff value for patients aged > 75 years was set at 4.0 ng mL^{-1}.

Similarly, if the recommended threshold for prostate biopsies in young men is set at 2.0 ng mL^{-1}, the prostate cancer risk in our cohort of patients is very low.

A minimum of 0.2 ng mL^{-1} was chosen in our study to exclude patients undergoing therapies that could lower the PSA value. For each patient, a retrospective history of all PSA values for the last 10 years was recorded to create a database enrolling subjects with at least five PSA assessments for at least 5 years.

The main bias of our retrospective research, as occurs in many other studies on screening populations, is that the risk of prostate cancer is consistent at any PSA value or range: failure to reach a certain cutoff cannot assure us about the absence of the neoplasm. We tried to minimize this risk by selecting an elderly population with PSA set < 2.0 ng mL^{-1}, which is a value in accordance with most recent suggestions about age-related PSA values. Another bias is the lack of clinical information: we tried to reduce this inaccuracy by excluding patients with two or more PSA assessments per year, thus avoiding the risk of clinical prostatis, diagnosis or recurrence of prostate cancer.

Beyond these biases, we think that the volume of the cohort in this large-scale study must be highlighted, with a total of 1 327 PSA values followed retrospectively for a minimum of 5 years, and thus representing the main impact and power of the research. In addition, the recent publication of similar studies [22] shows that this is a very current and relevant theme in the diagnosis of prostate cancer.

Our outcomes strengthen the point of view of Scales *et al*. [23], who analyzed the benefit of PSA testing in men older than 75 years and concluded that up to a third of those patients have an average life expectancy of < 10 years.

As suggested in the recent 'prostate, lung, colorectal and ovarian cancer screening trial' [24], screening steps can be optimized. The authors of that study concluded that screening every 5 years for baseline PSA < 1 ng mL^{-1} and every 2 years for PSA 1–2 ng mL^{-1} could result in a 50% reduction in PSA tests and in < 1.5% of men missing earlier positive screens. Our outcomes confirm that yearly repeated PSA assessment in an elderly population, with a potential life expectancy of < 10 years and with normal PSA values at baseline, may have low significance in urological practice and screening programs.

However, although repeated PSA assessments lose significance in older population, a recent study by Ulmert *et al.* [25] showed the importance of PSA before the age of 50 years, invoking this marker as a predictor of prostate cancer up to 25 years later. This outcome confirms the need for a risk-stratified screening approach for clinically significant diseases.

Even though the popularity of PSA is widely debated owing to its lack of sensitivity and specificity and the absence of an agreed-upon threshold, it still remains the most powerful marker in the management of prostate cancer diagnosis. PSAV has gained popularity for improving the usefulness of this indicator, and several studies have focused on the variation characterizing cancerous degeneration. Longitudinal assessment of PSA in an elderly and supposedly healthy population may help define its physiological kinetics. Our study represents a long-term retrospective PSA observation in a population aged > 75 years: PSA variation from the first to the last and from the highest to the lowest values seems to be insignificant. Even if followed up year by year, PSA fluctuations seem insignificant.

These outcomes help to define the possible phases of a screening program, especially if the program is targeted at elderly patients with a life expectancy lower than 10 years, with a low risk for prostate cancer. Physicians and urologists should consider these findings and apply them in their urological practice.

References

1 Polascik TJ, Oesterling JE, Partin AW. Prostate specific antigen: a decade of discovery – what we have learned and where we are going. J Urol l999; 162: 293–306.
2 Catalona WJ, Richie JP, Ahmann FR, Hudson MA, Scardino PT, *et al.* Comparison of digital rectal examination and serum prostate specific antigen in the early detection of prostate cancer. Results of a multicenter clinical trial of 6 630 men. J Urol 1994; 151: 1283–90.
3 Dai B, Ye DW, Kong YY, Shen YJ, Wang BH. Individualized prostate biopsy strategy for Chinese patients with different prostate-specific antigen levels. Asian J Androl 2008; 10: 325–31.
4 Lodding P, Aus G, Bergdahl S, Frösing R, Lilja H, *et al.* Characteristics of screening detected prostate cancer in men 50 to 66 years elderly with 3 to 4 ng/mL prostate specific antigen. J Urol 1998; 159: 899–903.
5 Sun L, Moul JW, Hotaling JM, Rampersaud E, Dahm P, *et al.* Prostate-specific antigen (PSA) and PSA velocity for prostate cancer detection in men aged < 50 years. BJU Int 2007; 99: 753–7.
6 Hara N, Kitamura Y, Saito T, Komatsubara S. Total and free prostate-specific antigen indexes in prostate cancer screening: value and limitation for Japanese populations. Asian J Androl 2006; 8: 429–34.
7 Carter HB, Pearson JD, Metter EJ, Brant LJ, Chan DW, *et al.* Longitudinal evaluation of prostate-specific antigen levels in men with and without prostate disease. JAMA 1992; 267: 2215–20.
8 Pearson JD, Carter HB. Natural history of changes in prostate specific antigen in early stage prostate cancer. J Urol 1994; 152: 1743–8.
9 Carter HB, Pearson JD, Waclawiw Z, Metter EJ, Chan DW, *et al.* Prostate-specific antigen variability in men without prostate cancer: Effect of sampling interval and number of repeat measurements on prostate-specific antigen velocity. Urology 1995; 45: 591–6.
10 Smith DS, Catalona WJ. Rate change in serum prostate specific antigen levels as method for prostate cancer detection. J Urol 1994; 152: 1163–7.
11 Eastham JA, Riedel E, Scardino PT, Shike M, Fleisher M, *et al.*; Polyp Prevention Trial Study Group. Variation of serum prostate-specific antigen levels: an evaluation of year-to-year fluctuations. JAMA 2003; 289: 2695–700.
12 Krejcarek SC, Chen MH, Renshaw AA, Loffredo M, Sussman B, *et al*. Prediagnostic prostate-specific antigen velocity and probability of detecting high-grade prostate cancer. Urology 2007; 69: 515–9.
13 D'Amico AV, Renshaw AA, Sussman B, Chen MH. Pretreatment PSA velocity and risk of death from prostate cancer following external beam radiation therapy. JAMA 2005; 294: 440–7.
14 D'Amico AV, Chen MH, Roehl KA, Catalona WJ. Preoperative PSA velocity and the risk of death from prostate cancer after radical prostatectomy. N Engl J Med 2004; 351: 125–35.
15 Carter HB, Ferrucci L, Kettermann A, Landis P, Wright EJ, *et al.* Detection of life-threatening prostate cancer with prostate-specific antigen velocity during a window of curability. J Natl Cancer Inst 2006; 21: 1521–7.
16 Kabalin JN, McNeal JE, Johnstone IM, Stamey TA. Serum prostate-specific antigen and the biologic progression of prostate cancer. Urology 1995; 46: 65–70.
17 Tchetgen MB, Song JT, Strawderman M, Jacobsen SJ, Oesterling JE. Ejaculation increases the serum prostate-specific antigen concentration. Urology 1996; 47: 511–6.
18 Sutcliffe S, Zenilman JM, Ghanem KG, Jadack RA, Sokoll LJ, *et al*. Sexually transmitted infections and prostatic inflammation/cell damage as measured by serum prostate specific antigen concentration. J Urol 2006; 175: 1937–42.
19 Roehrborn CG, Pickens GJ, Carmody T 3rd. Variability of repeated serum prostate-specific antigen (PSA) measurements within less than 90 days in a well-defined patient population. Urology 1996; 47: 59–66.
20 Riehmann M, Rhodes PR, Cook TD, Grose GS, Bruskewitz RC. Analysis of variation in prostate-specific antigen values. Urology 1993; 42: 390–7.
21 Ito K, Yamamoto T, Kubota Y, Suzuki K, Fukabori Y, *et al.* Usefulness of age-specific reference range of prostate-specific antigen for Japanese men older than 60 years in mass screening for prostate cancer. Urology 2000; 56: 278–82.
22 Berger AP, Deibl M, Strasak A, Bektic J, Pelzer AE, *et al.* Large-scale study of clinical impact of PSA velocity: long-term PSA kinetics as method of differentiating men with from those without prostate cancer. Urology 2007; 69: 134–8.
23 Scales CD Jr, Curtis LH, Norris RD, Schulman KA, Albala DM, *et al*. Prostate specific antigen testing in men older than 75 years in the United States. J Urol 2006; 176: 511–4.
24 Crawford ED, Pinsky PF, Chia D, Kramer BS, Fagerstrom RM, *et al*. Prostate specific antigen changes as related to the initial prostate specific antigen: data from the prostate, lung, colorectal and ovarian cancer screening trial. J Urol 2006; 175: 1286–90.
25 Ulmert D, Cronin AM, Björk T, O'Brien MF, Scardino PT, *et al*. Prostate-specific antigen at or before age 50 as a predictor of advanced prostate cancer diagnosed up to 25 years later: a case-control study. BMC Med 2008; 15: 6.