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Serum prostate-specific antigen (PSA) concentration is positively associated with rate of disease reclassification on subsequent active surveillance prostate biopsy in men with low PSA density

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Abstract

- To investigate the association between serum prostate-specific antigen (PSA) concentration at active surveillance (AS) entry and disease reclassification on subsequent AS biopsy ('biopsy reclassification') in men with low PSA density (PSAD).
- To investigate whether a clinically meaningful PSA threshold for AS eligibility/ineligibility for men with low PSAD can be identified based on risk of subsequent biopsy reclassification.
- We included men enrolled in the Johns Hopkins AS Study (JHAS) who had a PSAD of <0.15 ng/mL/g (640 men).
- We estimated the incidence rates (IRs; per 100 person years) and hazard ratios (HR) of biopsy reclassification (Gleason score ≥ 7, any Gleason pattern 4 or 5, ≥ 3 positive cores, or ≥ 50% cancer involvement/biopsy core) for categories of serum PSA concentration at the time of entry into AS.

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Conflict of Interest

The author(s) indicated no potential conflicts of interest

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- We generated predicted IRs using Poisson regression to adjust for age and prostate volume, mean percentage free PSA (ratio of free to total PSA) and maximum percentage biopsy core involvement with cancer.
- The unadjusted IRs (per 100 person years) of biopsy reclassification across serum PSA concentration at entry into JHAS showed, in general, an increase; however, the pattern was not linear with higher IRs in the group 4 to <6 ng/mL (14.2, 95% confidence interval [CI] 11.8–17.2%) when compared with 6 to <8 ng/mL (8.4, 95% CI 5.7–12.3%) but almost similar IRs when compared with the group 8 to <10 ng/mL (14.8, 95% CI 8.4–26.1%).
- The adjusted predicted IRs of reclassification showed a similar non-linear increase in IRs, whereby the rates around 4 ng/mL were similar to the rates around 10 ng/mL.

Conclusion—Risk for biopsy reclassification increased non-linearly across PSA concentration in men with low PSAD, whereby no obvious clinically meaningful threshold could be identified. This information could be incorporated into decision-making for AS. However, longer follow-up times are needed to warrant final conclusions.

Keywords

active surveillance; PSA; patient selection

Introduction

Active surveillance (AS) is a viable alternative to immediate treatment for many patients with low-risk prostate cancer. Because only men whose disease status is reclassified during surveillance and men who cannot live with the diagnosis of untreated cancer any longer will ultimately be treated [1,2], this strategy reduces overtreatment of men with low-risk disease.

The National Comprehensive Cancer Network (NCCN) recommends that men with very-low-risk prostate cancer and a life expectancy of <20 years be managed with AS rather than with curative intervention [3]. However, the best method of defining low-risk and very-low-risk prostate cancer is not clear. The NCCN defines very low risk as: clinical stage T1c, Gleason score ≤6, PSA concentration of <10 ng/mL, <3 biopsy cores with cancer, 50% cancer in any core, and PSA density (PSAD) of <0.15 ng/mL/g. These are the criteria for eligibility for the Johns Hopkins (JH) AS programme [2], with one exception, men who have a PSA concentration of ≥10 ng/mL, but a PSAD of <0.15 ng/mL/g are eligible, if they meet all other criteria. Although various PSAD thresholds have been suggested in the past, there is evidence in the literature that 0.15 ng/mL/g seems to be a rational choice [2,4]. The option of AS and the criteria for eligibility are applied uniformly at our institution.

Although it has been assumed that the risk for reclassification increases with increasing serum PSA concentration [5], knowledge about the pattern of this association in men in AS with low PSAD, including in men with a PSA concentration of ≥10 ng/mL, is inadequate. Today, a threshold for serum PSA of <10 ng/mL is usually applied [3] to define eligibility for AS, whereby the rationale for the use of the threshold at 10 ng/mL is that the probability of organ-confined disease is lower and the probability of non-organ-confined disease including seminal vesicle invasion and lymph node metastases is substantially higher for a PSA concentration of ≥10 ng/mL [6–8]. However, it remains to be determined whether this threshold is optimal in patients with prostate cancer otherwise eligible for AS and with low PSAD as well. To address these questions, we included men with a low PSAD enrolled in the JH AS Study (JHAS) and we compared the risk of disease reclassification on surveillance biopsies ('biopsy reclassification') across the spectrum of PSA concentrations.

Patients and Methods

We included in the analysis patients enrolled in the JHAS, a prospective cohort initiated in 1995 that includes almost 1000 patients through to July 2011 [2]. The JHAS was approved by the Institutional Review Board at the Johns Hopkins Medical Institutions and all patients provided informed consent.

To be eligible for inclusion in the JHAS, patients must have had clinical stage T1c prostate cancer with a PSAD of <0.15 ng/mL/g, Gleason score ≤ 6 , no Gleason pattern 4 or 5, ≤ 2 biopsy cores with cancer, and a maximum of 50% involvement of any core with cancer. All urologists at JH offer AS to men who meet the entry criteria. Since 2005, 54.1% of eligible men who considered AS entered the programme. Some men enrolled in AS did not meet all criteria due to co-morbidities or personal preference. In these men, the single but mandatory inclusion criterion was Gleason score ≤ 6 on the initial biopsy with no Gleason pattern 4 or 5.

Details of cohort follow-up have been described [9]. Briefly, participants were followed through semi-annual PSA measurements (total and free) with DRE and annual 12–14 core surveillance biopsy (transition zone biopsies obtained routinely since 2009). Curative treatment is recommended after disease reclassification on surveillance biopsy [9]. When possible, all surveillance visits and procedures have been performed at Johns Hopkins Hospital. Medical and pathology records are obtained for patients receiving outside care. By July 2011, 19 men in the JHAS had died, but none from prostate cancer.

The current analyses are restricted to patients who met all of the JHAS criteria for very-low-risk prostate cancer. We excluded 172 men with a PSAD of ≥ 0.15 ng/mL/g, 13 men with stage $> T1c$ disease, and 26 men with unfavourable findings on the initial diagnostic prostate biopsy. We also excluded 39 men with missing prostate volume and one man with unverified pathological findings for the entry prostate biopsy. We excluded 95 men who did not have at least one surveillance prostate cancer biopsy after entry. After these exclusions, 640 of the 986 men (64.9%) in the JHAS were included in the analysis.

The ratio of free to total PSA, i.e. the percentage free PSA (%fPSA), a significant predictor of disease reclassification on the first surveillance biopsy [10], was available at entry for only 4% of the men (23 men), although %fPSA was available at most of the times of surveillance biopsy. Hence, we calculated the mean %fPSA for each man and used only this mean value for all the men in the analysis. Study outcomes were disease status reclassification on a surveillance biopsy, defined as a Gleason score ≥ 7 and/or Gleason pattern 4 or 5 (grade reclassification), and/or ≥ 3 positive cores and/or $>50\%$ cancer involvement per biopsy core (volume reclassification).

Time on AS was calculated as time from entry to the date on which biopsy reclassification occurred, date of the last biopsy before exit from JHAS for other reasons, date of the last biopsy before death, or the date of the last biopsy before the end of follow-up for this study in July 2011, whichever occurred first.

We applied PSA thresholds ranging from 2 to 10 ng/mL, in 1-unit intervals (2 vs <2 , 3 vs <3 , 4 vs <4 , 5 vs <5 , 6 vs <6 , 7 vs <7 , 8 vs <8 , 9 vs <9 and 10 vs <10 ng/mL; nine binary comparisons were made) at the time of AS entry and then compared with the risk of biopsy reclassification in men in the higher compared with men in the lower PSA concentration groups. We calculated the number of events, estimated the cumulative incidence at a follow-up time of 55 months (the minimum of the maximum follow-up time to the last event over the nine binary comparisons made, which was in men with PSA concentration of ≥ 10 ng/mL) using the Kaplan–Meier method, and calculated the unadjusted

incidence rates (IRs) per 100 person years for biopsy reclassification. Differences in the cumulative incidence between men with higher and lower PSA concentrations defined by each of the nine thresholds were tested using the log-rank test.

Cox proportional hazards regression was used to estimate the association between higher PSA concentration (vs lower) and risk of biopsy reclassification adjusting for age, prostate volume, mean %fPSA and maximum percentage biopsy core involvement. Schoenfeld residuals were used to assess the proportional hazards assumption.

Further, unadjusted IRs of biopsy reclassification (any upgrade and upgrade in Gleason score) were calculated by PSA concentration for intervals of 2 ng/mL (<2, 2 to <4, 4 to <6, 6 to <8, 8 to <10, and ≥10 ng/mL). Poisson regression adjusting for age and prostate volume was used to generate predicted IRs across PSA concentrations, which we then plotted. In the graph, we truncated the distribution at a PSA concentration of >15 ng/mL (one man), but the value remained in the regression models. In the analysis for grade reclassification, men with a first event of volume reclassification were censored at that event time. We repeated the analysis adjusting additionally for mean %fPSA and maximum percentage core involvement with prostate cancer.

Based on these analyses, we categorised men into low-, intermediate-, and high-risk for biopsy reclassification using several sets of PSA thresholds (low-, intermediate-, and high-risk, respectively (analysis 1: <4, 4 to <8 and ≥8 ng/mL; analysis 2: <3, 3 to <8 and ≥8 ng/mL; analysis 3: <2, 2 to <8 and ≥8 ng/mL). We did not use a threshold of ≥10 ng/mL to define high risk because the number of men with a PSA concentration of ≥10 ng/mL was small and the adjusted hazard ratios (HRs) of biopsy reclassification comparing men ≥8 ng/mL with concentrations below and comparing men ≥10 ng/mL with concentrations below were almost the same. For calculation of the *P*-trend across the risk categories, we used Cox proportional hazards regression adjusting for age, prostate volume, mean %fPSA and maximum percentage core involvement with prostate cancer.

Two-sided tests were performed and a *P* < 0.05 was considered to indicate statistical significance.

Results

In all, 640 men were included in the analysis. At entry into AS, the mean (median, range) age was 65 (65, 48–82) years, the mean (median, range) PSA concentration was 4.5 (4.4, 0.24–19) ng/mL and the mean (median, range) PSAD was 0.09 (0.09, 0.004–0.14) ng/mL/g (Table 1). The mean (median, range) time at risk was 38 (27, 3–165) months. Overall, there were 213 biopsy reclassifications, 44 upgrades in Gleason score only, 125 upgrades in volume only and 44 upgrades in both, Gleason score and volume (21%), simultaneously. The mean (median, range) time to event was 29 (20, 3–147) months.

Table 2 summarises the cumulative incidences of biopsy reclassification, the IRs per 100 person years and the adjusted HRs for the nine PSA thresholds ranging from 2 to 10 ng/mL. We found a minimum and a maximum cumulative incidence, respectively, of 17 (95% CI 10–28)% in the low and 51 (95% CI 36–68)% in the high PSA concentration groups when comparing higher and lower PSA concentration groups with thresholds at 2 and 8 ng/mL, respectively. There were statistically significant differences in unadjusted biopsy reclassification rates between higher and lower PSA concentration groups using thresholds of 2, 3, or 4 ng/mL; however, the rates were not statistically significantly different when using higher thresholds. After adjusting for age, prostate volume, mean %fPSA, and maximum percentage of core involvement, the HRs of biopsy reclassification were

statistically significantly above 1 when comparing higher and lower PSA concentration groups using thresholds of 2, 3 or 4 ng/mL, while the HRs were not significant when using higher PSA concentration thresholds. When comparing higher and lower PSA concentration groups using thresholds at 8 or 10 ng/mL, the HRs of biopsy reclassification were above 1 and were of similar magnitude, but were not statistically significant.

The unadjusted IRs of biopsy reclassification across serum PSA concentration at entry into JHAS using categories with 2 ng/mL intervals showed, in general, an increase (Table 3); however, the pattern was non-linear with higher IRs (per 100 person years) in the group 4 to <6 ng/mL (IR 14.2%, 95% CI 11.8–17.2) when compared with 6 to <8 ng/mL (IR 8.4%, 95% CI 5.7–12.3) but almost similar IRs when compared with the group 8 to <10 ng/mL (IR 14.8%, 95% CI 8.4–26.1). The age and prostate volume adjusted predicted IRs of biopsy reclassification showed a similar non-linear increase in IRs whereby the rates around 4 ng/mL were similar to the rates around 10 ng/mL as shown in Fig. 1a for upgrade in volume and/or Gleason score and in Fig. 1b for upgrade in Gleason score only. Additional adjustment for mean %fPSA and maximum percentage biopsy core involvement with cancer did not change this pattern. Based on these predicted rates, no obvious clinically meaningful threshold could be identified for either outcome.

Next, we classified the men into PSA risk categories (low, intermediate and high) based on the preceding results, and compared the risk of biopsy reclassification among the categories as shown in Table 4. Several different thresholds were used to define the PSA risk categories. When using <4 ng/mL as the low-risk (reference) group, the adjusted HRs were 1.48 (95% CI 1.01–2.17) for the intermediate-risk (4 to <8 ng/mL) and 2.42 (95% CI 1.04–5.54) for the high-risk (>8 ng/mL) groups (P -trend = 0.019). When using <3 ng/mL as the low-risk (reference) group, the corresponding HRs were 1.93 (95% CI 1.17–3.17) and 3.47 (95% CI 1.36–8.83; P -trend = 0.004) and when using <2 ng/mL as the low-risk (reference) group, the corresponding HRs were 3.13 (95% CI 1.58–6.19) and 6.02 (95% CI 2.09–17.41; P -trend <0.001).

Discussion

In this prospective study of men with low PSAD enrolled in the JHAS, the biopsy reclassification rate generally increased with increasing PSA concentration, but the association was not linear. Taking into account age and prostate volume, the predicted biopsy reclassification rate in men with a PSA concentration of around 4 ng/mL was almost the same as the rate in men with a PSA concentration around 10 ng/mL. Additional adjustment for mean %fPSA and maximum percentage biopsy core involvement with cancer did not change this pattern. However, it remains unclear if the rates around 4 ng/mL are higher or the rates >10 ng/mL are lower than expected. Of note, the protocol at our institution does not exclude men with a PSA concentration of >10 ng/mL from AS, as long as PSA density is <0.15 ng/mL/g. Based on these predicted rates, no obvious clinically meaningful threshold for AS eligibility/ineligibility was identified for men with low PSAD.

Using a PSAD of <0.15 ng/mL/g and not additionally a PSA concentration of <10 ng/mL as inclusion criterion for AS, stands in contrast to most AS protocols. The rationale for the use of a limit of 10 ng/mL is that the probability of organ-confined disease is lower and the probability of non-organ-confined disease including seminal vesicle invasion and lymph node metastases is substantially higher for a PSA concentration of >10 ng/mL [6–8]. Based on the relationship between PSA and disease extent at prostatectomy, the current NCCN guidelines [3] recommend a PSA concentration threshold 10 ng/mL for classification of very-low- and low-risk disease. However, PSAD was not considered in the aforementioned studies [6–8], and to the best of our knowledge the validity of any given PSA threshold in

predicting biopsy reclassification among men in AS with a PSAD of <0.15 ng/mL/g has been never evaluated.

In the present data, the unadjusted and adjusted predicted IRs of biopsy reclassification indicated that men with a PSA concentration of ≥ 10 ng/mL had a higher risk than men with low PSA concentrations (<4 ng/mL); however, neither the unadjusted nor the age- and prostate volume-adjusted predicted IRs supported the selection of a particular threshold for deeming men ineligible for AS. While the rate of biopsy reclassification generally increased with increasing PSA concentration, the rate around 4 ng/mL was higher than would have been expected (based on the rates in men with PSA concentrations around 2 and 6 ng/mL) and it approaches that of men with a PSA of around 10 ng/mL. Further work is needed to determine whether referral and/or treatment-decision factors might explain this pattern.

We were not able to identify an optimal PSA concentration threshold that could be used for AS decision-making. However, it might be, that in some men with large prostates, PSA concentration and PSAD provide no or limited additional information about the presence of high-grade cancer anyway and based on the evidence that high-grade cancers produce less PSA on a volume for volume basis as compared with lower grade cancer [11,12]. It may be that refined and personalised risk stratification in patients entering AS could improve safety, and that especially men with large prostates should have earlier and extended follow-up biopsies and possibly MRI to reduce the rate of misclassification at entry into AS. However, to find a reasonable balance between gain of additional safety vs costs and potential adverse effects of extended prostate biopsies remains challenging and a topic of further investigation.

Several aspects of the present study require discussion:

1. It might be that the association between PSA concentration at AS entry and risk of biopsy reclassification during AS follow-up will change with longer follow-up. Due to the few men with a PSA concentration of ≥ 10 ng/mL, we could not determine with precision their risk of biopsy reclassification, although they did not appear to have a substantially higher risk than men with a PSA of ≥ 8 to <10 ng/mL.
2. The JHAS is a highly selected group and our results may not be generalizable to AS populations in which less stringent inclusion criteria have been applied, especially in cohorts in which low PSAD was not an inclusion criterion.
3. We had missing data on prostate volume and PSAD for 4% of the JHAS cohort; these men were excluded from the analysis. However, since the JHAS inclusion criteria are stringently and uniformly applied in our institution, we may reasonably assume that these patients would not have been significantly different from the ones remaining in the study. This is of crucial importance, as we assume that the exclusion of these patients did not result in a selection bias.
4. As only 76 men subsequently underwent prostatectomy, we could not determine whether different PSA concentration thresholds are associated with different likelihoods of harbouring a higher grade tumour.
5. Biopsy reclassification whether by cancer volume or grade, may be an imperfect proxy for the biological potential of prostate cancer.
6. We did not adjust for multiple testing in the analyses in which we used multiple thresholds because the goal was to evaluate the influence of shifting the threshold.
7. Finally, biopsy reclassification does not distinguish between misclassification and 'true' disease progression.

Strengths of the present study are the homogenous AS population due to stringent and uniformly applied inclusion criteria at our institution, the very few missing data due to high compliance with follow-up procedures, and a rigorous analytical approach.

In conclusion, risk for biopsy reclassification on subsequent AS prostate biopsies increased non-linearly across PSA concentrations in men with low PSAD, whereby no obvious clinically meaningful threshold PSA concentration for AS eligibility/ineligibility could be identified. This information could be incorporated into decision-making for AS. However, longer follow-up times are needed to warrant final conclusions.

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Abbreviations

AS	active surveillance
HR	hazard ratio
NCCN	National Comprehensive Cancer Network
%fPSA	percentage free PSA (ratio of free to total PSA)
PSAD	PSA density
IR	incidence rate
JH(AS)	Johns Hopkins (Active Surveillance Study)

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Fig. 1.

A, Age and prostate volume adjusted IRs (per 100 person years) of biopsy reclassification on surveillance biopsy as a function of serum PSA concentration at AS entry. The solid line represents the estimated IR from a Poisson regression model and the shaded area the 95% CI around the estimate. The one PSA concentration of 15 ng/mL was truncated for plotting. At the top of the figure the unadjusted IRs are shown in PSA concentration intervals of 2 ng/mL. **B**, Age and prostate volume adjusted IR (per 100 person years) of disease status reclassification by upgrade on surveillance biopsy as a function of serum PSA concentration at AS entry. The solid line represents the estimated IR from a Poisson regression model and the shaded area the 95% CI around the estimate. The one PSA concentration of 15 ng/mL was truncated for plotting. At the top of the figure the unadjusted IRs are shown in PSA concentration intervals of 2 ng/mL.

Table 1

Baseline characteristics of men with a PSAD of <0.15 ng/mL/g enrolled in the JHAS.

Variable	Value
Number of patients	640
Mean (median, range):	
Age, years	65.3 (65.6, 45.8–82.6)
PSA concentration, ng/mL	4.5 (4.4, 0.24–19)
PSAD, ng/mL/g	0.09 (0.09, 0.004–0.14)
Mean %fPSA	21.2 (20.2, 4.1–62.7)
Prostate volume, mL	53 (48, 7.7–211)
Maximum percentage biopsy core involvement	8.5 (1, 1.0–50)
N (%):	
Race:	
White/Caucasian	579 (90)
African-American/Black	38 (6)
Asian	7 (1)
Hispanic	4 (≈1)
Others	12 (2)
Family history of prostate cancer*:	
Positive in any relatives	110 (17)
Number of affected relatives	122
Positive in relatives aged < 75 years	63 (9.8)
Number of affected relatives aged < 75 years	78

* In first degree relatives, overall and restricted for relatives aged <75 years at diagnosis.

Table 2

Cumulative incidence of biopsy reclassification, IRs and adjusted HRs comparing higher and lower PSA concentrations at AS entry when using nine thresholds in men with a PSAD of <0.15 ng/mL/g in the JHAS.

PSA concentration threshold, ng/mL	Number of events, n/N		Cumulative incidence (95% CI), %		IR (95% CI), %		HR (95% CI) ***
	<Threshold	Threshold	<Threshold	Threshold	<Threshold	Threshold	
2	15/90	198/550	17 (10–28)	42 (37–46)	4.2 (2.5–7.0)	12 (10.4–13.8)	<0.01 2.9 (1.49–5.76)
3	32/144	181/496	25 (17–34)	42 (37–47)	6.1 (4.3–8.6)	12.2 (10.6–14.2)	<0.01 1.84 (1.12–3.01)
4	63/245	150/395	29 (23–37)	43 (38–49)	7.6 (5.9–9.7)	12.7 (10.9–14.9)	<0.01 1.46 (1.00–2.13)
5	135/407	78/233	38 (33–44)	37 (32–46)	10.7 (9.0–12.7)	10.4 (8.3–13.0)	0.86 0.68 (0.46–0.99)
6	169/505	44/135	38 (33–43)	40 (32–50)	10.7 (9.2–12.5)	10.1 (7.5–13.6)	0.74 0.87 (0.55–1.37)
7	187/563	26/77	38 (33–43)	41 (29–54)	10.5 (9.1–12.1)	11.2 (7.6–16.4)	0.76 1.33 (0.72–2.41)
8	195/594	18/46	37 (33–42)	51 (36–68)	10.4 (9.0–11.9)	14.4 (9.1–22.8)	0.19 1.57 (0.76–3.22)
9	204/613	9/27	38 (34–43)	42 (26–67)	10.6 (9.2–12.1)	10.9 (5.7–21.0)	0.89 0.94 (0.35–2.52)
10	207/624	6/16	38 (34–42)	50 (27–79)	10.5 (9.2–12.1)	14.3 (6.4–31.8)	0.45 1.61 (0.47–5.49)

* Kaplan–Meier estimates at the minimum follow-up of 1658 days (≈55 month);

** per 100 person years;

*** HR, Cox adjusted HR (adjusted for age, prostate volume, mean %tPSA, maximum percentage biopsy core involvement);

† Log-rank test for equality of survival;

‡ Two-tailed IR comparison.

IRs per 100 person years and multivariable adjusted HRs for biopsy reclassification (upgrade in prostate cancer volume and/or Gleason score) by PSA concentration categories in 2 ng/mL intervals in men with a PSAD of <0.15 ng/mL/g in the JHAS.

Table 3

PSA concentration category, ng/mL	Number of patients	Crude number of events	IR (95% CI), %*	HR (95% CI)**	P	P-trend
<2	90	15	4.2 (2.5–7.0)	1		0.009
2 to <4	155	48	10.1 (7.6–13.4)	2.84 (1.39–5.8)	0.004	
4 to <6	261	106	14.2 (11.8–17.2)	3.46 (1.71–7.01)	0.001	
6 to <8	89	26	8.4 (5.7–12.3)	2.14 (1.08–5.84)	0.032	
8 to <10	29	12	14.8 (8.4–26.1)	5.42 (1.75–16.79)	0.003	
10	16	6	14.3 (6.4–31.8)	6.81 (1.48–31.21)	0.013	

* Per 100 person years;

** HR, Cox adjusted HR (adjusted for age, prostate volume, mean %fPSA, maximum percentage biopsy core involvement).

Multivariable adjusted hazard ratios (HR) of biopsy reclassification by low, intermediate and high PSA groups, men with PSAD < 0.15 ng/ml/g in the Johns Hopkins Active Surveillance Cohort.

Table 4

Risk group	PSA groups		Number of patients	Median PSA concentration, ng/mL	HR (95% CI)*	P-trend
	PSA concentration, ng/mL					
Analysis 1						
Low	<4		245	2.64	1	0.019
Intermediate	4 to <8		349	5.04	1.48 (1.01–2.17)	
High	8		46	9.30	2.41 (1.04–5.54)	
Analysis 2						
Low	<3		144	1.745	1	0.004
Intermediate	3 to <8		450	4.80	1.93 (1.17–3.17)	
High	8		46	9.30	3.47 (1.36–8.83)	
Analysis 3						
Low	<2		90	1.14	1	<0.001
Intermediate	2 to <8		504	4.50	3.13 (1.58–6.19)	
High	8		46	9.30	6.02 (2.09–17.41)	

* HR, Cox adjusted HR (adjusted for age, prostate volume, mean %PSA, maximum percentage biopsy core involvement).