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Racial Disparities in Prostate Cancer: Prostate-Cancer Specific Mortality Across Grade Groups in African American vs White Men, 2010-2020: A SEER Analysis

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Racial Disparities in Prostate Cancer: Prostate-Cancer Specific Mortality Across Grade Groups in African American vs White Men, 2010-2020: A SEER Analysis

By

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B.A., Rice University, 2017

Thesis Committee Chair: Kevin Ward, Ph.D.

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Abstract

Racial Disparities in Prostate Cancer: Prostate-Cancer Specific Mortality Across Grade Groups in African American vs White Men, 2010-2020: A SEER Analysis

By Natalie Polacek

Background: Prostate cancer is one of the most common cancer types among American men, and prostate cancer specific mortality (PCSM) rates are almost double in African American compared to White men. While racial disparities in PCSM have been narrowing over time, prior studies have shown that African Americans have a higher risk of prostate cancer death compared to White men among those diagnosed with low-risk disease. The objective of this study was to build off prior research to determine whether the risk of PCSM differs by race for each of the five clinical grade groups.

Methods: A retrospective cohort analysis was performed on de-identified data from 289,521 males diagnosed with prostate cancer from 2010–2020 in the Surveillance, Epidemiology, and End Results (SEER) database. Fine-Gray competing risks regression models were built to analyze the effect of race, grade group, and a race *x* grade group interaction term on PCSM after adjusting for prognostic and sociodemographic covariates. Subdistribution hazard ratios and 95% confidence intervals were defined for the primary exposures and predictors.

Results: After a median follow-up of 57 months, 5,170 males (975 [1.86% of] African American and 4,195 [1.77% of] White men), died from prostate cancer. The Fine-Gray competing risks regression with the race *x* grade group interaction term found a statistically significant difference in PCSM among certain grade groups. In grade groups 1 and 2, African American men had a significantly higher risk of PCSM compared to White men (1: FG HR 1.60, 95% CI [1.32, 1.94]; 2: FG HR 1.21, 95% CI [1.02, 1.45]). In grade groups 3 and 4, no significant difference in PCSM was observed between African American and White men (3: FG HR 1.04, 95% CI [0.87, 1.25]); 4: (FG HR 0.95, 95% CI [0.82, 1.10]). In grade group 5, African American men had a significantly lower risk of PCSM compared to White men (FG HR 0.85, 95% CI [0.75, 0.97]). All covariates were significantly associated with PCSM.

Conclusion: African American men were associated with a higher risk of PCSM compared to White men among those diagnosed with low-risk prostate cancer (i.e., grade groups 1 and 2). This finding is consistent with the previous literature and demonstrates the need to further study and characterize African American men with low-risk prostate cancer to reduce disparities in PCSM.

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Section 1: Introduction

Problem Statement

Prostate cancer mortality rates are known to be almost double in African American men compared to White men [1, 2]. According to the National Cancer Institute's Cancer Profiles, the age-adjusted death rate for prostate cancer from 2016-2020 is 37.5 for African American men and 17.8 for White men [3]. Autopsy data further show that prostate cancer volume and Gleason grade were greater in African American men at a younger age compared to White men [4].

Among men with low-risk disease with a Gleason 6, Mahal et al conducted two studies that found that African American patients had a higher risk of prostate cancer-specific mortality (PCSM) compared to nonblack patients. The first study used the Surveillance, Epidemiology, and End Results (SEER) database to identify men diagnosed with low-risk prostate cancer (Gleason $\leq$ 6) from 2004-2009 and found that, after a median follow-up of 46 months, African American men were significantly associated with increased risk of PCSM compared with White men (aHR 1.45, 95% CI 1.03-2.05) [5]. The second study used the SEER Prostate Active Surveillance/Watchful Waiting (AS/WW) database to identify men diagnosed with prostate cancer from 2010-2015 and found that, after a median follow-up of 36 months, African American patients with a Gleason 6 score had a higher risk of PCSM compared with nonblack patients (aHR 1.95, 95% CI 1.42-2.67), and did not observe a significant difference in PCSM among men with Gleason 7 to 10 scores (aHR 1.01, 95% CI 0.87-1.16), after adjusting for key covariates [6]. Wright et al also demonstrated that Gleason 3+4=7 and Gleason 4+3=7 tumors exhibited different recurrence/progression and PCSM rates; however, this difference was not further explored by race [7]. Currently, there are no studies to our knowledge focused on

whether there are significant differences in PCSM by race among men diagnosed with Gleason 3+4 = 7 (i.e., grade group 2) tumors, which is also classified as a low-risk disease.

Although there are race-specific differences in prostate cancer mortality, the disparities appear to be narrowing over time due to greater availability in screening and treatment options [2]. Wen et al evaluated the impact of clinical characteristics by race using data from the National Cancer Database (NCDB) for 526,690 patients with prostate cancer who underwent radical prostatectomy [8]. In their study, when adjustments were made for all clinical factors and nonclinical factors, the Black-White survival disparity narrowed from 51% to 20%. Regarding radiation therapy, Kodiyan et al also utilized the NCDB to compare overall survival between African American and White men [9]. The study reported that overall survival was equivalent between African American and White men in favorable risk (HR 0.928, 95% CI 0.583–1.477, p=0.753) and unfavorable-risk subgroups (HR 1.078,95% CI, 0.843–1.379, p=0.550) when treated with radiation therapy.

There is a need to further investigate if differences exist in prostate cancer-specific mortality (PCSM) across grade groups between African American men and White men, even after controlling for key clinical and demographic characteristics.

Thesis Purpose

To address this gap in research, the study builds off prior research to explore whether the risk of PCSM differs by race for each of the five grade groups. The study uses more recent data from the SEER registry, including males diagnosed with prostate cancer from 2010-2020, for a 10-year study period. The study also considers whether the patient's clinical tumor category, PSA level, age, and initial treatment approaches (i.e., radical prostatectomy and radiation therapy) are significant predictors of PCSM.

Section 2: Background Literature Review

Overview

Prostate cancer occurs only in men and is marked by an uncontrolled growth of cells in the prostate gland. The prostate gland is part of the male reproductive system and produces fluid that makes up a part of semen. Most prostate cancers are adenocarcinomas, which are cancers that develop from the gland cells that produce the prostate fluid. The American Cancer Society recommends that men make an informed decision with their healthcare provider to discuss when they should be screened for prostate cancer, beginning at age 50 for men who are at average risk.

Prostate cancer is one of the most common cancer types among American men. It accounts for 29 percent of all incident cases and 11 percent of estimated deaths among men with cancer in the United States as of 2023 [2]. After lung cancer, prostate cancer is the second leading cause of cancer death. Despite being the second leading cause of cancer death, the majority of prostate cancer cases are localized, and the 5-year relative survival rate for prostate cancer is 97.5% [10, 11]. The most common risk factors for prostate cancer are age, being African American, or having a family history of prostate cancer [10, 12, 13].

Prostate-Specific Antigen Screening

Prostate cancer screening commonly involves the prostate-specific antigen (PSA) test, which measures the level of PSA, a protein produced by prostate gland cells, in the blood. PSA levels of 4.0 ng/mL and lower are considered normal. A PSA level of up to 10 ng/mL reflects low-risk prostate cancer, 10-20 ng/mL reflects intermediate risk, and >20 ng/mL reflects high risk. Generally, the higher a man's PSA level, the higher the likelihood that he has prostate cancer [14]. Fluctuations in the rate of prostate cancer incidence were reflected by the changes

in behaviors associated with cancer risk and changes in medical practice through the diagnosis of localized tumors through PSA testing [2].

A dramatic surge in prostate cancer incidence rates in the 1990s occurred due to widespread increase in PSA testing among previously unscreened men [15]. The trend in prostate cancer incidence then rapidly declined as expected following the implementation of a new screening program and subsequently remained level from 1995 through 2007. In 2008, prostate cancer incidence again began to decline due to decreased utilization of PSA testing following recommendations from the US Preventive Services Task Force (USPSTF). The USPSTF recommended against routine screening for (i) men aged 75 years and older in 2008, and then (ii) all men in 2012. The discouragement against PSA testing is due to its likelihood of presenting false-positive results, overdiagnosis of prostate cancer cases, and treatment complications [16-18]. The decline in PSA screening resulted in the decreased prevalence of the diagnosis of localized tumors. Instead, there was an increase in the diagnosis of regional and distant-stage diagnoses [19, 20]. To improve early cancer detection while keeping overdiagnosis and overtreatment low, the USPTF modified their recommendation in 2018 to informed decision making for men aged 55 to 69 years undergoing PSA-based screening [21, 22]. There was a modestly steeper decline in PSA testing among African American men (11.6%) relative to White men (9.3%) between the 2012 and 2018 USPTF recommendations [23].

Fortunately, advances in technology have improved screening approaches that include the use of molecular markers and multiparametric magnetic resonance imaging (mpMRI) targeted biopsy. These approaches have become successful at detecting clinically significant tumors while mitigating overdiagnosis [24-26]. The PSA level and mpMRI are used to determine

the extent of the stage of the cancer, which describes how much cancer is in the body, where it has spread and the best way to treat it.

Prostate Cancer Grading (Gleason Score & Grade Group)

The Gleason score is important for determining prostate cancer prognosis and for clinical decision-making. The grade is based on the arrangement of the malignant cells within the tumor as well as other factors such as the degree of differentiation. If a male has a blood test exhibiting a higher-than-normal PSA level, or if the provider detects a lump or abnormality in the prostate during a DRE, then the provider may recommend a prostate core needle biopsy. Prostate cancer cells can be collected from either a biopsy or prostatectomy sample, and the Gleason grade is assigned based on the microscopic appearance of the prostate cells. The less glandular the microscopic appearance, the higher the Gleason grade, ranging from 1 to a maximum of 5. A Gleason grade of 1 would appear almost normal while a Gleason grade of 5 would not show any glandular features at all; just sheets of abnormal cells [27, 28]. The Gleason score is calculated by adding the two grades of cancer cells that make up the largest areas of the biopsy sample. The two grades consist of the primary and secondary patterns, which are based on a five-tier scale and then summed together to create the Gleason score. Scores usually range from 6 to 10 and are divided into three groups with 6 being considered low-grade; 7 being considered medium-grade; and 8, 9, and 10 being considered high-grade. A Gleason score of 6 is considered low-risk and less aggressive compared to higher Gleason scores; therefore, individuals with a Gleason score of 6 are less likely to be treated right away [7]. Instead, active surveillance is the preferred standard of care for patients with low-risk prostate cancer.

One of the limitations of the Gleason system is that men with a Gleason score 7 can experience differences in prostate cancer outcomes depending on the number coded for their

primary and secondary pattern. The Gleason 7 patterns can consist of either (1) a 3 primary pattern and 4 secondary pattern (i.e., 3+4), (2) a 4 primary pattern and 3 secondary pattern (i.e., 4+3), (3) a 2 primary pattern and 5 secondary pattern (i.e., 2+5), or (4) a 5 primary pattern and 2 secondary pattern (i.e., 5+2). However, the 2+5 and 5+2 patterns are extremely rare. Studies have found that outcomes differ between men with 3+4 and 4+3 tumors, where men with 4+3 tumors were at increased risk for prostate cancer-specific mortality (PCSM) [7, 29, 30]. Wright et al found that among men undergoing curative therapy, those with Gleason 4+3 vs 3+4 tumors had an increased risk of biochemical recurrence (HR 2.10, 95% CI 1.08-4.08) and PCSM (HR 3.17, 95% CI 1.04-9.67) [7].

More recently, grade groups have been introduced by the International Society for Urological Pathology (ISUP) as a new and alternative method of grading prostate cancer which classifies men with Gleason 7 into different grade groups depending on whether they have a 3+4 or 4+3 tumor pattern. Grade groups range from 1 being the most likely to grow and spread slowly, to 5 being the most likely to grow and spread quickly [31, 32]. The grade groups are equivalent to the following Gleason scores: (1) grade group 1 = Gleason 6; (2) grade group 2 = Gleason 3+4 = 7; (3) grade group 3 = Gleason 4+3 = 7; (4) grade group 4 = Gleason 8; (5) grade group 5 = Gleason 9-10 [31]. Each of the grade groups are associated with a distinct risk of biochemical prostate cancer recurrence.

While the Gleason system and grade groups are being used concurrently to determine prostate cancer prognosis, new staging systems and risk assessment tools are being developed to predict PCSM and risk of recurrence more accurately [29, 33].

Prostate Cancer Treatment Options

The National Comprehensive Cancer Network (NCCN) guidelines recommend treatment options for localized prostate cancer based on: PSA level, Gleason score or grade group, clinical stage, and comorbidity-adjusted life expectancy [34, 35]. Localized prostate cancer treatment options include active surveillance; radiation therapy that includes external beam radiation therapy (EBRT) and brachytherapy; and radical prostatectomy. Treatment recommendations will differ depending on what risk group the patient's prostate cancer falls under. All three treatments have their advantages and disadvantages; however, when comparing the efficacy of the treatments over a median of 10 years in the ProtecT trial, PCSM was low, irrespective of the treatment assigned, with no significant difference among treatments [36]. Surgery and radiation therapy were associated with lower incidences of disease progression than active surveillance.

Men with localized prostate cancer that is low-risk, Gleason 6 and Gleason 3+4 = 7 with less than 10% pattern 4, are recommended for active surveillance to reduce the risk of adverse outcomes from overtreatment [26, 34, 37]. The American Society of Clinical Oncology protocol recommends that patients undergoing active surveillance receive a digital rectal exam (DRE) at least once a year; a prostate biopsy within 6-12 months of diagnosis, then at least every two to five years; and a PSA test every three to six months [38]. Definitive treatment should be offered if the tumor shows signs of becoming more aggressive or advancing on the Gleason score.

Radical prostatectomy and radiation therapy remain the gold standard for localized intermediate and high-risk disease [26]. Radical prostatectomy is a surgical procedure to remove the entire prostate gland and surrounding lymph nodes. Patients who undergo radical prostatectomy are more likely to experience urinary incontinence and trouble obtaining or sustaining an erection compared with patients who choose radiation therapy [39]. EBRT is

typically given with the goal of eradicating local prostate cancer before it advances or metastasizes. The amount of radiation delivered to a targeted area is critically important in preventing recurrence and improving long-term outcomes. In patients with low-risk and very low-risk prostate cancer, brachytherapy is a preferred treatment option in patients with low-risk disease because it controls the cancer as effectively as surgery or EBRT with less risk of urinary incontinence and erectile dysfunction. For intermediate-risk prostate cancer, brachytherapy may be used alone for selected patients or in combination with EBRT [34].

Racial Disparities in Prostate Cancer

Prostate cancer is the most common cancer type in African American men and accounts for 37 percent of all new cancer diagnoses [2]. African American men experience an incidence of prostate cancer that is more than 70% higher than in White men and are also twice as likely to die from prostate cancer compared to White men [1, 2, 10, 40]. The determinants of the high rate of prostate cancer incidence and aggressiveness in African American relative to White men are multifactorial and could be attributed to genetic susceptibility, access to care, differences in treatment received, lower screening rates, and psychosocial stressors (i.e., discrimination, negative neighborhood effects, low socioeconomic status (SES), limited access to healthcare) [1, 41, 42]. Furthermore, African American men are disproportionately underrepresented in clinical trials, which could be crucial to identifying potential interventions that would improve prevention and clinical outcomes in African American men [1, 43-45].

Due to the increased risk of PCSM among African American men, it is recommended that they have discussions with their provider on getting prostate cancer screening beginning at age 45, and potentially 40 if they are deemed higher risk. Even though African American men are more likely to be screened and diagnosed at younger ages, they are also more likely to be

diagnosed with an advanced diagnosis and have higher PSA levels than White men [41, 46, 47]. In general, African American men derive more benefit from PSA screening and adopting a lower screening threshold for further prostate cancer evaluation [48, 49].

African American men are found to be more likely to experience adverse outcomes and to be less likely to receive definitive treatment for prostate cancer compared to White men. Among men with low-risk prostate cancer enrolled in active surveillance programs, African American men had a higher risk of progressing to a higher Gleason grade cancer, PCSM, and adverse pathology compared to White men [5, 6, 50, 51]. African American men with low-risk prostate cancer who were candidates for active surveillance but elected to undergo radical prostatectomy experienced significantly higher rates of disease upgrading, adverse pathology, and biochemical recurrence compared to White men [52, 53]. Moses et al reported that Black men diagnosed with Gleason 7 and Gleason 8-10 were less likely than White men to receive definitive treatment by either prostatectomy or radiation therapy for localized prostate cancer (OR 0.73, 95% CI 0.71–0.75) [54]. Even if assigned the same treatment, such as radiation therapy, African American men were associated with greater rates of treatment noncompletion compared to White men (OR 1.14, 95% CI 1.09-1.19) [55]. This finding further supports that African Americans experience disparities and barriers in access to care.

Fortunately, the disparities between African American and White patients have been narrowing over time, thanks to increases in screening and treatment options [2, 20, 45]. Despite the multiple factors involved, further mitigation of prostate cancer disparities will likely include efforts to increase African American enrollment in clinical trials that contribute towards better

outcomes, to ensure all men receive standardized prostate cancer treatments, and to improve access to medical care [44, 45].

Section 3: Study Design & Methods

Data Source

This retrospective cohort study used de-identified data from the November 2022 submission of the Surveillance, Epidemiology, and End Results (SEER) research data to identify males diagnosed with prostate cancer from 2010 – 2020 [56]. The SEER Program collects and publishes cancer incidence, survival, and treatment data from population-based registries. This version of the SEER dataset contains information from 17 population-based cancer registries (San Francisco-Oakland SMSA, San Jose-Monterey, Connecticut, Los Angeles, Alaska Natives, Atlanta, Rural Georgia, California excluding SF/SJM/LA, Hawaii, Iowa, New Mexico, Seattle-Puget Sound, Kentucky, Louisiana, New Jersey, Greater Georgia, and Utah), which covers roughly 26.5% of the US population based on the 2020 census [57].

Study Population

The SEER database identified 580,124 males diagnosed with prostate cancer from January 1, 2010 – December 31, 2020. The inclusion criteria for our study population included males who (1) had prostate cancer as their only primary cancer, (2) were either African American or White, (3) had localized prostate cancer, (4) were not identified as having prostate cancer from an autopsy or death certificate, and (5) had complete survival dates available or no 0 follow-up days. There were 315,312 males who satisfied the inclusion criteria.

Following the imposing of the inclusion criteria, the study population was further subset to males who had (1) a grade group between 1 and 5, (2) a known initial treatment, and (3)

available clinical T1-T3 staging information. The final study population for the analysis was 289,521 males (***Figure 1***).

Outcomes

The primary outcome was time to prostate cancer-specific mortality, which was measured in survival months from the case's date of diagnosis to death, that had to have occurred during the follow-up period through December 31, 2020. A competing risk was defined as a case who died from non-prostate cancer-related reasons during the follow-up period, thereby preventing the event of interest, prostate cancer-specific mortality, from occurring. Cases were censored if they were lost to follow-up or were alive by the time the follow-up period ended.

Exposure

The primary exposures of interest are race and grade group. Race was dichotomous and classified as African American and White, as accessed under the Race Recode variable by the SEER registry. Patients of other races were excluded from the analysis.

The grade group variable was derived from the Gleason Clinical Score and Gleason Clinical Patterns variables that were provided in the SEER registry. The grade group was ordinal, ranked from 1 through 5, with 1 being the lowest risk and 5 being the highest risk. Males who had a clinical Gleason score of 7, but who did not have a tumor pattern of 3+4 or 4+3, and whose clinical Gleason score was below 6 or missing, were excluded.

- If the clinical Gleason score = 6, then the grade group = 1;
- If the clinical Gleason patterns = 3+4, then the grade group = 2;
- If the clinical Gleason patterns = 4+3, then the grade group = 3;
- If the clinical Gleason score = 8, then the grade group = 4; and

- If the clinical Gleason score = 9 or 10, then the grade group = 5.

Covariates

Covariates included age at diagnosis, PSA lab value, known initial treatment approach, and clinical T staging information. The PSA lab values are skewed right and therefore log-transformed to ensure the PSA values follow a normal distribution. There were 31,177 observations from the final dataset with a missing log-PSA value (10.77%). This subset of the study population did have a higher percentage of individuals with a clinical grade group of 1 (53.63% vs. 44.20%) and a lower percentage that received an initial treatment (32.15% vs 61.94%) compared to the rest of the cohort. Since the characteristics of the population with missing log-PSA values were different from the rest of the cohort, a multiple imputation (MI) approach was utilized, assuming a monotone missing data pattern with data missing at random (MAR), to address and populate the missing values [58]. MI was conducted using the regression method, with the number of imputations set to eight.

The known initial treatment was defined as either receiving radical prostatectomy, radiation therapy, both, or not receiving any treatment. Males whose treatment status was indicated as unknown were excluded from the final study population and analyses.

The clinical T staging variable was classified as T1 (clinically inapparent tumor neither palpable nor visible by imaging), T2 (tumor confined within prostate), or T3 (tumor extends through the prostate capsule). For the 51,575 males diagnosed with prostate cancer between 2016 and 2017, there was no purely clinical T staging variable available in the SEER dataset. Therefore, additional coding was performed to recode the pathologic T variable into the clinical T staging variable for 13,565 males (26.30%) who did not have clinical T staging information available during these years.

Statistical Analysis

Baseline demographic and clinical characteristics were compared by race (***Table 1***) and grade group (***Table 2***). Categorical patient characteristics such as treatment approach and clinical tumor category were compared using chi-square tests. Continuous patient characteristics such as age and log-PSA were compared using one-way ANOVA. Crude cumulative incidence estimates of PCSM by race, grade group, and by race for each grade group were plotted to illustrate the crude cumulative failure rates over time due to PCSM (***Figure 2*** - ***Figure 8***).

After adjusting for demographic factors (age), treatment approaches (radical prostatectomy, radiation therapy, both, none), clinical tumor category (T1, T2, T3), and log-PSA, a Fine-Gray univariable and multivariable competing risks regression was used to assess the effect of race and grade group, with a race *x* grade group interaction term, on PCSM and non-PCSM in 289,521 men (237,191 White; 52,330 African American) with complete clinical information available, as described by Mahal et al [5, 6]. Univariable analysis was conducted to examine the association between each covariate and the occurrence of PCSM and non-PCSM. Predictors identified as statistically significant in the univariable analysis were included in the multivariable model. The interaction term of race *x* grade group was included in the final multivariable model with all the statistically significant predictors to estimate adjusted hazard ratios. A cause-specific Cox model was also run to compare the estimates of covariates from the cause-specific hazard function to those of the Fine-Gray subdistribution hazard function.

Crude and adjusted hazard ratios were reported with 95% confidence intervals and *p*-values, when applicable. The threshold of .05 was used to determine statistical significance.

Statistical analyses were performed using Statistical Analysis Software (SAS) version 9.4 (SAS Institute Inc., Cary, NC).

Section 4: Results

Study Population

A total of 580,124 males were identified as having a prostate cancer diagnosis from 2010 – 2020 in the SEER registry data. Of these, 264,812 (45.65%) were excluded due to (1) having more than one primary; (2) not being an African American or White male; (3) not having localized prostate cancer; (4) being identified from an autopsy or death certificate; and (5) having incomplete survival dates with 0 follow-up days. To enhance data completeness, an additional 25,791 males were excluded if (1) they did not have a grade group 1-5 tumor; (2) their treatment status was unknown; and (3) they were reported having a clinical T4 tumor or no clinical T despite having already excluded males who did not have localized prostate cancer. The final study population included 289,521 males (***Figure 1***).

Table 1 presents the baseline clinical and demographic characteristics of the study population. Of 289,521 males in the study population, 52,330 males were African American (18.07%) and 237,191 were White (81.93%). African American men had a higher proportion of their population with a clinical grade group between 2-5 compared to White men (60.07% vs 54.80%), while White men had a higher proportion of their population with a clinical grade group of 1 compared to African American men (45.20% vs 39.93%). African Americans compared to White males had a higher log-PSA value (4.23 vs 4.14), were more likely to receive radiation therapy (41.22% vs 34.17%) or both treatments (0.52% vs 0.47%), were more likely to be diagnosed with T1 (i.e., clinically inapparent) tumors (71.41% vs 64.81%), and were younger at diagnosis (63.28 years vs 66.13 years). There were 5,170 males (1.79%) from the study

population who died due to prostate cancer, with the percentage of PCSM slightly higher among African American men (1.86%) compared to White men (1.77%). There were 23,750 males (8.20%) who died from non-prostate cancer related causes, where the non-PCSM was also slightly higher among African American men (9.08%) compared to White men (8.01%). In ***Table 2***, the racial and survival characteristics by grade group illustrates that the racial breakdown is proportional for grade groups 2-4 where African American men comprise 19-21% of the sub-population, whereas White men comprise 79-81%. In grade groups 1 and 5, the proportion of African American men is slightly lower, comprising 16-18% of the sub-population, while the White men comprise 82-84%. Among the men who received at least one type of initial treatment (radical prostatectomy, radiation therapy, or both), only 46% of the men with grade group 1 tumors received treatment compared to 68-80% of men with grade group 2-4 tumors. This table shows a positive correlation in the percentage of men between grade group severity and PCSM, with PCSM occurring in 0.46% of men in grade group 1 to 11.71% of men in grade group 5. Additionally, the median survival months decreases as the grade group increases in severity. ***Table 3*** compares the distribution of PCSM and median survival months by race and grade group. PCSM is greater among African American men compared to White men from grade groups 1-4. Only in grade group 5 is the PCSM higher among White men compared to African American men (41.07% vs 32.10%). With the exception of grade group 1 among African American men, the median survival months decrease as the grade group severity increases, with the African American men having shorter survival months than the White men across grade groups 1,3, 4, and 5. The descriptive statistics of the study population may indicate that

African American men have a higher likelihood of PCSM compared to White men, although the magnitude of the difference is small.

Cumulative Incidence Estimates of PCSM

After a median follow up of 57 months, 5,170 males (975 [1.86% of] African American and 4,195 [1.77% of] White men), died from prostate cancer. Crude cumulative incidence estimates of PCSM by race, grade group, and by race for each grade group were plotted ***(Figure 2 – Figure 8***). By race, the cumulative incidence estimates of PCSM were significantly higher for African American men compared with White men, with 5-year PCSM rates of 1.69% and 1.57%, respectively, and 10-year PCSM rates of 3.89% and 3.45%, respectively (P = 0.0074; ***Figure 2***). By grade group, the cumulative incidence estimates of PCSM were significantly different across grade groups, with the 5- and 10-year PCSM rates increasing as the grade group severity increased (*5-year PCSM rates*: grade group 1: 0.33%, grade group 2: 0.63%, grade group 3: 1.64%, grade group 4: 4.07%, grade group 5: 12.92%; *10-year PCSM rates*: grade group 1: 0.92%, grade group 2: 2.12%, grade group 3: 4.89%, grade group 4: 9.79%, grade group 5: 22.88% [P < 0.0001; ***Figure 3***]).

Within grade groups, the cumulative incidence estimates of PCSM were significantly higher for African American men compared with White men for grade groups 1 and 2. For grade group 1, the 5-year PCSM rates of African American and White men were 0.52% and 0.29%, respectively, while the 10-year PCSM rates were 1.20% and 0.87%, respectively (P < 0.0001; ***Figure 4***). For grade group 2, the 5-year PCSM rates of African American and White men were 0.67% and 0.62%, respectively, while the 10-year PCSM rates were 2.85% and 1.95%, respectively (P = 0.0049; ***Figure 5***). There was no significant difference in the cumulative incidence estimates of PCSM between African American and White men for grade groups 3 and

4. For grade group 3, the 5-year PCSM rates of African American and White men were 1.78% and 1.60%, respectively, while the 10-year PCSM rates were 5.17% and 4.82%, respectively (P = 0.36; ***Figure 6***). For grade group 4, the 5-year PCSM rates of African American and White men were 4.23% and 4.03%, respectively, while the 10-year PCSM rates were 9.48% and 9.86%, respectively (P = 0.79; ***Figure 7***). Within grade group 5, the cumulative incidence estimates of PCSM were significantly lower for African American compared with White men with 5-year PCSM rates of 11.36% and 13.26%, respectively, and 10-year PCSM rates of 19.96% and 23.47%, respectively (P = 0.0064; ***Figure 8***).

Model Assessment

All 289,521 observations were used for the model development and assessment. In the univariate analysis, all 6 variables included were statistically significant in the risk of PCSM, considering that grade group, initial treatment approach, and clinical tumor category were divided into categories of more than 2 levels (***Table 4***). There was increased risk of PCSM among African American compared to White men (HR 1.10, 95% CI [1.02, 1.18]); for every 1 ng/mL increase in log-PSA (HR 2.91, 95% CI [2.82, 3.01]); for every one-year increase in age (HR 1.11, 95% CI [1.10, 1.11]); for each grade group compared to grade group 1 (2: HR 2.16, 95% CI [1.94, 2.41]; 3: HR 5.04, 95% CI [4.52, 5.63]; 4: HR 11.56, 95% CI [10.47, 12.77]; and 5: HR 34.36, 95% CI [31.37, 37.65]); and for each clinical tumor category compared to T1 (T2: HR 1.62, 95% CI [1.53, 1.71] and T3: HR 2.020, 95% CI [1.29, 3.17]). Meanwhile, all of the treatment approaches were associated with a decreased risk of PCSM compared to those who did not receive any treatment (Radical Prostatectomy: HR 0.07, 95% CI [0.06, 0.08]; Radiation Therapy: HR 0.56, 95% CI [0.53, 0.59]; Both Treatments: HR 0.58, 95% CI [0.39, 0.85]).

Risk Factors Associated with PCSM

All six variables were included for the multivariate Fine-Gray competing risks regression (***Table 4***). In the multivariate model without the race *x* grade group interaction term, the risk of PCSM was not significant between African American and White men (FG HR 1.02, 95% CI [0.95, 1.10]) after adjusting for the covariates. When including the race *x* grade group interaction term in the multivariate model, it was found to be significant. After adjusting for covariates in the multivariate model with the interaction term, there was a statistically significant difference in PCSM among certain grade groups. In grade groups 1 and 2, African American men had a significantly higher risk of PCSM compared to White men (1: FG HR 1.60, 95% CI [1.32, 1.94]; 2: FG HR 1.21, 95% CI [1.02, 1.45]). In grade groups 3 and 4, no significant difference in PCSM was observed between African American and White men (3: FG HR 1.04, 95% CI [0.87, 1.25]); 4: (FG HR 0.95, 95% CI [0.82, 1.10]). In grade group 5, African American men had a significantly lower risk of PCSM compared to White men (FG HR 0.85, 95% CI [0.75, 0.97]). All covariates in both multivariate models, without and with the race *x* grade group interaction term, were significantly associated with PCSM (***Table 4***). Males who received radical prostatectomy, radiation therapy, or both were significantly associated with lower risk of PCSM compared to not receiving any treatment, while a one-year increase in age, a one-ng/mL increase in log-PSA and increase in the severity of clinical tumor categories were significantly associated with higher risk of PCSM.

A multivariable cause-specific hazard model was performed on the dataset, where all observations that did not experience PCSM were censored (***Table 5***). Both the cause-specific hazard model and Fine Gray regression model yielded similar hazard ratios between African American and White men within each grade group, as well as for the covariates.

Risk Factors Associated with Non-PCSM

Similarly, all six variables were included for the multivariable Fine-Gray competing risks regression for non-PCSM (***Table 6***). In the multivariable model without the race *x* grade group interaction term, the risk of non-PCSM was significantly higher in African American men compared to White men (FG HR 1.44, 95% CI [1.39, 1.49]) after adjusting for the covariates. When including the interaction term, African Americans had a higher risk of non-PCSM compared to White men within each grade group (1: FG HR 1.58, 95% CI [1.50, 1.67]; 2: FG HR 1.45, 95% CI [1.37, 1.55]; 3: FG HR 1.38, 95% CI [1.27, 1.50]; 4: FG HR 1.26, 95% CI [1.15, 1.38]; and 5: FG HR 1.30, 95% CI [1.16, 1.45]). All covariates, except for clinical tumor category T3 vs. T1, were significantly associated with risk of non-PCSM in both multivariable models without and with the interaction term (***Table 6***). Radical prostatectomy, radiation therapy, or both were significantly associated with lower risk of non-PCSM compared to not receiving any treatment, while a one-year increase in age, one ng/mL increase in log-PSA, and clinical tumor category T2 vs. T1 were significantly associated with increased risk of non-PCSM.

Section 5: Discussion

To our knowledge, this is the first study to explore whether racial disparities in PCSM exist between African American and White men by clinical grade group. Specifically, this present study found that PCSM rates were significantly different between African American and White men for grade groups 1, 2, and 5; and not significantly different for grade groups 3 and 4. In grade groups 1 and 2, for prostate cancer that is considered low-risk, African American men had a significantly higher risk of PCSM compared to White men.

This present study's findings are consistent with the two studies by Mahal et al, where both studies found that African American men with low-risk prostate cancer (i.e., clinical

Gleason score 6) had a higher risk of PCSM compared to White/non-Black men [5, 6]. However, these studies did not explore whether differences in PCSM by race existed for other clinical Gleason scores. Particularly for clinical Gleason 7, studies have found that patients with a clinical Gleason score 7 can experience different prognosis outcomes depending on the number coded for the primary and secondary patterns of the tumor [7, 29, 30]. By reassigning patients with clinical Gleason 7 into grade groups 2 or 3, this study found a significantly higher risk of PCSM in African American than White men in grade group 2, and no significant difference in risk of PCSM between African American and White men in grade group 3.

Specifically, the present findings from the multivariate model with the race *x* grade group interaction term indicate that among men who were diagnosed with prostate cancer in grade groups 1 and 2, African American men have a 60% and 21% increased risk, respectively, of PCSM compared to White men, even after adjusting for PSA, age, initial treatment, and clinical tumor stage. Among men classified with grade groups 3 and 4 prostate cancer, there was no significant difference of increased PCSM risk was observed between African American and White men. In grade group 5; however, African American men were 15% less likely to die of prostate cancer compared to White men. The results of PCSM risk by grade group were consistent when utilizing the Fine-Gray competing risks regression model and the cause-specific regression model. Among all five grade groups, the differences between the crude PCSM rates were small after 5-years of follow-up but increased after a longer follow-up period of 10-years.

Among the study population's baseline demographic characteristics, African American men were more likely to present with a higher clinical grade group (grade groups 2-5: 60.07% vs 54.80%; $P < .001$), a higher log-PSA (median, 4.2 vs 4.1; $P < .001$), were more likely to receive

radiation therapy (41.22% vs 34.17%) or both treatments (0.52% vs 0.47%), and were more likely to present with a clinical T1 at diagnosis (71.41% vs 64.81%; P < .001) compared to White men. Given the presentation of these baseline characteristics, it is possible that African American men may have harbored more aggressive forms of prostate cancer which could have contributed to the disparity in PCSM in the low-risk grade groups despite having a higher proportion of the population presenting with a clinically inapparent tumor that is not palpable and receiving at least one initial treatment intervention.

When looking at the specific types of treatments received, a lower proportion of African American men received radical prostatectomy only (23.05% vs 28.22%; P < .0001), while a higher proportion received radiation therapy (41.22% vs 34.17%; P < .0001) when compared to White men. In the Fine-Gray multivariable competing risks regression, men who received radical prostatectomy only had a statistically significant 88% reduction in PCSM, while men who received radiation therapy only had a statistically significant 59% reduction in PCSM, after adjusting for covariates. Clinicians and male patients could have selected upon the treatment intervention depending on the patient's preference or additional disease characteristics that are not currently captured in the SEER registry. If African American men were the ones disproportionately affected by adverse disease characteristics, that could also serve as an underlying reason for the disparity in PCSM.

There is the possibility that some of the males diagnosed with clinical grade group 1 prostate cancer could have been understaged or undergraded. This is illustrated by the 45.5 median survival months observed for African American men diagnosed with clinical grade group 1, which is noticeably shorter than the median survival months for African American men

diagnosed with clinical grade groups 2, 3, and 4, at 64.5, 55, and 48.5 months, respectively (***Table 3***). This misclassification could be attributed to either the male having only received a clinical biopsy and no surgical treatment, or due to erroneous coding with respect to clinical grading and cause of death.

The present study's findings on the risks of PCSM by grade groups between African American and White men appear to corroborate the prior literature that disparity gaps between the two racial groups exist but are narrowing. The fact that the present study found a gap in PCSM between African American and White men for low-risk grade groups despite adjusting for differences in PSA, treatment type, age, and tumor stage indicates that additional strategies are still needed to reduce disparities in PCSM. To determine these strategies, there needs to be increased efforts to enroll African American men in prostate cancer studies, particularly those with a low-risk grade group.

Strengths

The sample size and 10-year duration of this study provides a representation of racial disparities in PCSM by clinical grade group in the United States and an ample follow-up to confirm that the magnitude of the observed disparities increase over time, respectively. The findings highlight that African American men assigned to a low-risk grade group are at increased risk of PCSM, even after adjusting for sociodemographic factors and cancer characteristics.

This study was also novel in its approach to exploring PCSM disparities by clinical grade group as opposed to the Gleason scoring system. By separating out individuals with a clinical Gleason 7 into grade groups 2 and 3, the study identified differences in the risk of PCSM by race in the two groups. This finding supports the move towards utilizing grade groups as the method of grading prostate cancer given that males are experiencing differences in prostate cancer

outcomes based on whether they have a 3+4 and 4+3 tumor pattern that are both currently classified as a clinical Gleason 7.

Limitations

Although this study continues to uphold findings from previous studies that racial disparities in PCSM exist among men with low-risk prostate cancer, including those classified with grade group 2, limitations of the data should be taken into consideration when reviewing the results. First, the SEER Program changed how it collected cancer staging information between 2016-2017. For cancers diagnosed during these two years, SEER registries transitioned from collecting cancer stage information using Collaborative Stage (CS) to collecting stage using the TNM classification and creating a combined T that is derived based on the clinical and pathologic T. This was a different method compared to the cases diagnosed between 2010-2015 and 2018-2020 where clinical and pathological T staging information were collected and provided separately. Since the dataset did not contain a purely clinical T staging variable for cases diagnosed between 2016-2017, the present authors made the decision to recode the pathologic T to the clinical T. This impacted 13,565 males (4.70%) in the final study population, 83.62% of Whites and 16.38% of African Americans. While there was not complete confidence that the pathologic T was the same as the clinical T, this was decided upon after verifying that among the males diagnosed between 2010-2015 and 2018-2020 who received a prostatectomy, 21,619 of them (32.47%) had a matching clinical T and pathologic T, which consisted of 86.79% of Whites and 13.21% of African Americans. The racial breakdowns among those with a recoded pathologic T to clinical T and with matching clinical T and pathologic T are slightly different from the racial breakdown of the final study population. The proportion of African American men impacted is slightly lower than the proportion of African Americans in the final study population

(18.07%), whereas the proportion of White men impacted is slightly higher than the proportion of White men in the final study population (81.93%).

Second, there were 31,177 observations (10.77%) from the final study population with a missing log-PSA value. As discussed in the Methods section, the subset of the population with missing log-PSA information had noticeably different baseline characteristics compared to the rest of the cohort. When running the Fine-Gray competing risks regression on the dataset with and without the log-PSA imputation, a difference was observed between the results within grade group 2. When log-PSA was imputed, African American men had a significantly higher risk of PCSM compared to White men. When log-PSA was not imputed, there was no significant difference in PCSM risk between the two races.

Third, the data source used for this analysis did not distinguish between men who received no treatment and active surveillance. If information on men receiving active surveillance as an initial treatment was provided, this could have enabled better controlling for differences in treatment management and inform whether African American men on active surveillance were at greater risk for PCSM compared to White men.

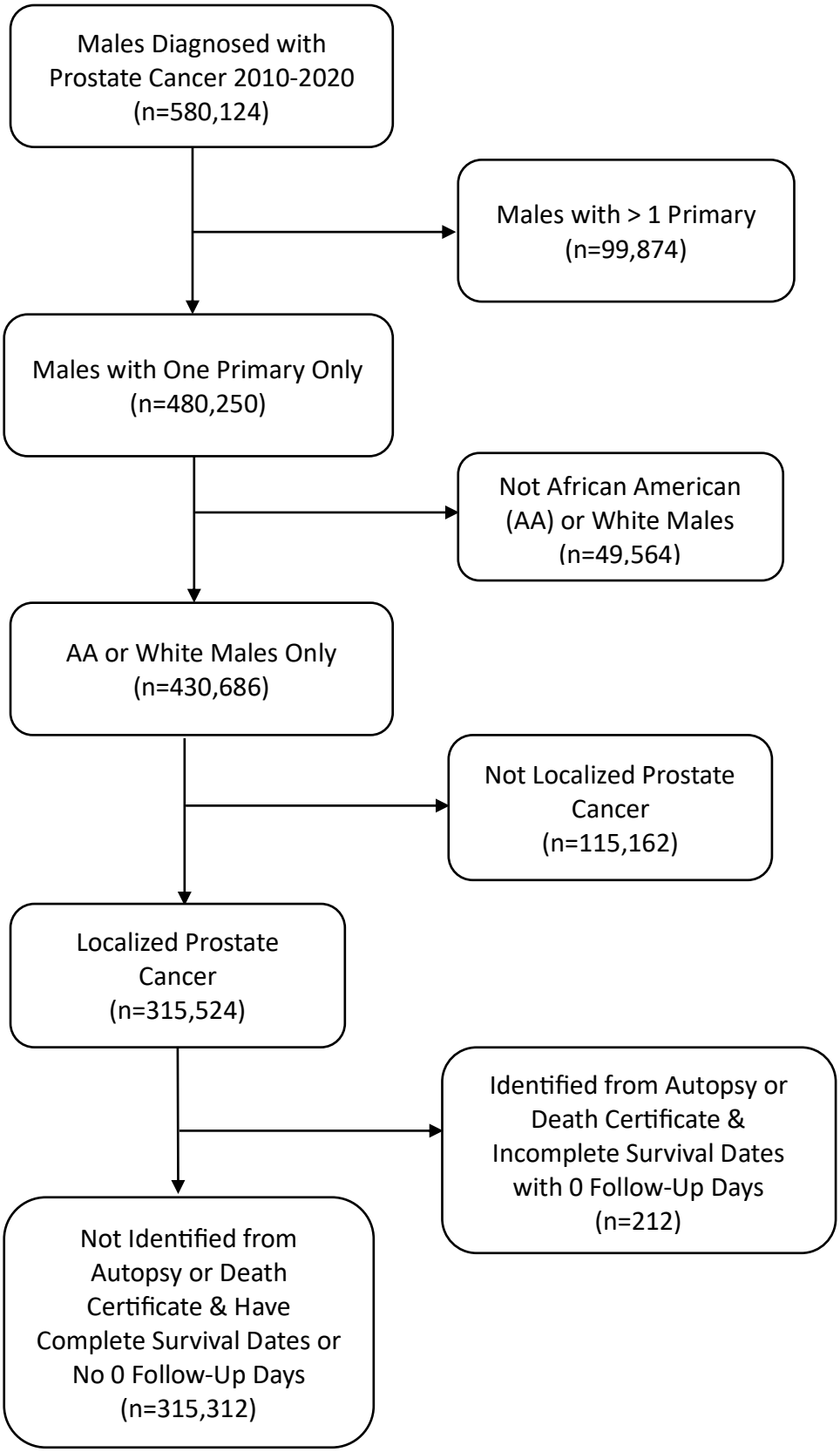
Conclusion & Recommendations

Despite the study's potential limitations, the magnitude of the study population (n=289,521) included in this analysis continues to substantiate previous findings that African American men with low-risk prostate cancer experience worse outcomes and increased risk of PCSM relative to non-African American males, independent of clinical and demographic characteristics. Although the rates of PCSM were small, especially among those in the low-risk grade groups, the disparities in the crude PCSM rate were greater after a longer follow-up period. Notably, the present study identified this disparity in grade groups 1 and 2, whereas

previous literature has only looked at whether these disparities were present in clinical Gleason 6. These findings demonstrate the need to further study and characterize African American men with low-risk prostate cancer. Future research should consider including additional covariates, including whether a patient received active surveillance as a treatment option; additional sociodemographic characteristics, such as income, education, marital status, and residence; and patterns of care to assess their differences by race and their impact on PCSM risk.

Figures and Tables

Figure 1 Consort Diagram: Inclusion Criteria



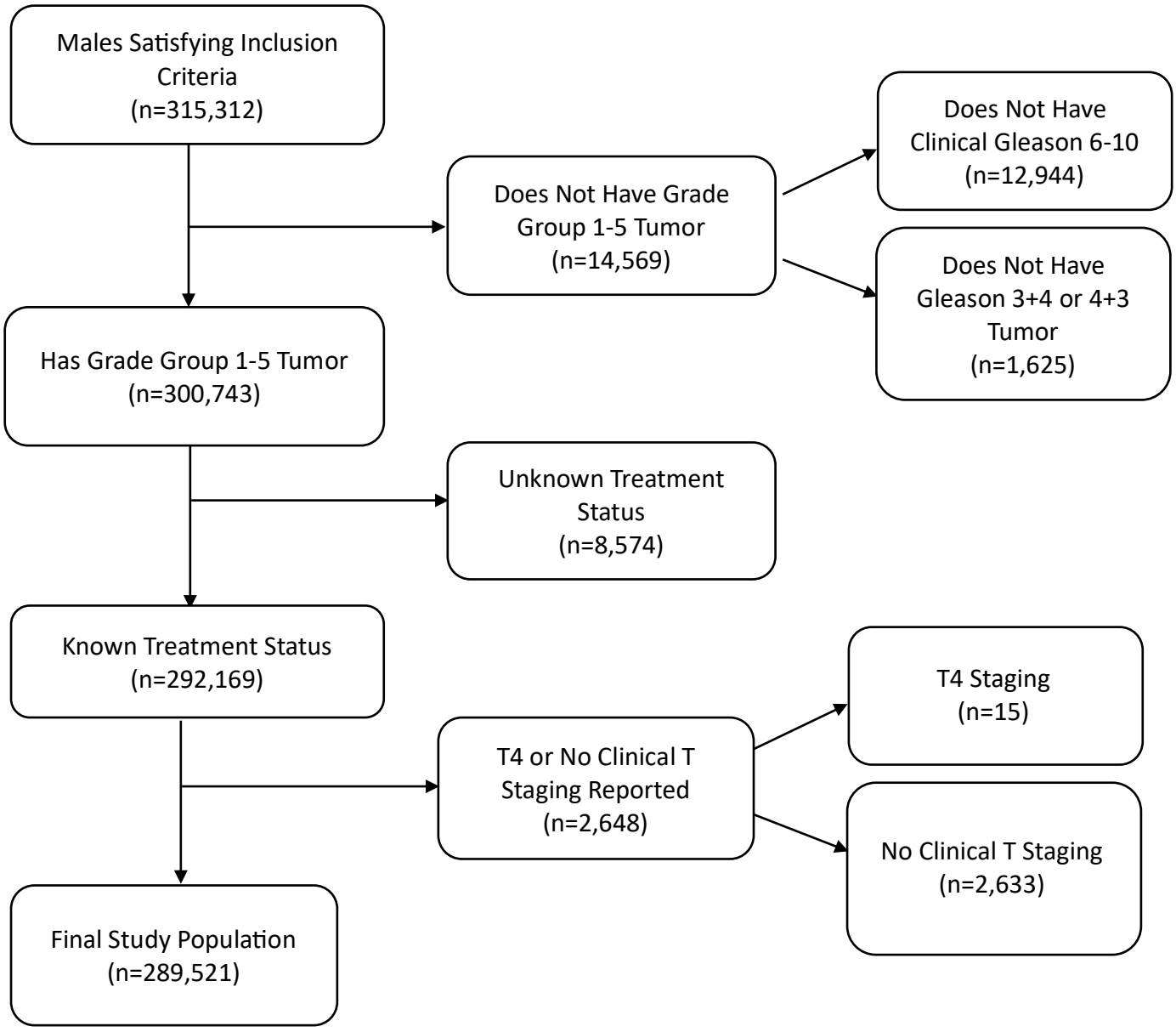

Males Satisfying Inclusion Criteria (n=315,312)
Does Not Have Grade Group 1-5 Tumor (n=14,569)
Does Not Have Clinical Gleason 6-10 (n=12,944)
Does Not Have Gleason 3+4 or 4+3 Tumor (n=1,625)
Has Grade Group 1-5 Tumor (n=300,743)
Unknown Treatment Status (n=8,574)
Known Treatment Status (n=292,169)
T4 or No Clinical T Staging Reported (n=2,648)
T4 Staging (n=15)
No Clinical T Staging (n=2,633)
Final Study Population (n=289,521)

Table 1. Baseline Clinical & Demographic Characteristics of Patients Diagnosed with Prostate Cancer, by Race

Variable	**Summary Statistic**			
	All Patients $n = 289{,}521$	African American (AA) $n = 52{,}330$ (18.07%)	White $n = 237{,}191$ (81.93%)	P
Grade Groups (%)				< 0.0001
1	128,094 (44.24%)	20,895 (39.93%)	107,199 (45.20%)	
2	80,626 (27.85%)	15,399 (29.43%)	65,227(27.50%)	
3	37,553 (12.97%)	7,700 (14.71%)	29,853 (12.59%)	
4	25,863 (8.93%)	5,168 (9.88%)	20,695 (8.73%)	
5	17,385 (6.00%)	3,168 (6.05%)	14,217 (5.99%)	
Log-PSA (ng/mL) $\boldsymbol{Median}$ $(\boldsymbol{IQR})$	$4.16\ (3.87 - 4.56)$	$4.23\ (3.93 - 4.71)$	$4.14\ (3.87 - 4.54)$	< 0.0001
Initial Treatment Approach (%)				< 0.0001
None	106,506 (36.79%)	18,419 (35.20%)	88,087 (37.14%)	
Radical Prostatectomy Only	79,009 (27.29%)	12,064 (23.05%)	66,945 (28.22%)	
Radiation Therapy Only	102,619 (35.44%)	21,573 (41.22%)	81,046 (34.17%)	
Both	1,387 (0.48%)	274 (0.52%)	1,113 (0.47%)	
Clinical Tumor Category (%)				< 0.0001
T1	191,081 (66.00%)	37,368 (71.41%)	157,313 (64.81%)	
T2	97,724 (33.75%)	14,838 (28.35%)	82,886 (34.94%)	
T3	716 (0.25%)	124 (0.24%)	592 (0.25%)	
Age (Yrs) $\boldsymbol{Mean \pm SD}$	65.61 ± 8.48	63.28 ± 8.41	66.13 ± 8.41	< 0.0001
Median Survival Months	57	54	57	< 0.0001
Cause of Death (%)				< 0.0001
Alive	260,601 (90.01%)	46,605 (89.06%)	213,996 (90.22%)	
PCSM[1]	5,170 (1.79%)	975 (1.86%)	4,195 (1.77%)	
Non-PCSM	23,750 (8.20%)	4,750 (9.08%)	19,000 (8.01%)	

[1] Prostate Cancer-Specific Mortality

Table 2. Baseline Clinical & Demographic Characteristics of Patients Diagnosed with Prostate Cancer, by Grade Group

Variable	**Grade Group**					
	1 $n = 128{,}094$ (44.24%)	2 $n = 80{,}626$ (27.85%)	3 $n = 37{,}553$ (12.97%)	4 $n = 25{,}863$ (8.93%)	5 $n = 17{,}385$ (6.00%)	P
Race (%)						< 0.0001
AA	20,895 (16.31%)	15,399 (19.10%)	7,700 (20.50%)	5,168 (19.98%)	3,168 (18.22%)	
White	107,199 (83.69%)	65,227 (80.90%)	29,853 (79.50%)	20,695 (80.01%)	14,217 (81.78%)	
Log-PSA (ng/mL) $\boldsymbol{Median\ (IQR)}$	4.04 $(3.81 - 4.37)$	4.16 $(3.89 - 4.51)$	4.30 $(3.99 - 4.76)$	4.45 $(4.06 - 5.03)$	4.72 $(4.20 - 5.51)$	< 0.0001
Initial Treatment Approach (%)						< 0.0001
None	69,164 (53.99%)	18,543 (23.00%)	7,501 (19.97%)	5,794 (22.40%)	5,504 (31.66%)	
Radical Prostatectomy Only	30,877 (24.10%)	28,581 (35.45%)	10,993 (29.27%)	6,420 (24.82%)	2,138 (12.30%)	
Radiation Therapy Only	27,761 (21.67%)	33,103 (41.06%)	18,781 (50.01%)	13,384 (51.75%)	9,590 (55.16%)	
Both	292 (0.23%)	399 (0.49%)	278 (0.74%)	265 (1.02%)	153 (0.88%)	
Clinical Tumor Category (%)						< 0.0001
T1	93,463 (72.96%)	51,428 (63.79%)	22,580 (60.13%)	14,475 (55.97%)	9,135 (52.55%)	
T2	34,532 (26.96%)	28,971 (35.93%)	14,819 (39.46%)	11,265 (43.56%)	8,137 (46.80%)	
T3	99 (0.08%)	227 (0.28%)	154 (0.41%)	123 (0.48%)	113 (0.65%)	
Age (Yrs) $\boldsymbol{Mean \pm SD}$	63.85 ± 8.09	65.28 ± 8.17	67.31 ± 8.25	69.18 ± 8.42	71.11 ± 8.71	< 0.0001
Median Survival Months	67	54	47	48	40	< 0.0001
Cause of Death (%)						< 0.0001
Alive	118,873 (92.80%)	73,954 (91.72%)	33,433 (89.03%)	21,553 (83.34%)	12,788 (73.56%)	
PCSM	591 (0.46%)	698 (0.87%)	702 (1.87%)	1,143 (4.42%)	2,036 (11.71%)	
Non-PCSM	8,630 (6.74%)	5,974 (7.41%)	3,418 (9.10%)	3,167 (12.24%)	2,561 (14.73%)	

Table 3. Prostate Cancer-Specific Mortality of Patients Diagnosed with Prostate Cancer, by Race and Grade Group

	AA		White	
Grade Group	PCSM $n = 975$	Median Survival Months	PCSM $n = 4{,}195$	Median Survival Months
1	130 (13.33%)	45.5	461 (10.99%)	60
2	162 (16.62%)	64.5	536 (12.78%)	59
3	148 (15.18%)	55	554 (13.21%)	56
4	222 (22.77%)	48.5	921 (21.95%)	49
5	313 (32.10%)	33	1,723 (41.07%)	35

Figure 2 Cumulative Incidence of PCSM by Race

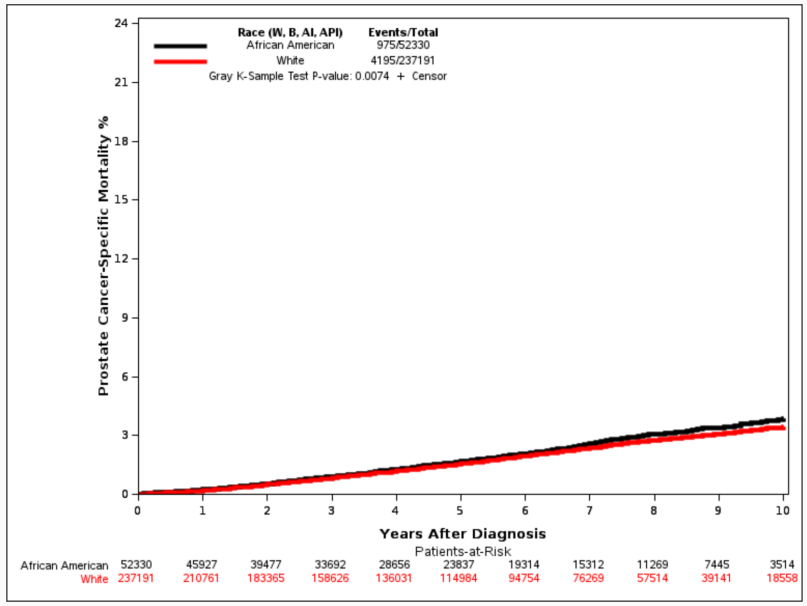


Figure 3 Cumulative Incidence of PCSM by Grade Group

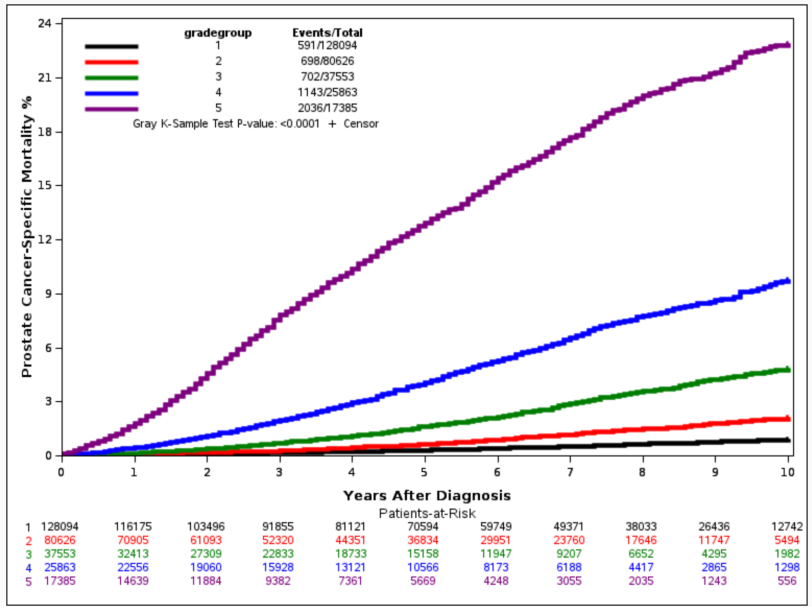


Figure 4 Cumulative Incidence of PCSM by Race in Grade Group 1

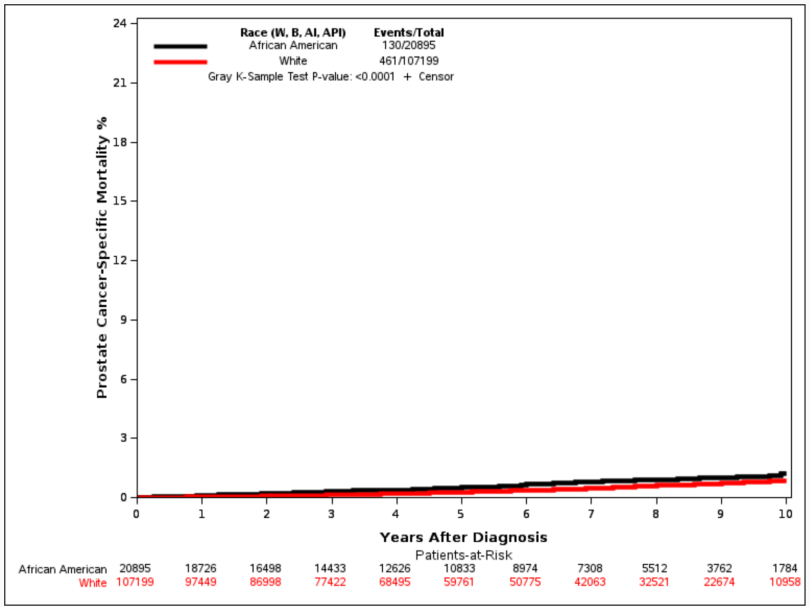


Figure 5 Cumulative Incidence of PCSM by Race in Grade Group 2

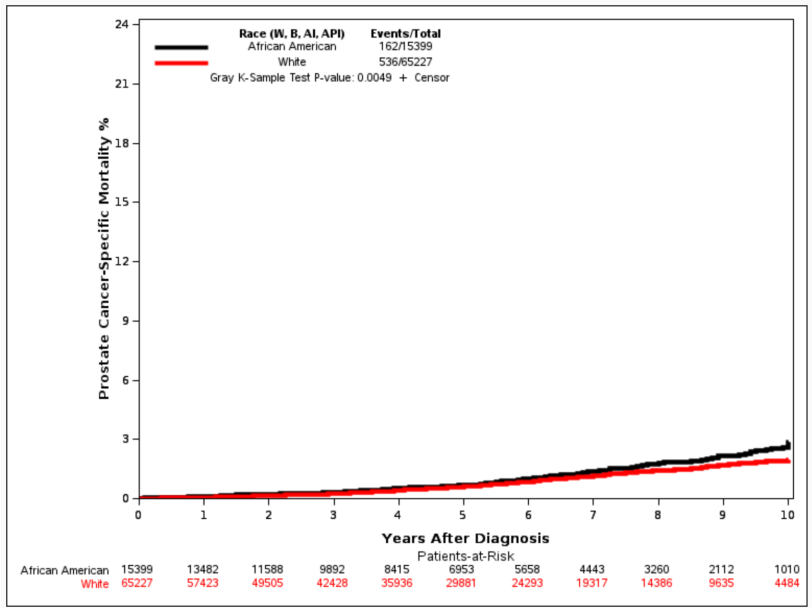


Figure 6 Cumulative Incidence of PCSM by Race in Grade Group 3

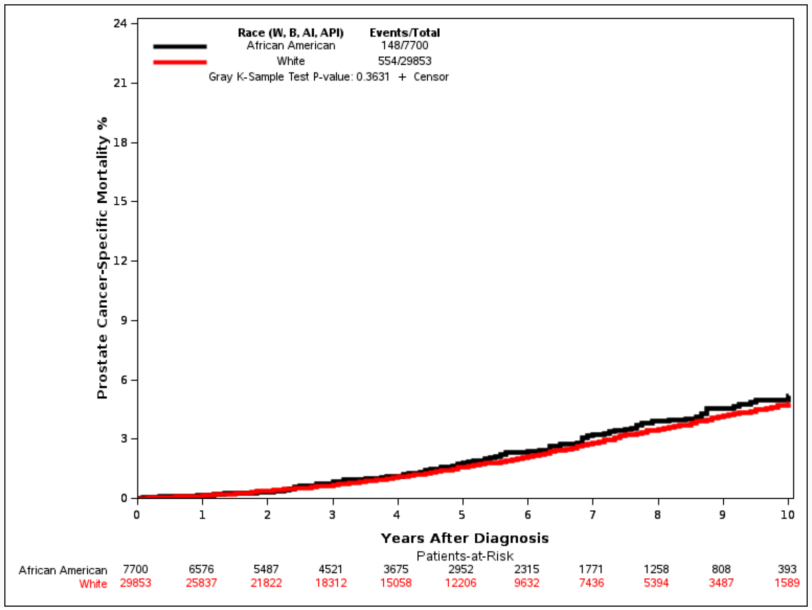


Figure 7 Cumulative Incidence of PCSM by Race in Grade Group 4

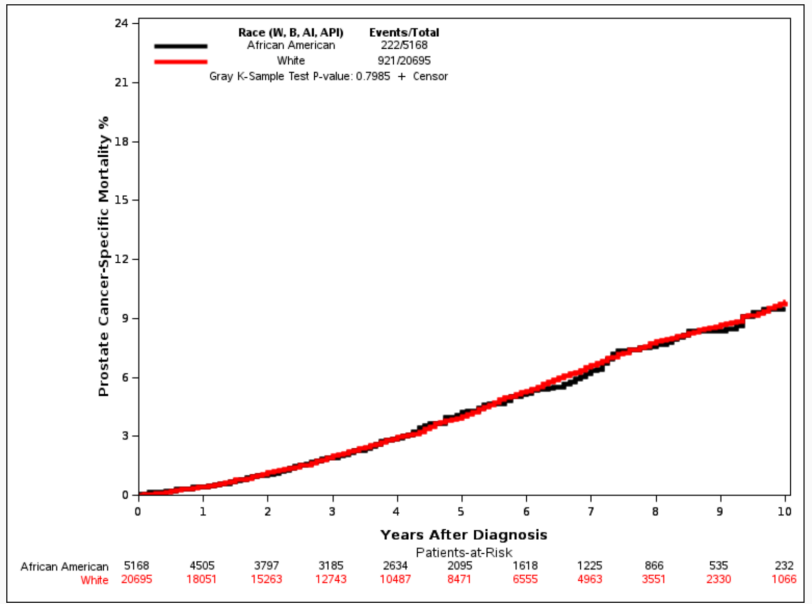


Figure 8 Cumulative Incidence of PCSM by Race in Grade Group 5

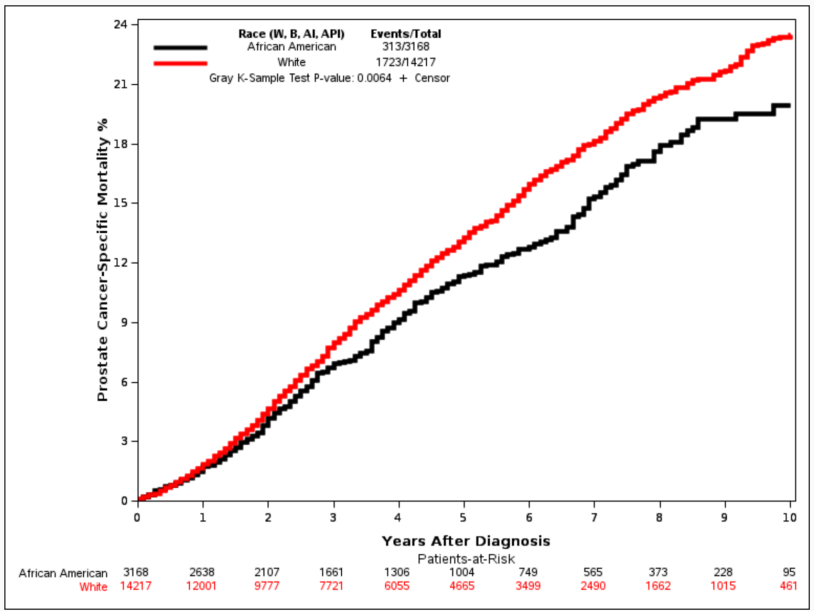


Table 4 Fine-Gray Competing Risks Regression Analysis of PCSM of White and AA Men

Variable	Univariable		Multivariable		Multivariable with Interaction	
	Crude HR (95% CI)	***P***	**Sub-Distribution HR (95% CI)**	***P***	**Sub-Distribution HR (95% CI)**	***P***
Race x Grade Group (GG)						
GG 1: AA vs White	–		–		1.599 (1.316, 1.942)	< 0.0001
GG 2: AA vs White	–		–		1.2124 (1.017, 1.446)	0.0317
GG 3: AA vs White	–		–		1.041 (0.867, 1.248)	0.6683
GG 4: AA vs White	–		–		0.951 (0.820, 1.103)	0.5038
GG 5: AA vs White	–		–		0.854 (0.752, 0.969)	0.0147
Race						
White	1.0 (ref)		1.0 (ref)		–	
AA	1.098 (1.024, 1.177)	0.00087	1.023 (0.950, 1.102)	0.5486	–	
Grade Group						
1	1.0 (ref)		1.0 (ref)		–	
2	2.163 (1.938, 2.413)	< 0.0001	2.526 (2.254, 2.831)	< 0.0001	–	
3	5.044 (4.521, 5.627)	< 0.0001	4.811 (4.274, 5.415)	< 0.0001	–	
4	11.561 (10.470, 12.766)	< 0.0001	8.894 (7.931, 9.973)	< 0.0001	–	
5	34.363 (31.360, 37.654)	< 0.0001	19.288 (17.214, 21.613)	< 0.0001	–	
Log-PSA (ng/mL)	2.914 (2.821, 3.010)	< 0.0001	1.488 (1.433, 1.545)	< 0.0001	1.492 (1.437, 1.549)	< 0.0001
Initial Treatment Approach						
None	1.0 (ref)		1.0 (ref)		1.0 (ref)	
Radical Prostatectomy Only	0.072 (0.063, 0.084)	< 0.0001	0.120 (0.103, 0.139)	< 0.0001	0.120 (0.103, 0.139)	< 0.0001
Radiation Therapy Only	0.555 (0.525, 0.588)	< 0.0001	0.409 (0.385, 0.435)	< 0.0001	0.407 (0.383, 0.433)	< 0.0001
Both	0.576 (0.390, 0.852)	0.0057	0.462 (0.313, 0.681)	< 0.0001	0.458 (0.311, 0.675)	< 0.0001
Age	1.108 (1.103, 1.112)	< 0.0001	1.029 (1.025, 1.033)	< 0.0001	1.028 (1.025, 1.032)	< 0.0001
Clinical Tumor Category						
1	1.0 (ref)		1.0 (ref)		1.0 (ref)	
2	1.622 (1.534, 1.714)	< 0.0001	1.133 (1.070, 1.200)	< 0.0001	1.131 (1.068, 1.198)	< 0.0001
3	2.020 (1.288, 3.166)	0.0022	1.860 (1.156, 2.993)	0.0105	1.843 (1.145, 2.967)	0.0118

Table 5 Cause-Specific Regression Analysis of PCSM of White and AA Men

Variable	Multivariable		Multivariable with Interaction	
	Cause-Specific HR (95% CI)	*P*	Cause-Specific HR (95% CI)	*P*
Race x Grade Group (GG)				
GG 1: AA vs White	–		1.697 (1.397, 2.062)	< 0.0001
GG 2: AA vs White	–		1.261 (1.057, 1.505)	0.01
GG 3: AA vs White	–		1.085 (0.904, 1.302)	0.3789
GG 4: AA vs White	–		0.982 (0.847, 1.139)	0.8147
GG 5: AA vs White	–		0.850 (0.751, 0.961)	0.0094
Race				
White	1.0 (ref)		–	
AA	1.048 (0.974, 1.126)	0.2084	–	
Grade Group				
1	1.0 (ref)		–	
2	2.645 (2.365, 2.957)	< 0.0001	–	
3	5.148 (4.593, 5.770)	< 0.0001	–	
4	9.697 (8.707, 10.800)	< 0.0001	–	
5	22.388 (20.178, 24.839)	< 0.0001	–	
Log-PSA (ng/mL)	1.536 (1.486, 1.588)	< 0.0001	1.541 (1.490, 1.593)	< 0.0001
Initial Treatment Approach				
None	1.0 (ref)		1.0 (ref)	
Radical Prostatectomy	0.109 (0.094, 0.126)	< 0.0001	0.109 (0.094, 0.126)	< 0.0001
Radiation Therapy	0.357 (0.336, 0.379)	< 0.0001	0.355 (0.334, 0.377)	< 0.0001
Both	0.416 (0.279, 0.618)	< 0.0001	0.412 (0.277, 0.613)	< 0.0001
Age	1.044 (1.040, 1.047)	< 0.0001	1.043 (1.039, 1.047)	< 0.0001
Clinical Tumor Category				
1	1.0 (ref)		1.0 (ref)	
2	1.131 (1.069, 1.196)	< 0.0001	1.128 (1.066, 1.193)	< 0.0001
3	1.863 (1.182, 2.935)	0.0073	1.843 (1.170, 2.905)	0.0084

Table 6 Fine-Gray Competing Risks Regression Analysis of Non-PCSM of White and AA Men

Variable	Univariable		Multivariable		Multivariable with Interaction	
	Crude HR (95% CI)	***P***	**Sub-Distribution HR (95% CI)**	***P***	**Sub-Distribution HR (95% CI)**	***P***
Race x Grade Group (GG)						
GG 1: AA vs White	–		–		1.579 (1.497, 1.665)	< 0.0001
GG 2: AA vs White	–		–		1.453 (1.366, 1.546)	< 0.0001
GG 3: AA vs White	–		–		1.380 (1.269, 1.501)	< 0.0001
GG 4: AA vs White	–		–		1.258 (1.148, 1.378)	< 0.0001
GG 5: AA vs White	–		–		1.298 (1.160, 1.452)	< 0.0001
Race						
White	1.0 (ref)		1.0 (ref)		–	
AA	1.200 (1.163, 1.239)	< 0.0001	1.441 (1.394, 1.489)	< 0.0001	–	
Grade Group						
1	1.0 (ref)		1.0 (ref)		–	
2	1.294 (1.252, 1.337)	< 0.0001	1.234 (1.192, 1.277)	< 0.0001	–	
3	1.749 (1.681, 1.819)	< 0.0001	1.343 (1.287, 1.401)	< 0.0001	–	
4	2.291 (2.200, 2.387)	< 0.0001	1.423 (1.360, 1.490)	< 0.0001	–	
5	2.978 (2.849, 3.114)	< 0.0001	1.403 (1.332, 1.478)	< 0.0001	–	
Log-PSA (ng/mL)	1.580 (1.554, 1.607)	< 0.0001	1.122 (1.100, 1.145)	< 0.0001	1.124 (1.101, 1.147)	< 0.0001
Initial Treatment Approach						
None	1.0 (ref)		1.0 (ref)		1.0 (ref)	
Radical Prostatectomy Only	0.198 (0.189, 0.207)	< 0.0001	0.373 (0.355, 0.391)	< 0.0001	0.372 (0.355, 0.391)	< 0.0001
Radiation Therapy Only	0.727 (0.708, 0.747)	< 0.0001	0.711 (0.691, 0.731)	< 0.0001	0.709 (0.689, 0.730)	< 0.0001
Both	0.206 (0.149, 0.284)	< 0.0001	0.331 (0.240, 0.457)	< 0.0001	0.330 (0.239, 0.455)	< 0.0001
Age	1.109 (1.107, 1.111)	< 0.0001	1.087 (1.085, 1.089)	< 0.0001	1.087 (1.085, 1.089)	< 0.0001
Clinical Tumor Category						
1	1.0 (ref)		1.0 (ref)		1.0 (ref)	
2	1.158 (1.128, 1.190)	< 0.0001	1.059 (1.031, 1.088)	< 0.0001	1.058 (1.030, 1.087)	< 0.0001
3	0.555 (0.380, 0.809)	0.0022	0.881 (0.599, 1.296)	0.5202	0.878 (0.596, 1.292)	0.5079

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