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Do Racial Differences In Prostate Size Explain Higher Serum PSA Concentrations Among Black Men?

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Abstract

Objectives—Black men have higher serum PSA values than white men. As levels of serum PSA directly correlate with prostate size, we hypothesized that elevated serum PSA values in black men may be due, at least partially, to larger prostate size among black men.

Methods—The study population consisted of two cohorts: 1) 1,410 men undergoing radical prostatectomy between 1988 and 2005 at five equal access medical centers comprising the SEARCH Database; and 2) 9,601 men undergoing radical prostatectomy between 1988 and 2004

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at the Johns Hopkins Hospital. We evaluated the association between race and serum PSA and prostate weight using multivariable linear regression while adjusting for demographic and clinico-pathological cancer characteristics.

Results—In both cohorts, black men had higher serum PSA values ($p \leq 0.001$). After adjusting for either demographic characteristics or demographic and cancer-specific characteristics, there were no significant associations between race and prostate size in either cohort. After adjusting for multiple demographic, clinical, and pathological cancer-specific characteristics, black men had 15% higher serum PSA values relative to white men in both the SEARCH ($p = 0.001$) and Hopkins cohorts ($p < 0.001$).

Conclusions—In this study of patients undergoing radical prostatectomy in two very different practice settings, black men in both cohorts had higher serum PSA values relative to white men despite adjustment for demographic and cancer-specific characteristics, including prostate weight. The lack of significant association between race and prostate size suggests alternative reasons are needed to explain higher serum PSA levels in black men.

INTRODUCTION

Population-based studies reveal that black men have higher serum prostate-specific antigen (PSA) values than white men.^{1, 2} Moreover, we³ and others^{4, 5} have consistently found that among men undergoing radical prostatectomy, black men present with higher serum PSA values. Given the strong positive association between prostate size and serum PSA,⁶ we hypothesize that black men have larger prostates than white men, which may, at least in part, explain the higher serum PSA values among black men. Although non-invasive imaging modalities such as transrectal ultrasound estimate prostate size with reasonable accuracy,⁷ there is not always a perfect correlation with prostate weight determined after radical prostatectomy. Therefore, prostate weight measured after radical prostatectomy represents the most reliable method to accurately determine the size of the entire organ. In order to test our hypothesis, we evaluated the association between race and serum PSA after adjusting for prostate weight among men treated with radical prostatectomy. As serum PSA also correlates with the extent of prostate cancer,⁸ we further controlled for cancer-specific characteristics. To increase the generality of our results, we included data from two different practice settings: a tertiary care referral center (Johns Hopkins Hospital), and multiple equal access medical centers using the Shared Equal Access Regional Cancer Hospital (SEARCH) database.³

MATERIALS AND METHODS

SEARCH Database study population

After obtaining Institutional Review Board (IRB) approval from each institution, data from patients treated with radical prostatectomy from 1988 to 2005 at the Veterans Affairs (VA) Health Care Facilities in West Los Angeles, Palo Alto, San Francisco, and Augusta, Georgia, and the San Diego Naval Hospital were combined into the SEARCH database.³ This database includes information on patient age at the time of surgery, race, height, weight, clinical stage, grade of cancer on diagnostic biopsies, pre-operative serum PSA, surgical specimen pathology (specimen weight, tumor grade, stage, and surgical margin status), and follow-up serum PSA data for a mean and median of 47 and 37 months (range: 1 to 172 months). Patients that were treated with either pre-operative androgen deprivation therapy or radiation therapy were excluded from our analysis. Of the 2,139 patients in the SEARCH database, we excluded 404 patients with missing data for weight of the radical prostatectomy specimen and 109 patients with missing data for pre-operative serum PSA values. Men who were neither black nor white were excluded ($n = 193$) due to limited

numbers of men from other races. An additional 23 men diagnosed from a transurethral resection specimen (clinical stage T1a/T1b) were also excluded as this affects prostate size and serum PSA, resulting in a study population of 1,410.

Prostatectomy specimens were sectioned per each institution's protocol.³ All institutions determined prostate weight by measurement of the gross weight of the entire specimen, including seminal vesicles and tips of the vasa.

Johns Hopkins Hospital study population

After obtaining IRB approval and informed consent when appropriate, consecutive patients treated with anatomic retropubic radical prostatectomy for prostate adenocarcinoma from 1988 to 2004 at the Johns Hopkins Hospital were identified. Men that were treated with either pre-operative hormonal therapy (luteinizing hormone releasing hormone agonist, anti-androgen or 5-alpha reductase type II inhibitor) or radiation therapy were excluded. Men diagnosed from a transurethral resection specimen (clinical stage T1a/T1b) were excluded as this affects prostate size and serum PSA. Men who were neither black nor white were excluded due to limited numbers of men from other races. Of the remaining 10,000 men, we excluded 300 patients with missing data for weight of the radical prostatectomy specimen and 99 patients with missing data for pre-operative serum PSA, resulting in a study population of 9,601.

Prostatectomy specimens were sectioned as previously described.⁹ Prostate weight was determined by measurement of the gross radical prostatectomy specimen weight, including seminal vesicles and tips of the vasa.

Statistical analysis

The distribution of clinicopathological characteristics was compared between races using chi-square analysis for categorical variables and rank-sum analysis for continuous variables. The associations between race and the outcome variables of prostate size and serum PSA were examined using a multivariable linear regression analysis. Both prostate size and serum PSA were examined as continuous variables after logarithmic transformation. In the models, we mutually adjusted for body mass index (BMI; weight in kilograms/height in meters squared; <25.0, 25.0–29.9, 30.0–34.9, ≥ 35.0 kg/m²), height (quartiles), age (continuous), year of surgery (continuous), clinical stage (T1 vs. T2/3), pathological Gleason sum (2–6, 7, and 8–10) and the following pathological features: positive surgical margins, extracapsular extension, seminal vesicle invasion, and lymph node metastasis.

The distribution of all clinicopathological variables was similar among the five centers contributing to the SEARCH database. Therefore, data from all five centers was combined for analyses. All statistical analyses were performed using STATA 9.1 (Stata Corp., College Station, TX).

RESULTS

Baseline Patient Characteristics

In both the SEARCH and Hopkins cohort, black men had significantly higher serum PSA values ($p \leq 0.001$, table 1). Additionally, black men in both cohorts were significantly younger ($p < 0.001$), more likely to have clinical T1 disease ($p < 0.001$), and more likely to be treated in recent years ($p < 0.001$) than white men. In the Hopkins series, black men were also significantly more likely to be obese ($p < 0.001$), and have higher biopsy ($p = 0.02$) and pathological Gleason sum cancers ($p = 0.001$) than white men.

Race and prostate size

We sought to determine whether racial differences in prostate size could explain the racial disparity in serum PSA. After adjusting for the pre-operative demographic clinical characteristics of age, BMI, height, year of surgery, and center (SEARCH Database only), there was no significant association between race and prostate size in either the SEARCH ($p=0.58$) or Hopkins cohorts ($p=0.17$). We further evaluated the association between race and prostate size by adjusting for demographic and cancer-specific characteristics including clinical stage, percent of biopsy cores with cancer (SEARCH Database only), pathological Gleason sum, and pathological findings. Analogous to the findings which were only adjusted for demographics, after adjustments for clinicopathological characteristics, there remained no significant association between race and prostate size in either the SEARCH ($p=0.42$) or Hopkins cohorts ($p=0.12$).

Race and PSA

While serum PSA is positively associated with larger prostate size, it is also associated with larger tumors.⁸ Therefore, in the current study, an alternative explanation for the higher serum PSA values among black men with prostate cancer would be larger tumor size. Because exact tumor volumes were not recorded in either dataset, we used percent of biopsy cores with cancer (SEARCH Database only) as well as pathological features of the radical prostatectomy specimen, such as margin status and pathological stage, as surrogates of tumor volume. After adjusting for multiple demographic, clinical, and pathological cancer characteristics, black men had 15% higher serum PSA values relative to white men in both the SEARCH ($p=0.001$) and Hopkins series ($p<0.001$, table 2).

DISCUSSION

Multiple studies have found that black race is associated with increased serum PSA values.^{1, 2} As serum PSA is positively associated with prostate size,⁶ we hypothesized that racial differences in prostate size may underlie the observed racial disparities in serum PSA values. In this study of over 1,000 men from multiple equal access medical centers and over 9,000 men from a tertiary care referral center, we found that among men undergoing radical prostatectomy for early stage prostate cancer, black men had higher serum PSA values than white men although there was no significant difference in prostate size between races. In addition, further adjustment for cancer characteristics did not account for the racial disparity in serum PSA values. Our study represents the largest study to date to address this issue and suggests that racial differences in prostate size do not account for the observed racial differences in serum PSA. Alternative reasons are needed to explain the higher serum PSA values observed in black men.

In the current study, which examined only men with prostate cancer, black men had 15% higher serum PSA values both in the multiple equal access medical centers of the SEARCH database as well as a tertiary care referral center. One possible explanation for the higher serum PSA values among black men is that black men may have a greater degree of inflammation within the prostate.¹⁰ However, this hypothesis was tested in a previous study examining radical prostatectomy specimens via close step-sectioning which found no significant differences in the amount or degree of inflammation within the prostate between black and white men.¹⁰

In light of these observations and based upon the known association between prostate size and serum PSA,⁶ we hypothesized that differences in prostate size may account for differences in serum PSA between the two races. To examine this issue, we analyzed prostate weight from two very large cohorts of men treated with radical prostatectomy.

While studying men with prostate cancer introduces the potential bias of serum PSA production by the cancer, it nonetheless allows an exact measurement of prostate size, which otherwise can only be estimated via non-invasive modalities. In this study, we found no significant differences in prostate size between the races. Moreover, after further adjusting for racial differences in cancer characteristics, black men still had significantly higher serum PSA values relative to white men. Our results mirror those from a previous smaller study of 155 white and 46 black men that also found no significant differences in prostate weight of the radical prostatectomy specimen between black and white men.¹¹ In addition, this prior study revealed that despite significant differences in tumor volume between black and white men, this also could not completely account for the racial disparity in serum PSA. Likewise, we found that further adjustment for cancer-specific characteristics did not completely account for racial differences in serum PSA. Finally, it should be noted that other studies have also found no difference in radical prostatectomy weight between black and white men.^{4, 5}

Given our findings, the question remains what accounts for the observed differences in serum PSA between black and white men? As androgens regulate cellular PSA production, perhaps differences in androgenic activity between black and white men could explain racial differences in serum PSA values. Some studies have suggested that black men in their teens and early twenties have significantly, albeit slightly, higher testosterone levels relative to similarly aged white men.¹² In addition, black men are more likely to possess genetic polymorphisms that favor increased androgen activity such as shorter CAG tri-nucleotide repeats in the androgen receptor gene¹³ and a possibly less active variant of the CYP3A4 gene, which encodes a protein involved in the oxidative deactivation of testosterone.¹⁴ Finally, increased androgen activity among black men was suggested by a study which found that benign and malignant prostate tissue from black men had both a greater number of cells staining positive for the androgen receptor as well as more intense staining within positive cells.¹⁵ Although androgens regulate cellular PSA production they also affect prostate size.¹⁶ Therefore, higher androgenicity among black men would be expected to result in larger sized prostates. However, we did not observe a racial difference in prostate size in the current study. This may suggest a lack of significant biological differences in androgenicity between black and white races. Alternatively, a biological effect of greater androgenicity among black men, if existent, may be blunted by alterations in other hormones that also regulate prostate size, such as estrogen, insulin, and insulin-like-growth factor 1.^{16–18} Data on serum and tissue hormonal concentrations were not available in either cohort in this study. Thus, we were unable to evaluate any possible association between hormonal concentrations, prostate size, and serum PSA values.

Another possible cause of racial differences in serum PSA values may involve polymorphisms within the PSA gene itself. A single-nucleotide polymorphism resulting in an adenine to guanine substitution at position –158 of the PSA promoter region has been correlated with alterations in serum PSA values.¹⁹ To date, no studies have been performed to assess the prevalence of this polymorphism in different ethnic or racial groups. Thus, it remains possible that the distribution of this polymorphism may differ between races and therefore account for at least some, if not all, of the differences in serum PSA values between black and white men.

In the current study, we used total weight of the radical prostatectomy specimen as a surrogate for benign prostate size. Thus, both the weights of the seminal vesicles and tips of the vasa were included in this measurement. As the weight of the cancer was not available in our cohorts, we could not subtract this quantity from the total weight of the radical prostatectomy specimen. However, a contemporary series of patients undergoing radical prostatectomy reveals that prostate cancer volumes are typically in the range of 1–2 cm³.²⁰

Although the impact of a 1–2 cm³ cancer volume on the total weight of a radical prostatectomy specimen (typically 40–50 grams) is probably slight, it remains possible that tumor volume, in very large cancers, may markedly affect total prostate weight.

Another consideration that may explain racial differences in serum PSA is based on PSA production by prostate epithelial cells. A lack of statistical difference in prostate size between black and white men does not necessarily imply that prostate epithelial cell content is equivalent between the two races. It remains possible that racial differences in serum PSA values may be due to a decreased stromal to epithelial cell ratio in black men relative to white men. Although not available in our study, this type of analysis may prove fruitful in future studies investigating the cause of racial differences in serum PSA. Finally, all patients had prostate cancer and underwent surgery for their disease. Therefore, although the current findings suggest no significant association between race and prostate size in men with prostate cancer, these findings need to be confirmed using population-based studies of men with and without prostate disease. In addition, the degree to which our results may be influenced by selection bias is unknown.

CONCLUSIONS

In this study, we observed that black men had higher serum PSA values relative to white men in two large cohorts of patients undergoing radical prostatectomy. After adjusting for demographic and cancer-specific variables, including prostate size, serum PSA values remained significantly higher among black men. The current findings suggest that differences in prostate size do not exist between black and white men and therefore alternative reasons are needed to explain racial differences in serum PSA values.

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TABLE 1

Clinical and pathological features of men undergoing radical prostatectomy

	SEARCH Database			Johns Hopkins Hospital		
	White	Black	p-value*	White	Black	p-value*
No. patients	945 (67)	465 (33)		9,069 (94)	533 (6)	
Age at surgery (yr)	62.7 ± 6.5	60.9 ± 6.8	<0.001 [†]	58.1 ± 6.4	56.7 ± 6.8	<0.001 [†]
Year of surgery, median	1998	1999	<0.001 [†]	1998	1999	<0.001 [†]
Body mass index (kg/m ²)			0.17			<0.001
<25.0	225 (28)	99 (23)		2,582 (30)	100 (19)	
25.0 – 29.9	393 (48)	201 (48)		4,777 (55)	287 (55)	
30.0 – 34.9	146 (18)	84 (20)		1,191 (14)	100 (19)	
≥35.0	54 (7)	39 (9)		136 (2)	34 (7)	
PSA (ng/ml)			0.001 [†]			<0.001 [†]
Mean	8.8 ± 7.8	10.4 ± 11.3		7.6 ± 6.4	9.2 ± 8.1	
Median	6.6	7.5		6.0	7.0	
Percent of cores with cancer			0.17 [†]			
Mean	34.6 ± 24.2	35.7 ± 23.3		data not available		
Median	30	33.3		data not available		
Biopsy Gleason score (n)			0.04			0.02
2–6	639 (69)	323 (71)		7,101 (79)	391 (74)	
7	207 (22)	114 (25)		1,651 (18)	121 (23)	
8–10	76 (8)	21 (5)		277 (3)	20 (4)	
Clinical Stage (n)			<0.001			<0.001
T1	386 (42)	259 (57)		5,565 (61)	381 (72)	
T2/T3	535 (58)	196 (43)		3,489 (39)	150 (28)	
Prostate weight (g)			0.51			0.87
Mean	44.6 ± 21.5	45.4 ± 25.4		56.6 ± 20.9	57.3 ± 23.4	
Median	40	39		52	52	
Pathological Gleason score (n)			0.15			0.001
2–6	509 (55)	238 (52)		5,736 (63)	295 (55)	
7	326 (35)	187 (40)		2,813 (31)	201 (38)	

	SEARCH Database			Johns Hopkins Hospital		
	White	Black	p-value *	White	Black	p-value *
8-10	88 (10)	37 (8)		500 (6)	36 (7)	
Positive surgical margins (n)	312 (33)	164 (35)	0.42	1,143 (13)	85 (16)	0.03
Capsular penetration (n)	240 (25)	96 (21)	0.05	3,249 (36)	193 (36)	0.93
Seminal vesicle invasion (n)	75 (8)	45 (10)	0.27	495 (5)	34 (6)	0.37
Positive lymph nodes (n)	21 (3)	6 (2)	0.21	261 (3)	10 (2)	0.17

* p-value from chi-square comparing black vs. white, except where noted

† p-value from rank-sum

Table 2

Mean pre-operative serum PSA values by race*

	Mean PSA $\pm$ Standard error (ng/ml)	
	SEARCH Database	Johns Hopkins Hospital
White men	6.7 $\pm$ 1.0	5.9 $\pm$ 1.0
Black men	7.7 $\pm$ 1.0	6.8 $\pm$ 1.0
p-value	0.001	<0.001

* Mean PSA values were mutually adjusted for age, height, body mass index, year of surgery, clinical stage, percent of cores with cancer (SEARCH database only), prostate weight, pathological Gleason sum, surgical margin status, extracapsular extension, seminal vesicle invasion, lymph node metastasis, and center (SEARCH database only).