PSA Dynamics

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Stacy Loeb and H. Ballentine Carter

Prostate-specific antigen (PSA) is widely used today for the diagnosis and management of men with prostate cancer. It is well known that PSA screening has led to a major stage migration, with most prostate cancers now diagnosed at a localized, curable stage [1]. Epidemiologic studies have also shown that prostate cancer mortality rates are lowest in areas where the rates of distant-stage disease are lowest, and distant-stage disease is lowest in areas with the highest PSA utilization [2]. Finally, randomized trials of PSA screening have recently been reported. The European Randomized Study of Screening for Prostate Cancer (ERSPC) and the Goteborg population-based screening trial (including a subset of Swedish ERSPC participants) reported a 21% and 44% relative reduction in prostate cancer mortality with screening at 11 and 14 years, respectively [3, 4]. The US Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial reported no difference in mortality with screening in the overall results [5].

In addition to its use in screening, PSA is also widely used for assessing disease extent after diagnosis of prostate cancer and for monitoring patients who have undergone treatment for the disease [6]. Even though widely used for two decades, interpretation of PSA values can be confusing both when used for diagnosis and management. There is increasing recognition of a wide variety of influences on PSA, including genetic variations, certain classes of medications (e.g., statins), obesity, and differences in assay standardization [7–11].

Correspondingly, there has been increasing interest in PSA changes (dynamics), which may provide important information beyond an absolute PSA value for assessing the risk of cancer, cancer significance, and death from prostate cancer after curative intervention. This chapter will review the role of PSA dynamics in the diagnosis and management of men with prostate cancer with an emphasis on diagnosis and assessment of disease significance.

Introduction to PSA Dynamics

The most commonly used metrics to describe changes in PSA are PSA velocity and PSA doubling time. PSA velocity (PSAV) is the rate of change in PSA or the change corrected for the elapsed time usually expressed in ng/ml per year (i.e., annualized), whereas PSA doubling time (PSADT) reflects "growth" of PSA and is the time to double the marker, usually expressed in months or years. PSADT is calculated from the slope of the regression of the log-transformed PSA on time and thus assumes an exponential

S. Loeb, M.D.
Department of Urology, New York University,
New York, NY, USA

H.B. Carter, M.D. (✉)
Department of Urology, Marburg 403,
Johns Hopkins School of Medicine, 600 N Wolfe Street,
Baltimore, MD 21287, USA
e-mail: hcarter@jhmi.edu

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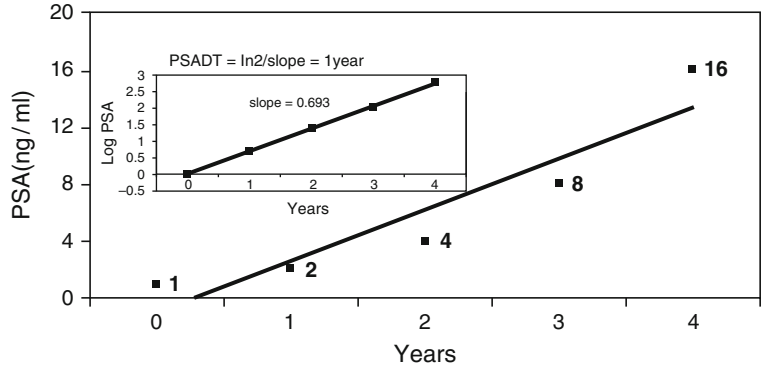

Fig. 4.1 Prostate-specific antigen (PSA) as a function of time (years). *Line* represents regression of PSA on time. *Inset* is log transformation of PSA as a function of time. *PSADT* PSA doubling time, *ln* natural logarithm

relationship between PSA and time. PSADT could be constant while PSA is increasing exponentially (see Fig. 4.1).

The slope of the line of the regression of PSA on time is the rate of change in PSA or PSA velocity (PSAV). The equation that describes a straight line is $y = mx + b$, where m is the slope and b is the intercept. This approach assumes a linear relationship between PSA and time as shown in Fig. 4.1. The slope (PSAV) in this example is 3.6 ng/ml per year over 4 years. Another method for calculating PSAV is the running average or the simple PSAV (change divided by time) between 2 points, plus the PSAV between the next 2 points, all divided by 2. For example, the average rate of change in Fig. 4.1 for year 2–4 is ([8 ng/ml-4 ng/ml]/1 year) + ([16 ng/ml-8 ng/ml]/1 year)/2 = 6 ng/ml/year. For PSADT, one can plot the log-transformed PSA on time for the above example (see figure inset), then apply the following formula: ln (2)/slope = PSADT. The ln2 = 0.693 and the slope = 0.693 giving a PSADT of 1 year.

Some studies have suggested that PSAV should be calculated using three repeated PSA measurements over an interval of at least 18 months to optimize its accuracy for prostate cancer detection [12–14] whereas more recent studies have shown predictive value using PSAV calculated over a 12-month time interval [15]. Prior studies have compared the different methods of PSAV calculation and demonstrated how the measurement will differ depending upon the time interval over which it is calculated (e.g., 12 vs. 18 months or longer) [16].

PSA Dynamics: Predicting the Presence of Prostate Cancer

There can be substantial changes or variability in serum PSA between measurements in the presence or absence of prostate cancer [17–20]. The short-term changes in PSA are primarily a result of physiologic variation [18]. Numerous studies have shown that men who harbor prostate cancer have more rapid rises in PSA when compared to those without the disease [12, 13, 21–26], which is useful for assessing the risk that prostate cancer is present.

Using frozen sera to measure PSA from many years earlier, Carter and colleagues found that at 5–10 years before clinical diagnosis, the median PSAV for men with localized prostate cancer (0.27 ng/ml/year) and metastatic disease (1.33 ng/ml/year) were significantly greater when compared to those men with BPH (0.09 ng/ml/year) and controls (0.01 ng/ml/year) (see Fig. 4.2) [12]. Even at 10–15 years prior to clinical diagnosis, the median PSAV for men with localized prostate cancer (0.14 ng/ml/year) and metastatic disease (0.30 ng/ml/year) were significantly greater when compared to controls (0.02 ng/ml/year) but not those with BPH (0.09 ng/ml/year). In that study,

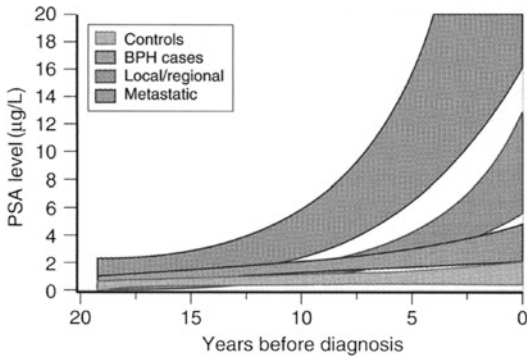

Fig. 4.2 The *curves* represent the average PSA levels and the 95% confidence limits of PSA among men without prostate disease (*bottom curve*), men with BPH who underwent simple prostatectomy (*next to bottom*), localized prostate cancer (*third from bottom*), and metastatic prostate cancer (*top curve*) as a function of years before diagnosis (prostate cancer), simple prostatectomy (BPH), or last visit to the BLSA indicated by time 0. Men in this study were diagnosed prior to the PSA era and were more likely to have life-threatening disease when compared to men diagnosed today (Adapted from Carter et al. [12])

72% of men with cancer and 5% of men without cancer had a PSAV >0.75 ng/ml/year. The specificity of PSA velocity using a cut point of 0.75 ng/ml/year remained high (over 90%) when PSA levels were between 4 and 10 ng/ml or below 4 ng/ml, but sensitivity for cancer detection was 11% at levels below 4 ng/ml compared with 79% for levels between 4 and 10 ng/ml.

More recent studies have demonstrated that PSA velocity might be useful for prostate cancer detection among men with PSA levels below 4.0 ng/ml. In a longitudinal aging study, the cumulative probability of freedom from prostate cancer at 10 years after a baseline PSA between 2 and 4 ng/ml was 97.1% (range 91.4–100%) and 35.2% (range 14.0–56.4%) when the PSAV was less than and greater than 0.1 ng/ml/year, respectively [27]. However, Roobol et al. did not find that PSAV was an independent predictor of a prostate cancer diagnosis at the second screening round of the Rotterdam ERSPC when PSA was less than 4.0 ng/ml, although the calculations were based upon two PSA measurements separated by a 4-year screening interval [28]. By contrast, in 22,019 men with PSA <4 ng/ml from a large PSA screening study in the US, a PSAV >0.4 ng/ml/year was a stronger predictor of prostate cancer on multivariate analysis than age, race, or family history [29].

The 2012 National Comprehensive Cancer Network Guidelines recommend considering a biopsy for men with a PSA ≤2.5 ng/ml and PSAV ≥0.35 ng/ml/year [30]. This was recently challenged by one study using data from the Prostate Cancer Prevention Trial (PCPT), in which PSAV was a significant independent predictor of biopsy outcome but was associated with only a small improvement in predictive accuracy [31]. Thus, the authors concluded that biopsy should be based on total PSA rather than a PSAV indication. However, emerging data suggest that men with a PSAV >0.4 ng/ml/year prior to a prostate cancer diagnosis are 50% less likely to meet published criteria for insignificant disease [32]. Another recent study from the Baltimore Longitudinal Study of Aging (BLSA) showed that the probability of life-threatening prostate cancer was 3% for men with a PSA <3 ng/ml; however, this increased to 13.6% if the PSAV was greater than 0.4 ng/ml/year [33]. Thus, PSAV may be more useful in enhancing the specificity of screening for clinically significant prostate cancer, as will be discussed in the next section.

Overall, Table 4.1 compares the PSAV findings in men with and without prostate cancer from several studies with different designs (i.e., prospective and retrospective). Differences in PSAV between studies may reflect differences in cohort age, absolute PSA levels, and cancer grade and extent—all of which can influence PSAV. Indeed, PSAV increases directly with PSA [34], which should be taken into consideration for proper clinical interpretation. For example, among men without prostate cancer from the BLSA, the mean PSAV was 0.02 ± 0.29 ng/ml/year for observations at PSA levels <3 ng/ml compared to 0.3 ± 0.59 ng/ml/year at a PSA of 3–10 ng/ml [33]. PSAV may also be influenced by age [13], with some data suggesting improved performance characteristics in young men [35]. However, age-related differences in the prevalence of confounding conditions (such as BPH and prostatitis [36]) may be more important determinants than age

Table 4.1 Average PSA velocity (PSAV) in men with and without prostate cancer

		PSAV (ng/ml per year)	
Study	Study design	No cancer	Cancer
Carter et al. [12, 13]	Longitudinal aging study	0.04	0.75
Oesterling et al. [26]	Longitudinal BPH study	0.04	–
Berger et al. [25]	Invitational screening over 10 years	0.03	0.4
Raaijmakers et al. [24]	Randomized screening at 4-year interval	0.09	0.62
Loeb et al. [35]	Invitational screening over 10 years	0–0.1	0.6–0.7[a]

[a]Depending upon age decade

itself. Finally, changes in PSA are greater for men with high-grade cancers when compared to low-grade cancers [37, 38].

Of note, there is also evidence that PSA kinetics are useful for prostate cancer risk assessment in men taking medications known to affect PSA levels, such as 5-alpha-reductase inhibitors (5-ARIs). For example, Etzioni et al. demonstrated that in contrast to the expected decreasing PSA levels for men taking finasteride, those diagnosed with prostate cancer had a rising annual PSA by approximately 15% for interval cases and 7% for cases diagnosed on empiric biopsy at the end of the trial [37]. Thus, a rise in the PSA level during treatment with 5ARIs can indicate the need for prompt biopsy.

PSA Dynamics: Prediction of Life-Threatening Disease

Before Curative Intervention

D'Amico et al. demonstrated that PSAV in the year prior to treatment of presumed localized prostate cancer was associated with the probability of prostate cancer death after curative intervention [15, 39]. In a landmark study, the authors evaluated PSAV in the year prior to surgery for men with clinically localized disease [15]. They found that when compared to a PSA velocity below 2 ng/ml/year in the year prior to diagnosis, a PSA velocity greater than 2 ng/ml/year was associated with a tenfold greater risk of prostate cancer death in the 7 years after surgery. Thus, failure of local therapy among men with presumed localized disease was associated with a higher PSAV. This seminal observation suggested that PSA velocity could be useful in assessing the biological behavior of prostate cancer prior to treatment. The authors have made the same observations after radiation therapy for prostate cancer [39]. In addition, Sengupta et al. showed that both PSAV and PSADT were significant predictors of radical prostatectomy outcomes at a median follow-up of 7 years [40].

It seems intuitive that PSA would rise faster in those men with high-grade cancer when compared to those with lower-grade cancers if PSA gains access to the systemic circulation by alterations in prostatic architecture caused by cancer. In addition, PSA may have greater access to the circulation in men with micrometastatic deposits compared to those with organ confined disease. Data from the PCPT have shown that men with high-grade cancers have faster PSA rises (annual percent change in PSA) in PSA compared to those with lower-grade cancers [37]. In the end of study biopsies (biopsies done not for elevated PSA or abnormal digital rectal examination) in the PCPT, men with high-grade cancers (Gleason score 7 and above) had an annual PSA change of 11–12% compared to those with low-grade cancers (Gleason score ≤6) where annual changes were 5–6% (i.e., twofold higher for high-grade cancers vs. low-grade cancers). For a man with a PSA of 2.5 ng/ml, this would translate into a PSAV of 0.3 ng/ml/year for high-grade cancer and 0.15 ng/ml/year for low-grade cancer.

Overall, the data from D'Amico et al. demonstrated that a higher PSAV in the year before diagnosis was associated with a greater likelihood that presumed localized disease would not be cured with local therapy (radiation and

surgery) [15, 39]. This leads to the question whether PSAV could help identify those men with life-threatening cancers at a time when cure might still be possible. Among men enrolled in a longitudinal aging study, PSAV evaluated 10–15 years prior to diagnosis (when absolute PSA levels were below 4.0 ng/ml in most men) predicted cancer-specific survival 25 years later [41]. Using a PSAV cutoff of 0.35 ng/ml/year, cancer-specific survival was 92% (84–96) for those with a PSAV of 0.35 ng/ml/year or less compared to 54% (15–82) for men with a PSAV more than 0.35 ng/ml per year ($p=0.0001$). The relative risk of prostate cancer death was 4.7 (1.3–16.5) for participants with a PSAV more than 0.35 ng/ml/year compared to those whose PSAV ≤0.35 ng/ml/year ($p=.02$). These data suggest that even among men with PSA levels that are traditionally considered to be low (below 4.0 ng/ml), the rate of rise in PSA may provide an early warning sign to identify those men at risk for life-threatening disease. This suggests that overdiagnosis and overtreatment might be reduced through an evaluation of the rate at which PSA rises (PSAV) rather than relying on a single dichotomous PSA cut point.

PSADT has also been studied in relation to treatment outcomes. Among men undergoing active surveillance, some groups have used PSADT after diagnosis to assess for progressive disease [42], whereas others have found a poor correlation between PSADT with adverse pathology on repeat surveillance biopsy or subsequent radical prostatectomy [43].

For men undergoing definitive treatment, the data are similarly controversial. In the study by Sengupta et al., PSADT was a robust predictor of clinical progression and prostate cancer death after radical prostatectomy [40]. By contrast, other studies have found that PSAV during the 5 years prior to prostate cancer diagnosis improved the prediction of life-threatening disease, while PSADT did not [44].

A systematic review of studies published prior to 2007 concluded that there was little evidence that pretreatment PSA kinetics provide incremental value above PSA alone [45]. However, the negative findings in this study may reflect the outcome of combining together studies using PSAV or PSADT in heterogeneous patient populations to predict a divergent set of endpoints. In this regard, an updated systematic review of studies focusing on a single PSA dynamic to predict clinically significant or life-threatening prostate cancer would be useful, particularly given the rapidly expanding literature on this topic.

After Failed Curative Intervention

It has been estimated that 20–40% of men who undergo curative intervention for presumed localized prostate cancer with radiotherapy or surgery will have evidence of biochemical failure over the 10 years after treatment [46]. Because a detectable or rising PSA after treatment is not a valid surrogate for clinical relapse (radiographic or physical evidence of disease) or more importantly overall survival, it is difficult to identify which patients will benefit from further treatment [46–51]. In a series of men with a detectable PSA after surgical treatment of prostate cancer followed without additional treatments, 34% developed metastatic disease at a median of 8 years after PSA failure, and of these 43% (or 15% of those with metastatic disease) died of prostate cancer at a median of 5 years later [47]. Ward et al. found that 29% of men who experienced biochemical failure progressed to clinical failure, and 8% died of prostate cancer at a median of 10 years after clinical failure was documented [48]. Thus, biochemical failure after curative intervention is not synonymous with death from prostate cancer but instead represents a heterogeneous state that is a continuum from insignificant disease to the development of metastatic disease and death.

The management of biochemical failure after curative intervention is complicated by this uncertainty regarding future progression to clinically apparent disease and the inability to accurately determine by imaging if microscopic disease is localized or distant. Since salvage therapy is associated with potential morbidity and most men with biochemical failure after definitive therapy will not develop metastatic disease or die

Table 4.2 Distributions of PSA doubling time (PSADT) after failure of local therapy

Study (# of subjects)	PSADT (months)	Distribution (%) of subjects
D'Amico et al. [49] ($n=8,669$)	<3	12
	3–5.9	16
	6–11.9	28
	≥12	44
Freedland et al. [50] ($n=379$)	<3	6
	3–5.9	15
	6–11.9	29
	≥12	50
Stephenson et al. [51] ($n=501$)	<7.4	50
	>7.4	50
Ward et al. [48] ($n=211$)	<7.3	50
	>7.3	50

from prostate cancer within 10 years [47, 48], it is important to identify those with a significant recurrence for whom further treatment may be most beneficial.

In this regard, D'Amico et al. showed that PSADT is a surrogate endpoint for prostate cancer mortality and overall mortality among men with biochemical failure, independent of curative treatment received (radiation or surgery) [49]. In their study, the posttreatment PSADT was statistically significantly associated with time to prostate cancer-specific and all-cause mortality. A PSADT of less than 3 months was associated with a median time to prostate cancer-specific mortality of 6 years and a hazard ratio of 19.6 for prostate cancer-specific mortality. These results were confirmed by Freedland et al. who followed untreated men with biochemical failure after radical prostatectomy [50]. Overall, the proportion of patients with postoperative biochemical failure with a PSADT less than 3 months is around 10% (Table 4.2). However, due to the imminent risk of metastatic disease in these men, a PSADT <3 months may be a useful marker for a subset who would benefit from early salvage therapy.

In fact, the continuum of PSADT provides a useful surrogate endpoint for prostate cancer-specific mortality for those with biochemical failure after curative intervention [49]. In the study by Freedland et al., PSADT, pathological Gleason score, and time from surgery to biochemical recurrence were all significant risk factors for time to prostate cancer-specific mortality [50]. However, a PSADT below 9 months was associated with a higher risk of prostate cancer death when compared to time from surgery to recurrence (≤3 vs. >3 years) and pathological Gleason score (≥8 vs. <8). Thus, PSADT should be used in the decision-making process when determining the need for salvage treatments in those with biochemical failure after curative intervention. Accordingly, the authors calculated estimates of the risk of biochemical recurrence at 15 years after biochemical failure as a function of PSADT, grade, and time from surgery to recurrence to help physicians and patients choose management options (Table 4.3) [50].

Conversely, D'Amico et al. identified a subset of patients who appear to have clinically insignificant PSA failure and might be spared from salvage therapy [52]. A PSADT ≥12 months and a pretreatment PSAV <0.5 ng/ml/year (12% of population) were associated with maintenance of a minimally detectable PSA and associated with pathological features at surgery that were not different from those who did not sustain PSA failure. Further follow-up may identify a larger proportion of patients with biochemical failure after curative intervention who should consider surveillance instead of salvage therapy.

Conclusions

Evaluation of PSA changes over time (PSA dynamics) is a method that can be used to help assess the risk of prostate cancer detection. Accumulating data suggest that there is no PSA level below which we can reassure a man that prostate cancer is not present. Therefore, instead of performing a biopsy on all men who reach a given PSA threshold, another approach would be to evaluate the rate at which the PSA rises and use this information as part of the decision-making process regarding the need for biopsy. Although the data on PSAV as a predictor of overall prostate cancer risk are more controversial, a large body of evidence demonstrates that PSAV correlates with the likelihood that life-threatening

Table 4.3 Estimated risk of prostate cancer-specific survival 15 years after biochemical failure following surgery

	Risk estimate, % (95% confidence interval)			
	Recurrence >3 year after surgery		Recurrence ≤3 year after surgery	
PSADT (mo)	Gleason score <8	Gleason score ≥8	Gleason score	Gleason <8 score ≥8
≥15	94(87–100)	87(79–92)	81(57–93)	62(32–85)
9–14.9	86(57–97)	72(35–92)	59(24–87)	31(7–72)
3–8.9	59(32–81)	30(10–63)	16(4–49)	1(<1–51)
<3	19(5–51)	2(<1–38)	<1(<1–26)	<1(<1–2)

Adapted from Freedland et al. [50]

disease is present. Thus, a PSAV-based screening approach might help reduce the overdiagnosis and overtreatment of prostate cancer that has occurred with PSA screening. PSA dynamics are also useful predictors of treatment outcomes. Finally, among men with biochemical recurrence after curative intervention, PSA doubling time is a surrogate for survival and can be used to help identify those men with life-threatening recurrence who are most likely to benefit from salvage treatments.

Editorial Commentary:
If fraternal twins present to different urologists with PSA values of 4.1 and 3.9, respectively, the traditional threshold (4.0) would lead to a recommendation for biopsy in the first one but reassurance and a recommendation to repeat the laboratory test in 1 year in the second. Obviously this would be flawed thinking, as their actual likelihood of having cancer is essentially—if not exactly—the same.

Thus, it has become clear that thresholds or cutoffs are artificial and misleading. Delving deeper using tools such as PSAV allows us to more fully explore and understand prostate cancer risk assessment. Although a recent study has challenged empiric use of this concept, the authors demonstrate that taking PSA dynamics into account improves our ability to identify real risk, even if incrementally. Even more importantly, PSAV appears to improve identification of the higher-grade cancers whose detection has the potential to improve outcomes.

–J. Stephen Jones

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