Dissecting the Dynamics of Serum Prostate-Specific Antigen

Robin T. Vollmer, MD

Key Words: Serum prostate-specific antigen; PSA; PSA velocity; Dynamics; Kinetics; Prostate cancer; Tumor volume; Tumor histology

Abstract

I have examined more than 800 values of serum prostate-specific antigen (PSA) in 119 American Veterans during the time before their diagnosis of prostate cancer. These values appear to follow an exponential model with respect to time. Specifically, the model comprises a sum of 2 exponential functions: one for an early, slowly rising component of PSA and a second for a later, faster rising component. The parameters of each component comprise an amplitude and a relative velocity. Whereas the relative velocity of the slow component is significantly associated with the volume of benign tissue, both the amplitude and relative velocity of the fast component are significantly associated with the volume of tumor. The results suggest that at the time of diagnosis of prostate cancer the level and velocity of PSA reflect the combination of slow and fast components. Thus, this model provides insight into how benign and malignant tissues in the prostate determine the dynamics of PSA.

Early investigators of serum prostate specific antigen (PSA) discovered that the level of PSA was proportional to the amount of tumor in the prostate. If we symbolize serum PSA as $y$ and tumor volume as $V_c$, then mathematically this proportionality between PSA and tumor volume can be written as:

$$y = \alpha \cdot V_c$$  (Equation 1)

In this equation, $\alpha$ represents the proportionality constant. Very soon thereafter some of the same investigators found that the rate of increase in PSA related positively to the stage of prostate cancer, and later this rate became known as PSA velocity. In calculus, the first derivative of Equation 1 with respect to time, $t$, yields the change in PSA with time as follows:

$$\frac{dy}{dt} = \alpha \cdot \frac{dV_c}{dt}$$  (Equation 2)

Thus, PSA velocity (that is, $\frac{dy}{dt}$) should reflect the rate of increase in tumor volume. For this reason, there has been considerable interest in using PSA velocity as an indirect measure for the rate of tumor growth.

Some of these same early investigators also observed that the rate of rise in PSA was correlated with the level of PSA. Mathematically, this observation suggests that:

$$\frac{dy}{dt} = \beta \cdot y$$  (Equation 3)

Here, $\beta$ represents another proportionality constant. In calculus, Equation 3 is a differential equation whose solution is:

$$y = y_0 \cdot \exp(\beta \cdot t)$$  (Equation 4)

where $y_0$ symbolizes the value of PSA at time 0, and $\exp$ stands for the exponential function. Thus, the empirical
observations made by Stamey et al1 and Stamey and Kabalin,2 together with logical and mathematical developments, imply that PSA should have an exponential relationship with time, and this has been observed by many who have studied the time-related dynamics of PSA. The exponential relationship between PSA and time and Equation 3 are equivalent observations. Consequently, PSA velocity and level of PSA cannot be statistically independent of one another.22,25

If we solve Equation 3 for β, we get:

Equation 5

\[ \beta = \frac{dy}{dt}/y = \text{PSA velocity/PSA} \]

In other words, β is equal to PSA velocity divided by PSA, and its units are 1/time. For this reason, β has been described as a relative velocity of PSA, that is, a PSA velocity relative to the level of PSA, and several studies have examined its importance in prostate cancer.22,25

Another dynamic PSA variable is the PSA doubling time, which we symbolize here as td. The doubling time is closely related to β. For example, if we take the natural logarithm of Equation 4 we get:

Equation 6

\[ \log(y/y_0) = \beta \times t \]

Consider the situation when the final value of PSA is twice that of the initial value. In this circumstance, y/y0 equals 2, and the time t becomes the doubling time, td. Thus,

Equation 7

\[ td = \log(2)/\beta \]

In other words, td is approximately equal to 0.693/β. The potential importance to β and td can be seen in what follows. If we combine the results of Equations 1, 2, and 3 we get:

Equation 8

\[ dy/dt = \beta \times y = \beta \times \alpha \times V_c = \alpha \times dV_c/dt \]

implying that:

Equation 9

\[ dV_c/dt = \beta \times V_c \]

Thus, β should be equal to the relative velocity of tumor growth, and this result explains how there can be so much interest in either relative velocity or the doubling time of PSA.

The problem with the foregoing development and most of the cited studies, of course, is that the contribution of benign tissues to the dynamics of PSA is largely ignored. Theoretical analysis, common sense, and empirical data suggest that any observed level of PSA is due to the sum of benign and malignant tissues.49,51 Because each of these tissues can influence the dynamics of PSA in a distinct way, herein I explore the contributions of benign and malignant tissues to the dynamics of PSA.

Materials and Methods

The study population comprised 119 men who underwent prostatectomy at the Veterans Affairs Medical Center (Durham, NC) and who had at least 4 measurements of serum PSA made before their diagnosis, with these measurements taking place during a time lapse long enough so that at least 1 measurement occurred more than 11 months before their diagnosis. There were no other inclusion or exclusion criteria. Their prostates were completely examined histologically, and grade, pathologic stage, and percentage of tissue with tumor were recorded. The volume of tumor, Vc, was estimated as the percentage of tissue with tumor multiplied times the mass of prostate tissue, and the volume of benign tissue was estimated as the remainder.51 Other details about the study men are given in Table 1. The study was approved by the local Veterans Affairs Medical Center Institutional Review Board.

Exponential Model

We start with the hypothesis that the evolution of serum PSA in men with prostate cancer is due to 2 components: an early one with a slow rise in PSA and a later one with a faster rise in PSA. The early, slow component corresponds to benign enlargement of the prostate with age. The second, fast component corresponds to the development and growth of prostate cancer. In keeping with prior observations of exponential rises in serum PSA, I also assumed that both components should be approximately exponential with respect to time. In mathematical terminology, the slow component can then be written as:

Equation 10

\[ \text{Slow PSA} = \alpha s \times \exp(\beta s \times t) \]

Here, αs is the amplitude of the slow component, and, as before, t symbolizes the current time, which in this study is the time to diagnosis. Consequently, all times have negative values, and the time of diagnosis is when t equals 0. βs is the relative velocity of the slow component. The fast component can be written as:

Equation 11

\[ \text{Fast PSA} = \alpha f \times \exp(\beta f \times t) \]

Here, αf symbolizes the amplitude and βf the relative velocity of the fast component. Total serum PSA can then be modeled as the sum of slow and fast components:

Table 1

Characteristics of Study Population*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>119</td>
</tr>
<tr>
<td>Age (y)</td>
<td>62 (50-74)</td>
</tr>
<tr>
<td>Gleason score</td>
<td>7 (5-9)</td>
</tr>
<tr>
<td>No. with stage pT3</td>
<td>27</td>
</tr>
<tr>
<td>No. of prostate-specific antigen values</td>
<td>7 (5-17)</td>
</tr>
<tr>
<td>Estimated volume of cancer (cc)</td>
<td>5.2 (0.09-64.6)</td>
</tr>
</tbody>
</table>

* Data are given as mean (range) unless otherwise indicated.
Equation 12

Total PSA = \( \alpha_s \exp(\beta_s t) + \alpha_f \exp(\beta_f t) \)

For each patient, Equation 12 was fitted to the observed values of serum PSA measured before the time of diagnosis. In other words, parameters \( \alpha_s, \beta_s, \alpha_f, \) and \( \beta_f \) were derived to obtain an approximately least-squares fit of Equation 12 to the data. In doing so, values of \( \alpha_s \) and \( \beta_s \) were estimated first, then values of \( \alpha_f \) and \( \beta_f \) were obtained by least-squares technique, given the initial values of \( \alpha_s \) and \( \beta_s \). Adjustments were made so that all 4 dynamic parameters were equal to or greater than zero.

Finally, statistical methods included linear regression, the Kruskal-Wallis nonparametric test, and logistic regression, and these analyses were performed with S-PLUS software (MathSoft, Seattle, WA).

Results

Fit of the Exponential Model

Figure 1 shows plots of serum PSA values vs time for 4 typical patients in this study. In all plots, the points represent the observed values of PSA, and the smooth lines represent the fits obtained with the exponential function of Equation 12. The time axis is given in months before diagnosis of prostate cancer. The upper left plot shows a patient with 8 values of PSA collected during a 10-year period before the diagnosis, and it demonstrates how the exponential model follows the trend in PSA when there are small erratic departures from the trend. The upper right plot shows a patient with just 4 values of PSA collected during 33 months before diagnosis, and this plot demonstrates how the exponential model can fit the trend in PSA even when there are limited samples and a relatively small rise in PSA. The lower left plot shows a patient who had 6 samples of PSA taken during the 5 years before diagnosis, and these demonstrate how the model fits an early slow rise in PSA followed by a dramatic rise. Finally, the lower right plot shows how the exponential model fits a series of 6 values of PSA gathered during 19 months before diagnosis in a man who undoubtedly had prostate cancer at the time of the first measurement. Not only does the model fit his rise in PSA, but it was also able to determine a component of slowly rising PSA with an amplitude of just 1.47 and a relative velocity of just 0.00864.

Figure 2 shows a plot of all observed values of PSA in 119 patients on the horizontal axis vs values obtained from the exponential model on the vertical axis. Altogether, the plot...
comprises 851 values of PSA. The straight line shows where the points should lie if there was a perfect fit, and the proximity of the points to this line demonstrates that the exponential model fit these patients’ values of serum PSA well. Figure 3 provides additional information about how the exponential model fit PSA data. Figure 3 shows the frequency distribution of absolute differences between observed values of PSA and those predicted by the exponential fit. Because most of the differences appear close to zero, the plot shows again how well the model fit the data. The average difference between observed and predicted values of PSA was just –0.02 ng/mL, and 75% of the predicted values of PSA fell between –0.6 and 0.4 ng/mL of the observed values.

Values of the Dynamic Parameters

The values of $\alpha_s$, $\beta_s$, $\alpha_f$, and $\beta_f$ obtained from the exponential model are summarized in Table 2. Although $\alpha_s$ tended to be lower than $\alpha_f$, and $\beta_s$ tended to be lower than $\beta_f$, there were significant overlaps between the parameters of slow and fast components. Furthermore, for some patients $\alpha_f$ was 0, suggesting that the slow component was all that was necessary to fit the data.

Substituting the time of diagnosis (ie, $t = 0$) into Equation 12 demonstrates that the expected value of PSA at diagnosis equals the sum of $\alpha_s$ and $\alpha_f$. In these patients, this sum showed that the slow component comprised, on average, 42% of the value of PSA at the time of diagnosis (range, 1%-100%). By contrast, the fast component comprised, on average, 58% of PSA (range, 0%-99%). Thus, the model and its results suggest that the value of PSA at the time of diagnosis for an average patient is a composite of both slow and fast PSA components. Similarly, one can estimate PSA velocity by calculating the derivative of Equation 12 with respect to time, and this yields:

$$\text{PSA Velocity} = \beta_s \cdot \alpha_s \cdot \exp(\beta_s \cdot t) + \beta_f \cdot \alpha_f \cdot \exp(\beta_f \cdot t)$$

PSA Velocity at the time of diagnosis as:

$$\text{PSA Velocity} = \beta_s \cdot \alpha_s + \beta_f \cdot \alpha_f$$

Thus, at the time of diagnosis, PSA velocity should also be a composite of slow and fast components. In this study, PSA velocity at the time of diagnosis averaged 0.25 ng/(mL * month) [range, 0.01-2.52 ng/(mL * month)]. The slow component comprised, on average, 25% of PSA velocity (range, 0.2%-100%), and the fast component comprised, on average, 75% of PSA velocity (range, 0%-100%). Thus, at the time of diagnosis, the fast component was reflected more in PSA velocity than in the level of PSA.

<table>
<thead>
<tr>
<th>Table 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Values and Ranges of Prostate-Specific Antigen Dynamic Parameters*</td>
</tr>
<tr>
<td>Variable</td>
</tr>
<tr>
<td>----</td>
</tr>
<tr>
<td>$\alpha_s$</td>
</tr>
<tr>
<td>$\beta_s$</td>
</tr>
<tr>
<td>$\alpha_f$</td>
</tr>
<tr>
<td>$\beta_f$</td>
</tr>
</tbody>
</table>

* $\alpha_s$ is the amplitude of the slow component in Equation 12. $\beta_s$ is the relative velocity of the slow component, and $\alpha_f$ and $\beta_f$ are the analogous parameters for the fast component.
Relationships Between PSA Dynamic Parameters and Prostate Histologic Features

Table 3 shows the results of linear regression analyses relating the estimated volumes of benign (Vb) and malignant (Vc) prostate tissue compartments to the dynamic variables of the exponential model. The entries in the table are P values for tests of association. For example, the first column of P values demonstrates that Vb was significantly associated with βs, the relative velocity of the slow component in the exponential model, but not with αs, the amplitude of the slow component. Vb had a borderline association with αf, the amplitude of the fast component (P = .08). By contrast, the second column of P values demonstrates that Vc was significantly associated with both αf and βf of the fast component in the exponential model, but Vc was not associated with either of the dynamic parameters for the slow component.

Kruskal-Wallis tests demonstrated that there was a borderline association between Gleason score and αf, the amplitude of the fast component (P = .08); however, there was no association between Gleason score and any of the remaining 3 dynamic PSA variables (P > .3).

Finally, logistic regression analysis demonstrated that there was a significant association between presence of pT3 stage and αf, the amplitude of the fast component (P = .0008); however, there was no association between pT3 stage and any of the remaining 3 dynamic PSA variables (P > .4).

Discussion

The exponential model of this study was derived from 4 assumptions: (1) that serum PSA is due to a sum of 2 PSA components released respectively from benign and malignant tissues, (2) that each component of PSA follows approximately an exponential function with respect to time, (3) that benign tissues result in a slower rise in PSA over longer time, and (4) that malignant tissues result in a faster rise in PSA over a shorter time. These 4 assumptions are nothing more than a codification of early empirical observations made about the kinetics of serum PSA in men with and without tumor (eg, see Carter et al3).

The most important result of this study is that the exponential model and its Equation 12 fit observed prediagnostic values of PSA very well. Furthermore, the model’s amplitude parameter for the slow component was closely associated with the volume of benign tissue, but neither of the parameters for the slow component related to the volume of tumor. By contrast, the parameters for the fast component were closely associated with the volume of the tumor, and αf was significantly associated with pathologic stage. Thus, the results appear to support the aforementioned assumptions. Furthermore, the results suggest that serial measurements of prediagnostic PSA for most men with prostate cancer are likely to reflect benign and cancerous tissues right up to the time of diagnosis, and both the level and velocity of PSA are probably composites of both slow and fast components of PSA. This result may then partly explain how neither the level nor the velocity of PSA can be 100% specific and 100% sensitive for the presence of prostate cancer. The results also hint that at the time of diagnosis, PSA velocity may potentially provide more information than the level of PSA. For example, Equation 14 suggests that whenever βf is much larger than βs, PSA velocity will be mostly due to the product βf * αf, that is, it will reflect both the relative velocity and amplitude of the fast component. In fact, the results demonstrated that for an average patient, 75% of PSA velocity could be attributed to the fast component.

Although the exponential model introduced herein deals with pretreatment levels of PSA, including during expectant management, the situation changes after prostatectomy. If all of the benign prostate tissue has been removed, then it is likely that the slow component will disappear because most, if not all, benign prostate tissues disappear. Thus, after prostatectomy, any residual levels of PSA should follow a single exponential equation like that in Equation 4. In this circumstance, Equation 3 implies that PSA velocity will not be statistically independent of the level of PSA, but will reflect both the level and the relative velocity of PSA. However, suggest that after prostatectomy, β or td should provide more independent prognostic information. After radiation treatment, the situation is less straightforward because of residual benign tissues. In this setting, there is the potential for both slow and fast components of PSA, and Equation 12 may still apply. It is also likely that the values of αs, βs, αf, and βf would change to become, for example, smaller.

Finally, this is a preliminary report of the exponential model done mostly to see if the model fits observed data on prediagnostic values of PSA and to see how the results relate to anatomic features of benign and malignant tissues. Because of limited numbers of clinical outcomes, I have not explored whether this model or its dynamic parameters provide useful

<table>
<thead>
<tr>
<th>PSA Variables</th>
<th>Vb</th>
<th>Vc</th>
</tr>
</thead>
<tbody>
<tr>
<td>αs</td>
<td>&gt; .1</td>
<td>&gt; .4</td>
</tr>
<tr>
<td>βs</td>
<td>0</td>
<td>&gt; .3</td>
</tr>
<tr>
<td>αf</td>
<td>.08</td>
<td>.01</td>
</tr>
<tr>
<td>βf</td>
<td>&gt; .3</td>
<td>.00</td>
</tr>
</tbody>
</table>

PSA, prostate-specific antigen.

* Vb is the estimated benign tissue volume, and Vc is the estimated tumor volume.

The units for both α and β are cubic centimeters. Entries in the table are P values for tests of association between the PSA dynamic parameters and Vb and Vc, respectively.

© American Society for Clinical Pathology
diagnostic or prognostic information but would be happy to make the model available to those who may have sufficient data for such studies.

From Laboratory Medicine, VA and Duke University Medical Centers, Durham, NC.

Address reprint requests to Dr Vollmer: Laboratory Medicine 113, VA Medical Center, 508 Fulton St, Durham, NC 27705.

References


