African-American men with prostate cancer have larger tumor volume than Caucasian men despite no difference in serum prostate specific antigen

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Introduction: *Prior studies suggest that among men with low grade prostate cancer, African Americans (AA) produce less prostate-specific antigen (PSA) than Caucasians. We investigated racial differences in PSA, PSA density (PSAD), and tumor volume among men with prostate cancer, regardless of tumor grade. These racial differences, if present, would suggest that AA men may benefit from different screening, surveillance, and treatment regiments compared to Caucasians.*

Materials and methods: *We identified men from our institutional prostate cancer database that underwent radical prostatectomy between 2012 and 2015. Clinicopathologic parameters were compared by race. Multivariable linear regression was then performed to identify factors associated with PSA, PSAD, and tumor volume, adjusting for race, age, body mass index, and pathologic parameters.*

Results: *A total of 255 men were included in the analysis, including 182 (71.4%) Caucasian and 73 (28.6%) AA. PSA (10.2 versus 8.1, p = 0.13) and PSAD (0.23 versus 0.22, p = 0.73) did not differ significantly between AA and Caucasian men. In contrast, tumor volume was significantly greater in AA men (13.4 versus 9.6 grams, p = 0.01). In multivariable linear regression analysis, AA race was not associated with PSA (p = 0.80) or PSAD (p = 0.41), but was significantly associated with increased tumor volume (p < 0.01).*

Conclusions: *AA men who underwent radical prostatectomy in this analysis had larger tumor volume than Caucasian men despite having similar PSA levels. This association suggests that prostate cancers in AA men may produce less PSA than in Caucasian men. These findings have implications for prostate cancer screening and treatment, as PSA may underestimate the presence or extent of cancer in AA men.*

Key Words: prostatic neoplasms, prostate-specific antigen, tumor volume, African Americans, European continental ancestry group

Introduction

Prostate cancer is a heterogeneous disease, and prior studies have shown that incidence and mortality rates, and tumor aggressiveness vary among men of different ethnic groups.[1] In particular, African American suffer from a disproportionately high burden of prostate cancer morbidity and mortality. From 2007-2011, the incidence of prostate cancer in AA men exceeded that of Caucasian men by more than 50%, and the mortality rate in AA men was more than double that of Caucasians.[1]

Several studies have investigated racial differences in prostate-specific antigen (PSA) levels and tumor volume among men with prostate cancer.[2-13] A recent publication found that AA men with low grade prostate cancer had lower PSAD than Caucasian men, despite comparable tumor volumes.[13] These findings suggest that PSA thresholds used to recommend prostate biopsy, select men for active surveillance, and risk stratify men prior to treatment may need to

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be adjusted for ethnicity. This study, however, was limited to men with Gleason 6 tumors and excluded those with higher grade disease.

In the current study, we assess racial differences in PSA, PSAD, and tumor volume among men treated with radical prostatectomy (RP). We did not limit our analysis to men with low grade tumors, but instead included all tumor grades to determine whether racial differences in these parameters persist in more aggressive tumors. Identification of such racial differences, if present, may alter prostate cancer screening and treatment recommendations for AA men relative to Caucasians.

Materials and methods

We identified Caucasian and AA men from our institutional prostate cancer database that underwent RP between 2012 and 2015. All men had clinically localized disease at the time of diagnosis. All racial and ethnicity data was self-reported by individual patients prior to inclusion in the database. Men of non-Caucasian or AA races were excluded.

Additional demographic and clinical information, including age at time of RP, body mass index (BMI), and PSA at time of last biopsy were collected. Pathologic parameters following radical prostatectomy were also analyzed, including prostate specimen weight, Gleason grade group, T stage, and percent of specimen involved by tumor. All pathology specimens were reviewed by pathologists with expertise in genitourinary pathology at our academic medical center.

Prostate specimen weight on pathology reports at our institution included the weight of the prostate and seminal vesicles. To estimate the corrected prostate weight, we subtracted the average weight of the seminal vesicles (6.4 grams) from the specimen weight.[14] PSAD was calculated by dividing the most recent PSA value prior to surgery by the corrected prostate weight.

The percent of specimen involved by tumor was obtained from pathology reports, which was an approximation by the pathologist following RP. To estimates tumor volume, the prostate specimen weight was multiplied by the percent of specimen involving tumor.

Demographic and clinicopathologic variables were compared between Caucasian and AA men using chi-squared analysis for categorical variables and the two-sided t-test for comparison of means.

Multivariable linear regression analyses were then used to identify variables associated with preoperative PSA level and PSAD. Covariates in the model included race, age, BMI, pathological T stage, Gleason score, prostate specimen volume, and tumor volume. A separate multivariable model was then used to identify factors associated with tumor volume. This model included race, age, BMI, T stage, and Gleason score. Stepwise regression models were then used further characterize variables associated with PSA, PSAD and tumor volume. For all of our analysis, results with two sided $p < 0.05$ were considered significant. All analyses were performed using Stata version 14.1 (College Station, TX, USA).

Results

A total of 255 men undergoing RP for prostate cancer at our institution between 2012-2015 were analyzed, including 182 (71.4%) Caucasian and 73 (28.6%) AA men. Demographic parameters for these men are shown in Table 1.

TABLE 1. **Comparison of demographic factors by race**

	Caucasian n (%)	**African-American n (%)**	**p value**
Race	182 (71.4)	73 (28.6)	
Age (y)			
Mean	61.2	60.3	0.39
< 60	72 (39.6)	36 (49.3)	0.35
60-65	59 (32.4)	19 (26.0)	
> 65	51 (28.0)	18 (24.7)	
Body mass index (kg/m^2)			
Mean	29.1	29.6	0.54
< 25	32 (17.6)	16 (21.9)	0.25
25-< 30	83 (45.6)	25 (34.3)	
≥ 30	67 (36.8)	32 (43.8)	

Univariate comparisons of clinicopathologic data by race are shown in Table 2. No significant difference was observed between races in Gleason score distribution (p = 0.59). AA men exhibited a trend towards higher pathological stage (p = 0.01) and specimen weights (p = 0.06), and had significantly larger tumor volume than Caucasians (p = 0.04). Despite larger tumor volumes, there was no difference in PSA (p = 0.32) or PSAD (p = 0.55) between AA and Caucasian men.

Multivariate regression models comparing factors associated with PSA, PSAD, and tumor volume are shown in Table 3. Tumor volume was strongly associated with PSA level (p < 0.001), whereas race, age BMI, T-stage, and Gleason score were insignificant. Tumor volume showed a similar significant association with PSAD (p < 0.001), whereas age (p = 0.02) and BMI (p = 0.047) were found to have inverse associations with PSAD. Despite no racial differences in PSA and PSAD, African American race was strongly associated with larger tumor volume (p = 0.006).

Results of stepwise regression models for factors associated with PSA, PSAD, and tumor volume are shown in supplemental Tables 4, 5, and 6, respectively.

TABLE 2. **Comparison of clinicopathologic factors by race**

	Caucasian n (%)	**African-American n (%)**	**p value**
Pathological stage			
pT2	140 (76.9)	45 (61.6)	0.01
pT3 or pT4	42 (23.1)	28 (38.4)	
Gleason Score			
3+3	46 (25.6)	23 (31.9)	0.59
3+4	87 (48.3)	29 (40.3)	
4+3	26 (14.4)	13 (18.1)	
≥ 4+4	21 (11.7)	7 (9.7)	
Specimen weight (g)			
Mean	44.8	49.7	0.07
≤ 35	65 (35.7)	17 (23.3)	0.06
35-50	69 (37.9)	27 (37.0)	
> 50	48 (26.4)	29 (39.7	
% specimen involving tumor (%)			
Mean	23.4	26.2	0.29
≤ 10	61 (33.5)	17 (23.3)	0.28
10-25	61 (33.5)	28 (38.4)	
> 25	60 (33.0)	28 (38.4)	
Tumor volume (g)			
Mean	9.6	13.4	0.01
≤ 5	65 (35.7)	15 (20.6)	0.04
> 5-10	53 (29.1)	22 (30.1	
> 10	64 (35.2)	36 (49.3)	
Prostate-specific antigen (PSA) (ng/mL)			
Mean	8.110.2	0.13	
≤ 5	71 (39.0)	22 (30.1)	0.32
5-10	78 (42.9)	33 (45.2)	
> 10	33 (18.1)	18 (24.7	
PSAD (ng/mL/g)			
Mean	0.22	0.23	0.73
≤ 0.15	86 (47.3)	31 (42.5)	0.55
0.15-0.25	53 (29.1)	20 (27.4)	
> 0.25	43 (23.6)	22 (30.1)	

TABLE 3. **Multivariable regression models of factors associated with PSA, PSAD, and tumor volume**

	Factors associated with PSA			Factors associated with PSAD			Factors associated with tumor volume		
Variable	**Coef.**	**p value**	**95% CI**	**Coef.**	**p value**	**95% CI**	**Coef.**	**p value**	**95% CI**
Race									
Caucasian	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
African-American	-0.29	0.80	-2.53-1.96	-0.02	0.41	-0.08-0.03	3.30	0.006	0.98-5.63
Age (y)	-0.07	0.37	-0.21-0.08	-0.004	0.02	-0.01--0.001	-0.03	0.73	-0.13-0.18
BMI (kg/m^2)	-0.13	0.21	-0.33--0.07	-0.01	0.047	-0.01--0.0001	0.14	0.17	-0.06-0.35
T stage									
T2	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
T3a	0.72	0.67	-2.58-4.01	0.04	0.36	-0.04-0.12	0.38	0.831	-3.10-3.85
T3b	1.85	0.34	-1.94-5.64	0.09	0.07	-0.01-0.18	10.67	< 0.001	6.91-14.43
T4	-8.31	0.19	-20.74-4.12	-0.11	0.49	-0.42-0.20	23.64	< 0.001	10.89-36.40
Gleason score									
3+3	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
3+4	0.08	0.95	-2.41-2.57	0.06	0.07	-0.005-0.12	3.57	0.007	0.98-6.15
4+3	2.58	0.18	-1.23-6.39	0.11	0.03	0.01-0.20	6.82	0.001	2.89-10.74
4+4	-2.67	0.30	-7.77-2.44	0.08	0.22	-0.05-0.20	8.79	0.001	3.52-14.05
≥ 9	1.95	0.47	-3.38-7.28	0.13	0.06	-0.003-0.26	5.64	0.047	0.07-11.22
Tumor volume (g)	0.54	< 0.001	0.42-0.66	0.01	< 0.001	0.003-0.01			

Tumor volume remained strongly associated with PSA ($p < 0.001$) and PSAD ($p < 0.001$) and AA race remained a strong predictor of increased tumor volume ($p = 0.006$).

TABLE 4. **Stepwise regression analysis: factors associated with PSA**

	Factors associated with PSA		
Variable	**Coef.**	**p value**	**95% CI**
Tumor volume (g)	0.58	< 0.001	0.48-0.68

TABLE 5. **Stepwise regression analysis: factors associated with PSAD**

	Factors associated with PSAD		
Variable	**Coef.**	**p value**	**95% CI**
Tumor volume (g)	0.007	< 0.001	0.004-0.010
T stage			
T2	Ref	Ref	Ref
T3a	0.057	0.15	-0.020-0.13
T3b	0.14	0.001	0.06-0.22
T4	-0.057	0.70	0.08-0.16

Discussion

In the current analysis of Caucasian and AA men undergoing radical prostatectomy, we found no

TABLE 6. **Stepwise regression analysis: factors associated with tumor volume**

	Factors associated with tumor volume		
Variable	**Coef.**	**p value**	**95% CI**
Race			
Caucasian	Ref	Ref	Ref
African-American	3.30	0.006	0.98-5.63
T stage			
T2	Ref	Ref	Ref
T3a	0.67	0.70	-2.77-4.12
T3b	10.77	< 0.001	7.04-14.51
T4	24.57	< 0.001	11.89-37.26
Gleason score			
3+3	Ref	Ref	Ref
3+4	3.51	0.007	0.95-6.07
4+3	6.67	0.001	2.84-10.50
4+4	8.58	0.001	3.37-13.79
≥ 9	5.32	0.060	-0.23-10.87

differences in PSA or PSA density by race despite significantly larger tumor volumes in AA men. These findings suggest that AA men may produce less PSA per unit volume of tumor and that PSA may therefore underestimate the true extent of disease in AA men.

Our analysis attempted to adjust for other factors that may potentially influence PSA levels, including age, BMI, pathological tumor stage, and Gleason score. These factors did not differ significantly by race, and in multivariable analyses including these factors as covariates, AA race was not significantly associated with PSA or PSAD. At first glance, the results of the current study appear to stand in contrast to those of a recent publication by Kryvenko et al, who reported lower PSAD in AA men with Gleason 6 prostate cancer compared to Caucasian men.[13] However, with further scrutiny, our results are similar in that each study suggests decreased PSA production in AA men. Kryvenko et al reported lower PSAD in AA men despite larger overall prostate size and comparable tumor volume. This observation suggests that either benign prostate tissue or cancerous tissue in AA men produces less PSA than a comparable amount of tissue in Caucasians. Our analysis found larger cancer volumes in AA men, but similar PSA and PSAD, which also could be explained by decreased PSA production by either cancerous or non-cancerous tissue in AA patients.

Multiple investigators have published similar studies investigating racial differences in PSA levels and tumor volume.[2-13] In contrast to our results, the majority of these studies found that AA men with prostate cancer had higher PSA levels than Caucasian men. Many of these studies, however, included heterogeneous patient populations and did not account for factors such as BMI which are known to influence PSA levels through hemodilution.[15-17] Furthermore, many of the previously published did not perform multivariable analyses to control for covariates known to influence PSA level. Our analysis attempted limit patient heterogeneity by excluding patients with metastatic prostate cancer, while also including patients of varying tumor grade to determine if racial differences in PSA production were present in poorly differentiated prostate tumors. Furthermore, we attempted to control for factors known to influence PSA production such as patient age and BMI.

Racial differences in tumor volume have also been studied extensively in the published literature.[7,9,11-13] The majority of such studies found that AA men tended to have larger tumor volume than Caucasians, results that are consistent with our study findings. This larger tumor volume in AA may partially contribute to the increased prostate cancer morbidity and mortality in AA men compared to Caucasians.

The results of the current study carry several clinical implications potentially applicable to screening, risk stratification, and selection of appropriate treatment strategy. Should AA men truly produce less PSA per unit tumor volume, PSA may underestimate the true extent of cancer present at the time of diagnosis. When screening for prostate cancer, this finding would argue that the PSA threshold prompting prostate biopsy should be lower in AA men compared to Caucasians, despite no current recommendations suggesting that PSA should be adjusted by race. It has also been shown that among men suspected of having clinically indolent disease at the time of biopsy, AA men are more likely to be upstaged or upgraded after radical prostatectomy.[18] This poor risk stratification in AA men could be explained by decreased PSA production in AA men relative to Caucasians. Finally, PSAD is often used to identify men with low risk cancer who are potential candidate for active surveillance, as PSAD is known to correlate closely with tumor volume.[19] Prior studies have shown that commonly employed surveillance eligibility criteria function poorly in AA populations, and often fail to identify men with more aggressive disease.[20] This limitation of traditional AS eligibility criteria may be due to the inability of PSA and PSAD to accurately reflect tumor volume in AA men.

There are limitations to the current study. The sample size was relatively modest which may limit statistical power to identify differences between races. There was no centralized review of pathology specimens, although all specimens were reviewed by pathologists with expertise in genitourinary pathology. Furthermore, tumor volume was not measured directly, but instead calculated using prostate size and the percentage of the specimen involved by tumor. Although this method is likely to be less accurate than direct measurement, the same technique has been used to estimate tumor volume in several studies in the published literature.[11,12]

Our findings suggest that PSA and PSAD levels are similar in AA and Caucasian men with prostate cancer, despite significantly larger tumor volumes in AAs. This observation could be explained by the decreased production of PSA per unit tumor volume in AA men compared to Caucasians. Similar findings have been previously reported in the literature, but additional validation is needed. The clinical implications of this observation are significant, and suggest that PSA potentially should be adjusted for race when evaluating patients for prostate biopsy, performing pre-treatment risk stratification, or selecting appropriate management strategy for men with prostate cancer. □

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