Published in final edited form as:

Br J Med Surg Urol. 2012 July 1; 5(4): 162–168. doi:10.1016/j.bjmsu.2011.08.006.

PSA Velocity and Doubling Time in Diagnosis and Prognosis of Prostate Cancer

Andrew J. Vickers and

Memorial Sloan-Kettering Cancer Center, 307 E. 63rd Street, 2nd Floor, New York, NY 10065, USA

Simon F. Brewster

Department of Urology and Nuffield Department of Surgery (University of Oxford), Churchill Hospital, Oxford, OX3 7LJ, UK

Abstract

Cancer is a growth process and it is natural that we should be concerned with how the routinely used marker of prostate cancer tumour burden – PSA – changes over time. Such change is measured by PSA velocity or PSA doubling time, described in general as “PSA kinetics”. However, it turns out that calculation of PSA velocity and doubling time is far from straightforward. More than 20 different methods have been proposed, and many of these give quite divergent results. There is clear evidence that PSA kinetics are critical for understanding prognosis in advanced or relapsed prostate cancer. However, PSA kinetics have no value for men with an untreated prostate: neither PSA velocity nor doubling time have any role in diagnosing prostate cancer or providing a prognosis for men before treatment.

Keywords

Prostatic neoplasms; prostate specific antigen

Introduction

Cancer is a growth process and it is natural that we should be concerned with how measures of tumour burden change. An obvious example would be tumour response, a ubiquitous concept in research and clinical care for advanced cancer. After a patient is treated with an agent and then scanned, we are interested not in the absolute size of a tumour, but whether it grew or shrank in response to treatment. In the case of prostate cancer, we rely strongly on prostate-specific antigen (PSA) as a marker; it makes sense that our focus should similarly be not so much on absolute PSA level, but on how this has changed over time.

Change in PSA over time is formalised in the concepts of PSA velocity and PSA doubling time. PSA velocity is given in ng/ml/year and can be thought of as a prediction: for example, a patient with a current PSA of 2 ng/ml and a PSA velocity of 0.5 ng/ml/year would be expected to have a PSA of 2.5 ng/ml in 12 months time. PSA doubling time is the number of

© 2011 British Association of Urological Surgeons. Published by Elsevier Ltd. All rights reserved.

Corresponding Author: Andrew J. Vickers, Memorial Sloan-Kettering Cancer Center, 307 E. 63rd Street, 2nd Floor, Phone #: 646-735-8142 Fax #: 646-735-0032, vickersa@mskcc.org.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

months it would take for PSA to increase two-fold. The PSA doubling time of our example patient would therefore be 48 months. For patients with relatively constant PSA, such as a change from 6 to 6.1 ng/ml over the course of a year, doubling time become rather unstable and such patients are normally categorized in terms of “doubling time > 10 years” or similar.

In this paper, we will review data on the value of PSA velocity and doubling time, which when considered together are termed “PSA kinetics”. We will make three points. First, calculation of PSA velocity and doubling time is far from straightforward, with wide variation between different methods. Second, PSA kinetics are critical for understanding prognosis in advanced or relapsed prostate cancer. Third, PSA kinetics have no value for men with an untreated prostate; neither PSA velocity nor doubling time have any role in diagnosing prostate cancer or providing a prognosis for men before treatment.

Calculating PSA kinetics

Although conceptually simple, PSA velocity and doubling time can pose considerable challenges in practical application. For example, take two patients with yearly PSAs of 1, 1.9, 2.0 and 2.1 vs. 1, 1.3, 1.7 and 2.1. The approach widely used in clinical practice is simply to ignore the middle values and subtract the initial value from the final value, dividing by time. This would give both patients a PSA velocity of 0.37 ng/ml/year, something which does not seem to reflect rather different PSA histories. An alternative would be to conduct what is known as “ordinary least squares regression”; in simple terms, a line of best fit. This gives PSA velocities of 0.34 and 0.37 ng/ml/year, and therefore does seem to reflect a clinical intuition that the second patient is more likely to have a higher PSA in a year’s time. Note, however, that a regression is not simple to conduct in routine practice as it involves a complex mathematical calculation.

But now imagine that the second patient had a 10-year history with annual PSAs of 0.5, 0.55, 0.6, 0.65, 0.7, 0.8 and 0.9, before those given above. In this case, the PSA velocity from ordinary least squares regression is 0.14 ng/ml/year. As this is somewhat lower than what we might expect, it would seem prudent to have a rule for the period of time over which PSA is measured, excluding PSA measures taken many years before. Alternatively, it has been suggested that PSA values be logarithmically transformed before analysis.

Yet even these approaches would be incomplete. Assume that we insisted only the most recent 3 years of PSA were analysed, but that the patient had additional PSAs of 1.8 and 2 in the months preceding the final PSA of 2.1. The estimate of PSA velocity is now 0.34 compared to 0.37 ng/ml. One view is that PSAs measured close together constitute statistical “noise” and that, as such, a certain minimum period is required between PSA measures. Similarly, consider a patient who had just two PSAs 1.8 and 2.1, measured 6 months apart. It would seem rather unsound to claim that the patient had a PSA velocity of 0.6 ng/ml/year. So a sensible additional requirement might be that at least three PSAs are required over a minimum total length of time.

It should become obvious that it is possible to construct a number of different definitions for PSA kinetics, with different methods of calculation (e.g. log transformed or not) and eligible PSAs (how many, over what period of time, with what minimum time period between measures). For example, the “MSKCC” method calculates a regression slope on the basis of all PSA values taken; the “Thompson” method log transforms PSA before calculating the slope and only includes PSAs within 3 years; the “Sengupta” definition is based on untransformed PSAs within 2 years, but also specifies that PSA measures have to be at least 3 months apart; the method of “Smith” involves log transformation and the specification that at least three PSAs have to be taken at least 4 months apart [1]. As a result, it is not untypical for researchers to examine 5 or 10 different definitions of PSA kinetics in a

research study [2, 3]. In the most exhaustive study of its type, O'Brien and colleagues identified no fewer than 22 different definitions of PSA velocity and doubling time. Applying these different definitions to a data set led to some interesting findings. First, for many definitions, PSA velocity cannot be calculated for a significant proportion of patients. As an example, take the case of a man who has a PSA test at, say, age 57, then again at 61, where an elevated value led to biopsy and diagnosis. Because the Smith definition requires at least 3 PSA values, it could not be applied to this man. Indeed, O'Brien found that PSA velocity according to Smith could be calculated for fewer than half of men presenting at a major cancer centre [1]. The second major finding of the O'Brien papers is that values of PSA kinetics can vary widely between different definitions. For example, one man in the data set has PSA velocities of 0.27, 0.76, 1.47, 2.64 and 32.0 ng/ml/year for each of five different definitions.

Remarkably, the O'Brien papers actually underestimate the complexity and variety of PSA kinetic algorithms. This is because new methods are developed every year. One novel approach is the "risk count" method: PSA velocity is recalculated for every historical PSA value and the number of times that PSA velocity exceeds a certain threshold calculated[4]. Ketterman et al. have developed an even more complex algorithm for determining whether a man in a screening program should undergo biopsy[5]. In brief, each time a PSA level is obtained, the physician conducts "a linear regression of PSA and log PSA on time using the first three measures, and separately at each measure beyond the third PSA measure (using all previous data)". Following this, the physician should compare R^2 statistics to determine if the patient has reached a transition point. If so, the physician would calculate the "derivative of the linear regression of logPSA on time to obtain the PSA [velocity]". It strains credibility to think that such an algorithm could be implemented in clinical practice, especially given that the supporting evidence is rather weak: the algorithm was one of five attempted on a data set with 11 events.

PSA kinetics in relapsed or advanced prostate cancer

Prostate cancer patients treated by surgery or radiotherapy typically experience a decrease in PSA to a stable nadir. If PSA subsequently rises, the patient is said to have relapsed. Various investigators have examined whether the rate of this PSA rise is prognostic. Indeed, one of the first references to PSA doubling time was in a paper examining PSA changes at relapse [6].

An early indication that PSA kinetics at relapse predicted subsequent mortality included 94 patients with recurrence after radiotherapy. The risk of prostate cancer death within five-years of relapse was 50% for patients with a PSA doubling time of 12 months or less compared to 10% for patients with a doubling time greater than 12 months[7]. Other authors have clearly demonstrated that PSA doubling time adds information to other available predictors. Pound et al. created an algorithm for calculating risk of metastasis after relapse following radical prostatectomy. For patients with Gleason less than 8, though not for those with Gleason 8+, PSA doubling time strongly separated risk of subsequent metastasis, even after adjusting for time between surgery and relapse [8]. Freedland et al. similarly reported that PSA doubling time has a very strong influence on the risk of cancer-specific death after relapse in surgical patients. In a multivariable model, doubling times < 3 months and 3 – 8.9 months were associated with hazard ratios of 25 and 8 respectively; in comparison, the hazard ratio for a high Gleason score was 1.35 [9]. PSA doubling time has now been incorporated into predictive models for use at the time of relapse [10, 11].

There is also evidence that PSA kinetics can be of benefit for making treatment decisions after relapse. In a cohort of over 1000 men with relapse after radical prostatectomy, Moul et

al. analyzed the risk of metastasis for patient receiving early compared to delayed androgen deprivation therapy. Early treatment was only found to be more effective in high risk patients, defined in terms of either Gleason grade or short PSA doubling time[12].

The relationship between PSA kinetics and disease progression in patients with metastatic and castrate-resistant prostate cancer is less clear than at the time of relapse. Still, a preponderance of data suggests that a short doubling time is associated with a poorer prognosis in patients with castration-resistant prostate cancer. In a typical study, PSA doubling time was analysed for 250 patients on chemotherapy. Median survival was 16.5 months in patients with a doubling time lower than the median (45 days) compared to 26 months for patients with longer doubling times[13]. Similar findings have been reported by other investigators[14] although in some cases, the association between doubling time and survival has been relatively modest[15].

PSA kinetics in men with an untreated prostate

It has been suggested that PSA velocity and doubling time are of value for diagnosis and prognosis in men before prostate cancer treatment. This includes long-term prediction of the future risk of prostate cancer[16]; indication for biopsy[17]; eligibility for active surveillance[18]; monitoring of patients on active surveillance[19]; risk of recurrence after initial treatment[20] and risk of lethal cancer after curative treatment[21]. Proponents of PSA velocity make practice-altering clinical recommendations; for example, men without an elevated PSA or a positive DRE should undergo biopsy if PSA velocity is high[22], or that men with low risk cancer should receive immediate curative treatment if they have recently experienced a recent large rise in PSA[18].

The evidence for these claims is surprisingly weak. For example, to uphold claims that men with a low PSA/normal DRE should be biopsied if they have a high PSA velocity, we would require evidence that, for an important proportion of such men, cancer would become incurable if biopsy were delayed until PSA rose above a cut-point, such as 4 ng/ml. In its absence, we might request data on the results of biopsies driven by high PSA velocity without other indications. But neither type of study is cited by advocates of PSA velocity. Instead, the recommendation to biopsy on the basis of PSA velocity is based on a single cohort, the Baltimore Longitudinal Study of Aging (BLSA). An initial paper found a correlation between changes in PSA and prostate cancer diagnosed 7 – 25 years subsequently[23]; in particular, almost all men who subsequently developed cancer had a PSA velocity $>0.75\text{ng/ml/year}$. A later study correlated PSA changes and the development of subsequent fatal disease [16]. It is not at all obvious that an inflated long-term risk of aggressive cancer indicates immediate biopsy.

Furthermore, there are serious problems with the BLSA study. First, the authors stated that a cut-point PSA velocity of 0.35 ng/ml/year distinguished lethal prostate cancer, and this later hardened into a recommendation in Guidelines to biopsy such men[22]. However, the cut-point was not chosen on the basis of an analysis of clinical consequences, but on a visual inspection of the receiver-operating-characteristics curve: “ 0.35 ng/ml/year could be one reasonable choice — among others — to balance sensitivity and specificity for detection of life threatening cancer”. Second, the conclusions were based on a rather small number of events, 18 prostate cancer cases in the first paper, 20 cancer deaths in the second. This is a particular problem because it makes it difficult to determine whether PSA velocity adds information to PSA alone. This is an absolutely critical question. The clinician has a PSA level in front of them: should they act on the basis of the PSA level or look up past PSAs and then undertake what can be a complex calculation?

By way of analogy, tall players generally have an advantage at basketball, and they also tend to have large feet. This creates a statistical association between shoe size and basketball ability. However, it would be odd to claim on these grounds alone that a school basketball coach should start measuring shoe size before choosing a squad; it would need to be shown that shoe size is able to predict basketball ability over and above height. In statistical terms, predictions are assessed in terms of a concordance index – in some cases, described as an “area-under-the-curve” – which ranges from 0.5 (no better than a coin flip) to 1 (perfect discrimination). One basic question is whether a new marker, such as PSA velocity, could improve the concordance index of an existing marker, such as PSA. This question was not addressed in the BLSA study.

Subsequently, however, my own group used data from the Malmo cohort to determine the added value of PSA velocity. We found that PSA predicted long-term risk of prostate cancer with a concordance index of 0.771. We then created a statistical model including both PSA and PSA velocity. Although PSA velocity was a statistically significant predictor of prostate cancer risk, it added nothing to the predictiveness of PSA, indeed, the concordance index of the combined model was identical to three decimal places [24].

This story has played out repeatedly in the literature. A paper is published showing a statistical association between PSA velocity and outcome, often in a relatively limited number of cases, and the authors make strong claims with respect to the implications for clinical practice. A larger replication study is then reported that examines the clinical value of the PSA velocity and concludes that it is of no benefit. A summary of some of the most well-known studies is given in table 1. In general, the studies supporting prostate cancer velocity are based on clinical cohorts (i.e. men who happened to be treated at a particular hospital), with small number of events. Most critically, none examined the marginal value of PSA velocity, that is, whether it increased the predictive accuracy of standard predictors such as PSA, stage and grade. In contrast, the papers suggesting that PSA velocity is not helpful are typically based on randomized trials or prospective cohort studies with large numbers of events, and did address the specific question of whether PSA velocity increases predictiveness.

One particularly difficult clinical problem is management of men with elevated PSA after negative biopsy. Again, it would seem logical that PSA velocity would be predictive: if a man's PSA continued to rise after negative biopsy, this would lead to a much greater level of suspicion than if PSA was stable, or declined. But again, the data do not support this apparently common sense conclusion, with changes in PSA being a poor predictor of subsequent biopsy outcome. The concordance index of PSA velocity was 0.55, little better than a coin flip[25]. Nonetheless, as the risk of aggressive disease rises once PSA is above 10 ng/ml, it is reasonable to track the absolute level of PSA over time.

Conclusion

Changes in PSA – PSA velocity and doubling-time – can be difficult to calculate, with a large number of different methods proposed. There is a body of evidence confirming that the rate of PSA changes in locally-recurrent and advanced prostate cancer has prognostic value for metastasis-free and cancer-specific survival. This suggests patients with advanced or relapsed disease who have rapid PSA doubling times should be offered earlier or more aggressive treatments, or entered into clinical trials of new agents. Conversely, there is good evidence that PSA velocity has no role for men with an untreated prostate; PSA velocity should not be used to recommend biopsy, determine eligibility for active surveillance versus curative treatment, or give prognosis as to the risk of post-treatment failure.

This of course opens the question of how PSA should be used in men before curative treatment. With respect to prognosis, prognostic models have been proposed for endpoints such as biochemical recurrence[26], survival after radical prostatectomy[27] or conservative management[28] and long-term risk of prostate cancer death for men considering prostate cancer screening[29]. These models generally incorporate information about absolute PSA level along with grade and stage.

Conversely, diagnosis of prostate cancer often involves a complex series of sequentially-dependent decisions. Take the following four patients as illustrative examples: a patient with a history of prostate symptoms and a PSA that rises and falls; a patient whose first ever PSA is elevated and remains high on repeat testing after a few months; a patient treated with Finasteride for symptoms, whose PSA has risen steadily after an initial fall; a patient with a very dramatic jump in PSA and evidence of infection, whose PSA is sharply reduced after antibiotic therapy. Even if each of these four patients had the same current PSA, such as 5 ng/ml, our estimate of risk would vary widely. The patient with fluctuating PSA and prostate symptoms, for example, is surely at lower risk than the patient on Finasteride with a rising PSA, for whom prostate cancer must be seen as the most likely cause of PSA increases.

The data quite clearly demonstrate that there is no rationale for formal calculation of PSA velocity and application of simplistic thresholds, such as 0.35 ng/ml/year. However, this does not imply that PSA monitoring should be abandoned, or that clinicians should ignore PSA histories. An elevated PSA should prompt *consideration* of biopsy: whether a man should be *recommended* for biopsy depends on a number of factors, including clinical judgment, informed where appropriate by the course of PSA over time.

Acknowledgments

Supported in part by funds from David H. Koch provided through the Prostate Cancer Foundation, the Sidney Kimmel Center for Prostate and Urologic Cancers and P50-CA92629 SPORE grant from the National Cancer Institute to Dr. P. T. Scardino.

Abbreviations

PSA	prostate specific antigen
DRE	digital rectal examination
BLSA	Baltimore Longitudinal Study of Aging

References

1. O'Brien MF, Cronin AM, Fearn PA, Smith B, Stasi J, Guillonneau B, et al. Pretreatment prostate-specific antigen (PSA) velocity and doubling time are associated with outcome but neither improves prediction of outcome beyond pretreatment PSA alone in patients treated with radical prostatectomy. *J Clin Oncol.* 2009; 27:3591–7. [PubMed: 19506163]
2. Thompson IM, Ankerst DP, Chi C, Goodman PJ, Tangen CM, Lucia MS, et al. Assessing prostate cancer risk: results from the Prostate Cancer Prevention Trial. *J Natl Cancer Inst.* 2006; 98:529–34. [PubMed: 16622122]
3. Vickers AJ, Till C, Tangen CM, Lilja H, Thompson IM. An empirical evaluation of guidelines on prostate-specific antigen velocity in prostate cancer detection. *J Natl Cancer Inst.* 2011; 103:462–9. [PubMed: 21350221]
4. Carter HB, Kettermann A, Ferrucci L, Landis P, Metter EJ. Prostate-specific antigen velocity risk count assessment: a new concept for detection of life-threatening prostate cancer during window of curability. *Urology.* 2007; 70:685–90. [PubMed: 17991538]

5. Kettermann AE, Ferrucci L, Trock BJ, Metter EJ, Loeb S, Carter HB. Interpretation of the prostate-specific antigen history in assessing life-threatening prostate cancer. *BJU Int.* 2010; 106:1284–90. discussion 90–2. [PubMed: 20477823]
6. D'Amico AV, Hanks GE. Linear regressive analysis using prostate-specific antigen doubling time for predicting tumor biology and clinical outcome in prostate cancer. *Cancer.* 1993; 72:2638–43. [PubMed: 7691393]
7. D'Amico AV, Cote K, Loffredo M, Renshaw AA, Schultz D. Determinants of prostate cancer-specific survival after radiation therapy for patients with clinically localized prostate cancer. *J Clin Oncol.* 2002; 20:4567–73. [PubMed: 12454114]
8. Pound CR, Partin AW, Eisenberger MA, Chan DW, Pearson JD, Walsh PC. Natural history of progression after PSA elevation following radical prostatectomy. *JAMA.* 1999; 281:1591–7. [PubMed: 10235151]
9. Freedland SJ, Humphreys EB, Mangold LA, Eisenberger M, Dorey FJ, Walsh PC, et al. Death in patients with recurrent prostate cancer after radical prostatectomy: prostate-specific antigen doubling time subgroups and their associated contributions to all-cause mortality. *J Clin Oncol.* 2007; 25:1765–71. [PubMed: 17470867]
10. Dotan ZA, Bianco FJ Jr, Rabbani F, Eastham JA, Fearn P, Scher HI, et al. Pattern of prostate-specific antigen (PSA) failure dictates the probability of a positive bone scan in patients with an increasing PSA after radical prostatectomy. *J Clin Oncol.* 2005; 23:1962–8. [PubMed: 15774789]
11. Stephenson AJ, Scardino PT, Kattan MW, Pisansky TM, Slawin KM, Klein EA, et al. Predicting the outcome of salvage radiation therapy for recurrent prostate cancer after radical prostatectomy. *J Clin Oncol.* 2007; 25:2035–41. [PubMed: 17513807]
12. Moul JW, Wu H, Sun L, McLeod DG, Ameling C, Donahue T, et al. Early versus delayed hormonal therapy for prostate specific antigen only recurrence of prostate cancer after radical prostatectomy. *J Urol.* 2004; 171:1141–7. [PubMed: 14767288]
13. Oudard S, Banu E, Scotte F, Banu A, Medioni J, Beuzeboc P, et al. Prostate-specific antigen doubling time before onset of chemotherapy as a predictor of survival for hormone-refractory prostate cancer patients. *Ann Oncol.* 2007; 18:1828–33. [PubMed: 17846024]
14. Semeniuk RC, Venner PM, North S. Prostate-specific antigen doubling time is associated with survival in men with hormone-refractory prostate cancer. *Urology.* 2006; 68:565–9. [PubMed: 17010728]
15. Armstrong AJ, Garrett-Mayer ES, Yang YC, de Wit R, Tannock IF, Eisenberger M. A contemporary prognostic nomogram for men with hormone-refractory metastatic prostate cancer: a TAX327 study analysis. *Clin Cancer Res.* 2007; 13:6396–403. [PubMed: 17975152]
16. Carter HB, Ferrucci L, Kettermann A, Landis P, Wright EJ, Epstein JI, et al. Detection of life-threatening prostate cancer with prostate-specific antigen velocity during a window of curability. *J Natl Cancer Inst.* 2006; 98:1521–7. [PubMed: 17077354]
17. Loeb S, Roehl KA, Catalona WJ, Nadler RB. Prostate specific antigen velocity threshold for predicting prostate cancer in young men. *J Urol.* 2007; 177:899–902. [PubMed: 17296371]
18. Khatami A, Aus G, Damber JE, Lilja H, Lodding P, Hugosson J. PSA doubling time predicts the outcome after active surveillance in screening-detected prostate cancer: results from the European randomized study of screening for prostate cancer, Sweden section. *Int J Cancer.* 2007; 120:170–4. [PubMed: 17013897]
19. van den Bergh RC, Roemeling S, Roobol MJ, Wolters T, Schroder FH, Bangma CH. Prostate-specific antigen kinetics in clinical decision-making during active surveillance for early prostate cancer—a review. *Eur Urol.* 2008; 54:505–16. [PubMed: 18585845]
20. Palma D, Tyldesley S, Blood P, Liu M, Morris J, Pickles T. Pretreatment PSA velocity as a predictor of disease outcome following radical radiation therapy. *Int J Radiat Oncol Biol Phys.* 2007; 67:1425–9. [PubMed: 17394943]
21. 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. [PubMed: 15247353]

22. Prostate Cancer Early Detection. National Comprehensive Cancer Network; NCCN Clinical Practice Guidelines in Oncology. [Cited 2010 February 3]. Available from: URL: http://www.nccn.org/professionals/physician_gls/PDF/prostate_detection.pdf
23. Carter HB, Pearson JD, Metter EJ, Brant LJ, Chan DW, Andres R, et al. Longitudinal evaluation of prostate-specific antigen levels in men with and without prostate disease. *JAMA*. 1992; 267:2215–20. [PubMed: 1372942]
24. Ulmert D, Serio AM, O'Brien MF, Becker C, Eastham JA, Scardino PT, et al. Long-term prediction of prostate cancer: prostate-specific antigen (PSA) velocity is predictive but does not improve the predictive accuracy of a single PSA measurement 15 years or more before cancer diagnosis in a large, representative, unscreened population. *J Clin Oncol*. 2008; 26:835–41. [PubMed: 18281654]
25. Vickers AJ, Wolters T, Savage CJ, Cronin AM, O'Brien MF, Roobol MJ, et al. Prostate specific antigen velocity does not aid prostate cancer detection in men with prior negative biopsy. *J Urol*. 2010; 184:907–12. [PubMed: 20643434]
26. Stephenson AJ, Scardino PT, Eastham JA, Bianco FJ Jr, Dotan ZA, Fearn PA, et al. Preoperative nomogram predicting the 10-year probability of prostate cancer recurrence after radical prostatectomy. *J Natl Cancer Inst*. 2006; 98:715–7. [PubMed: 16705126]
27. Eggener SE, Scardino PT, Walsh PC, Han M, Partin AW, Trock BJ, et al. Predicting 15-year prostate cancer specific mortality after radical prostatectomy. *J Urol*. 2011; 185:869–75. [PubMed: 21239008]
28. Kattan MW, Cuzick J, Fisher G, Berney DM, Oliver T, Foster CS, et al. Nomogram incorporating PSA level to predict cancer-specific survival for men with clinically localized prostate cancer managed without curative intent. *Cancer*. 2008; 112:69–74. [PubMed: 18000803]
29. Vickers AJ, Cronin AM, Bjork T, Manjer J, Nilsson PM, Dahlin A, et al. Prostate specific antigen concentration at age 60 and death or metastasis from prostate cancer: case-control study. *BMJ*. 2010; 341:c4521. [PubMed: 20843935]
30. Vickers AJ, Wolters T, Savage CJ, Cronin AM, O'Brien MF, Pettersson K, et al. Prostate-specific antigen velocity for early detection of prostate cancer: result from a large, representative, population-based cohort. *Eur Urol*. 2009; 56:753–60. [PubMed: 19682790]
31. 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. [PubMed: 16046650]
32. Stephenson AJ, Kattan MW, Eastham JA, Bianco FJ Jr, Yossepowitch O, Vickers AJ, et al. Prostate cancer-specific mortality after radical prostatectomy for patients treated in the prostate-specific antigen era. *J Clin Oncol*. 2009; 27:4300–5. [PubMed: 19636023]
33. Ross AE, Loeb S, Landis P, Partin AW, Epstein JI, Kettermann A, et al. Prostate-specific antigen kinetics during follow-up are an unreliable trigger for intervention in a prostate cancer surveillance program. *J Clin Oncol*. 2010; 28:2810–6. [PubMed: 20439642]
34. Fall K, Garmo H, Andren O, Bill-Axelsson A, Adolfsson J, Adami HO, et al. Prostate-specific antigen levels as a predictor of lethal prostate cancer. *J Natl Cancer Inst*. 2007; 99:526–32. [PubMed: 17405997]
35. O'Brien MF, Cronin AM, Fearn PA, Savage CJ, Smith B, Stasi J, et al. Evaluation of prediagnostic prostate-specific antigen dynamics as predictors of death from prostate cancer in patients treated conservatively. *Int J Cancer*. 2011; 128:2373–81. [PubMed: 20658531]

Table 1

Examples of the results of typical studies on PSA velocity in men before treatment.

Study	Design	Events	Endpoint	Examined marginal value?	PSA velocity helpful?
BLSA[16]	Prospective cohort study	20	Prostate cancer death in men prior to diagnosis	No	Yes
Malmö[24]	Prospective cohort study	82	Advanced cancer in men prior to diagnosis	Yes	No
Loeb[17]	Prospective cohort	346	Diagnosis of prostate cancer during screening	No	Yes
PCPT [3]	Randomized trial	1211 (any) 256 (high grade)	Prostate cancer on biopsy	Yes	No
ERSPC [30]	Randomized trial	710 (any) 144 (high grade)	Prostate cancer on biopsy	Yes	No
D'Amico [31]	Clinical cohort	28	Prostate cancer death in men treated with radiotherapy	No	Yes
D'Amico [21]	Clinical cohort	27	Prostate cancer death in men treated with surgery	No	Yes
Stephenson[32]	Clinical cohort	117	Prostate cancer death in men treated with surgery	Yes	No
Khatami[18]	Clinical cohort	104	Progression on active surveillance	No	Yes
Ross[33]	Prospective cohort study	102	Progression on active surveillance	No	No
SPCG4 [34]	Randomized trial	34	Prostate cancer death in men managed conservatively after diagnosis	Yes	No
O'Brien[35]	Prospective cohort study	119	Prostate cancer death in men treated conservatively	Yes	No