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Impact of Race on Survival in Patients With Clinically Nonmetastatic Prostate Cancer who Deferred Primary Treatment

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Abstract

BACKGROUND—Prostate cancer (PCa) racial disparity studies typically focus on survival differences after curative treatment. The authors of this report hypothesized that comparing mortality rates between African American (AA) and Caucasian American (CA) patients who deferred primary treatment for clinically nonmetastatic PCa may provide a better assessment of the impact of race on the natural course of PCa.

METHODS—The pathology database of the New York Veterans Administration Medical Center (VAMC), an equal access-of-care facility, was searched for patients with biopsy-proven PCa. Inclusion criteria included 1) no evidence of metastatic disease or death within 3 years after diagnosis, 2) no primary treatment, and 3) a minimum of 5 years of follow-up for survivors.

RESULTS—In total, 518 patients met inclusion criteria between 1990 and 2005. AA patients were younger ($P=.02$) and had higher median prostate-specific antigen (PSA) levels ($P=.001$) at the time of diagnosis compared with CA patients. In a multivariate model, higher Gleason score and PSA level were associated with increased mortality ($P=.001$ and $P=.03$, respectively), but race was not a predictor of death from PCa.

CONCLUSIONS—The current data suggested that race did not have a major impact on survival in patients with PCa who deferred primary treatment for clinically nonmetastatic disease.

Keywords

prostate cancer; race; survival; surveillance; nonmetastatic

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CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

INTRODUCTION

Several groups have sought to identify differences in outcome between African American (AA) and Caucasian American (CA) patients with prostate cancer (PCa) who receive primary treatment. Those studies have demonstrated consistently that, with time, differences in outcome by race diminished when adjusted for pathologic features.¹⁻⁴ Because the Veterans Administration Medical Center (VAMC) New York Harbor Healthcare System is a US government health center for veterans, the management and care provided to all patients is standardized. It is noteworthy that a relatively high percentage of AA patients present for treatment at the VAMC, as reported previously by several groups, including ours.⁵⁻⁸

We previously reported that, at our equal-access institution, whereas disparities in pathologic stage, pretreatment prostate-specific antigen (PSA), and age at diagnosis between AA and CA patients narrowed over time, AA patients continued to have significantly worse Gleason scores, suggesting that biologic factors may have a role in the poor outcome of men with PCa in this population.⁵ The impact of socioeconomic factors, such as income, literacy, and access to care, on the disparities observed in PCa outcome between AA and CA patients has been extensively studied.⁹⁻¹¹ Data suggest that, even when controlling for socioeconomic factors, AA ancestry remained an independent predictor of disease recurrence or mortality.⁹ Disparities in education and literacy have been identified as predictive of poorer outcome from PCa.¹² In this regard, we recently examined AA patients with different income and education levels and reported that socioeconomic factors had a limited impact on PSA recurrence in AA men who underwent radical prostatectomy (RP).¹³

The natural course of newly diagnosed PCa is difficult to predict, because very little is known about its progression when untreated. RP and radiotherapy (XRT) have emerged as the standard of care, and several studies have indicated decreasing trends toward watchful waiting, an approach with noncurative intent.^{14, 15} Studies also have suggested that many newly diagnosed PCas are indolent and may not progress clinically to the degree that curative intervention is required.¹⁶⁻¹⁸ Curative attempts for these patients may represent invasive over treatment, resulting in an increased risk of significant morbidity.¹⁶ In the current study, we sought to determine differences in survival between AA and CA patients diagnosed with clinically nonmetastatic PCa who deferred primary treatment in an attempt to assess the contribution of racial differences on the natural progression of PCa.

MATERIALS AND METHODS

Study Population

We evaluated men who were diagnosed with PCa between 1990 and 2005 at the Brooklyn and Manhattan Campuses of the VAMC. Inclusion criteria included: 1) biopsy-proven PCa, 2) no evidence of metastatic disease or death within 3 years after diagnosis, 3) no treatment with curative intent (RP or XRT), and 4) a minimum of 5 years of follow-up for survivors. We included patients who were diagnosed in 1990 to ensure availability of documented baseline PSA levels after the US Food and Drug Administration approved PSA testing and its widespread use in the following years. We concluded in 2005 to ensure a minimum of 5 years of follow-up data.

The VAMC is an equal access-of-care facility. All patients had PSA evaluations and digital rectal examination (DRE) at age 50 years by their primary care physician at the VAMC. If PSA >4 ng/mL and/or DRE revealed abnormal findings, then patients were referred to the urology clinic for assessment and biopsy. The patients who were included in this study were identified with biopsy-proven, positive PCa; and imaging studies (bone scans and computed tomography [CT] scans of the abdomen and pelvis) did not reveal image-based evidence of

PCa progression. Patients declined definitive treatment and requested watchful waiting only. Patients who were diagnosed with clinically nonmetastatic PCa and who did not undergo RP or receive XRT (including brachytherapy and external-beam radiotherapy) were considered to have not been treated with curative intent. Clinically nonmetastatic PCa was defined based on lack of evidence of extension beyond the prostate using both CT scans of the abdomen and pelvis as well as bone scans.

Palliative treatments, including transurethral resection of the prostate (TURP) to relieve urinary obstruction, hormone therapy, palliative radiotherapy to relieve local PCa progression or bone metastases, or chemotherapy and combinations thereof were given at least 1 year after a biopsy-proven diagnosis of PCa. Use of 5-alpha-reductase inhibitors to relieve symptoms of prostatic hyperplasia was not considered an exclusion criterion. The study was approved both by the Institutional Review Board and by the Office of Research and Development of the Veterans Administration New York Harbor Healthcare System.

The clinicopathologic variables analyzed included: race, age at diagnosis, PSA at diagnosis, Gleason score, type of treatments, diagnosis of other cancer, duration of follow-up, and status at last follow-up. Patients self-identified their race during the hospital registration process, which was confirmed further by a review of the clinical notes in the computerized medical chart. Patients were categorized as either "AA," or "CA," or "other." Patients of African or African Caribbean origin were considered AAs. Patients whose race did not definitively fall into 1 of these categories or who self-identified as "other" were excluded. Age at diagnosis was calculated from the date of birth to the date of the first positive biopsy. PSA levels at diagnosis were recorded and grouped into 3 categories: <10 ng/mL, 10 to 100 ng/mL, and >100 ng/mL. Pathologic Gleason scores in all patients were determined by the centralized pathology review process (P.L.) and grouped according to scores <7, 7, and >7. Treatment information was extracted from electronic medical charts and progress notes. Patient status at the time of data retrieval, including date of last follow-up, living/deceased, and cause of death were determined by electronic medical chart review. The date of death routinely is verified independently in the medical record electronic system, which has been in place at the VAMC since 1996. In cases of equivocal cause of death in the medical record, final designation was determined by an oncologist (I.O.) after extensive and exhaustive analysis of all hospital documentation. Causes of death that could not be assigned to any of these categories were designated as "unclassified." It is worth noting that the VAMC employs a computerized data system that takes full advantage of its comprehensive care. VAMC patients are likely to be screened, diagnosed, and treated within the VAMC medical system, ensuring continuity and quality of data. Follow-up information was obtained by reviewing electronic medical records from standard examinations conducted at the VAMC, and there was no difference in the follow-up of PCa based on the patient's race.

Statistical Analysis

The primary outcome of our study was death from PCa or from other competing causes with consideration of information specifically on race but also on patient age, Gleason score, PSA, type of treatment, and occurrence of other cancer. Differences in demographic and clinical information between the AA and CA men were tested using *t* tests for continuous variables, such as age, and using the chi-square test or the Fisher-exact test (when any cell frequencies were <5) for categorical variables, such as Gleason score and type of treatment. The cumulative incidence functions (CIF) were calculated by using *cmprsk*CIFs in the R software package (R Foundation for Statistical Computing, Vienna, Austria) and are plotted for the overall group and for all covariates by their respective categories for death because of PCa. Univariate and multivariate Cox regression analyses with competing risks were performed to identify variables predictive of death from PCa using STATA version 11 (STATA, College Station, Tex).^{19, 20} Subhazard ratios (SHRs), their 95% confidence

interval, and corresponding p-values also were reported. *P* values for the subhazard ratios were computed with the Gray test.¹⁶ The median follow-up for the entire cohort was computed based on survivors (n=193).

RESULTS

African American Patients Present at a Younger Age and With Higher PSA When Compared With Caucasian American Patients

Table 1 lists the characteristics of both groups and indicates that AA patients were younger at the time of diagnosis (72.0 years vs 73.6 years; *P*=.02) and had a significantly higher median PSA (18.0 ng/mL vs 11.5 ng/mL; *P*=.001). There also was a trend toward statistically significant differences in Gleason score between AA patients and CA patients (*P*=.08).

Nonprostate Cancer-Related Illness Was the Leading Cause of Death for Both African Americans and Caucasians Americans

At the end of follow-up, more AA patients had died of PCa than CA patients (14% vs 11%, respectively), although the difference was not statistically significant (*P*=.81). After a median follow-up of 8.1 years, 193 patients (37%) remained alive with PCa, 64 patients (13%) had died of PCa, 203 patients (39%) had died of other causes, and 58 patients (11%) had died of unclassified causes (Table 1). Both AA patients and CA patients were more than twice as likely to die from other causes compared with PCa-related causes of death (AA, 39%; CA, 39%). It is noteworthy that, when the median follow-up was compared between the 2 groups, a *P* value of .89 indicated almost no difference.

Race Is Not a Significant Predictor of Mortality in Patients Treated With Noncurative Intent

AA men had a higher probability of death compared with CA men at all time points, but the difference was not statistically significant (*P*=.42) (Table 2, Fig. 1A). Factors that were associated significantly with worse survival included higher PSA (Table 2, Fig. 1B), higher Gleason score (Table 2, Fig. 1C), and any palliative treatment intervention versus follow-up with no intervention only (*P*<.001) (Table 2) in univariate analysis. A multivariate Cox regression model with competing risk revealed that the only 2 variables that remained significant predictors of mortality were a Gleason score of 7 (hazard ratio [HR], 2.59; 95% confidence interval [CI], 1.14–5.89; *P*=.02), a Gleason score >7 (HR, 4.02; 95% CI, 1.75–9.22; *P*=.001), and a PSA level >100 ng/mL (HR, 2.59; 95% CI, 1.14–5.89; *P*=.03) (Table 2). Race, age, and treatment intervention were not significant predictors of PCa-related death on multivariate analysis. Nevertheless, because the deaths were few, the model estimates should not be over interpreted.

Caucasian Americans Had Slightly Longer Follow-Up Compared With African Americans in the Subset of Patients who Did Not Receive any Form of Palliative Prostate Cancer Treatment

We also compared mortality between AA patients and CA patients who did not receive any PCa-related palliative intervention at any point during follow-up. The cohorts of men who ultimately underwent TURP (n=47), received palliative XRT (n=83), or received hormones (n=306) for symptomatic relief (at least 1 year postdiagnosis) were excluded from the subset analysis.

The baseline clinicopathologic features and survival data for this subset (n=158) are presented in Table 3. AA patients in this no-treatment subset presented with a significantly higher PSA than CA patients (7.6 ng/mL vs 6.0 ng/mL, respectively; *P*=.03), but there was no significant difference in Gleason score between racial groups (*P*=.95) (Table 3). The

majority of patients from both racial groups in this no-treatment subset had Gleason scores <7 (AA, 75%; CA, 77%). CA patients had a slightly longer follow-up than AA patients (6.7 years vs 6.4 years, respectively), but the difference was not statistically significant ($P=.42$). In this cohort, the cumulative incidence of PCa at 4 years was 1.6% in AAs compared with 0% in CAs, but very few patients of either racial group died from PCa (AA, $n=3$; CA, $n=1$).

DISCUSSION

Several studies have reported that AAs are more likely to elect for deferred treatment than CAs when controlling for stage and grade of disease and also are more likely to receive fewer interventions during the watchful-waiting period.^{21, 22} However, to our knowledge, no study has examined the impact of race on survival in patients with PCa who deferred primary treatments. In our study of AA and CA patients who were managed at the VAMC in New York, an equal-access facility, we observed that AA patients were younger and presented with higher PSA values compared with CA patients. However, race was not an independent variable for PCa-related mortality. Our data revealed that high PSA and Gleason score, the 2 factors most strongly associated with outcome in patients who are treated with curative intent,^{23, 24} remained significant factors in patients who forego such treatment.

Watchful waiting remains controversial, because as it is not clear which patients should be considered to have low-risk PCa. Surveillance criteria according to Epstein et al. recommend PSA <10 ng/mL, clinical T1 or T2a tumors, a PSA density <0.15 ng/mL per gram, <1 of 3 biopsy cores positive, and absence of Gleason pattern 4 and 5 on biopsy for defining low-risk PCa.^{25, 26} Other studies have included patients with Gleason scores as high as 8, diagnostic PSA levels >20 ng/mL, <50% biopsypositive cores, and clinical T3 disease.^{26–29} Bastian et al. identified 8 different definitions of low-risk PCa.²⁷ In addition, there is a lack of consensus regarding the appropriate follow-up interval for surveillance. The literature reflects at least 7 different time frames for each of the following clinical tests: DRE, PSA, rebiopsy, and transrectal ultrasound.^{27, 30–34} Increases in PSA screening have resulted in more patients of both races being diagnosed with PCa and referred to physicians for discussion of treatment options.³⁵ However, our results suggest that the differences between these criteria are negligible and that the overall risk of PCa mortality may be overstated. In fact, the majority of both AA patients and CA patients in our total sample would be categorized as high risk according to the standards mentioned above. Thus, it is reasonable to assume that these patients would be indicated for curative intent; yet, within a 5-year follow-up period, very few actually died a PCa-related death. It is noteworthy that we did not attempt to identify criteria for active surveillance or its impact on race. Our objective was to examine the impact of race on individuals who have chosen to defer primary treatment as the closest clinical scenario to the natural course of the disease, which, to our knowledge, has not been examined before.

Several points need to be considered in interpreting our data. The first, and most important, is the *reason* patients decided to defer primary treatment for their clinically nonmetastatic PCa. Although it is very difficult to assess comorbidity scores for a study cohort in retrospect, a review of the notes revealed that all treatment options, including XRT, were discussed with the patients. This leads us to assume that patients deferred primary treatment because of concerns of the effect of treatment on their quality of life (potency and urinary incontinence) rather than baseline comorbidity. Nevertheless, the lack of documentable data on comorbidities is a limitation of the study. In fact, we have attempted to extract this information from reviewing the patient's electronic charts; however, wide variations in descriptions complicated the generation of objective, measurable data that can be categorized. Second, it is possible that there is a true difference between PCa progression in

AA patients and CA patients that might be revealed with longer follow-up of our cohort. We argue that long follow-up is needed when investigators compare mortality between the screened population and those who are not screened.^{36–38} Our study cohort, however, is fundamentally different. All patients were screened by the same medical staff in the same institution, and we are reporting on all patients who were diagnosed with PCa. In fact, the median follow-up in our study is much longer than that in the published data.^{31, 39, 40}

We observed differences between the larger study cohort and the subset that included patients who did not receive any form of treatment and only underwent watchful waiting. Both AA patients and CA patients in that subset were younger, had less comorbidity, and presented with lower PSA levels and Gleason scores. These clinicopathologic features suggest that patients in the subset were appropriate candidates for conventional “watchful waiting.” It is important to note that these tumors, both indolent and completely unaltered by treatment, closely approximate the natural course of PCa. In this subgroup, we did observe that the median survival of AA patients was >3 years shorter than that of CA patients. Because there were only 4 PCa-related deaths in this cohort (n=158), however, we are unable to draw firm conclusions regarding the impact of PCa on the observed difference in survival. It is possible that biologic differences between AA tumors and CA tumors are present early in the disease course and, thus, can adversely affect the outcome of patients who have tumors otherwise deemed slow growing and not clinically relevant.

The large percentage of deaths from non-PCa-related illness among both AAs and CAs revisits the long-held conclusion that most patients who have PCa die *with* disease and not *from* it. In this regard, previously published studies that compared conservative management of PCa with mortality excluded patients aged >75 years, patients with baseline PSA values >100 ng/mL, those with significant comorbidities, and those diagnosed with other cancers associated with a high risk of death.^{41–43} Those studies concurred with our findings of the prognostic importance of both the PSA level and the Gleason score in death from PCa. The cohorts in those previous studies differed from the PCa patient population studied at the VAMC, in which 36% were aged >75 years, 9% presented with PSA levels >100 ng/mL, and 24% had been diagnosed with other cancers. It is important to note that, despite the high percentage of secondary cancer diagnoses, <12% identified another cancer as the cause of death.

Although the high prevalence of serious comorbidities muddles efforts to assess the natural course of PCa, it is consistent with the aging population most affected by PCa and represents realistic concerns for both patients and health care providers. Recent studies suggest that the risks and complications associated with curative interventions are related more to comorbidities than to chronological age,⁴⁴ although, in clinical practice, age overwhelmingly influences treatment decisions.⁴⁵ These treatments may include palliation by hormone therapy, which is associated with an increased risk of metabolic syndrome, bone fractures, and cardiovascular mortality. The high percentage of patients in our cohort with Gleason scores >7 whose average median follow-up was >8 years suggests that PCa in this population is not the main cause of death; therefore, we recommend that decisions regarding treatment should heavily weigh the risks of death against the quality of life.

The inclusion of patients with several comorbidities may be realistic for assessing overall mortality but also confounds comparisons by race. Putt et al. reported that comorbidities were more prevalent among AAs than CAs but that the effect on mortality was smaller for AAs. That study demonstrated that the absolute mortality differences between AAs and CAs were greatest for men with no comorbidities and narrowed with increasing comorbidities. This may explain, in part, the findings of our study and suggests further studies in an equal access-to-care facility where levels of patients’ overall health vary.⁴⁶

In conclusion, race was not an independent predictor of mortality in patients with nonmetastatic PCa who deferred primary treatment. In addition, the current results indicate that non-PCa-related illness is the major cause of death in this patient cohort. Significant predictors of mortality included Gleason score and PSA, suggesting that these variables, and not race, should factor most prominently in the counseling of both AA and CA patients who wish to defer curative treatment in light of palliative methods or watchful waiting/active surveillance.

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Figure 1.

Predicted cumulative incidence functions for prostate cancer are illustrated according to potential risk factors. The cumulative incidence functions were calculated by using R package cmprskCIFs (R Foundation for Statistical Computing, Vienna, Austria) and are plotted for the overall group and for all covariates according to their respective categories of death from prostate cancer. (A) The predicted cumulative incidence functions for prostate cancer did not reflect any differences in outcome according to race. (B) The predicted cumulative incidence functions for prostate cancer revealed significant differences in outcome according to prostate-specific antigen (PSA) level. (C) The predicted cumulative

incidence functions for prostate cancer revealed a significant difference in outcome according to Gleason score.

Table 1

Baseline Characteristics of Patients With 518 Prostate Cancer who Deferred Primary Treatment

Variable	No. of Patients (%)		<i>P</i>
	AA, n=280	CA, n=238	
Age at diagnosis, y			
Median [IQR]	73 [68–76]	74 [69–79]	
Mean ± SD	72.0 ± 7.5	73.6 ± 7.5	
<65	47 (17)	25 (11)	
65–75	153 (55)	109 (46)	.02
>75	80 (29)	104 (44)	
PSA, ng/mL			
Median [IQR]	18.0 [8.0–50.3]	11.5 [6.0–38.6]	.001
Missing	13 (5)	14 (6)	
<10	84 (30)	99 (42)	
10–100	151 (54)	111 (47)	
>100	32 (11)	14 (6)	
Gleason score			
<7	119 (43)	119 (50)	
7	98 (35)	62 (26)	.08
>7	63 (23)	57 (24)	
Clinical status at last follow-up			
Alive with disease	101 (36)	92 (39)	
Died of PCa	38 (14)	26 (11)	.81
Died of other causes	110 (39)	93 (39)	
Died of unclassified causes	31 (11)	27 (11)	
Cumulative incidence of PCa death (%)			
2 y	(1.08)	(91.27)	
4 y	(2.18)	(2.98)	
6 y	(5.24)	(6.99)	
8 y	(9.55)	(6.99)	
Median follow-up, y ^a	8.7	7.8	.89

Abbreviations: AA, African American; CA, Caucasian American; IQR, interquartile range; PCa, prostate carcinoma; PSA, prostate-specific antigen; SD, standard deviation.

^aThe median follow-up was calculated based on survivors.

Table 2

Univariate and Multivariate Analysis of Risk Factors for 518 Patients With Prostate Cancer who Deferred Primary Treatment

Variable	Unadjusted Univariate Analysis: SHR (95% CI)	<i>p</i> ^a	Adjusted Multivariable Analysis: SHR (95% CI)	<i>p</i> ^a
Race				
CA	Ref		Ref	
AA	1.23 (0.75–2.02)	.42	0.93 (0.54–1.60)	.8
Age, y				
<65	Ref		Ref	
65–75	0.61 (0.31–1.22)	.16	0.57 (0.27–1.20)	.14
>75	0.84 (0.42–1.71)	.64	0.76 (0.35–1.64)	.49
PSA, ng/mL				
<10	Ref		Ref	
10–100	4.62 (1.98–10.80)	<.0001	2.36 (0.94–5.91)	.07
>100	9.74 (3.76–25.24)	<.0001	3.27 (1.12–9.56)	.03
Gleason Score				
<7	Ref		Ref	
7	3.43 (1.70–6.94)	.001	2.59 (1.14–5.89)	.02
>7	6.46 (3.29–12.72)	<.0001	4.02 (1.75–9.22)	.001
Palliative treatment				
No	Ref		Ref	
Yes	6.16 (2.23–16.99)	<.0001	2.08 (0.63–6.84)	.23

Abbreviations: AA, African American; CA, Caucasian American; IQR, interquartile range; Ref, reference category; PCa, prostate carcinoma; PSA, prostate-specific antigen; SHR, subhazard ratio.

^a*P* values were calculated using the Gray test.

Table 3

Baseline Characteristics of 158 Patients With Prostate Cancer who Did Not Receive Palliative Treatments

Variable	No. of Patients (%)	
	AA, n=71	CA, n=87
Age at diagnosis, y		
Mean $\pm$ SD	71.7 $\pm$ 6.9	71.7 $\pm$ 8.4
<65	10 (14)	14 (16)
65–75	42 (59)	42 (48)
>75	19 (27)	31 (36)
PSA, ng/mL		
Median [IQR]	7.6 [4.9–14.9]	6 [3.8–10.7]
Missing	3 (4)	7 (8)
<10	41 (58)	57 (66)
10–100	27 (38)	23 (26)
>100	0 (0)	0 (0)
Gleason score		
<7	53 (75)	67 (77)
7	15 (21)	17 (20)
>7	3 (4)	3 (3)
Clinical status at last follow-up		
Alive with disease	29 (41)	43 (49)
Died of PCa	3 (4)	1 (1)
Died of other causes	30 (42)	30 (34)
Died of unclassified causes	9 (13)	13 (15)
Cumulative incidence of PCa death (%)		
2 y	(0)	(0)
4 y	(0)	(0)
6 y	(1.6)	(0)
8 y	(5.7)	(0)
Median follow-up, y ^a	6.4	6.7

Abbreviations: AA, African American; CA, Caucasian American; IQR, interquartile range; PCa, prostate carcinoma; PSA, prostate-specific antigen; SD, standard deviation.

^aThe median follow-up was calculated based on survivors.