Trajectories of prostate-specific antigen after treatment for prostate cancer

Ziyue Wu,[1] Mihaela Aslan,[2,3] Haiqun Lin,[4] John Ko,[2] Krishnan Radhakrishnan,[2] Carolyn K Wells,[3] Edward Uchio,[5] John Concato[2,3]

[1]Biostatistics, Yale University School of Public Health, New Haven, Connecticut, USA
[2]Department of Veterans Affairs Connecticut Healthcare System, Clinical Epidemiology Research Center, Veterans Affairs Medical Center (VAMC), West Haven, Connecticut, USA
[3]Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut, USA
[4]Department of Biostatistics, Yale University School of Public Health, Decatur, Georgia, USA
[5]Department of Urology, University of California, Irvine, California, USA

Correspondence to
Dr John Concato, Department of Veterans Affairs Connecticut Healthcare System, Clinical Epidemiology Research Center, Veterans Affairs Medical Center (VAMC), West Haven, CT 06516, USA; john.concato@yale.edu

Accepted 5 November 2017

ABSTRACT

Prostate-specific antigen (PSA) measurements after primary treatment reflect residual tumor burden among men with prostate cancer. Using a mixture model analysis, we identified distinct trajectories of post-treatment PSA measurements and evaluated their associations with prostate cancer mortality. The study sample included 623 US Veterans treated for prostate cancer with curative intent during 1991–1995; 225 men received surgery and 398 men received radiation therapy. Post-treatment PSA measurements over a 2-year period for each patient were evaluated in latent class mixture models using the SAS TRAJ procedure, and groups of men with distinct trajectories of PSA were identified. These groups were then assessed for associations with 10-year prostate cancer mortality using proportional hazards analysis. Analyses identified three distinct groups—representing patterns of both initial values and changes in PSA over time—after surgery (n=172/31/14) and radiation therapy (n=253/103/22). Men in groups with patterns of higher (compared with the group with lowest) PSA values tended to have worse survival experience: HRs for prostate cancer mortality were 3.45 (P=0.18) and 22.7 (P<0.001) for surgery, and 2.70 (P=0.005) and 18.1 (P<0.001) for radiation therapy. The results indicate that PSA measurements after surgery or radiation therapy with curative intent include groups of men with a diverse spectrum of prognosis for prostate cancer mortality. Although contemporary PSA levels are lower than those observed in the study sample, the corresponding trajectory patterns may become evident shortly after the time of diagnosis and treatment.

Significance of this study

What is already known about this subject?

- Although prostate-specific antigen (PSA) is controversial as a screening test, evidence supports its use as a tumor marker to assess prognosis after treatment for prostate cancer.
- Trends in PSA measurements are typically reported as velocity or doubling time, but are often based on recent (eg, two or several) test results for a patient.
- The trajectory of PSA—as the time course of this variable using all available measurements—can provide clinically relevant information regarding prognosis after primary treatment for prostate cancer.

What are the new findings?

- Among men treated for prostate cancer with surgery or radiation therapy in the 1990s, analyses identified three PSA trajectory patterns for each treatment modality.
- During 10 years of follow-up, the worst PSA trajectories (ie, patterns with higher PSA values) were associated with increased risk of long-term prostate cancer mortality.
- PSA trajectories can become evident soon after primary treatment.

How might these results change the focus of research or clinical practice?

- Mixture model approaches, as a clustering procedure, can be useful in clinical research to identify discrete subpopulations of patients.
- If replicated in contemporary study populations, prognosis among men receiving surgery or radiation therapy for prostate cancer can be inferred from early post-treatment PSA trajectories.

INTRODUCTION

Prostate-specific antigen (PSA) was found initially to be useful as a tumor marker after men were diagnosed with prostate cancer.[1] Despite subsequent adoption of PSA as a screening test, its effectiveness in reducing mortality remains controversial.[2–4] Trends in measurements of PSA—often called PSA kinetics, and involving calculations such as velocity or doubling time—can be described conceptually as representing a corresponding trajectory, both before[5 6] and after[7 8] primary treatment with curative intent. In clinical practice, calculations of PSA velocity and doubling time often involve laboratory values from two (or several) recent consecutive time points, with secondary treatment initiated if a threshold value of PSA is exceeded. Although this approach is a relevant 'moving' assessment, it represents a limited use of available data.[9]

Our objective, among men receiving primary treatment for prostate cancer, was to identify

To cite: Wu Z, Aslan M, Lin H, *et al*. *J Investig Med* Published Online First: [*please include* Day Month Year]. doi:10.1136/jim-2017-000627

Table 1 Baseline characteristics of men (n=623) receiving primary treatment for prostate cancer and with multiple prostate-specific antigen (PSA) tests

Characteristics	Surgery (n=225)	Radiation (n=398)	P value	Total (n=623)
Age (years)			<0.001	
50–59	19 (8.4%)	8 (2.0%)		27 (4.3%)
60–69	143 (63.6%)	134 (33.7%)		277 (44.5%)
70–79	63 (28.0%)	242 (60.8%)		305 (49.0%)
≥80	0 (0%)	14 (3.5%)		14 (2.2%)
Race			0.83	
Black	27 (12%)	42 (10.6%)		69 (11.1%)
White	198 (88%)	356 (89.4%)		554 (88.9%)
Comorbidity (Charlson)			<0.001	
0 (none)	91 (40.4%)	103 (25.9%)		194 (31.1%)
1 (mild)	70 (31.1%)	131 (32.9%)		201 (32.3%)
2 (moderate)	47 (20.9%)	93 (23.4%)		140 (22.5%)
3 (severe)	17 (7.7%)	71 (17.8%)		88 (14.1%)
Anatomic stage			0.04	
Localized	221 (98.2%)	374 (94.0%)		595 (95.5%)
Regional	4 (1.8%)	24 (6.0%)		28 (4.5%)
Histologic grade			0.046	
Well	57 (25.3%)	81 (20.4%)		138 (22.2%)
Moderate	147 (65.3%)	254 (63.8%)		401 (64.4%)
Poor	21 (9.4%)	63 (15.8%)		84 (13.5%)
Baseline PSA (ng/mL)			<0.001	
0 to <4.0	39 (17.3%)	38 (9.5%)		77 (12.4%)
4.0 to <10.0	105 (46.7%)	157 (39.5%)		262 (42.1%)
10.0 to <20.0	49 (21.8%)	118 (29.6%)		167 (26.8%)
≥20.0	29 (12.9%)	84 (21.1%)		113 (18.1%)
Unknown	3 (1.3%)	1 (0.3%)		4 (0.6%)

and evaluate clinically relevant PSA trajectories among groups of patients, as determined by the magnitude and pattern of change of post-treatment PSA values. We sought specifically to (1) identify distinct groups of patients based on their PSA values (trajectories) during the initial 2 years post-treatment; and (2) evaluate associations between PSA trajectory groups and prostate cancer mortality over 10 years. Although the data set analyzed is from early in the PSA era, the proposed methodological approach is still clinically relevant.

METHODS

Patients and clinical information

In prior research approved by relevant institutional review boards, a source population of 64,545 male Veterans older than 50 years receiving outpatient care during 1989 or 1990 at nine Veterans Affairs (VA) medical centers in New England was identified,[10] and a search of pathology registries identified 1,313 men with incident prostate cancer diagnosed from January 1991 through December 1995. A comprehensive review of medical records and death registries, available for 1,270 men, determined each patient's clinical characteristics and mortality follow-up. Complete data were available for 1,156 men regarding date of treatment (zero-time),[11] types of treatment, and date/cause of death.

Six baseline characteristics were of interest, measured up to the time of primary treatment of prostate cancer: age and race (obtained from an outpatient database and from medical record review); tumor anatomic stage and histologic grade (from biopsy and imaging tests); and medical comorbidity score and pretreatment PSA values (from medical record review). Vital status for each patient was determined through December 2006, using data from the VA Patient Treatment File, the VA Beneficiary Identifier Locator System, or the National Death Index.[10] Mortality due to prostate cancer was identified by a comprehensive medical record review.[10]

Methodological considerations

At the nine VA medical centers involved, different criteria were used for clinical reporting of very low PSA values; some laboratories coded the lower limit of detection for PSA as 0.04 ng/mL, whereas others coded the minimal value as 0.1 ng/mL. This discrepancy could cause low PSA values to aggregate at the two corresponding threshold levels, and such a pattern would significantly affect the analysis by generating two clusters (one linked to 0.04 ng/mL, and the other to 0.1 ng/mL). Accordingly, all PSA measurements lower than 0.1 ng/mL were recoded as 0.1 ng/mL. (All affected men received surgery; PSA values for men receiving radiation therapy were larger than 0.1 ng/mL, and no data were reclassified.)

To avoid unstable mathematical results, calculations were based on PSA tests separated by more than 14 days; shorter intervals were considered retesting. In addition, results after prostatectomy (only) were assessed as of 6 weeks postprocedure, when PSA usually becomes undetectable; all postradiation PSA values were included.

Although most VA-treated patients tend to remain in the VA healthcare system, the frequency of PSA testing tended to wane over the course of follow-up for some patients. In addition, information on PSA trajectory is most meaningful in the period relatively soon after primary treatment. Accordingly, and seeking to balance clinical relevance with ample data for analyses, mixture model analyses (see below) were conducted for each patient over a period of up to 2 years after initial treatment, or until secondary therapy (potentially affecting PSA) was documented. Using a parallel justification, prostate cancer mortality was assessed over 10 years, providing a relevant period of virtually complete follow-up.

Statistical analyses

Baseline characteristics were compared using χ^2 or χ^2 for linear trend tests, as appropriate. A mixture model[12] approach was used to identify groups of patients with similar longitudinal patterns of post-treatment PSA values, thereby characterizing PSA trajectories over time. (Of note, similar approaches have been used to identify trajectories describing recovery of urinary function after radical prostatectomy,[13] among other topics.) The TRAJ module of SAS V.9.3[14] was used for estimating group-based trajectory models, with different polynomial orders of time as model covariates. Natural logarithm transformations were used to

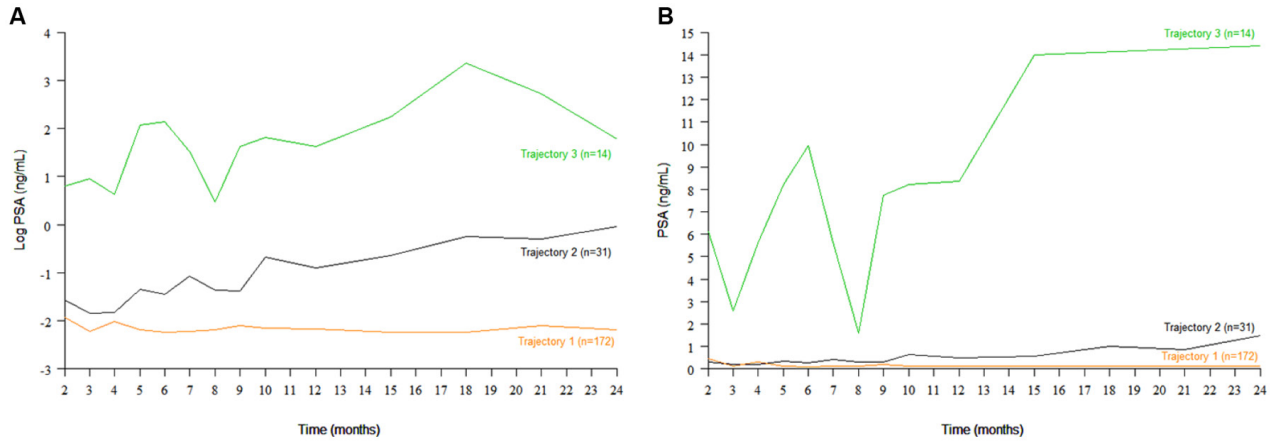

Figure 1 Mean values of prostate-specific antigen (PSA) values for clusters of patients after surgery (n=217), both on a natural logarithmic scale (A), and for the corresponding groups on an ng/mL scale (B). The y-axis on (B) includes mean PSA values up to 20 ng/mL, allowing for better visualization of results for groups 1 and 2; two data points (for group 3 only, at 18 and 21 months) are not shown.

normalize the PSA values, given a skewed distribution of measurements, and months were used as the time covariate. Maximum likelihood estimation was used to obtain model parameters, and models with 1–6 mixture components were fitted separately. For both the postsurgery and postradiation study populations, several candidate models—varying the number of clusters or 'groups'—were ranked according to Bayesian information criterion (BIC) values, with a smaller absolute value indicating better fit. If BIC values were similar, clinical judgment was used to select the optimal number of groups.

After model selection, posterior probabilities of group membership were calculated, and each patient was then assigned to the group with the highest posterior probability of membership. Model validation was conducted by calculating the Jaccard coefficient[15]—a stability index, ranging from 0 to 1, indicating similarity between bootstrapped (n=50) samples.

In subsequent analyses, and separately for men receiving surgery or radiation therapy, the association of PSA group membership with prostate cancer mortality was assessed using proportional hazard analysis. Give the limited number of outcomes, as well as the focus of this research, covariates were not included in the models. Stratified Kaplan-Meier survival curves were plotted; HRs, P values and 95% CIs were reported. Finally, in a descriptive analysis of the derived groups, we report on the median and IQR values for the last pretreatment and first post-treatment PSA results; these prominent measurements help to inform initial post-treatment assessments in clinical settings.

RESULTS

Baseline characteristics and overall outcomes

Among 643 men receiving prostatectomy or radiation therapy with curative intent, 623 (97%) had multiple follow-up PSA values, representing the study population for our analysis. The median age was 70 years old; most of the patients were white (n=556, 89%), with a median PSA value of 8.9 ng/mL (IQR 5.6–16.7) at diagnosis. When

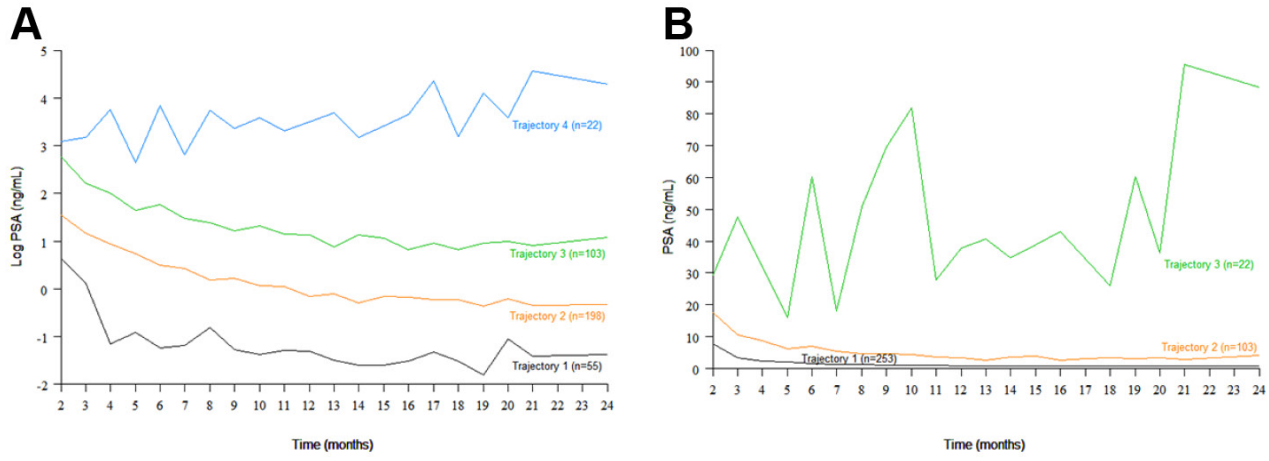

Figure 2 Mean values of prostate-specific antigen (PSA) for clusters of patients after radiation therapy (n=378), both on a natural logarithmic scale (A) and on an ng/mL scale (B) with clusters 1 and 2 combined to form group 1 (see text). The y-axis on (B) includes mean PSA values up to 100 ng/mL, allowing for better visualization of results for groups 1 and 2; two data points (for group 3 only, at 4 and 17 months) are not shown.

Table 2 Associations of group membership with prostate cancer mortality

Effect	HR	P value	95% CI
Surgery patients (n=217)			
Group 2 versus 1	3.45	0.18	0.58 to 20.6
Group 3 versus 1	22.7	<0.001	5.42 to 95.5
Radiation patients* (n=378)			
Group 2 versus 1	2.70	0.005	1.35 to 5.40
Group 3 versus 1	18.1	<0.001	8.26 to 39.8

*Four initial clusters were combined into three groups; specifically, the two lowest clusters were combined into group 1.

stratified by treatment, patients receiving radiation therapy (compared with patients receiving surgery) tended to be older, with more comorbidity and more extensive disease as reflected by anatomic stage, histologic grade, and baseline PSA values (see table 1). During a median follow-up of 11.9 (IQR 8.0–13.5) years after surgery, and 8.9 (IQR 4.9–12.1) years after radiation therapy, median values of 12 (IQR 8–17) and 13 (IQR 8–19) PSA test results, respectively, were documented. During this post-treatment follow-up period, prostate cancer mortality was identified in 58/623 (9.3%) men, including 10/225 (4.4%) after surgery and 48/398 (12.1%) after radiation therapy, with a median time to death of 7.7 (IQR 6.8–9.0) years after surgery and 5.1 (IQR 3.1–8.9) years after radiation therapy.

PSA trajectories

Focusing on patients with available PSA values during the initial 2-year window after primary treatment, analyses were based on n=217 men after surgery and n=378 men after radiation therapy (n=595 total); 28 men with PSA values available only after the 2-year period were excluded. Reflecting clinical practice in 1991–1995, early in the 'PSA era', the median PSA values were 7.4 ng/mL for patients receiving surgery and 10.0 ng/mL for patients receiving radiation therapy; the median age was 67 years for patients receiving surgery and 72 years for patients receiving radiation.

For men receiving surgery, the optimal mathematical output of the TRAJ procedure generated three initial clusters, with 172 (79.3%), 31 (14.3%), and 14 (6.4%) patients. The Jaccard coefficients for these groups were 0.83, 0.98, and 0.88, respectively. As shown in figure 1A, and with PSA on a natural logarithmic scale, the mean PSA values in group 1 were stable at low levels throughout follow-up, whereas the mean PSA values in group 2 were low initially but increased afterwards. The mean PSA values in group 3 were elevated during the 2-year follow-up period. These distinctions are shown on a conventional scale for PSA in figure 1B, with an upper limit of 15 ng/mL on the y-axis used to provide better visualization of low values.

For men receiving radiation therapy, the optimal mathematical output of the TRAJ procedure generated four initial clusters, with 55 (14.6%), 198 (52.4%), 103 (27.2%), and 22 (5.8%) patients. The Jaccard coefficients for these groups were 0.89, 0.90, 0.87, and 0.85, respectively. As shown in figure 2A, with PSA again on a natural logarithmic scale, the mean PSA levels in the two lowest value clusters decreased over the first year, and then kept relatively constant at low levels (ie, both with natural logarithm (ln) PSA values <0 in later months, corresponding to PSA <1.0 ng/mL) thereafter. These two low-PSA clusters were therefore subsequently combined, based on clinical judgment and in favor of parsimony. The next highest cluster (with actual PSA values in the single-digit range) was retained independently, as was the highest cluster (with actual PSA values in the double-digit range). These distinctions are shown on a conventional scale in figure 2B, with an upper limit of 100 ng/mL on the y-axis used to provide better visualization of relatively lower values.

Prostate cancer mortality

Patients in groups with higher PSA trajectories had worse prostate cancer survival, and assessments of group membership and prostate cancer mortality had mostly statistically significant (unadjusted) associations (see table 2 and figure 3A,B). Specifically, and with group 1 as the reference, postsurgery patients had an HR of 3.45 (95% CI 0.58 to20.6; P=0.18) for group 2, and 22.7 (95% CI 5.42

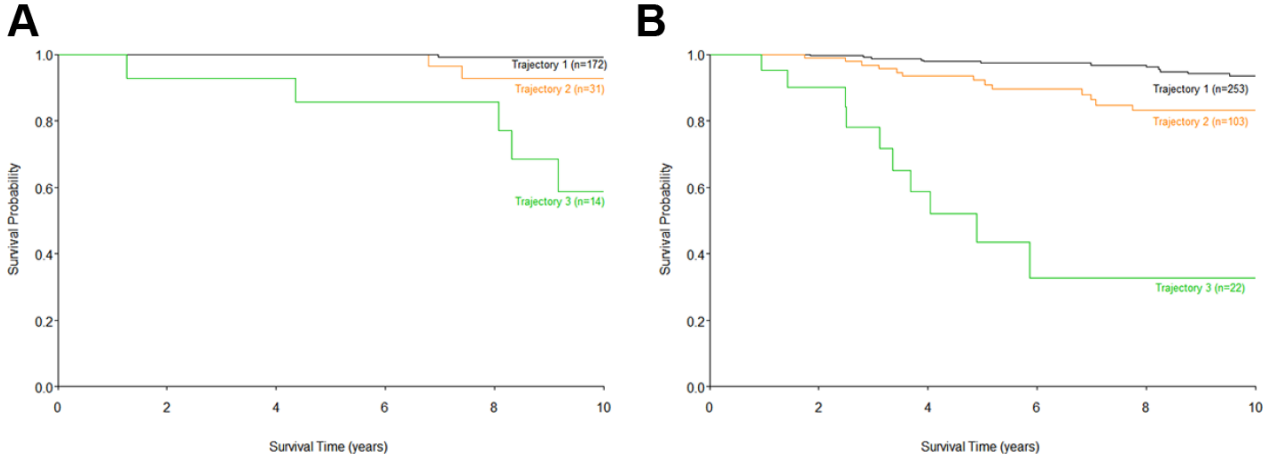

Figure 3 Survival after surgery (A; n=217) and radiation therapy (B; n=378) based on group membership, reflecting prostate-specific antigen trajectories, as shown in figure 2.

to 95.5; P<0.001) for group 3. (Survival curves for groups 2 and 3 cross due to small numbers of participants, but an overall pattern is evident.) After radiation therapy, and with group 1 as the reference, HRs were 2.7 (95% CI 1.35 to 5.40; P=0.005) for group 2 and 18.1 (95% CI 8.26 to 39.8; P<0.001) for group 3.

Additional analyses

Sensitivity analyses were conducted without the 2-year and 10-year time frames, respectively, for determining group membership and the association of group membership with mortality. These results were similar (data not shown).

DISCUSSION

Among men receiving primary treatment for prostate cancer, analyses using latent class mixture models generated a clinically relevant number of PSA trajectories (groups) that were stable after bootstrap resampling. In addition, survival analyses among the men in postsurgery and postradiation groups indicated a significantly different mortality experience corresponding to each cluster. Overall, patients with worse (higher) PSA trajectories tended to have higher hazards of dying from prostate cancer.

The current results—showing that patients with worse trajectories of PSA are more likely to die from prostate cancer—suggest that early recognition of different underlying 'types' of prostate cancer, in terms of aggressiveness, is feasible. Of note, the trajectories were identified using data from the 1990s, when primary treatment was administered for patients with higher PSA values than are observed in current practice. In addition, evaluation for metastases was largely accomplished using CT and bone scan imaging, and adjuvant/neoadjuvant hormone therapy was not commonly used—given that randomized evidence of its effectiveness was not yet available.[16] These 'older' practice patterns yielded a wider range of PSA values to evaluate for trajectory patterns, yet the underlying biology of prostate cancer would be unaffected. As evidence of the representativeness of our analyses, data from the same time period[17] show prostate cancer mortality similar to our findings, in contrast to more recent studies.[18]

Strengths and limitations of the current research include a well-characterized study population, although with a modest number of prostate cancer deaths and corresponding wide CIs for results. The study population was assembled early in the PSA era, as discussed above, and the analyses focused on one (of many possible) methods of clustering longitudinal PSA measurements. We also did not evaluate the direct impact of treatment on mortality, but therapies delivered in a contiguous region, within a national healthcare system, can be expected to have a comparable impact. Also as mentioned above, recent evidence[18] confirms that prostate cancer mortality after treatment is currently considerably lower than we found, presumably attributable to advances in patient care. Such reports support the relevance of our findings, in that our approach helps to identify post-treatment patients at risk for mortality.

As a separate issue, and from a broad perspective, the impact of PSA trajectory should always be considered along with other clinical and laboratory factors of each patient. In the current context, the study population was assembled from multiple sites, the analyses were based on data from a thorough medical record review, and the assessment of PSA kinetics rigorously evaluated attributes of cluster stability. Finally, our results should be replicated in a more contemporary study population.

In the setting of patients being followed after primary treatment for prostate cancer, the current results confirm clinicians' experience that post-treatment PSA trajectory is predictive of prostate cancer mortality. The corresponding patterns (clusters) of PSA measurements become evident early in a patient's clinical course.

Contributors EU and JC developed the study design and drafted the manuscript. ZW, MA and HL conducted the analyses. KR and CKW provided critical feedback. All authors participated in revisions of the manuscript.

Disclaimer The content of this manuscript is the responsibility of the authors alone and does not necessarily reflect the views or policies of the Department of Veterans Affairs or the US Government.

Competing interests None declared.

Provenance and peer review Not commissioned; externally peer reviewed.

Author note ZW is now with Emory University in Atlanta, Georgia, USA.

REFERENCES

1 Lange PH, Ercole CJ, Lightner DJ, *et al*. The value of serum prostate specific antigen determinations before and after radical prostatectomy. *J Urol* 1989;141:873–9.
2 Barry MJ. Screening for prostate cancer—the controversy that refuses to die. *N Engl J Med* 2009;360:1351–4.
3 Hayes JH, Barry MJ. Screening for prostate cancer with the prostate-specific antigen test: a review of current evidence. *JAMA* 2014;311:1143–9.
4 Kim EH, Andriole GL. Prostate-specific antigen-based screening: controversy and guidelines. *BMC Med* 2015;13:61.
5 Carter HB, Pearson JD, Metter EJ, *et al*. Longitudinal evaluation of prostate-specific antigen levels in men with and without prostate disease. *JAMA* 1992;267:2215–20.
6 Schmid HP, McNeal JE, Stamey TA. Observations on the doubling time of prostate cancer. The use of serial prostate-specific antigen in patients with untreated disease as a measure of increasing cancer volume. *Cancer* 1993;71:2031–40.
7 D'Amico AV, Moul JW, Carroll PR, *et al*. Surrogate end point for prostate cancer-specific mortality after radical prostatectomy or radiation therapy. *J Natl Cancer Inst* 2003;95:1376–83.
8 Freedland SJ, Humphreys EB, Mangold LA, *et al*. Risk of prostate cancer-specific mortality following biochemical recurrence after radical prostatectomy. *JAMA* 2005;294:433–9.
9 Vickers AJ, Brewster SF. PSA Velocity and doubling time in diagnosis and prognosis of prostate cancer. *Br J Med Surg Urol* 2012;5:162–8.
10 Concato J, Jain D, Uchio E, *et al*. Molecular markers and death from prostate cancer. *Ann Intern Med* 2009;150:595–603.
11 Concato J. Challenges in prognostic analysis. *Cancer* 2001;91:1607–14.
12 Bryk AS, Raudenbush SW. Application of hierarchical linear models to assessing change. *Psychol Bull* 1987;101:147–58.
13 Anderson CB, Kaufman MR, Dietrich MS, *et al*. Recovery of urinary function after radical prostatectomy: identification of trajectory cluster groups. *J Urol* 2012;187:1346–51.
14 Jones BL, Nagin DS, Roeder K. A SAS procedure based on mixture models for estimating developmental trajectories. *Sociol Methods Res* 2001;29:374–93.
15 Hennig C. Cluster-wise assessment of cluster stability. *Comput Stat Data Anal* 2007;52:258–71.
16 Bolla M, Gonzalez D, Warde P, *et al*. Improved survival in patients with locally advanced prostate cancer treated with radiotherapy and goserelin. *N Engl J Med* 1997;337:295–300.
17 Gerber GS, Thisted RA, Scardino PT, *et al*. Results of radical prostatectomy in men with clinically localized prostate cancer. *JAMA* 1996;276:615–9.
18 Hamdy FC, Donovan JL, Lane JA, *et al*. 10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer. *N Engl J Med* 2016;375:1415–24.