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Racial variation in prostate cancer upgrading and upstaging among men with low risk clinical characteristics

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Abstract

Background: African-American (AA) men suffer a higher prostate cancer burden than other groups.

Objective: We aim to determine the role of race in the likelihood of adverse pathology at surgery and whether outcomes were worse for AA men.

Design, setting, and participants: We studied men with low risk prostate cancer (CaP) diagnosed in 1990-2012 and treated with radical prostatectomy (RP) at UCSF and CaPSURE centers. Low clinical risk was defined as diagnostic PSA ≤10 ng/ml, biopsy Gleason grade 2-6, and stage cT1/2. Outcome variables were adverse pathology at surgery. Associations between race and the outcomes were evaluated with logistic regression.

Results and limitations: Of the 9,304 men diagnosed with CaP, 8,999 underwent RP within 1 year. Men were 273 AA (6.5%), 3,771 Caucasian (89.1%) and 187 Other race/ethnic groups (4.4%). AA men had a significantly younger mean age of 58.7 years (SD 7.06) and fewer AA men (85%) were married/partnered. Upgrade (34%) and upstage (13%) rates did not significantly differ between the 3 groups. Positive surgical margin (PSM) rate was significantly higher in AA men (31%) versus Caucasian (21%) and Other men (20%), $p<0.01$. We found an association between race group and PSM rate ($p<0.03$) with higher odds of PSM in AA men versus Caucasian men (OR 1.64 95%CI 1.08-2.47). No associations between race and rates of upgrading and upstaging were found. This study was limited by the relatively low proportion of AA men in the cohort.

Conclusions: AA men had a higher likelihood of PSM compared to Caucasian men. However, rates of upgrading and upstaging did not vary between the race groups.

Keywords: Prostate Cancer, racial disparities, radical prostatectomy, pathologic outcomes

Introduction

Prostate cancer (CaP) is the leading non-cutaneous cancer for men, with an estimated incidence of 238,590 and related deaths reaching 29,720 in 2013 [1]. Use of PSA testing has led to earlier detection resulting in increased diagnosis and treatment and, in turn, reducing the proportion of CaP metastasis and disease specific mortality. Nevertheless, African American (AA) men are known to suffer a substantial and disproportionate CaP burden, with studies showing a higher incidence, more advanced stages at diagnosis, more aggressive tumors, and poorer outcomes than other racial groups [2-5].

CaP management decisions depend on stage and grade of the disease, among other prognostic factors. Men with clinically low-risk disease are often well suited for active surveillance rather than immediate treatment. However, despite improvements in clinical and pathological assessment, there are considerable levels of upgrading and upstaging between biopsy and surgical treatment. Upgrading and upstaging are well described in men otherwise eligible for active surveillance who instead undergo surgery as primary treatment [6,7]. Depending on the criteria for defining active surveillance eligibility, upgrading occurs in 23% to 35% of cases.

Although upgrading may be related to the natural history of CaP, it may also be due to sampling error that is unveiled by more complete pathologic examination of the prostatic specimen after radical prostatectomy (RP).

A recently published study [7] compared AA and Caucasian men diagnosed with very low risk disease who were candidates for active surveillance but elected to undergo immediate RP. This study found a significantly lower rate of organ confined-cancers, a higher rate of Gleason upgrading and a higher average postoperative risk score in AA men. These findings were observed in a single-institution cohort, and may not be generalizable. Therefore, using a broader cohort from multiple institutions across the United States we assessed whether patient race was associated with likelihood of upgrading and upstaging at RP for patients with disease that was presumed to be very low risk by established criteria. We also evaluated whether outcomes were worse for AA men compared to Caucasian and other men including Asian, Pacific Islander, Latino, and Native American men.

Methods

The current study included men diagnosed with CaP in 1990-2012 and treated with RP within 1 year of diagnosis. Participants are enrolled in the Urologic Oncology Data Base (UODB) maintained at the UCSF Department of Urology or the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) registry, a national longitudinal disease registry including men treated at 43 practice sites across the U.S. [8]. All study subjects consented to participate in research under central institutional review board supervision and underwent surgery at UCSF or at one of the CaPSURE sites. Patients in both cohorts are followed until death or study withdrawal.

Both the UODB and CaPSURE studies gather demographic, clinical and surgical pathology data. The exposure variable was patient race, self-reported as AA, Caucasian or Other (Asian, Pacific Islander, Native American, Latino/Hispanic, Mixed). Independent variables were age at diagnosis, relationship/marital status, PSA at diagnosis, clinical TNM stage, biopsy Gleason grade, biopsy cores sampled and positive, and percentage of tissue positive. In addition, CaPSURE patients reported education level, insurance coverage, body mass index, and medical history at diagnosis including cardiovascular disease, diabetes, kidney/urinary conditions, lung disease, other cancers, alcohol use, and smoking. Outcome variables were defined as adverse pathology at prostatectomy (Gleason upgrade to at least 3+4 and/or upstage to pT3 or pN1, or positive surgical margins (PSM)).

Participants were diagnosed with low clinical risk defined as PSA<10 ng/ml, biopsy Gleason grade 2-6, and clinical stage cT1/2a according to NCCN 2012 guidelines. Patients were further classified as meeting strict eligibility criteria for active surveillance (AS) according to both the Johns Hopkins and UCSF criteria. The Hopkins criteria—also echoed in the NCCN definition of “very low risk” disease—include biopsy Gleason grade 2-6 with no 4/5 pattern, PSA density ≤0.15 cc, stage cT1, <3 positive biopsy cores, and ≤50% of any single core positive [9]. The UCSF criteria are slightly broader: biopsy Gleason 2-6, diagnostic PSA ≤10 ng/ml, stage cT1/2, ≤33% cores positive, and ≤50% of any single positive core [10]. Patients were classified into 3 risk groups: met Hopkins criteria, met UCSF criteria but not Hopkins, and met neither set of criteria (no man met UCSF but not Hopkins criteria). Post-operative risk was defined using the validated UCSF Cancer of the Prostate Risk Assessment (CAPRA-S) score, a measure computed from surgical pathology findings to predict risk of cancer recurrence following RP [11].

Independent characteristics were compared between the 3 race groups (AA, Caucasian, Other) and between the 3 risk groups (Hopkins, UCSF, Neither) using frequency tables and chi-square for categorical variables and means and ANOVA for continuous variables.

Associations between race and outcome variables were evaluated with logistic regression. Models were adjusted for age at diagnosis, relationship status, number of biopsy cores sampled, clinical risk group, individual clinical site, surgical approach (open vs. robotic laparoscopic RP), and year of diagnosis. Secondary analyses of patient subsets were run to address other factors that could influence outcomes. A model of patients who met each set of AS eligibility criteria was run to assess race groups who undergo similar follow up regimens. We also modeled subsets of patients treated only at academic and at community-based sites to account for variations in practice patterns. Model covariates were selected a priori and assessed for inter-item correlations. A 2-tailed p-value <0.05 was considered significant. Analyses were completed using SAS 9.2 (Cary, IN).

Results

Between the UODB and CaPSURE databases, 9304 individuals were diagnosed with CaP in the period 1990-2012, 8999 of whom underwent RP within 1 year of diagnosis. Of those, 4231 met the criteria for low risk CaP and formed the study cohort. The racial distribution of the cohort included 273 AA (6.5%), 3,771 Caucasian (89.1%), and 187 Other (4.4%) men. Demographics, comorbidities, and clinical characteristics are presented in **Table 1**. AA men were diagnosed with CaP at a younger mean (SD) age of 58.7 years (7.1) compared to Caucasian and Other

groups, p<0.01. Fewer AA men (85%) were married/partnered compared to Caucasian (92%) and Other men (90%), p<0.01.

In CaPSURE, level of education was higher in Caucasian men. AA men had higher rates of comorbidities compared to Caucasian and Other men. Most AA men (79%) were treated at community-based rather than academic centers compared to 60% of Caucasians and 66% of Other men, p<0.01.

AA men had the lowest mean (SD) number of biopsy cores sampled (7.9 (3.34)) and highest percentage of positive cores (35.5% (24.25)), both p<0.01. Fifty percent of AA men met UCSF AS eligibility criteria compared 63% of Caucasian men and 68% of Other men, p<0.01. More AA men (35%) and Caucasian men (37%) met Johns Hopkins criteria compared to 26% of Other men, p=0.01. Rates of open versus laparoscopic surgery were higher for AA men (82%) and Caucasian men (81%) compared to Other men (73%, p<0.01). Median follow up after RP was 61 months (interquartile range 30-100).

Pathologic outcomes after surgery are presented in **Table 2**. The percentage of overall upgrade was 34% and did not differ significantly between groups. The pattern of Gleason grade for all patients was 67% with 2-6, 30% with 3+4, and 3% with 4+3 or higher. The upstage rate, 13%, also was similar across the groups. Positive lymph nodes occurred in 14 Caucasian men (<1%) and in no AA or Other men. Extracapsular extension (ECE) occurred in 12% of all men while seminal vesicle involvement (SVI) was found in 2% of patients with no statistical differences between groups. The proportion of CAPRA-S >=3 was lower in AA men but the difference was not statistically significant. The PSM rate was significantly higher in AA (31%) compared to the Caucasian (21%) and Other (20%) groups, p<0.01.

Comparisons of patients based on AS eligibility criteria (**Table 2**) showed significantly higher proportions of upgrade (44%), upstage (19%), ECE (18%), SVI (3%), and PSM (28%) in men meeting eligibility criteria for AS. These proportions were lowest in men meeting Johns Hopkins criteria alone, p<0.01. Likewise, rates of upstage/pN1, upgrade and CAPRA-S ≥3 were significantly higher in men meeting neither set of eligibility criteria for AS.

Associations of race group with surgical pathology outcomes were evaluated in a series of logistic regression models, adjusted for clinical variables, year of diagnosis and individual clinical site (**Table 3**). Race group was associated with surgical margin status (p=0.03) such that AA men had higher odds of PSM than both Caucasian (OR 1.64 95%CI 1.08-2.47) and Other men (OR 1.41 95%CI 0.90-2.23). Race was not associated with upgrade (OR: 1.452 CI:0.96-2.17 p=0.77) compared to Caucasian and Other men combined. AA men tended to have higher, though not statistically significant, rates of upstaging (OR: 1.44 CI:0.99-2.10 p=0.06).

In subset analysis, race and PSM remained similarly associated among patients meeting the UCSF eligibility criteria for AS (2.44 95%CI 1.39-4.29 for AA men versus Caucasian men, p<0.01). In a subset of patients treated at community-based sites only, odds of PSM again were significantly higher for AA men (OR 2.05 95% CI 1.29-3.26, p=0.01) compared to Caucasian men. Race and PSM were not associated in men meeting Johns Hopkins AS criteria or among those treated only at academic sites, nor was race associated with upgrading, upstaging, or CAPRA-S ≥3 in any subset models.

Discussion

The literature indicates that genetic predisposition and environmental factors contribute to racial disparities observed in CaP patients. Among the biological differences, higher levels of circulating androgens [12] and higher proportions of susceptibility alleles in the metabolism pathways for androgens [13] may contribute to a higher disease burden in black men. An important environmental factor is the high consumption of animal fat which is reported to be both common in AA diets and associated with increased risk of CaP [14]. Moreover, AA men may suffer more from traumatic stress related to CaP than non-AA men [15,16].

There is a mixed picture regarding higher CaP aggressiveness in AA men. Many studies have found more advanced disease at diagnosis [17], while other studies show poorer survival in AA men compared to other racial groups [1]. Conversely, some studies report no differences in age and clinical stage at diagnosis between AA and Caucasian men in settings of equal access to healthcare [18] and similar overall mortality rates across racial groups after treatment for CaP [19]. These disparate findings were derived mainly from retrospective data of cohorts with varying sociodemographic characteristics, clinical risk, treatment regimens, and follow up. Among CaP men managed with AS, AA race has been linked to discontinuation of surveillance followed by active treatment [20]. After RP for all-risk localized disease, AA men have been found to have more adverse pathologic features [21].

In our study, AA men had higher rates of comorbidities, lower levels of education and less comprehensive insurance coverage than other racial groups. These differences corroborate findings of many studies [17,19] and may partially explain treatment patterns for AA men. Following progression during AS, a lower proportion of AA men undergo RP [22] and instead are treated most frequently with

radiation or another non-surgical therapy for CaP [23]. Such treatment patterns, together with the referral populations represented by UODB and CaPSURE sites, may in part explain the lower representation of AA men in our cohort.

A recent study from Johns Hopkins [7] compared AA and Caucasian men diagnosed with very low risk CaP who underwent immediate RP and found that AA race was strongly and independently associated with upgrade and upstage after surgery. While these findings were notable because favorable outcomes had been expected among such a low risk group, the cohort was from a single academic institution which may limit the generalizability of the results. In contrast, our study did not find statistically significant differences in upgrading and upstaging rates between AA and Caucasian men, suggesting that, with equal access to care and comparable baseline clinical characteristics, CaP pathologic outcomes may be similar across racial groups, as put forth by other studies [18,25,26].

It should be noted that neither the Hopkins study nor our study evaluated tumor location and size. In another analysis of the same Hopkins cohort, Sundi et al. [27] reported that AA men diagnosed with very low risk CaP were more likely to have Gleason $\geq$ 7 (37% vs 11%, $p<0.001$) and tumor volume $\geq$0.5 cm3 (45% vs 21%, $p=0.001$) at RP, compared to Caucasian men. Among those who upgraded, the dominant nodule was more frequently anterior in AA men than in Caucasian men. At UCSF, anterior biopsies are part of the standard schema [28], which may improve the chances of identifying tumors among AA men and explain why upgrading and upstaging rates are similar by race at UCSF. Unfortunately, the CaPSURE study does not collect information on tumor location that would have allowed us to evaluate the impact of anterior findings in this combined UCSF-CaPSURE analysis.

The rate of PSM in AA men was higher than the two other groups and this difference persisted among subsets of men who met UCSF eligibility criteria for AS

and those treated only at community-based practices. While this finding is inconsistent with some previous studies [29], PSM rate is associated with higher risks of biochemical recurrence and cancer-specific mortality in AA men who have undergone RP [30]. What explains the relationship between AA race and risk of PSM is unclear. However, anatomic pelvic variations are believed to increase the risk of PSM during RP in AA men due to steeper symphysis pubis angles and smaller mid-pelvis areas in AA men compared to white men [31]. In this situation, the risk of apical PSM is higher.

We acknowledge limitations to the current study. First, the proportion of AA men in the cohort is smaller than the national average. In addition, some demographic and all comorbidity data were unavailable for UCSF patients, preventing adjustment for such characteristics in multivariate models. Finally, upgrading and upstaging are far from perfect surrogates for aggressive biology. The fact that a man may have some indication of worse-than-expected pathology after surgery—particularly low-volume Gleason pattern 4 or focal ECE—does not mean that he would have progressed to incurable disease without treatment, nor that he was a poor candidate for AS. We do not have detailed information on tumor location for all men, and thus cannot validate previously reported findings regarding higher incidence of anterior tumors among AA men [27].

Strengths of this study are the broad, nationwide sample of participants from community-based, academic, and Veteran's sites and the comprehensive follow-up provided by AS programs. Our study represents one of the largest reported cohorts (n=273) of low risk AA men who qualify for AS with a median follow up of 56 months.

Conclusion

We studied patients who underwent RP within a year of follow up. AA men were younger, had lower levels of education and insurance coverage, and higher rates of comorbidities than Caucasian and Other race groups. The groups had similar clinical characteristics before surgery and CaP upgrade and upstage rates after RP. However, higher PSM was associated with AA race. Studies with larger representation of AA men are badly needed to better assess the role of race/ethnicity in CaP pathologic outcomes after RP.

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Table 1. Patient characteristics at diagnosis of 9,304 men managed at UCSF and CaPSURE sites

	African American (n=273)	Caucasian (N=3771)	Other (N=187)	*p*
Age (years), mean (sd)	58.7 (7.06)	60.0 (6.90)	60.5 (7.00)	<0.01
Married/partnered, n (%)	157 (85)	2914 (92)	150 (90)	<0.01
Education level*, n (%)				<0.01
Some high school	50 (31)	164 (8)	12 (24)	
High school degree	38 (23)	532 (24)	13 (25)	
Some college	36 (23)	441 (20)	16 (31)	
College degree	38 (23)	1040 (48)	10 (20)	
Insurance*, n (%)				<0.01
Medicare + Supplement	33 (15)	604 (23)	15 (23)	
Medicare only	19 (8)	191 (7)	6 (9)	
Private or Veteran	152 (69)	1801 (68)	40 (63)	
Other	17 (8)	38 (2)	3 (5)	
Stroke*, n (%)	7 (4)	95 (4)	5 (9)	0.20
Obesity (BMI 30-34.9)*, n (%)	39 (26)	425 (20)	11 (22)	0.20
Heart disease, n (%)	14 (8)	297 (14)	7 (13)	0.16
Hypertension*, n (%)	99 (59)	827 (38)	20 (38)	<0.01
Diabetes*, n (%)	27 (16)	149 (7)	7 (13)	<0.01
Smoking*, n (%)	36 (23)	192 (9)	5 (10)	<0.01
7+ drinks per week*, n (%)	21 (28)	402 (31)	6 (29)	0.78
PSA (ng/ml), median (IQR)	5.6 (4.5-7.2)	5.2 (4.2-6.5)	5.4 (4.3-6.6)	<0.01
Biopsy cores sampled, mean (sd)	7.9 (3.34)	9.2 (4.02)	9.9 (4.93)	<.01
Number of positive cores, mean (sd)	2.5 (1.62)	2.4 (1.83)	2.3 (1.90)	0.70
Percentage positive cores, mean (sd)	35.5 (24.25)	30.8 (23.31)	29.3 (24.97)	<0.01
Clinical T-stage, n (%)				
T1	171 (63)	2099 (56)	91 (49)	0.01
T2	102 (37)	1672 (44)	96 (51)	
Clinical CAPRA risk score, mean (sd)	1.6 (0.75)	1.5 (0.69)	1.5 (0.68)	0.16
Met UCSF criteria for AS, n (%)	121 (50)	2139 (63)	113 (68)	<0.01
Met Hopkins criteria for AS, n (%)	83 (35)	1177 (37)	37 (26)	0.01

Values may not sum to total N due to missing data
**Data available only for CaPSURE patients*
BMI, body mass index
PSA, prostate specific antigen
CAPRA, Cancer of the Prostate Risk Assessment
n, number
sd, standard deviation
IQR, interquartile range

Table 2: Postoperative pathologic outcomes of 9,304 men managed at UCSF and CaPSURE sites

	RACE/ETHNICITY				ACTIVE SURVEILLANCE CRITERIA			
	African American (N=273)	Caucasian (N=3771)	Other (N=187)	*p*	Hopkins Criteria (N=1297)	UCSF Criteria (N=901)	Neither (N=1201)	*p*
RP approach, n (%)				<0.01				0.02
Open retropubic	224 (82)	3053 (81)	137 (73)		1055 (81)	719 (80)	949 (79)	
Robotic	22 (8)	578 (15)	43 (23)		186 (14)	160 (18)	208 (17)	
Other	27 (10)	139 (4)	70 (4)		56 (4)	21 (2)	44 (4)	
Gleason grade, n (%)				0.27				<.01
2-6	176 (68)	2393 (67)	115 (65)		960 (78)	562 (63)	641 (56)	
7 (3+4)	75 (29)	1077 (30)	54 (31)		234 (19)	291 (33)	462 (40)	
7 (4+3)	0 (0)	43 (1)	5 (3)		8 (1)	18 (2)	8 (1)	
8-10	6 (2)	81 (2)	3 (2)		21 (2)	15 (2)	33 (3)	
Upgrade, n (%)	71 (34)	1003 (33)	49 (33)	0.98	263 (22)	314 (36)	411 (44)	<.01
T-stage, n (%)				0.36				<.01
T2	199 (87)	3043 (87)	144 (84)		1078 (93)	763 (87)	877 (81)	
T3	30 (13)	425 (12)	26 (15)		84 (7)	106 (12)	204 (19)	
T4	1 (<1)	12 (<1)	2 (1)		1 (<1)	5 (1)	5 (<1)	
ECE, n (%)	24 (11)	377 (11)	27 (16)	0.20	71 (6)	94 (11)	185 (18)	<.01
SVI, n (%)	6 (2)	75 (2)	4 (2)	0.93	16 (1)	19 (2)	34 (3)	0.02
Upstage/pN1, n (%)	31 (13)	440 (13)	28 (16)	0.36	86 (7)	111 (13)	209 (19)	<.01
Upgrade and/or Upstage, n (%)	89 (36)	1221 (34)	62 (35)	0.78	283 (24)	355 (40)	507 (45)	<.01
Positive margin, n(%)	76 (31)	746 (21)	35 (20)	<.01	202 (17)	197 (22)	318 (28)	<.01
CAPRA-S >=3, n (%)	3 (10)	180 (18)	26 (22)	0.23	17 (8)	58 (18)	79 (23)	<.01

Values may not sum to total N due to missing data
RP, radical prostatectomy
ECE, extracapsular extension
SVI, seminal vesicle invasion
CAPRA-S, Surgical Cancer of the Prostate Risk Assessment
n, number

Table 3: Multivariate logistic regression results with surgical pathology outcomes (All low risk patients) of 9,304 men managed at UCSF and CaPSURE sites

OUTCOME	INDEPENDENT VARIABLE	*p*	Odds ratio	95%CI lower limit	95%CI upper limit
Upgrade	Race African American vs Caucasian	0.13	1.438	0.959	2.157
	Race African American vs Other	.	0.824	0.545	1.245
	Age at diagnosis (years)	<.01	1.036	1.023	1.049
	Relationship Yes vs No	0.87	1.119	0.826	1.517
	PSA at diagnosis (ng/ml)	<.01	1.114	1.064	1.166
	Biopsy cores percent positive	<.01	1.019	1.014	1.023
	Surgical approach Lap vs Open	0.64	0.891	0.663	1.198
	Surgical approach Other vs Open	.	1.168	0.665	2.049
	Year of diagnosis	<.01	1.056	1.026	1.088
	Individual clinical site (Categorical)	<.01	Not	shown	
Upstage/ pN1	Race African American vs Caucasian	0.64	1.153	0.665	1.998
	Race African American vs Other	.	1.242	0.736	2.098
	Age at diagnosis (years)	<0.01	1.030	1.012	1.048
	Relationship Yes vs No	0.77	1.066	0.697	1.632
	PSA at diagnosis (ng/ml)	<0.01	1.164	1.096	1.236
	Biopsy cores percent positive	<0.01	1.019	1.014	1.023
	Surgical approach Lap vs Open	0.49	0.716	0.319	1.609
	Surgical approach Other vs Open	.	1.190	0.800	1.772
	Year of diagnosis	0.05	0.964	0.929	1.000
	Individual clinical site (Categorical)	0.13	Not	shown	
Positive surgical margins	Race African American vs Caucasian	0.03	1.635	1.081	2.473
	Race African American vs Other	.	1.413	0.897	2.227
	Age at diagnosis (years)	0.26	1.008	0.994	1.022
	Relationship Yes vs No	0.19	0.805	0.580	1.118
	PSA at diagnosis (ng/ml)	<.01	1.121	1.069	1.176
	Biopsy cores percent positive	<.01	1.013	1.009	1.017
	Surgical approach Lap vs Open	0.91	1.088	0.619	1.911
	Surgical approach Other vs Open	.	1.058	0.754	1.484
	Year of diagnosis	0.03	0.967	0.939	0.996
	Individual clinical site (Categorical)	<.01	Not	shown	

PSA, prostate specific antigen
Lap, laparoscopic surgical approach