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Sociodemographic and clinical predictors of switching to active treatment among a large ethnically diverse cohort of men with low-risk prostate cancer on observational management

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Abstract

Purpose—To determine the clinical and sociodemographic predictors of beginning an active treatment among an ethnically diverse population of men with low-risk prostate cancer initially on observational management.

Materials and Methods—We retrospectively studied men diagnosed with low-risk prostate cancer between 2004 and 2012 at Kaiser Permanente Northern California, who did not receive any treatment within the first year of diagnosis and had at least two years of follow-up. We used Cox proportional hazards regression models to determine factors associated with time from diagnosis until active treatment.

Results—We identified 2,228 eligible men who were initially on observation, and 27% began an active treatment during follow-up (median 2.9 years). Non-Hispanic Black men were marginally more likely to begin an active treatment (hazard ratio [HR] 1.3, 95% CI 1.0–1.7) than non-Hispanic White men, independent of baseline and follow-up clinical measures. Among men who remained on observation, non-Hispanic Black men were re-biopsied within 24 months of diagnosis at slightly lower rates than non-Hispanic White men (HR 0.70, 95% CI 0.6–1.0). Gleason grade progression (HR 3.3, 95% CI 2.7–4.1) and a PSA doubling time < 48 months (HR 2.9, 95% CI 2.3–3.7) were associated with initiation of active treatment, independent of race.

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Conclusions—Sociodemographic factors, such as ethnicity and education, may independently influence a patient's decision to pursue active treatment and their utilization of serial biopsies during active surveillance. These factors are important in further studies of prostate cancer treatment decision making.

Keywords

Active surveillance; Disease progression; Early detection; Expectant management; Prostate-specific antigen; Prostatic neoplasms

Introduction

The use of active surveillance (AS) as a management strategy for low-risk prostate cancer (PCa) has been increasing over the last decade.¹ Current US guidelines recommend observational management, AS or watchful waiting (WW), as strategies for men who are at low-risk of disease progression,^{2–4} thereby avoiding active treatment (AT) unless clinical measures indicate disease progression or the patient requests AT.^{5, 6} Results from prostate-specific antigen (PSA) testing and repeat biopsies are used to determine PCa progression and prompt cessation of observational management.⁷ Recent systematic reviews advocated serial prostate biopsies to accurately detect disease progression,⁶ because PSA kinetics are not effective as the sole clinical trigger to prompt a switch to AT.⁸

Younger age and anxiety are associated with men switching from observation to more aggressive treatment.^{9, 10} However, few studies have examined non-clinical factors that influence surveillance and follow-up protocols in a sociodemographically diverse population. In addition, there is limited evidence on whether race/ethnicity and sociodemographic factors influence beginning more aggressive treatments within equal-access integrated healthcare systems with salaried providers.¹¹ We assessed the impact of sociodemographic and clinical factors in predicting whether men began an AT after initially choosing observational management among an ethnically diverse population of low-risk PCa patients receiving care in an integrated healthcare system.

Methods

Study design and population

The study population included men seen at Kaiser Permanente Northern California (KPNC), an integrated healthcare delivery system. The KPNC health system has comprehensive information from inpatient and outpatient diagnoses, clinical encounters, laboratory test values, and tumor-related characteristics. We identified men from the KPNC Cancer Registry diagnosed with low-risk PCa from 1/1/2004 to 12/31/2012. Low-risk PCa was defined using D'Amico/AUA criteria¹²: clinical stage T2a, PSA <10 ng/mL and Gleason score ≤ 6. Men on observational management, either AS or WW, were those who had not received AT within 12 months of their diagnosis and who were followed for at least two years after diagnosis. End of follow-up for the cohort was December 31, 2014. AT was defined as radical prostatectomy (RP), radiation therapy (RT), or androgen deprivation therapy (ADT).

We defined observational management as any use of AS or WW that included evidence of regular PSA monitoring (1 PSA/year) or repeat biopsies, as there was no uniform surveillance protocol implemented at KPNC during the study period. KPNC provided care in one of 12 KPNC service areas within the greater San Francisco Bay Area and Central Valley of California. The study was approved by the Kaiser Foundation Research Institute IRB and the Georgetown University IRB.

Demographic characteristics

We obtained age at diagnosis, race/ethnicity, date of diagnosis, census-tract educational attainment (percentage of the population 25 years or older living in the same census area as the individual with at least a college education), and KPNC service area.

Clinical characteristics

Elixhauser comorbidity index was computed for 30 individual health conditions diagnosed between 2 years before PCa diagnosis and up to 90 days after PCa diagnosis. We required an inpatient diagnosis and/or at least two outpatient diagnosis codes at least 30 days apart to minimize false-positives from “rule-out” diagnoses. We obtained the Gleason score from the first biopsy leading to the PCa diagnosis. There was no central pathological review and the Gleason grading was performed by various pathologists using the ISUP Modified Gleason System since 2005. However, due to volume (>2000) of new cases per year at KPNC, the pathologists have a robust practice in urological cancer. Diagnostic biopsies were performed under the general practice guidelines of the time period; 6 core biopsies in the earlier part of the study period with a transition to 12 core biopsies in the latter part of the study period. The baseline PSA level was defined as the serum PSA (ng/mL) measured within 6 months prior to diagnosis and examined using categorical (<4, 4–5, 6–7, and 8–10 ng/mL), and age-specific PSA cutoffs based on AUA criteria.¹³ We obtained follow-up PSA test results and derived the following variables: PSA slope,¹⁴ PSA doubling time (PSADT; <48 months vs. 48 months),¹⁵ and follow-up PSA intermediate-risk PCa status (any follow-up PSA>10 ng/mL: yes/no).¹⁶ More detailed methodology is available online (supplementary material).

Analytic Cohort

Of the 6,632 men diagnosed with PCa from January 1, 2004 to December 31, 2012, we identified 2,228 cases diagnosed with clinically localized low-risk PCa, who had not received any treatment within 12 months of their diagnosis and who were followed for at least two full years after diagnosis. Less than 2.6% of men were lost to follow-up through 2014.

Statistical analysis

We performed Cox proportional hazard regression models to estimate the risk, presented as hazard ratios (HRs) with 95% confidence intervals (95% CIs), of beginning an AT associated with sociodemographic and clinical characteristics, up to a maximum of 11 years after PCa diagnosis. Follow-up time started from the date of the diagnostic biopsy that led to pathologic confirmation of PCa, and continued until the time of the event (AT) or time of right-censoring (date of disenrollment, date of death, or end of follow-up), whichever

occurred first. We adjusted for age at diagnosis, race/ethnicity, T stage, baseline PSA, Gleason, census-tract educational attainment, Elixhauser comorbidity index, year of diagnosis and KPNC service area in all models. In models that examined sociodemographics, we also adjusted for Gleason grade progression status and follow-up PSA intermediate-risk PCa status. In models that examined clinical measures, models were adjusted for all variables mentioned above except the following: follow-up biopsy utilization did not adjust for Gleason grade progression; PSA slope and PSADT did not adjust for follow-up PSA intermediate-risk PCa status.

We also performed Cox proportional hazard regression models, adjusted for baseline variables, to examine the association between sociodemographics and time until follow-up biopsy utilization among men who remained on observational management. Follow-up time started from the date of the diagnostic biopsy, and continued until the time of the event (initial re-biopsy date within the first 24 months) or time of right-censoring (date of disenrollment, date of death, or end of follow-up).

In subgroup analyses, we conducted models that were restricted to men who had serial re-biopsies. In a sensitivity analysis, we excluded men whose Gleason grading was performed prior to the revised 2005 guidelines. Subjects with missing data were excluded, however all variables had less than 1% of data missing (except for follow-up biopsy status and Gleason progression status). All analyses were performed using SAS version 9.3. All statistical tests were two-sided and statistical significance was defined as $p < 0.05$.

Results

Table 1 presents sociodemographic and baseline clinical characteristics (N = 2,228). The median follow-up time was 2.9 years and overall survival was 96.0% (5 deaths were from PCa).

During the follow-up period, 27.2% men received AT (median=1.8 years), while 72.8% men remained on an observational management regimen (median follow-up 3.4 years) (Table 2). Men who began an AT were more likely to undergo RT (N = 355, 58.5%) than RP (N = 207, 34.1%), yet RPs occurred slightly earlier (75% within 2.5 years), compared to RT (75% within 3.2 years). Among men undergoing RT as their definitive treatment, 11.3% also received ADT (mean= 2 months prior to RT). Of men with ADT only (N=45), 50% received ADT within 3 years of diagnosis.

A majority of men (96.5%) received at least one follow-up PSA test, while 53% were re-biopsied (46% on observation, 74% with AT). The mean number of follow-up biopsies was 1.2 among men who switched to an AT, while only 0.7 among men who remained on observation. Re-biopsy utilization 24 months post-diagnosis did not significantly differ between Black and White men who began an AT (52% versus 56%, respectively). However, among men remaining on observation, Black men were re-biopsied slightly less often compared to White men (26% versus 32%, respectively; HR 0.7, 95% CI 0.6–1.0). However, when additionally adjusted for PSA progression within 24 months, race was not significant (HR 0.9, 95% CI 0.8–1.1). Men living in areas with higher census-level educational

attainment (HR 1.6, 95% CI 1.3–2.0, Q4 vs. Q1 [lowest]) and those diagnosed in more recent years (HR 1.1, 95% CI 1.0–1.1) were more likely to be re-biopsied. We conducted a chart review among men without pathological verification of Gleason progression but who began AT (N=157) and the top reasons for beginning AT were: treatment choice indecision (N=46), rise in PSA (N=36 [26 were White, 6 Black]), potential rebiopsy complications due to comorbidity (N=30) and physician recommendation for PSA only (N=21).

Men with a higher baseline PSA level (8–10 ng/mL) were associated with beginning AT (HR 1.4, 95% CI 1.1–1.8) compared to men with a lower PSA (4–5 ng/mL) (Table 3). Follow-up biopsy utilization (HR 2.9, 95% CI 2.4–3.5) was associated with beginning AT. Gleason grade progression (HR 3.3, 95% CI 2.7–4.1), PSA slope (HR 1.7, 95% CI 1.5–1.9) and PSADT < 48 months (HR 2.9, 95% CI 2.3–3.7) were associated with beginning AT. When we tested for interaction by ethnicity, models were not statistically significant.

Among sociodemographic factors, non-Hispanic Black men were marginally more likely to begin AT (HR 1.3, 95% CI 1.0–1.7) than non-Hispanic White men, with a majority of Black men choosing RT (39% RP versus 49% RT and 12% ADT). Men living in higher education areas (Q4 vs. Q1, HR 0.8, 95% CI 0.6–1.0) and those diagnosed in more recent years (HR 0.9, 95% CI 0.9–1.0) were slightly less likely to begin AT (Table 3). In a subgroup analysis of 1,140 men who adhered to a defined AS protocol with annual re-biopsies and PSA tests, sociodemographic predictors did not materially differ. In sensitivity analyses, results were robust as they remained similar after excluding men whose Gleason grade was scored prior to the revised guidelines in 2005 (supplementary material).

Discussion

Among men diagnosed with low-risk PCa, observational management is now a commonly used treatment option, as the potential harms arising from overtreatment are weighed against deferring therapies that may preempt disease progression. In this cohort of a large ethnically diverse population with medium-term follow-up, we found that non-Hispanic Black men were more likely than White men to begin an AT, independent of all clinical triggers, including PSA doubling time and Gleason progression.

There is mounting evidence that supports observation, particularly AS, as a safe method of disease management for patients with low-risk PCa.¹⁷ The overall rate of re-biopsy was lower in our cohort compared to other studies that monitored AS adherence,⁶ which likely reflects that our cohort mirrors a 'real-life' cohort of men who may or may not choose to follow surveillance plans for a wide variety of reasons. However, racial differences for uptake of AT among men managed under a stricter AS protocol, and who all underwent repeat biopsies, were similar to the entire cohort. While the results were only marginally significant, it suggests that race may be a factor for switching to an AT even among men on AS.

Tumor reclassification has been the primary clinical trigger that prompts AT among men on AS.^{18, 19} Gleason progression was associated with switching to an AT, and this did not vary by race. The rate of Gleason progression in our cohort (18%) among men who did undergo a

repeat biopsy was lower than reported elsewhere,⁶ perhaps reflecting concern about biopsy-related complications.²⁰

The large proportion of men who remained on observation without a follow-up biopsy appeared to be men with PSA-only surveillance. Measures of PSA kinetics to date have been deemed unreliable to function as a sole trigger to drive an AT intervention.⁸ Measures of PSA kinetics, including PSADT and PSA slope, were associated with switching to an AT, and appeared to drive treatment changes in our cohort.

A primary reason we examined whether sociodemographic and clinical factors predicted switching to an AT is that studies have primarily been performed in non-ethnically diverse populations.^{6, 21, 22} While use of observational management is becoming more common,^{23, 24} it is unknown whether AS is underutilized in minority populations, particularly within an equal-access healthcare system. Our study had a relatively large number of men from minority populations (31.1%). Black men were marginally more likely to switch to AT, a finding previously been reported in only two other studies.^{25, 26} Yet, evidence also suggests Black men are less likely to receive curative treatment for low-risk PCa than White men.^{11, 27} While race/ethnicity may play a factor in uptake of AT, the effect was modest. Gleason progression and PSA kinetics were both more influential predictors for switching to AT.

Ensuring greater adherence to strict AS criteria by use of serial re-biopsies in Black men and those living in areas with lower educational attainment is an important finding. Our results suggest that Black men who remained on observation had lower rates of serial rebiopsies. These results are important as clinicians may be increasingly hesitant to require men to have serial re-biopsies due to complications. Yet, Black men are known to have a greater likelihood of PCa progression,^{28, 29} which suggests that clinicians should be cautious about placing men on AS until better methods are devised to improve monitoring men on AS.

Other reasons for beginning an AT may include lack of patient awareness of AS, patient anxiety, physician anxiety about whether deferred treatment could result in poorer long-term outcomes, and the societal inclinations for treating all cancers.^{6, 30} Future studies are needed to prospectively examine a wider variety of clinical and non-clinical factors to provide a clearer assessment of the patient and physician related decision-making processes associated with treatment selection and discontinuation.

Strengths of this study included the large number of ethnically diverse patients spanning the most recent decade during which substantial changes have occurred in treatment practices for low-risk PCa. This is one of the few cohorts with sufficient sample sizes to examine whether the associations of clinical triggers for beginning AT varied by sociodemographic factors. In addition, our study included comprehensive clinical and laboratory data.

Limitations include those inherent to a retrospective observational design and the lack of some cancer-specific information (tumor density, size and positive cores). In addition, our data do not include patient-reported reasons for AT, patient-physician interactions or provider preferences. Lastly, greater follow-up time is needed to examine longer-term outcomes. Finally, our study may not be generalizable to other populations as it was limited

to a single integrated health system. However, KPNC includes a socioeconomically and racially diverse community.

In summary, Black men may be more likely than White men to begin an AT independent of follow-up clinical measures, a finding that suggests greater attention to race/ethnicity is needed. In addition, we were able to confirm previously identified clinical triggers of beginning AT, and these factors did not vary by sociodemographics. As delaying more aggressive treatments following a low-risk PCa diagnosis is becoming more common, non-clinical predictors may influence a man's decision on whether to end observational management. To better understand predictors for AT utilization, future studies of men with low-risk disease should include patient-reported outcomes and account for sociodemographic factors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Definitions of Abbreviations

ADT	Androgen deprivation therapy
AS	Active surveillance
AT	Active treatment
AUA	American Urological Association
CI	Confidence interval
HR	Hazard ratio
HMO	Health Maintenance Organization
IRB	Internal/institutional review board
KPNC	Kaiser Permanente Northern California
LRT	Likelihood ratio test
ng	Nanogram
mL	Milliliter
PCa	Prostate cancer
PSA	Prostate-specific antigen
PSADT	Prostate-specific antigen doubling time

RP	Radical prostatectomy
RT	Radiation therapy
WW	Watchful waiting

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Baseline patient and sociodemographic characteristics among men on observational management at one year post diagnosis of prostate cancer at KPNC

Table 1

Baseline characteristics	All men (N = 2,228)	Statistic	Remained on observational management (N = 1,621)	Statistic	Switched to active treatment (N = 607)	Statistic	P value *
Follow-up time, y							
Median (IQR)	2.9 (2.8)		3.4 (3.0)		1.8 (1.7)		
Age Group, y							
Median (IQR)	63 (11)		63 (11)		64 (10)		0.7582
Race/Ethnicity							
Hispanic	217 (9.9%)		159 (10.0%)		58 (9.6%)		0.0573
Non-Hispanic White	1514 (68.7%)		1101 (68.8%)		413 (68.4%)		
Non-Hispanic Black	254 (11.5%)		170 (10.7%)		84 (13.8%)		
Asian	218 (9.9%)		168 (10.5%)		50 (8.2%)		
Missing (or other)	25		23		2		
Year of Diagnosis, y							
2004	83 (3.7%)		50 (3.1%)		33 (5.4%)		0.0076
2005	106 (4.8%)		56 (3.5%)		50 (8.2%)		
2006	190 (8.5%)		125 (7.7%)		65 (10.7%)		
2007	180 (8.1%)		107 (6.6%)		73 (12.0%)		
2008	159 (7.1%)		109 (6.7%)		50 (8.2%)		
2009	250 (11.2%)		182 (11.2%)		68 (11.2%)		
2010	385 (17.3%)		276 (17.0%)		109 (18.0%)		
2011	428 (19.2%)		339 (20.9%)		89 (14.7%)		
2012	447 (20.1%)		377 (23.3%)		70 (11.5%)		0.1014
PSA at diagnosis, ng/mL							
<4	99 (4.4%)		78 (4.8%)		21 (3.4%)		
4–5	930 (41.7%)		692 (42.7%)		238 (39.1%)		
6–7	748 (33.6%)		537 (33.1%)		211 (34.8%)		
8–10	451 (20.2%)		314 (19.3%)		137 (22.7%)		
Median (IQR)	6 (2)		6 (2)		6 (2)		0.0943
PSA at diagnosis, age-specific upper limit ⁺							

Baseline characteristics	All men (N = 2,228) Statistic	Remained on observational management (N = 1,621) Statistic	Switched to active treatment (N = 607) Statistic	P-value*
Under	423 (19.0%)	310 (19.1%)	113 (18.6%)	
Over	1805 (81.0%)	1311 (80.9%)	494 (81.4%)	
Clinical T Stage				0.3902
T1	2137 (95.9%)	1551 (95.7%)	586 (96.4%)	
T2A	91 (4.1%)	70 (4.3%)	21 (3.6%)	
Diagnostic Gleason score				0.1314
5	12 (0.5%)	5 (0.3%)	7 (1.1%)	
6	2216 (99.5%)	1616 (99.7%)	600 (98.9%)	
Education, % pop 25+, College +				0.0558
Q1: 0–14%	474 (23.1%)	332 (22.3%)	142 (25.3%)	
Q2: 15–22%	461 (22.5%)	342 (22.9%)	119 (21.4%)	
Q3: 23–30%	542 (26.4%)	386 (25.9%)	156 (27.8%)	
Q4: 31% +	576 (28.1%)	433 (29.0%)	143 (25.6%)	
Missing	175	128	47	
Elixhauser index⁺⁺				0.7067
0	855 (38.4%)	636 (39.3%)	219 (36.0%)	
1	649 (29.1%)	474 (29.2%)	175 (29.1%)	
2	372 (16.7%)	256 (15.8%)	116 (19.0%)	
3+	352 (15.8%)	255 (15.8%)	97 (15.9%)	

Note: All statistics are counts and percentages (%), unless otherwise noted.

Abbreviations: PCa, Prostate Cancer; PSA, prostate-specific antigen; pop, population; IQR, interquartile range; y, years; ng/mL, nanograms per milliliter; Education % pop 25+ College +, percentage of men residing in the same census-tract population with at least a college education among those aged 25 years or older.

Data for KPNC service area is not shown due to table length.

⁺The age-specific reference range for serum PSA (95th percentile) for men aged 40 to 49 years is 0.0 to 2.5 ng/mL; for 50 to 59 years, 0.0 to 3.5 ng/mL; 60 to 69 years, 0.0 to 4.5 ng/mL; and 70 to 79 years, 0.0 to 6.5 ng/mL.

⁺⁺Elixhauser index: comorbid conditions diagnosed up to 2 years prior through 90 days prior to prostate cancer diagnosis.

* P-values were calculated using unadjusted Cox regression models to account for differential follow-up time.

Follow-up clinical characteristics among men on observational management during their first year following diagnosis of prostate cancer at KPNC

Table 2

Follow-up clinical characteristics	All men (N = 2,228) /Statistic	Remained on observational management (N = 1,621) /Statistic	Switched to active treatment /Statistic	N (N = 607) /Statistic	P value *
Follow-up Biopsy Utilization					
No	1036 (46.5%)	879 (54.2%)	157 (26.1%)		<0.0001
Yes	1192 (53.5%)	742 (45.8%)	450 (73.9%)		
Number of follow-up biopsies					
Median (IQR)	1 (1)	0 (1)	1 (2)		<0.0001
Gleason progression status ++					
No follow-up biopsies	1036 (46.5%)	879 (54.2%)	157 (26.1%)		<0.0001
Stable or downgraded	789 (35.4%)	610 (37.6%)	179 (29.2%)		
Progression	403 (18.1%)	132 (8.2%)	271 (44.5%)		
Number of follow-up PSA tests +					
Median (IQR)	9 (7)	8 (7)	12 (7)		<0.0001
PSA rise to intermediate Pca risk status (>10 ng/mL) +					
No	1525 (70.9%)	1147 (74.4%)	377 (62.1%)		<0.0001
Yes	625 (29.1%)	395 (25.6%)	230 (37.9%)		
PSA slope +					
Median (IQR)	0.35 (0.53)	0.31 (0.44)	0.59 (0.58)		<0.0001
Insufficient PSA tests to compute	915	538	377		
PSADT +					
48 months or not reached	930 (58.8%)	814 (64.7%)	116 (35.7%)		<0.0001
< 48 months	653 (41.3%)	444 (35.3%)	209 (64.3%)		
Insufficient PSA tests to compute	566	283	282		
Number of urological center visits					
Median (IQR)	9 (7)	8 (7)	12 (7)		<0.0001

Note: All statistics are counts and percentages (%), unless otherwise noted.

Abbreviations: PCa, Prostate Cancer; PSA, prostate-specific antigen; PSADT, PSA doubling time; IQR, interquartile range; y, years; ng/mL, nanograms per milliliter.

+ 79 men were missing a follow-up PSA test, all of which were men who remained on observational management.

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5 men were Gleason downgraded during rebiopsies and were collapsed into the stable Gleason category due to sample size restrictions.
* P-values were calculated using unadjusted Cox regression models to account for differential follow-up time.

Associations between baseline and follow-up clinical measures and beginning an active treatment among men initially on observational management for at least one year following diagnosis, with stratification by strict AS and rebiopsy usage

Table 3

	Entire cohort (N = 2,228)	HR (95% CI)	Men with stricter AS usage (N = 1,140)	HR (95% CI)
Clinical variables ⁺				
PSA at diagnosis, ng/mL				
<4	1.09 (0.69,1.75)		1.31 (0.78,2.19)	
4–5	1.00 (Referent)		1.00 (Referent)	
6–7	1.20 (0.99,1.47)		1.23 (0.97,1.55)	
8–10	1.41 (1.11,1.79)		1.58 (1.18,2.12)	
Follow-up biopsy utilization				
No	1.00 (Referent)		-	
Yes (1 re-biopsy)	2.89 (2.37,3.52)		-	
Gleason progression status				
No follow-up biopsies	0.59 (0.47,0.75)		-	
Stable or Downgraded	1.00 (Referent)		1.00 (Referent)	
Progression	3.34 (2.74,4.09)		3.56 (2.90,4.38)	
PSA rise to intermediate-risk PCa status (>10 ng/mL)				
No	1.00 (Referent)		1.00 (Referent)	
Yes	1.11 (0.91,1.35)		1.35 (1.07,1.69)	
PSADT < 48 months				
NA/Unable to calculate	9.02 (7.14,11.41)		11.07 (8.39,14.60)	
No	1.00 (Referent)		1.00 (Referent)	
Yes	2.90 (2.28,3.69)		2.71 (2.06,3.57)	
PSA Slope				
Continuous, per 1 unit	1.71 (1.54,1.89)		1.63 (1.45,1.84)	
Sociodemographic variables ⁺⁺				
Age, per 5 years	1.00 (0.94,1.07)		1.00 (0.93,1.08)	
Race/Ethnicity				
Hispanic	1.02 (0.77,1.37)		0.92 (0.64,1.31)	
Non-Hispanic White	1.00 (Referent)		1.00 (Referent)	

	Entire cohort (N = 2,228)	HR (95% CI)	Men with stricter AS usage (N = 1,140)	HR (95% CI)
Non-Hispanic Black	1.29 (1.00,1.66)		1.33 (0.99,1.79)	
Asian	0.87 (0.64,1.17)		0.88 (0.61,1.25)	
Education, % pop 25+, College +				
Q1: 0–14%	1.00 (Referent)		1.00 (Referent)	
Q2: 15–22%	0.84 (0.65,1.07)		0.80 (0.60,1.08)	
Q3: 23–30%	0.90 (0.71,1.13)		0.85 (0.64,1.13)	
Q4: 31%+	0.75 (0.59,0.96)		0.69 (0.51,0.92)	
Elixhauser index [†]				
0	1.00 (Referent)		1.00 (Referent)	
1	0.94 (0.76,1.16)		0.92 (0.72,1.18)	
2	1.10 (0.86,1.40)		1.08 (0.80,1.45)	
3+	1.00 (0.77,1.30)		0.90 (0.65,1.24)	
Year of diagnosis	0.94 (0.90,0.98)		0.98 (0.93,1.03)	

Abbreviations: PCa, Prostate Cancer; HR, hazard ratio; CI, confidence interval; pop, population; PSA, prostate-specific antigen; PSADT, PSA doubling time; y, years; ng/mL, nanograms per milliliter; Q, quartile; Education % pop 25+ College +, percentage of men residing in the same census-tract population with at least a college education among those aged 25 years or older.

Follow-up biopsy utilization did not adjust for Gleason grade progression. PSA slope did not adjust for PSA rise to intermediate risk PCa status. PSADT did not adjust for PSA rise to intermediate risk PCa status. Number of follow-up PSA tests did not adjust for PSA rise to intermediate risk PCa status.

Data for KPNC service area is not shown.

[†]Cox multivariable regression models were adjusted for the following covariates: Age at diagnosis, race/ethnicity, PSA level at diagnosis, T stage, education, Elixhauser index, KPNC service area, Gleason grade progression status, and PSA rise to intermediate risk PCa status unless otherwise specified.

^{††}Cox multivariable regression models were adjusted for the following covariates: Age at diagnosis, race/ethnicity, PSA level at diagnosis, T stage, education, Elixhauser index, KPNC service area, Gleason grade progression status, and PSA progression into intermediate risk status.