UCSF

UC San Francisco Previously Published Works

Title

Does larger tumor volume explain the higher prostate specific antigen levels in black men with prostate cancer--Results from the SEARCH database.

Permalink

<https://escholarship.org/uc/item/9xw0t71c>

Journal

Cancer epidemiology, 39(6)

ISSN

1877-7821

Authors

Klaassen, Zachary
Howard, Lauren
Terris, Martha K
et al.

Publication Date

2015-12-01

DOI

10.1016/j.canep.2015.09.007

Peer reviewed

Does larger tumor volume explain the higher prostate specific antigen levels in black men with prostate cancer—Results from the SEARCH database

Zachary Klaassen^a, Lauren Howard^b, Martha K. Terris^{a,c}, William J. Aronson^{d,e},
Matthew R. Cooperberg^{f,g}, Christopher L. Amling^h, Christopher J. Kane^{i,j},
Stephen J. Freedland^{k,l,*}

^a Medical College of Georgia—Georgia Regents University, Augusta, GA, United States

^b Duke University Medical Center, Durham, NC, United States

^c Augusta Veterans Affairs Medical Center, Augusta, GA, United States

^d West Los Angeles Veterans Affairs Medical Center, West Los Angeles, CA, United States

^e University of California, Los Angeles School of Medicine, Los Angeles, CA, United States

^f San Francisco Veterans Affairs Medical Center, San Francisco, CA, United States

^g University of California, San Francisco, CA, United States

^h Oregon Health & Sciences University, Portland, OR, United States

ⁱ San Diego Veterans Affairs Medical Center, San Diego, CA, United States

^j University of California, San Diego, CA, United States

^k Durham Veterans Affairs Medical Center, Durham, NC, United States

^l Cedars Sinai Medical Center, Los Angeles, CA, United States

ARTICLE INFO

Article history:

Received 25 June 2015

Received in revised form 25 August 2015

Accepted 12 September 2015

Available online 6 October 2015

Keywords:

Prostate cancer

PSA

Race

Radical prostatectomy

Tumor volume

ABSTRACT

Objectives: To assess whether larger tumor volume in black men explains higher presurgical PSA levels versus white men with prostate cancer.

Methods: We retrospectively analyzed 1904 men from the Shared Equal Access Regional Cancer Hospital database who underwent radical prostatectomy from 1990 to 2013. Geometric mean of tumor volume and preoperative PSA for each race were estimated from multivariable linear regression models.

Results: There were 1104 (58%) white men and 800 (42%) black men. Black men were younger (60.2 vs. 62.9 years, $p < 0.001$) had a higher PSA (6.7 vs. 6.0 ng/mL, $p < 0.001$), more positive margins (47 vs. 38%, $p < 0.001$), and seminal vesicle invasion (13 vs. 9%, $p = 0.007$). White patients had higher clinical stage ($p < 0.001$) and greater median tumor volume (6.0 vs. 5.3 gm, $p = 0.011$). After multivariable adjustment (except for PSA), white men had smaller mean tumor volumes (5.2 vs. 5.8 gm, $p = 0.011$). When further adjusted for PSA, there was no racial difference in mean tumor volume ($p = 0.34$). After multivariable adjustment, black men had higher mean PSAs vs. white men (7.5 vs. 6.1 ng/mL, $p < 0.001$). Results were similar after further adjusting for tumor volume: black men had 16% higher mean PSAs versus white men (7.4 vs. 6.2 ng/mL, $p < 0.001$).

Conclusions: In this study of men undergoing radical prostatectomy at multiple equal access medical centers, racial differences in tumor volume did not explain higher presurgical PSA levels in black versus white men. The exact reason for higher PSA values in black men remains unclear.

© 2015 Elsevier Ltd. All rights reserved.

1. Introduction

Multiple previous population-based studies have demonstrated that black men have higher prostate-specific antigen (PSA) values than white men [1,2]. Similar results have been seen among men with prostate cancer [3] and specifically among men undergoing radical prostatectomy [4–6]. There are multiple potential explanations for a higher serum PSA including larger prostate size and

* Corresponding author at: Department of Surgery, Division of Urology, Cedars Sinai Medical Center, 8635 West 3rd Street, Suite 1070W, Los Angeles, CA 90048, United States. Fax: +1 310 423 4711.

E-mail address: stephen.freedland@cshs.org (S.J. Freedland).

larger tumor size [7]. We previously showed that the inherent racial serum PSA differences in men undergoing radical prostatectomy were not explained by racial differences in prostate size [8].

An alternative explanation for higher serum PSA values among black men with prostate cancer may be increased tumor volume. Increasing tumor volume is associated with higher serum PSA [9–11]. Several studies have shown that among men with low-grade (Gleason ≤ 6) prostate cancer, black men had higher tumor volume compared to non-black men [12,13]. Furthermore, black men with cT1c prostate cancer undergoing radical prostatectomy had greater mean tumor volume and tumor per ng/mL of serum PSA compared to white men [14]. We hypothesized that larger tumor volume in black men may explain all or part of the higher presurgical PSA levels in black versus white men with prostate cancer. To test this hypothesis, we used a radical prostatectomy database of men treated at equal access centers with a large proportion of black patients to assess whether larger tumor volumes explains the inherent higher PSA levels in black versus white men.

2. Materials and methods

2.1. Study population

After obtaining Institutional Review Board approval, data on patients treated with radical prostatectomy from 1990 to 2013 at Veterans Affairs Medical Centers in West Los Angeles, San Diego and Palo Alto, California; Durham and Asheville, North Carolina; and Augusta, Georgia, were combined into the Shared Equal Access Regional Cancer Hospital (SEARCH) database [15]. This database includes information on patient age at the time of surgery, race, height, weight, clinical stage, grade of cancer on diagnostic biopsies, preoperative serum PSA value, surgical specimen pathology (specimen weight, tumor grade, tumor volume, stage and surgical margin status), and follow-up serum PSA data.

Patients treated with either preoperative androgen deprivation therapy or radiation therapy were excluded from analysis. Of the 5062 patients in the SEARCH Database, we excluded 2733 patients with missing data for tumor volume, 27 patients with missing data for PSA, and 128 patients who were neither white nor black because of limited numbers of men from other races. An additional 18 men diagnosed from a transurethral resection specimen (clinical stage T1a/T1b) were also excluded because this affects prostate size, tumor volume and serum PSA value. Finally, patients with missing data for pathologic Gleason sum ($n=5$), pathologic features ($n=52$), or BMI ($n=195$) were excluded. This resulted in a study population of 1904 patients.

Prostatectomy specimens were sectioned per each institution's protocol. All institutions determined prostate weight by measurement of the gross weight of the entire specimen, including seminal vesicles and tips of the vasa. In the pathology reports, we abstracted data for percent of the total prostatectomy specimen involved with cancer. This value was then used to calculate tumor volume as follows: tumor volume (gm) = [prostate weight (gm) $\times$ percent of prostate with tumor]/100. Preoperative BMI was calculated as weight in kg divided by height in m² (kg/m²).

2.2. Statistical analysis

The distribution of clinicopathologic characteristics was compared between races using Chi-square analysis for categorical variables and Wilcoxon rank-sum or *t*-tests for continuous variables. The associations between race and the outcome variables of tumor volume and preoperative serum PSA values were examined using linear regression. Both tumor volume and serum PSA value were examined as continuous variables after logarithmic transformation. In the models, we mutually adjusted for age (continuous), year of surgery (continuous), pathologic Gleason sum (2 to 6, 3 + 4, 4 + 3, and 8 to 10), BMI (continuous, log-

Table 1
Clinical and pathologic features of men undergoing radical prostatectomy.

Characteristic	White	Black	<i>p</i> value ^a
Patients, <i>n</i> (%)	1104 (58)	800 (42)	
Age at surgery, mean $\pm$ SD	62.9 $\pm$ 5.5	60.2 $\pm$ 6.4	<0.001 ^b
Median yr surgery	2008	2009	<0.001 ^c
BMI (kg/m ²), median (Q1–Q3)	28.0 (25.3–31.1)	28.1 (25.2–31.6)	0.93 ^c
PSA (ng/mL), median (Q1–Q3)	6.0 (4.4–8.3)	6.7 (5.0–10.4)	<0.001 ^c
Biopsy Gleason sum, <i>n</i> (%)			0.025
2–6	496 (45)	327 (41)	
3+4	293 (27)	264 (33)	
4+3	147 (14)	103 (13)	
8–10	157 (14)	101 (13)	
Clinical stage, <i>n</i> ^a (%)			<0.001
T1	625 (62)	550 (72)	
T2/T3	391 (38)	213 (28)	
Pathologic Gleason sum, <i>n</i> (%)			<0.001
2–6	297 (27)	143 (18)	
3+4	441 (40)	414 (52)	
4+3	191 (17)	157 (20)	
8–10	175 (16)	86 (11)	
Prostate weight (gm), median (Q1–Q3)	41.0 (32.5–53.2)	41.0 (32.6–53.0)	0.81 ^c
Tumor volume (gm), median (Q1–Q3)	6.0 (3.0–11.8)	5.3 (2.8–9.9)	0.011 ^c
Positive surgical margins, <i>n</i> (%)	416 (38)	379 (47)	<0.001
Extracapsular extension, <i>n</i> (%)	210 (19)	154 (19)	0.90
Seminal vesicle invasion, <i>n</i> (%)	103 (9)	106 (13)	0.007
Positive lymph nodes, <i>n</i> (%)	37 (3)	25 (3)	0.94

Values are number (percentage) unless otherwise stated.

SD = standard deviation; BMI = body mass index; PSA = prostate specific antigen; Q1 = 25th percentile; Q3 = 75th percentile.

^a *p* value from Chi-square comparing black vs. white, except when noted.

^a Clinical stage analyzed from 1779 patients with available data.

^b *p* value from *t*-test.

^c *p* value from Wilcoxon rank-sum.

transformed), and the following pathologic features (yes/no): positive surgical margins, extracapsular extension, seminal vesicle invasion, and lymph node metastasis (yes vs. no vs. not done). To adjust for case mix, and any racial differences or different ways centers calculated tumor volume, we included a categorical term for each center. The predicted geometric means of tumor volume and PSA for white and black patients were calculated by substituting the mean value of each covariate into the fitted regression model, calculating the mean predicted value, and log-transforming the mean. To quantify the variability of this prediction, we reported the geometric mean plus and minus the standard error of the estimate ($\exp(Y \pm SE(Y))$). All statistical analyses were performed using STATA 13.0 (Stata Corp., College Station, Texas). $p < 0.05$ was used for the level of statistical significance.

3. Results

3.1. Baseline patient characteristics

Table 1 lists the clinicopathological characteristics of the patient population, as categorized by race. In the study population, there were 1104 (58%) white patients and 800 (42%) black patients. Black patients were younger at surgery (60.2 vs. 62.9 years, $p < 0.001$), had a higher median presurgical serum PSA value (6.7 vs. 6.0 ng/mL, $p < 0.001$), and more often had positive surgical margins (47 vs. 38%, $p < 0.001$) and seminal vesicle invasion (13 vs. 9%, $p = 0.007$). White patients had higher clinical stage disease ($p < 0.001$) and greater median tumor volume (6.0 vs. 5.3 gm, $p = 0.011$). Overall, pathological Gleason scores ($p < 0.001$) significantly differed between the races, but with no consistent pattern in that black men had a higher percentage of Gleason 7 (3+4 and 4+3), while white men had a higher percentage of Gleason 2-6 or 8-10 prostate cancer.

3.2. Race and tumor volume

We examined whether there were racial differences in tumor volume (Table 2). After adjusting for demographics and cancer-specific characteristics (but not PSA), white patients had smaller adjusted mean tumor volume compared to black patients (5.2 vs. 5.8 gm, $p = 0.011$). However, when we further adjusted for log-transformed PSA there was no difference in adjusted mean tumor volume (white = 5.3 vs. black = 5.6 gm, $p = 0.34$).

3.3. Race and PSA

After adjusting for demographic and cancer-specific characteristics, black men had a higher mean presurgical PSA compared to white men (7.5 vs. 6.1 ng/mL, $p < 0.001$; Table 3). To assess whether this difference was due to tumor volume differences between the races, we repeated the analysis of PSA but also adjusted for tumor volume and again there was a significant difference in mean

preoperative PSA with black men having a 16% higher median presurgical PSA versus white men (7.4 vs. 6.2 ng/mL, $p < 0.001$).

4. Discussion

It is generally accepted that black men have higher PSA values compared to white men, although there has yet to be a clinicopathologic explanation for this difference. In the current analysis, we specifically assessed whether tumor volume would explain a higher presurgical PSA in black compared to white men. We found that adjusting for tumor volume had no/little effect on racial differences in PSA with black men having a 16% higher preoperative serum PSA value compared to white men on multivariable analysis. From these findings, we conclude that the explanation for higher PSA values in black men with prostate cancer is not related to tumor volume differences and further explanations are needed.

Earlier small clinical studies have attempted to explain the PSA variation between black and white men [14,16,17]. Moul et al. analyzed 155 white and 46 black patients with clinical stage T1–T3 prostate cancer undergoing radical prostatectomy [16]. They found that black men had higher pretreatment PSA and pathologic whole mount specimen 3-D tumor volume compared to white men. However, PSA values remained significantly higher in black men even after adjusting for 3-D tumor volume, gland volume, age, stage, and Gleason sum. Black men in our study were younger and had more favorable clinical stage compared to white men. Previous retrospective [18] and autopsy [19] studies demonstrated that older men have greater tumor volume. Similarly, stage of disease is a significant factor influencing tumor volume at the time of radical prostatectomy [20]. Despite these factors, after adjusting for demographic, clinicopathologic variables and tumor volume, black men in our study had a significantly greater presurgical PSA than white men.

An alternative explanation is perhaps black men have larger prostates. We previously tested this hypothesis using both the SEARCH database and tertiary referral center dataset [8]. In our prior study, we found no difference in prostate size between the two races and on multivariable analysis, black men had 15% greater serum PSA values [8]. Thus, it appears larger prostate size cannot explain the higher PSA values in black men with prostate cancer.

Since prostate size and tumor volume at radical prostatectomy in our cohort are not responsible for a significantly increased serum PSA in black men versus white men, what may account for these observed differences? Prostate inflammation may spuriously elevate serum PSA levels; if a racial difference in the prevalence of prostatitis exists, this may contribute to racial differences in PSA. In an effort to determine whether prostate inflammation varies by race, Zhang et al. analyzed 238 RP specimens in men with clinically localized prostate cancer at Walter Reed Army Medical Center between 1993 and 1997. They noted a statistically insignificant greater degree of inflammation in RP specimens of white compared to black men, which was not related to racial variation

Table 2
Adjusted tumor volume by race.

Race	Tumor volume (gm) ^a Geometric mean ($\pm$ standard error)	Tumor volume (gm) ^b Geometric mean ($\pm$ standard error)
White men	5.2 (5.1–5.3)	5.5 (5.2–5.5)
Black men	5.8 (5.6–6.0)	5.7 (5.4–5.7)
<i>p</i> value	0.011	0.34

^a Geometric mean of tumor volume adjusted for age, year of surgery, center, pathologic Gleason sum, BMI (continuous, log-transformed), surgical margin status, seminal vesicle invasion, extraprostatic extension, lymph node involvement.

^b Adjusted for variables above and log transformed PSA.

Table 3

Predicted preoperative serum PSA value by race.

Race	PSA (ng/mL) ^a Geometric mean (±standard error)	PSA (ng/mL) ^b Geometric mean (±standard error)
White men	6.1 (6.0–6.2)	6.2 (6.0–6.3)
Black men	7.5 (7.3–7.6)	7.4 (7.2–7.6)
<i>p</i> value	<0.001	<0.001

PSA = prostate specific antigen.

^a Median preoperative serum PSA values were adjusted for age, year of surgery, center, pathologic Gleason sum, BMI (continuous, log-transformed), surgical margin status, seminal vesicle invasion, extraprostatic extension, lymph node involvement.^b Adjusted for variables above and log transformed tumor volume.

in PSA [17]. Furthermore, it has been suggested that the role of subclinical prostatic inflammation is minimal for contributing to serum PSA in men without clinically detectable prostate cancer when the PSA is greater than 4.0 ng/mL [21]. As such, an inflammatory etiology for racial differences in PSA seems unlikely.

Given that androgens regulate cellular PSA production, racial differences in androgen activity and free testosterone between races may explain PSA differences. Previous immunochemistry and biomarker studies have identified increased androgen receptor protein expression in black compared to white men for both benign [22] and malignant prostate tissue [22,23]. Additionally, black men are more likely to possess shorter CAG trinucleotide repeats in exon 1 of the androgen receptor gene [24]. Analysis of radical prostatectomy specimens demonstrates increased PSA staining and higher Gleason score prostate cancer for short alleles of the CAG repeats in the androgen receptor gene [25]. However, results from the Prostate Cancer Prevention Trial have questioned the association of CAG repeat with prostate cancer risk, although this study did not specifically address an association with PSA [26]. Furthermore, a recent meta-analysis comparing hormone levels between black and white men confirmed that free testosterone levels were significantly higher in black than white men, translating to a racial difference of free testosterone ranging from 2.5 to 4.9% [27].

Another possible cause of genetic variation in PSA levels may involve single-nucleotide polymorphisms (SNP) [28–30]. A recent study by Bentmar-Holgersson et al. looked at 1744 men from the European Male Ageing Study and investigated whether SNPs in the androgen receptor were associated with greater PSA values [28]. They found that patients with SNP rs1204038 A-allele had a 65% higher risk of PSA >3 ng/mL compared to G-allele carriers. Whether there are racial differences in expression of rs1204038 A-allele has not been reported. Also, the North Carolina-Louisiana Cancer Project reported that in 1060 black Americans and 1087 European Americans with prostate cancer, three SNPs at the kallikrein-related peptidase 3 locus were significantly associated with serum PSA levels in black Americans but not in European Americans [26]. Taken together, these genetic studies provide evidence to suggest that genetic racial differences in PSA values exist.

This study is not without limitations. As with any retrospective study, the degree to which our results are influenced by selection bias is unknown. Also, many patients were missing tumor volume data—especially patients treated in earlier years. We only examined radical prostatectomy patients within the VA. Whether similar results would be seen for non-surgically treated men or men outside the VA system is unknown. Finally, tumor volumes were not measured exactly but using estimates, and thus our findings do require validation in other datasets. Furthermore, tumor volume location in the RP specimen was not available in the VA system, which may affect racial conclusions reported in this study [31]. Strengths of the study include the large dataset with a high proportion of black men all of whom had the data necessary for analysis.

5. Conclusions

Among patients undergoing radical prostatectomy, we found that black men had higher serum PSA values compared to white men. Despite adjusting for demographic and clinical characteristics, including tumor volume, serum PSA values remain significantly higher in black men. These results suggest that racial differences in PSA are not due to tumor volume differences alone. We speculate that race-specific variations in androgen biology may contribute to differences in the PSA production, but further study is needed to fully explain racial differences in PSA levels.

Conflict of interest

No disclosures for any authors.

Authorship contribution

Zachary Klaassen—Conception and design, acquisition of data, drafting and revising article, final approval.

Lauren Howard—Conception and design, acquisition of data, analysis and interpretation of data, revising article, final approval.

Martha K. Terris—Conception and design, revising article, final approval.

William J. Aronson—Conception and design, revising article, final approval.

Matthew R. Cooperberg—Conception and design, revising article, final approval.

Christopher L. Amling—Conception and design, revising article, final approval.

Christopher J. Kane—Conception and design, revising article, final approval.

Stephen J. Freedland—Conception and design, acquisition of data, analysis and interpretation of data, drafting and revising article, final approval.

Acknowledgements

Research support was received from the Department of Veterans Affairs, the National Institutes of Health (NIH) (grant R01CA100938 to Dr. Aronson), NIH Specialized Programs of Research Excellence Grant P50CA92131-01A1 (to Dr. Aronson), the Georgia Cancer Coalition (to Dr. Terris), and NIH grant K24CA160653 (to Dr. Freedland).

References

- [1] T.O. Morgan, S.J. Jacobsen, W.F. McCarthy, D.J. Jacobson, D.G. McLeod, J.W. Moul, Age-specific reference ranges for prostate-specific antigen in black men, *N. Engl. J. Med.* 335 (1996) 304–310.
- [2] R.J. Henderson, J.A. Eastham, D.J. Culpin, Prostate-specific antigen (PSA) and PSA density: racial differences in men without prostate cancer, *J. Natl. Cancer Inst.* 89 (1997) 134–138.
- [3] J.W. Moul, I.A. Sesterhenn, R.R. Connelly, et al., Prostate-specific antigen values at the time of prostate cancer diagnosis in African-American men, *JAMA* 274 (1995) 1277–1281.

- [4] S.J. Freedland, C.L. Amling, F. Dorey, Race as an outcome predictor after radical prostatectomy: results from the Shared Equal Access Regional Cancer Hospital (SEARCH) database, *Urology* 60 (2002) 670–674.
- [5] J.A. Eastham, M.W. Kattan, Disease recurrence in black and white men undergoing radical prostatectomy for clinical stage T1–T2 prostate cancer, *J. Urol.* 163 (2000) 143–145.
- [6] C.A. Pettaway, P. Troncso, E.I. Ramirez, D.A. Johnston, L. Steelhammer, R.J. Babaian, Prostate specific antigen and pathologic features of prostate cancer in black and white patients a comparative study based on radical prostatectomy specimens, *J. Urol.* 160 (1998) 437–442.
- [7] J.N. Kabalin, J.E. McNeal, I.M. Johnstone, T.A. Stamey, Serum prostate-specific antigen and the biologic progression of prostate cancer, *Urology* 46 (1995) 65–70.
- [8] J.C. Mavropoulos, A.W. Partin, C.L. Amling, Do racial differences in prostate size explain higher serum prostate-specific antigen concentrations among black men, *Urology* 69 (2007) 1138–1142.
- [9] C.R. Mitchell, E.C. Umbreit, L.J. Rangel, E.J. Bergstralh, R.J. Karnes, Does body mass index dilute the predictive property of prostate-specific antigen for tumor volume at radical prostatectomy, *Urology* 78 (2011) 868–872.
- [10] G.F. Carvalhal, S.N. Daudi, D. Kan, Correlation between serum prostate-specific antigen and cancer volume in prostate glands of different sizes, *Urology* 76 (2010) 1072–1076.
- [11] B.D. Figler, A.M. Reuther, N. Dhar, et al., Preoperative PSA is still predictive of cancer volume and grade in late PSA era, *Urology* 70 (2007) 711–716.
- [12] M. Tsivian, L.L. Banez, C.J. Keto, African-American men with low-grade prostate cancer have higher tumor burdens: results from the Duke Prostate Center, *Prostate Cancer Prostatic Dis.* 16 (2013) 91–94.
- [13] D. Sondi, O.N. Kryvenko, H.B. Carter, A.E. Ross, J.I. Epstein, E.M. Schaeffer, Pathological examination of radical prostatectomy specimens in men with very low risk disease at biopsy reveals distinct zonal distribution of cancer in black American men, *J. Urol.* 191 (2014) 60–67.
- [14] R.F. Sanchez-Ortiz, P. Troncso, R.J. Babaian, J. Lloreta, D.A. Johnston, C.A. Pettaway, African-American men with nonpalpable prostate cancer exhibit greater tumor volume than matched white men, *Cancer* 107 (2006) 75–82.
- [15] E.H. Allott, M.R. Abern, L. Gerber, Metformin does not affect risk of biochemical recurrence following radical prostatectomy: results from the SEARCH database, *Prostate Cancer Prostatic Dis.* 16 (2013) 391–397.
- [16] J.W. Moul, R.R. Connelly, R.M. Mooneyhan, Racial differences in tumor volume and prostate specific antigen among radical prostatectomy patients, *J. Urol.* 162 (1999) 394–397.
- [17] W. Zhang, I.A. Sesterhenn, R.R. Connelly, F.K. Mostofi, J.W. Moul, Inflammatory infiltrate (prostatitis) in whole mounted radical prostatectomy specimens from black and white patients is not an etiology for racial difference in prostate specific antigen, *J. Urol.* 163 (2000) 131–136.
- [18] L. Sun, A.A. Caire, C.N. Robertson, Men older than 70 years have higher risk prostate cancer and poorer survival in the early and late prostate specific antigen eras, *J. Urol.* 182 (2009) 2242–2248.
- [19] N.B. Delongchamps, C.Y. Wang, V. Chandan, Pathological characteristics of prostate cancer in elderly men, *J. Urol.* 182 (2009) 927–930.
- [20] C.K. Poulos, J.K. Daggy, L. Cheng, Prostate needle biopsies: multiple variables are predictive of final tumor volume in radical prostatectomy specimens, *Cancer* 101 (2004) 527–532.
- [21] C. Kwak, J.H. Ku, T. Kim, Effect of subclinical prostatic inflammation on serum PSA levels in men with clinically undetectable prostate cancer, *Urology* 62 (2003) 854–859.
- [22] K.E. Gaston, D. Kim, S. Singh, O.H. Ford 3rd, J.L. Mohler, Racial differences in androgen receptor expression in men with clinically localized prostate cancer, *J. Urol.* 170 (2003) 990–993.
- [23] H.S. Kim, D.M. Moreira, J. Jayachandran, Prostate biopsies from black men express higher levels of aggressive disease biomarkers than prostate biopsies from white men, *Prostate Cancer Prostatic Dis.* 14 (2011) 262–265.
- [24] R.A. Irvine, M.C. Yu, R.K. Ross, G.A. Coetzee, C.A.G. The, and GGC microsatellites of the androgen receptor gene are in linkage disequilibrium in men with prostate cancer, *Cancer Res.* 55 (1995) 1937–1940.
- [25] G. Rodriguez-Gonzalez, S. Cabrera, R. Ramirez-Moreno, Short alleles of both GGN and CAG repeats at the exon-1 of the androgen receptor gene are associated to increased PSA staining and a higher Gleason score in human prostatic cancer, *J. Steroid Biochem. Mol. Biol.* 113 (2009) 85–91.
- [26] D.K. Price, C.H. Chau, C. Till, Androgen receptor CAG repeat length and association with prostate cancer risk: results from the prostate cancer prevention trial, *J. Urol.* 184 (2010) 2297–2302.
- [27] A. Richard, S. Rohrmann, L. Zhang, Racial variation in sex steroid hormone concentration in black and white men: a meta-analysis, *Andrology* 2 (2014) 428–435.
- [28] M. Bentmar-Holgersson, A. Giwerzman, A. Bjartell, Androgen receptor polymorphism dependent variation in prostate specific antigen concentrations of European men, *Cancer Epidemiol. Biomarkers Prev.* 23 (2014) 2048–2056.
- [29] J.T. Bensen, Z. Xu, G.J. Smith, J.L. Mohler, E.T. Fontham, J.A. Taylor, Genetic polymorphism and prostate cancer aggressiveness: a case-only study of 1536 GWAS and candidate SNPs in African-Americans and European-Americans, *The Prostate* 73 (2013) 11–22.
- [30] W. Xue, R.A. Irvine, M.C. Yu, R.K. Ross, G.A. Coetzee, S.A. Ingles, Susceptibility to prostate cancer: interaction between genotypes and androgen receptor and prostate-specific antigen loci, *Cancer Res.* 60 (2000) 839–841.
- [31] D. Sondi, O.N. Kryvenko, H.B. Carter, A.E. Ross, J.I. Epstein, E.M. Schaeffer, Pathological examination of radical prostatectomy specimens in men with very low risk disease at biopsy reveals distinct zonal distribution of cancer in black American men, *J. Urol.* 191 (2014) 60–67.