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Risk of Pathological Upgrading and Up Staging among Men with Low Risk Prostate Cancer Varies by Race: Results from the National Cancer Database

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Abstract

Purpose: The impact of African-American race on oncologic outcomes for low risk prostate cancer is unclear due to conflicting data. We investigated the effect of African-American race on pathological upgrading and/or up staging at prostatectomy in men with clinically low risk prostate cancer.

Materials and Methods: We queried the National Cancer Database for men with low risk prostate cancer (clinical stage T2a or less, Gleason score 6 or less, prostate specific antigen less than 10 ng/ml) treated with radical prostatectomy between 2010 and 2013. The outcomes were pathological upgrading to Gleason score greater than 6 (primary) or Gleason score greater than 3+4=7 (secondary) and/or up staging (pathological T3–4 or N1 disease). The association between race and the end points was assessed using multivariable logistic regression. To further adjust for potential confounders, stratification by urban residence and comorbidity score, and subgroup analyses were performed.

Results: With adjustment for age, comorbidity, income, urban residence, T stage, prostate specific antigen and percentage of positive biopsy cores, African-American race conferred 1.2-fold higher odds of pathological upgrading to Gleason score greater than 6 and/or up staging (OR 1.2, 95% CI 1.1–1.3, $p < 0.01$). African-American race also was an independent predictor of pathological upgrading to Gleason score greater than 3+4=7 and/or up staging ($p = 0.03$).

Conclusions: African-American men with low risk prostate cancer are more likely to harbor higher risk disease, which may lead to adverse outcomes. This finding alone does not preclude

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active surveillance. However, race should be considered as men weigh the risks and benefits of active surveillance vs treatment.

Keywords

prostatic neoplasms; neoplasm grading; neoplasm staging; watchful waiting; African Continental Ancestry Group

AFRICAN-AMERICAN race is associated with increased prostate cancer incidence and mortality.

¹ It is unclear if racial disparities in PCa outcomes are due to coexisting factors (eg low socioeconomic status or poor health) or race itself. For men with low risk PCa this question is important because it directly influences treatment selection (active surveillance vs immediate treatment)² and it indirectly informs race specific age thresholds for PCa screening practices.³

Several studies have reported that AA race confers higher risks of cancer progression on active surveillance,^{4,5} upgrading at RP,⁶ biochemical recurrence after treatment⁷ and cancer specific mortality.⁸ However, in other studies race appears to have little effect on outcomes.^{9,10} We examined whether race was associated with pathological upgrading and/or up staging at RP in the NCDB. We chose this data set because it is comprehensive (captures 70% of new cancer diagnoses) and nationally representative.

MATERIALS AND METHODS

Data Source

The NCDB is a joint endeavor of the American Cancer Society and the Commission on Cancer of the American College of Surgeons. It is a comprehensive, hospital based oncology registry that includes data on 70% of incident cancer diagnoses in the United States. Institutional review board approval was obtained before using the prostate cancer Participant User File.

Study Population

We identified 51,057 men with clinically localized (cN0/ cM0) low risk prostate cancer (clinical stage T2a or less, Gleason score 6 or less, PSA less than 10 ng/ml) between 2010 and 2013 who underwent RP. This study period was chosen because data on the number of positive/total biopsy cores were only available from 2010 onward. Cases missing pathological stage or grade were excluded from analysis (1,930) as were cases missing income or county data (1,321). Race was classified as African-American or nonAfrican American. Other variables examined included patient age at diagnosis, CCI, household income, county of residence, clinical stage, pathological grade, percentage of biopsy cores positive and pathological stage.

Study Variables

CCI was reclassified as 1 or less and greater than 1. Median household income for each patient's area of residence was categorized by quartiles (less than \$38,000, \$38,000 to \$47,999, \$48,000 to \$62,999, \$63,000 or greater) based on 2012 American Community

Survey Data adjusted for 2012 inflation. County of residence was reclassified as urban and nonurban based on 2013 figures published by the U.S. Department of Agriculture Economic Research Service. The percentage of positive cores was obtained by dividing the number of positive cores by the total number of cores biopsied and was categorized by tertiles (less than 33%, 33% to 67%, greater than 67%).

Study Outcomes

UGUS was determined by comparing biopsy/clinical characteristics to pathological results. Upgrading was defined as an increase in Gleason score greater than 6 (primary outcome) or Gleason score greater than 3+4=7 (secondary outcome). Up staging was defined as the presence of pathological T3–4 or N1 disease. Upgrading, regardless of up staging, was assessed as a tertiary outcome. We performed multivariable logistic regressions to evaluate the association between race and UGUS, adjusting for age, CCI, race, income, county, clinical stage, PSA and percentage of positive cores to identify predictors of UGUS.

Statistical Analyses

Using the Pearson chi-square test, bivariate comparisons of pathological characteristics (Gleason score, T stage, N stage), surgical margin status and UGUS were performed between groups (AA vs nonAA). Using multivariable logistic regression we assessed for predictors of UGUS or upgrading regardless of up staging. For the primary outcome subanalyses were performed in 4 distinct subgroup strata defined by county of residence and Charlson score, namely urban, CCI 1 or less; urban, CCI greater than 1; nonurban, CCI 1 or less; and nonurban, CCI greater than 1. Statistical tests were performed using SAS® University Edition. All tests were 2-sided and statistical significance was assigned at $p < 0.05$.

RESULTS

There were 48,473 men in the final cohort, including 5,411 AA (11.2%) and 43,062 nonAA (88.8%). AA men were younger but had more comorbidities and lower incomes compared to their nonAA counterparts (table 1). In the final pathological specimen AA men were more likely to have Gleason score greater than 6 disease than nonAA men ($p < 0.01$) but there was no significant difference in pathological stage between the races ($p = 0.10$, table 2).

In terms of primary and secondary outcomes race significantly predicted UGUS. Compared to nonAA men, AA men had 1.2-fold higher odds of UGUS to Gleason greater than 6 (OR 1.2, 95% CI 1.1–1.3, $p < 0.01$, table 3) and 1.1-fold higher odds of UGUS to Gleason greater than 3+4=7 (OR 1.1, 95% CI 1.01–1.2, $p = 0.03$, table 4). Other significant predictors of UGUS to Gleason greater than 6 were increasing age ($p < 0.01$), urban residence ($p = 0.01$), higher PSA ($p < 0.01$) and 33% or more positive cores ($p < 0.01$). After stratifying men by county and CCI, AA race remained an independent predictor of UGUS to Gleason greater than 6 in men with CCI 1 or less residing in urban and nonurban areas, the 2 subgroups which accounted for the largest proportion (98.4%) of cases (table 5). In these healthy men AA race was associated with a 1.2 to 1.3-fold higher odds of UGUS compared to nonAA race ($p < 0.01$ and $p = 0.02$, respectively).

In terms of tertiary outcomes AA race was a strong independent predictor of upgrading to Gleason greater than 6 (OR 1.2, 95% CI 1.1–1.3, $p < 0.01$, supplementary table 1, <http://jurology.com/>) and upgrading to Gleason greater than 3+4=7 (OR 1.3, 95% CI 1.1–1.4, $p < 0.01$, supplementary table 2, <http://jurology.com/>).

DISCUSSION

Prior studies have suggested that AA race is associated with a higher risk of progression on active surveillance,^{4,5} pathological upgrading,⁶ biochemical recurrence after RP⁷ and cancer specific mortality after treatment.⁸ However, there have been conflicting reports. For example, Jalloh et al found no association between race and UGUS in an analysis of the University of California, San Francisco institutional database and the multi-practice CaPSURETM registry, although adverse pathological features were more common among AA men undergoing RP (positive margin rate 31% for AA vs 21% for nonAA, $p < 0.01$).⁹ Schreiber et al, analyzing the SEER (Surveillance, Epidemiology, and End Results) database, also found no association between race and UGUS.¹⁰ These prior studies (positive and negative) were retrospective, and results may have been influenced by various study biases including referral patterns, patient selection, regional variation and sampling of distinct geographic areas (SEER or Veterans Affairs studies).

In 2 prior NCDB studies it was incidentally observed that AA race was associated with UGUS, consistent with our findings. Weiner et al analyzed the effect of delayed RP in low risk cases and found that AA race was associated with 1.2-fold higher odds of UGUS ($p < 0.001$, sample size 26,884).¹¹ In a report on the effect of comorbidity in low risk cases Maurice et al similarly found that nonwhite race was associated with 1.1-fold higher odds of UGUS ($p = 0.001$, sample size 29,447).¹² Despite these robust sample sizes, neither study was designed to investigate the effect of race on UGUS and, therefore, did not adequately account for potential confounders, thereby limiting the race specific conclusions that can be drawn from these analyses.

In comparison, our study was a hypothesis driven investigation into the impact of race on UGUS specifically designed to address potential bias due to known confounders. A particular concern with prior studies was potential collinearity among race, health status and socioeconomic status for which multivariable logistic regression alone may have been insufficient to adjust.¹³ To account for this residual confounding we used stratification and multivariable modeling to further delineate the effect of race on pathological outcomes. We successfully showed that AA race independently predicted UGUS exclusive of other significant predictors, including age, demographics and clinical disease characteristics.

Study weaknesses include a retrospective design, susceptibility to bias from unmeasured confounders, lack of central pathological review and inability to adjust for family history of PCa. Furthermore, we did not analyze long-term oncologic outcomes, although recent work by Yamamoto et al supports the notion that UGUS may adversely affect long-term outcomes, ie PCa metastasis, for men on AS.¹⁴ Lastly, the NCDB lacks data on the percentage of core involvement with PCa and PSA density, precluding an analysis of the outcomes in AA men with very low risk PCa. Study strengths include a large sample size

(48,473), contemporary cohort and adjustment for known confounders (ie comorbidity, income, rural/urban status and clinical prognostic variables).

CONCLUSIONS

In a nationally representative sample of American men we observed significant racial disparities in the pathological features of clinically low risk PCa. Specifically, AA men have a higher chance of harboring higher risk cancers at RP. The increased odds of UGUS are most apparent in AA men with a low comorbidity burden. These results suggest that during individualized counseling for men with low risk PCa, race should be considered when discussing treatment options.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Abbreviations and Acronyms

AA	African-American
CCI	Charlson-Deyo comorbidity index
NCDB	National Cancer Database
PCa	prostate cancer
PSA	prostate specific antigen
RP	radical prostatectomy
UGUS	upgrading and/or up staging

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Table 1.**Baseline patient characteristics**

	AA	NonAA
<i>Clinical variables</i>		
Age:		
Mean (SD)	57.2 (7.1)	59.8 (6.9)
Median (IQR)	57 (52–62)	60 (55–65)
No. CCI (%):		
1 or Less	5,257 (97.2)	42,445 (98.6)
Greater than 1	154 (2.9)	617 (1.4)
<i>Demographic variables</i>		
No. income level (%):		
Less than \$38,000	1,723 (31.8)	4,430 (10.3)
\$38,000–\$47,999	1,206 (22.3)	8,449 (19.6)
\$48,000–\$62,999	1,182 (21.8)	11,929 (27.7)
\$63,000 or Greater	1,300 (24.0)	18,254 (42.4)
No. county (%):		
Urban	463 (8.6)	6,248 (14.5)
Nonurban	4,948 (91.4)	36,814 (85.5)
<i>Disease variables</i>		
No. T stage (%):		
1	5,113 (94.5)	38,897 (90.3)
2	298 (5.5)	4,165 (9.7)
PSA (ng/ml):		
Mean (SD)	5.2 (1.9)	5.0 (1.9)
Median (IQR)	5.0 (4.1–6.4)	4.8 (4.0–6.1)
% Pos cores:		
Mean (SD)	31.5 (23.1)	29.8 (23.2)
Median (IQR)	25.0 (16.7–41.7)	25.0 (11.8–41.7)

All values p <0.01.

Table 2.

Pathological outcomes

	Total No. (%)	No. AA (%)	No. NonAA (%)	p Value
<i>Pathological characteristics at RP</i>				
Gleason score:				<0.01
6 or Less	27,485 (56.7)	2,912 (53.8)	24,573 (57.1)	
3+4=7	18,205 (37.6)	2,142 (39.6)	16,063 (37.3)	
4+3=7	2,197 (4.5)	278 (5.1)	1,919 (4.5)	
8 or Greater	586 (1.2)	79 (1.5)	507 (1.2)	
T stage:				0.10
T2	44,129 (91.0)	4,927 (91.1)	39,202 (91.0)	
T3	4,314 (8.9)	477 (8.8)	3,837 (8.9)	
T4	30 (0.1)	7 (0.1)	23 (0.1)	
N stage:				<0.01
N0	27,829 (57.4)	3,182 (58.8)	24,647 (57.2)	
N1	68 (0.1)	15 (0.3)	53 (0.1)	
NX	20,576 (42.4)	2,214 (40.9)	18,362 (42.6)	
Surgical margin status:				0.14
Pos	7,335 (15.1)	865 (16.0)	6,470 (15.0)	
Neg	40,957 (84.5)	4,529 (83.7)	36,428 (84.6)	
Indeterminate	181 (0.4)	17 (0.3)	164 (0.4)	
<i>UGUS at RP</i>				
Gleason greater than 6 ± pT3-T4, pN1:				
Upgraded	20,988 (43.3)	2,499 (46.2)	18,489 (42.9)	<0.01
Up staged	4,371 (9.0)	488 (9.0)	3,883 (9.0)	1.00
Upgraded or up staged	22,081 (45.6)	2,639 (48.8)	19,442 (45.2)	<0.01
Gleason greater than 3+4=7 ± pT3-T4, pN1:				
Upgraded	2,783 (5.7)	357 (6.6)	2,426 (5.6)	<0.01
Upgraded or up staged	6,455 (13.3)	762 (14.1)	5,693 (13.2)	0.08

Table 3.

Multivariable logistic regression analysis of predictors of upgrading to Gleason greater than 6 and/or up staging

	OR	95% CI	p Value
Age	1.02	1.02–1.03	<0.01
CCI:			0.07
1 or Less	1.0	(referent)	
Greater than 1	1.1	1.0–1.3	
Race:			<0.01
NonAA	1.0	(referent)	
AA	1.2	1.1–1.3	
Income level:			0.34
Less than \$38,000	1.0	(referent)	
\$38,000–\$47,999	1.0	0.9–1.1	
\$48,000–\$62,999	1.1	1.0–1.1	
\$63,000 or Greater	1.0	1.0–1.1	
County:			0.01
Nonurban	1.0	(referent)	
Urban	1.1	1.02–1.1	
Clinical T stage:			0.63
1	1.0	(referent)	
2a	1.0	1.0–1.1	
PSA (ng/ml)	1.1	1.1–1.1	<0.01
% Pos cores:			<0.01
Less than 33	1.0	(referent)	
33–67	1.6	1.5–1.7	
Greater than 67	1.5	1.4–1.7	

Table 4.

Multivariable logistic regression analysis of predictors of upgrading to Gleason greater than 3+4=7 and/or up staging

	OR	95% CI	p Value
Age	1.03	1.03–1.04	<0.01
CCI:			0.20
1 or Less	1.0	(referent)	
Greater than 1	1.1	0.9–1.4	
Race:			0.03
NonAA	1.0	(referent)	
AA	1.1	1.01–1.2	
Income level:			0.54
Less than \$38,000	1.0	(referent)	
\$38,000–\$47,999	0.9	0.9–1.0	
\$48,000–\$62,999	1.0	0.9–1.0	
\$63,000 or Greater	0.9	0.9–1.0	
County:			0.87
Nonurban	1.0	(referent)	
Urban	1.0	0.93–1.1	
Clinical T stage:			<0.01
1	1.0	(referent)	
2a	1.2	1.1–1.3	
PSA (ng/ml)	1.1	1.1–1.2	<0.01
% Pos cores:			<0.01
Less than 33	1.0	(referent)	
33–67	1.5	1.4–1.6	
Greater than 67	1.8	1.6–2.0	

Table 5.

Predictors of UGUS at RP stratified by residence and comorbidity burden

	OR	95% CI	p Value
<i>Nonurban, CCI 1 or less (41,121)</i>			
Race:			<0.01
NonAA	1.0	(referent)	
AA	1.2	1.1–1.3	
Age	1.02	1.02–1.03	<0.01
PSA (ng/ml)	1.1	1.1–1.1	<0.01
% Pos cores:			<0.01
Less than 33	1.0	(referent)	
33–67	1.6	1.5–1.7	
Greater than 67	1.5	1.4–1.7	
<i>Urban, CCI 1 or less (6,581)</i>			
Race:			0.02
NonAA	1.0	(referent)	
AA	1.3	1.04–1.5	
Age	1.03	1.02–1.04	<0.01
PSA (ng/ml)	1.1	1.1–1.1	<0.01
% Pos cores:			<0.01
Less than 33	1.0	(referent)	
33–67	1.6	1.4–1.8	
Greater than 67	1.5	1.2–1.9	
<i>Nonurban, CCI greater than 1 (641)</i>			
Race:	1.1	0.8–1.7	0.55
NonAA	1.0	(referent)	
AA	1.0	0.7–1.5	
Age	1.0	1.0–1.0	0.07
PSA (ng/ml)	1.1	1.03–1.2	0.01
% Pos cores:			0.02
Less than 33	1.0	(referent)	
33–67	1.5	1.0–2.1	
Greater than 67	2.5	1.2–5.3	
<i>Urban, CCI greater than 1 (130)</i>			
Race:			0.08
NonAA	1.0	(referent)	
AA	0.4	0.1–1.1	
Age	1.0	1.0–1.1	0.19
PSA (ng/ml)	1.1	0.9–1.3	0.41
% Pos cores:			0.25
Less than 33	1.0	(referent)	
33–67	2.3	0.9–5.9	

	OR	95% CI	p Value
Greater than 67	1.7	0.1–38	

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