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Original Article

Racial disparities in biochemical recurrence of prostate cancer

Karishma Gupta[1,2], Vidushri Mehrotra[3], Pingfu Fu[4], Kyle Scarberry[1,2], Gregory T MacLennan[5], Sanjay Gupta[1,2,5,6,7,8,9]

[1]Urology Institute, University Hospitals Cleveland Medical Center, Cleveland, Ohio 44106, USA; [2]Department of Urology, Case Western Reserve University School of Medicine, Cleveland, Ohio 44106, USA; [3]College of Arts and Sciences, Case Western Reserve University, Cleveland, Ohio 44106, USA; [4]Department of Population and Quantitative Health Sciences, Case Western Reserve University, Cleveland, Ohio 44106, USA; [5]Department of Pathology, Case Western Reserve University School of Medicine, Cleveland, Ohio 44106, USA; [6]Department of Pharmacology, Case Western Reserve University, Cleveland, Ohio 44106, USA; [7]Department of Nutrition, Case Western Reserve University, Cleveland, Ohio 44106, USA; [8]Division of General Medical Sciences, Case Comprehensive Cancer Center, Cleveland, Ohio 44106, USA; [9]Department of Urology, Louis Stokes Cleveland Veterans Affairs Medical Center, Cleveland, Ohio 44106, USA

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Abstract: Background: The aim of this study was to determine the biochemical recurrence among Black and White American men with grade group 2-5 prostate cancer managed primarily by radical prostatectomy (RP). Methods: This was a single-institution, retrospective study evaluating biochemical recurrence by self-identified race. 163 patients who underwent RP at the University Hospitals Cleveland Medical Center between 2015-2021 were analyzed for racial differences in age at diagnosis, clinical stage, and preoperative serum prostate-specific antigen (PSA). Patients were followed for PSA recurrence (PSA ≥ 0.2 ng/ml). Multivariate analysis was used to determine clinical and pathologic variables that were significant in predicting biochemical recurrence after RP and to determine whether race was an independent predictor of biochemical recurrence-free survival (BCRFS). Results: Of 163 patients, 82 (50.3%) were Black Americans and 81 (49.7%) were White Americans with a median age of 62.7 ranging between 38.7 to 76.3 years. The grade-specific distribution of cancer 3+4 was 54.9% *versus* 65.4%; 4+3 was 25.6% *versus* 30.9%; 4+4 was 7.3% *versus* 2.5%; 4+5 was 12.2% *versus* 1.2% in Black American and White American men. Univariate analysis of BCRFS using Kaplan-Meier method demonstrated a significant difference among levels of Gleason score between Black Americans and White Americans (P = 0.041). Multivariable analysis after controlling the effects of age, Gleason score exhibited no significant difference of BCRFS comparing Black and White American men (P = 0.145). Specifically, the hazard of biochemical recurrence among Black Americans was 1.6 times (95% CI: 0.85-3.02) compared to White Americans (P = 0.145). Conclusion: Our study demonstrated a significant difference in BCRFS between Black and White American patients. Additional studies with larger sample size underlying this clinical disparity are warranted.

Keywords: Racial difference, prostate-specific antigen, prostate cancer, gleason score, biochemical recurrence

Introduction

Prostate cancer is the most prevalent malignancy among adult men and is the fifth highest cause of cancer mortality in the United States [1]. Due to the high disease burden of prostate cancer, it is important to characterize disparities in diagnosis, management, and recurrence in these patients. Racial differences in prostate cancer incidence and mortality are well described in the literature; the incidence in prostate cancer is approximately 66% greater in Black men compared to White men, and mortality rates for Black American men is 2-3 times higher [1]. These disparities are complex in nature and include biological determinants such as genetic susceptibility, presence of comorbidities, socioeconomic status, and cultural components [2, 3].

In contrast to this trend in incidence and mortality in prostate cancer, racial disparities in bio-

Table 1. Patient characteristics

	Black American (n = 82)	White American (n = 81)	*p*-value
Age (year)	61.1 (7.4)	63 (6.2)	0.085
Gleason score			
3+4	45	53	
4+3	21	25	0.016[£]
4+4	6	2	
4+5	10	1	

[£]When grouping 4+4 and 4+5 together, *p*-value = 0.007.

chemical recurrence are less understood. Determining biochemical recurrence after local treatment is critical in identifying treatment failure and pursuing salvage therapy. However, there is disagreement in the literature about the role of race as a predictor for biochemical recurrence after prostatectomy. Jeffers *et. al*. (2017) applied a statistical learning model method to a cohort of 1276 patients undergoing radical prostatectomy to evaluate the most important predictors for biochemical recurrence. They found that preoperative PSA levels were the most significant predictor, whereas race was not [4]. In another study, researchers stratified Black and White men by risk categories for biochemical recurrence and followed them for 20 years. They found that Black American men in the low-risk category had similar risk of biochemical recurrence as their higher risk White American counterparts [5]. This finding indicates that despite stratification into different risk groups, which should be better predictors of biochemical recurrence, there was still a racial disparity present with Black American men having greater rates of biochemical recurrence and a shorter interval between treatment and failure. Another study evaluating the implications of race on time to recurrence with the SEARCH database cohort found that Black American men were more likely to have biochemical recurrence, but this relationship was mitigated once clinical and pathological features were included in the model [6]. This study alludes to the potential complexity and nuance of the relationship between racial disparities in biochemical recurrence for prostate cancer. Therefore, further study in this area is of clinical relevance because of implications in pursuing ongoing treatment to prevent metastatic disease [7]. Knowing whether racial disparity exists in biochemical recurrence after radical prostatectomy would allow clinicians to make more appropriate therapy decisions throughout the course of disease management.

Racial disparities between Black American men and White men for biochemical recurrence of prostate cancer is continuously debated in the literature. There is evidence indicating that Black American patients are at higher risk of biochemical recurrence, while on the other hand there is also evidence indicating that race does not impact biochemical recurrence [8-10]. Given the conflicting results of race as a predictor of biochemical recurrence, we sought to evaluate this relationship in our institution. Our study evaluates biochemical recurrence free survival (BCRFS) for prostate cancer patients with self-identified race who underwent radical prostatectomy.

Materials and methods

Analytic cohort and data collection

This current research is a retrospective observational cohort study approved by the University Hospitals Cleveland Medical Center (UHCMC) Institutional Review Board (UH IRB#20190533), and the need for written informed consent was waived. Data was obtained among men who were managed by radical prostatectomy (RP) at University Hospitals Cleveland Medical Center from February 2013 to July 2020. A total of six different surgeons performed RP in this patient cohort.

Age and self-reported race were extracted from institutional data. Additional patient data included PSA at diagnosis, clinical stage, biopsy grade, pathologic TNM stage, pathologic grade. The TNM staging system was utilized to classify disease stage and the Gleason grading system was used to grade the biopsy specimens (**Table 1**). Biopsy and prostatectomy specimens were reviewed at University Hospitals by expert genitourinary pathologists. Men were excluded from the final cohort if there was missing data or incomplete follow-up after their surgical treatment. Eligibility criteria included a diagnosis of prostate cancer, treatment of prostate cancer by radical prostatectomy, self-identification as either white or black,

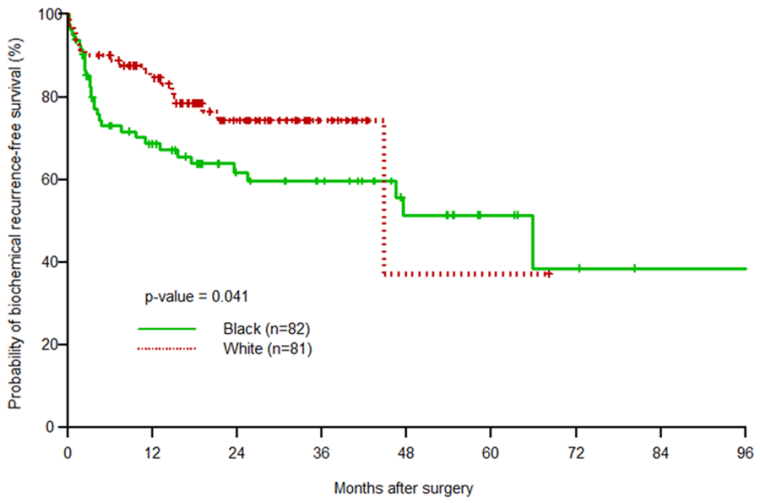

Figure 1. Kaplan-Meier estimation of biochemical recurrence free survival by race.

presence of pathologic data and post-operative follow-up. In total, 163 patients were identified, of whom 82 (50.3%) were black and 81 (49.7%) were white. Men with missing data points or unknown follow-up information were excluded from this analysis (n = 10). The following pathologic findings were evaluated: positive surgical margins, Gleason score, surgical margins, extracapsular extension, seminal vesicle invasion, and lymph node invasion. Post-operative follow-up consisted of PSA measurements. The primary outcomes evaluated during follow-up was biochemical recurrence following RP, which was defined as an initial PSA value of ≥ 0.2 ng/ml confirmed by a subsequent PSA of ≥ 0.2 ng/ml, in accordance with the American Urological Association Guidelines. The initial post-operative PSA values were obtained after 6 weeks to allow for washout of the residual serum PSA.

Statistical analysis

Descriptive statistics were performed using T-tests for continuous variables, Wilcoxon-Mann-Whitney rank sum tests for non-normally distributed continuous variables, and chi-squared tests for categorical variables. Biochemical recurrence-free survival (BCRFS) (time 0 was defined as the date of RP) were compared using the Kaplan-Meier method with Wilcoxon test for differences between the two cohorts [11]. All Kaplan-Meier analyses were censored at the date of last known follow-up. The effect of race on BCRFS was further examined using Cox regression controlling the effects of preoperative variables such as age, year of surgery, biopsy Gleason score, and clinical stage [12]. Univariate and multivariate analyses were performed comparing the primary outcome of BCRFS between the two cohorts. All statistical analyses were performed using SPSS software (version 16.01). *P*-values <0.05 (two-sided) were considered statistically significant.

Results

In total, 163 patients were included in the study comprising of 82 (50.3%) Black Americans and 81 (49.7%) White Americans. The median age for the study population was 62.7, ranging between 38.7 to 76.3 years. The median follow-up was 18 months, ranging from 0.23 to 100.46 months.

Univariate analysis of BCRFS using Kaplan-Meier method demonstrated a significant difference of BCRFS between Black and White men (p = 0.041) (**Figure 1**). There was a significant difference of BCRFS among levels of Gleason score between Black and White men with poor survival in the highest Gleason grade (**Figure 2**). Results from the multivariable analysis are provided in **Table 2**. After controlling the effects of age, year of surgery, biopsy Gleason score, and clinical stage, there was no significant difference of BCRFS comparing Black American and White men (P = 0.145). Specifically, the hazard of having biochemical recurrence for Black Americans was 1.6 times (95% CI: 0.85-3.02) of the hazard of having biochemical recurrence for White American men (P = 0.145).

Discussion

In our study, we found a significant difference between biochemical recurrence free survival (BCRFS) among Black American and White patients in the Kaplan-Meier estimation. However, once the multivariate analysis was

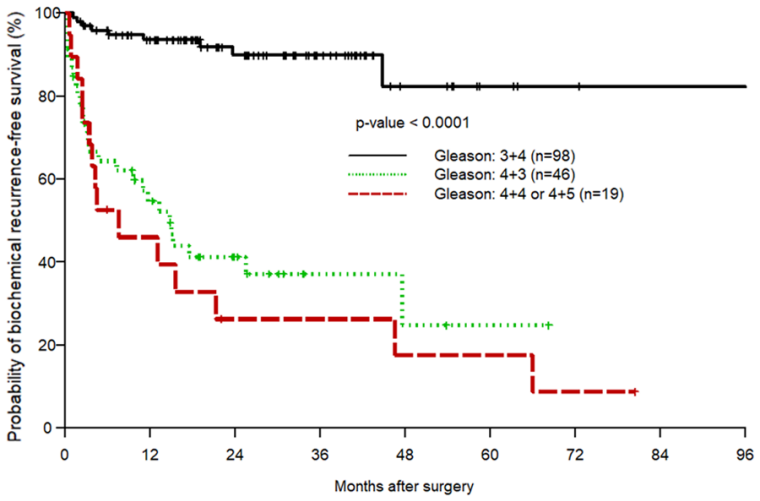

Figure 2. Kaplan-Meier estimation of biochemical recurrence free survival by Gleason score.

Table 2. Multivariable Cox regression analysis on biochemical recurrence free survival

	HR$^{£}$ (95% CI)	*p*-value
Race (Black vs. White)	1.6 (0.85, 3.02)	0.145
Age (per 1 year increase)	1.02 (0.97, 1.06)	0.436
Gleason score		
3+4 vs. 4+4 and 4+5 combined	0.1 (0.04, 0.24)	<0.0001
4+3 vs. 4+4 and 4+5 combined	0.92 (0.46, 1.82)	0.811

HR - Hazard Ratio; CI - Confidence Interval. HR$^{£}$, adjustment of factors between race, age and Gleason grade.

performed which controlled for age, year of surgery, biopsy Gleason score, and clinical stage, this effect was mitigated and no significant difference in BCRFS was observed. Patient data (**Table 1**) also demonstrated that Black patients had higher rates of NCCN high risk (Gleason Grade 4 or Gleason 4+4, Gleason Grade 5 or Gleason 4+5) compared to their White counterparts. Sub analysis by NCCN risk groups revealed that high grade cancer had lower BCRFS. These results indicate that the effect of race on BCRFS may not be a direct causal relationship, rather Gleason score may be a key mediator of this relationship.

The results of this study are in line with the SEARCH database cohort study, which also found that the relationship between race and biochemical recurrence was mitigated once clinical and pathological features were controlled for, including age and grading of the cancer [6]. Additionally, it is well demonstrated in the literature that Black American patients present with higher Gleason score prostate cancer compared to White patients [13, 14]. The results of the current study may suggest that pathological factors such as Gleason score may be a better predictor of BCRFS compared to race on its own. Since Black American men are known to present with higher grade cancer, Gleason score may be mediating the relationship between race and biochemical recurrence in some of the previous studies that found a significant effect. Further studies should focus on evaluating variables which may mediate the relationship between race and biochemical recurrence for prostate cancer patients. For example, while several papers in the existing body of literature hypothesize that biological factors underlie more aggressive prostate cancer in Black men, the exact differences in genetic or molecular components have yet to be validated. Hence, additional study in this area can help highlight factors that will truly impact prognosis, or drive diagnostic and therapeutic interventions. Future studies should also stratify the relationship between race and biochemical recurrence-based Gleason score and type of treatment (ex: radical prostatectomy *versus* brachytherapy). This will allow for further evaluation of risk categories for recurrence within multiple treatment options.

We acknowledge that our study has several limitations. First, our study is retrospective in nature and reflects the experiences of a single institution, which may introduce the potential of selection bias and limit generalizability. Second, the variables evaluated in this study were limited and only included: BCRFS, age, race, and Gleason score. Therefore, it could have been beneficial to socioeconomic variables, intensity of screening before diagnosis, prostate cancer specific survival, and overall survival between Black American and White patients in order to broaden the scope of the potential effect of race in prostate cancer outcomes. Additionally, our study population only

included 163 patients who underwent radical prostatectomy. This smaller sample size with patients who underwent the same procedure may create a homogenous study sample in which the results may not apply to patients who undergo other therapies at other locations.

The strengths of our study include evenly matched cohorts from a longitudinal study period incorporating data from all the surgeons who performed radical prostatectomy during the study period within our institution. A study strength attributable to the single-center study design was consistency in central pathology review of biopsy and surgical specimens throughout the study period.

In conclusion, our study found that among Black men and White men undergoing radical prostatectomy, Black American men were at increased risk of BCRFS in univariate but not multivariate analysis. Inclusion of age and Gleason score as covariates mitigated this relationship. Further studies are needed to better characterize the role of race in prostate cancer prognosis and disease recurrence.

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Disclosure of conflict of interest

None.

Address correspondence to: Dr. Sanjay Gupta, Department of Urology, The James and Eilleen Dicke Research Laboratory, Case Western Reserve University, 10900 Euclid Avenue, Cleveland, Ohio 44106, USA. Tel: (216) 368 6162; Fax: (216) 368 0213; E-mail: sanjay.gupta@case.edu

References

[1] Cronin KA, Lake AJ, Scott S, Sherman RL, Noone AM, Howlader N, Henley SJ, Anderson RN, Firth AU, Ma J, Kohler BA and Jemal A. Annual report to the nation on the status of cancer, part I: national cancer statistics. Cancer 2018; 124: 2785-2800.

[2] Freedland SJ and Isaacs WB. Explaining racial differences in prostate cancer in the United States: sociology or biology? Prostate 2005; 62: 243-252.

[3] Vidal AC, Oyekunle T, Howard LE, De Hoedt AM, Kane CJ, Terris MK, Cooperberg MR, Amling CL, Klaassen Z, Freedland SJ and Aronson WJ. Obesity, race, and long-term prostate cancer outcomes. Cancer 2020; 126: 3733-3741.

[4] Jeffers A, Sochat V, Kattan MW, Yu C, Melcon E, Yamoah K, Rebbeck TR and Whittemore AS. Predicting prostate cancer recurrence after radical prostatectomy. Prostate 2017; 77: 291-298.

[5] Faisal FA, Sundi D, Cooper JL, Humphreys EB, Partin AW, Han M, Ross AE and Schaeffer EM. Racial disparities in oncologic outcomes after radical prostatectomy: long-term follow-up. Urology 2014; 84:1434-1441.

[6] Hamilton RJ, Aronson WJ, Presti JC Jr, Terris MK, Kane CJ, Amling CL and Freedland SJ. Race, biochemical disease recurrence, and prostate-specific antigen doubling time after radical prostatectomy: results from the SEARCH database. Cancer 2007; 110: 2202-2209.

[7] Artibani W, Porcaro AB, De Marco V, Cerruto MA and Siracusano S. Management of biochemical recurrence after primary curative treatment for prostate cancer: a review. Urol Int 2018; 100: 251-262.

[8] Hart KB, Wood DP Jr, Tekyi-Mensah S, Porter AT, Pontes JE and Forman JD. The impact of race on biochemical disease-free survival in early-stage prostate cancer patients treated with surgery or radiation therapy. Int J Radiat Oncol Biol Phys 1999; 45: 1235-1238.

[9] Freedland SJ, Jalkut M, Dorey F, Sutter ME and Aronson WJ. Race is not an independent predictor of biochemical recurrence after radical prostatectomy in an equal access medical center. Urology 2000; 56: 87-91.

[10] Yamoah K, Deville C, Vapiwala N, Spangler E, Zeigler-Johnson CM, Malkowicz B, Lee DI, Kattan M, Dicker AP and Rebbeck TR. African American men with low-grade prostate cancer have increased disease recurrence after prostatectomy compared with Caucasian men. Urol Oncol 2015; 33: 70, e15-22.

[11] Kaplan EL and Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc 1958; 53: 457-481.

[12] Cox DR. Regression models and life-tables. J R Stat Soc Series B Stat Methodol 1972; 34: 187.

[13] Aziz H, Rotman M, Thelmo W, Chen P, Choi KN, Khil SU, Laungani GB, Brandys M, Ayr G and Macchia RJ. Radiation-treated carcinoma of prostate. Comparison of survival of black and white patients by Gleason's grading system. Am J Clin Oncol 1988; 11: 166-171.

[14] Woods SE, Messer J and Engel A. The influence of ethnicity on Gleason score. Journal of Men's Health 2008; 5: 314-317.