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14. ABSTRACT
Active surveillance (AS) is an appropriate method to avoid overtreatment for many men with early prostate cancer (PC). However, whether African-American (AA) men can safely undergo AS is controversial due to the higher risk of death from PC and the lack of data on AS in this population. We identified 5,774 men (1,456 AA, 4,318 non-Hispanic White (NHW)) that were initially managed with AS. Progression to definitive treatment was more common in AA men than NHW men (10-year cumulative incidence: 60.7% AA vs. 49.1% NHW, subdistribution hazard ratio (SHR) 1.18, p< 0.01). Of those who proceeded to treatment, progression to Gleason Score 7 or higher was the most common reason (52.3% AA vs 43.1%, p < 0.01). There were no significant differences in the cumulative incidence of metastases (10-year cumulative incidence: 1.96% AA vs. 2.80% NHW, SHR: 0.92, p=0.81), death from prostate cancer, (10-year cumulative incidence: 1.00% AA vs. 0.86% NHW, SHR: 1.16, p=0.69), or all-cause mortality (10-year cumulative incidence: 15.9% AA vs. 17.4% NHW, SHR: 0.91, p=0.14). Although progression to definitive treatment was higher, we found no evidence that metastasis or death from prostate cancer was more common in AA men.

15. SUBJECT TERMS
Prostate cancer, active surveillance, African-American, Race, Disparity

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1. Introduction:

Active surveillance (AS) is an appropriate method to avoid overtreatment for many men with early prostate cancer (PC). However, whether African-American men can safely undergo AS is controversial. Black men are 70% more likely to be diagnosed and 240% more likely to die from PC than White men suggesting their disease may behave more aggressively. Furthermore, very few Black men have been included in AS studies. We hypothesize that African-American men managed in a high quality, equal access health care system can safely undergo with AS with rates of disease progression and oncologic outcomes that are comparable to non-African-American patients. Our study will employ the novel dataset of Veterans Affairs Health System patients from within the VINCI research platform. To test our hypothesis, we will identify Black and White men with low-risk PC who underwent active surveillance. We will then determine the rates of PSA progression, pathologic upgrading, and subsequent definitive therapy. We will report cancer outcomes for Black and White men managed with AS. We will seek to identify specific triggers for definitive therapy by investigating risk factors for metastases and PCSM in those undergoing AS. We also hypothesize that NLP tools can extract information from unstructured or semi-structured health records. This will unlock an enormous amount of information to enhance outcomes research for this and many other projects. These data will serve to differentiate indolent from aggressive disease and improve the physical health and quality of life of African-American men with PC by limiting overtreatment and unnecessary side effects.

2. **Keywords:** Prostate cancer, active surveillance, African-American, Race, Disparity

3. Accomplishments:

a. What were the major goals of the project?

Major Task 1: Development of active surveillance cohort and assessment of follow-up

- Subtask 1: Obtain UCSD IRB
- Subtask 2: DoD-Level human research protection approval
- Subtask 3: Acquire and clean VINCI data in preparation for data analysis
- Subtask 4: Characterize the frequency of repeat PSA testing and prostate biopsy
- Subtask 5: Identify AS cohort defined by PSA frequency and repeat biopsy
- Subtask 6: Obtain important baseline covariates not included in standard structured databases through manual chart-review

Major Task 2: Investigate rates of disease progression and need for definitive treatment in men undergoing active surveillance

- Subtask 1: To determine the rates of PSA progression and PSA doubling time
- Subtask 2: To determine the rates of Gleason and volume upgrading on repeat biopsy
- Subtask 3: To determine the rate of subsequent definitive therapy

Major Task 3: Investigate oncologic outcomes and triggers for intervention in men undergoing active surveillance

- Subtask 1: To determine the rate of metastasis, prostate cancer-specific mortality and overall survival for African-American and White men managed with active surveillance
- Subtask 2: To identify specific triggers for definitive therapy in men undergoing active surveillance

Major Task 4: Development and validation of Natural Language Processing (NLP) algorithms

- Subtask 1: To develop NLP algorithm to extract and classify biopsy data from pathology reports
- Subtask 2: To validate the NLP biopsy algorithm in an independent group of patients
- Subtask 3: To develop NLP algorithm to identify the first diagnosis of metastases from radiology reports and clinical notes
- Subtask 4: To validate the NLP metastasis algorithm in an independent group of patients

b. What was accomplished under these goals?

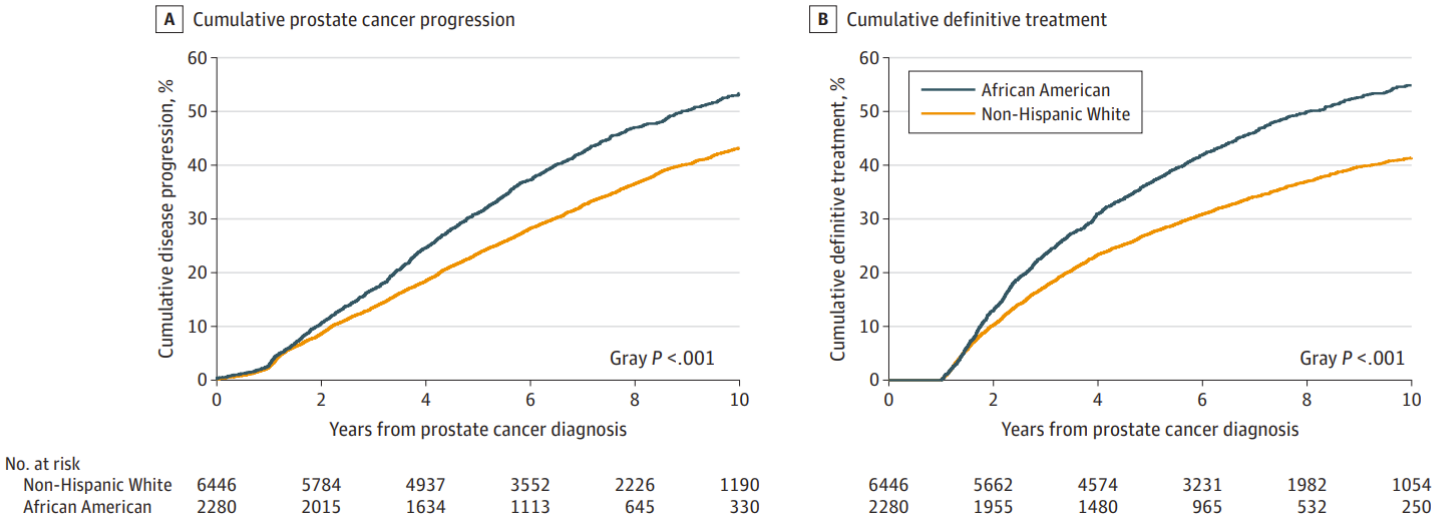
Major Task 1

Major Task 1 and all associated sub tasks were completed in the prior reporting period.

Major Task 2

During this reporting period Major task 2 and all subtasks were completed and published in the *Journal of the American Medical Association* (JAMA) (Deka et al, JAMA, 2020). Briefly, we sought to identify the rates of PSA progression, Gleason score progression, and need for definitive treatment for African American and Non-Hispanic White men undergoing active surveillance. We then sought to compare the rates to test the hypothesis that African American men would have higher risk of progression. We found that African American men were at significantly higher risk of disease progression (10-year cumulative incidence of disease progression: 59.9% vs 48.3%, $P < 0.001$) and required definitive treatment more frequently (10-year cumulative incidence of definitive treatment: 54.8% vs 41.4%, $P < 0.001$) (figure 1). These findings suggest that active surveillance in African American men requires heightened level of vigilance to avoid missing early disease progression and the opportunity to offer curative therapy.

Figure 1



Major Task 3

During this reporting period Major task 3, subtask 1 was completed and also published in the *Journal of the American Medical Association* (JAMA) (Deka et al, JAMA, 2020). Despite the higher risk of PSA and Gleason grade progression, we found that rates of metastases and death from cancer were very low for both African American men initially managed with active surveillance (Table 1).

Table 1

End point	10-y Cumulative incidence No. (%) African American men[a] (n = 2280)	Non-Hispanic White men[a] (n = 6446)	Absolute difference, % (95% CI)	Subdistribution hazard ratio (95% CI)
Disease progression[b]	1156 (59.9)	2610 (48.3)	11.6 (9.2 to 13.9)	1.3 (1.2 to 1.4)
Definitive treatment[c]	1137 (54.8)	2438 (41.4)	13.4 (11.0 to 15.7)	1.3 (1.2 to 1.4)
Metastasis[d]	30 (1.5)	79 (1.4)	0.1 (-0.4 to 0.6)	1.2 (0.8 to 1.9)
Prostate cancer-specific mortality	22 (1.1)	65 (1.0)	0.1 (-0.4 to 0.6)	1.2 (0.7 to 2.1)
Nonprostate cancer-specific mortality	387 (21.2)	1265 (22.4)	1.2 (-0.7 to 3.2)	1.0 (0.9 to 1.1)
All-cause mortality	409 (22.4)	1330 (23.5)	1.1 (-0.9 to 3.1)	1.0 (0.9 to 1.1)[e]

[a] Self-reported race.

[b] Disease progression was defined as an increase in prostate-specific antigen level greater than 10 ng/dL, pathologic Gleason score greater than 6 (Gleason Grade Group >1), or development of metastases at any point during follow-up.

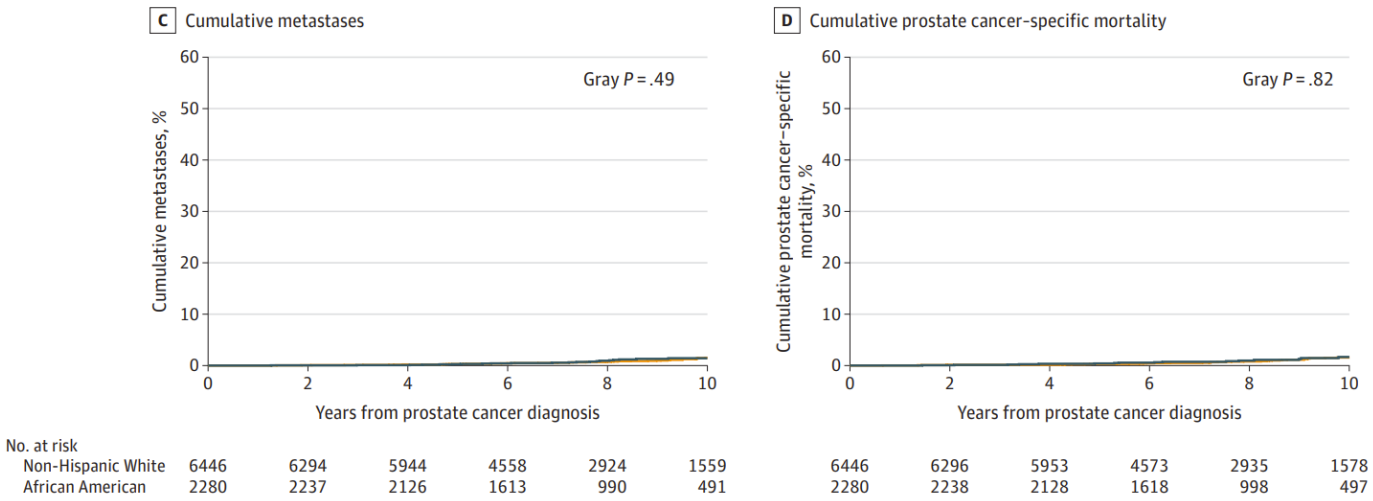
[c] Receipt of radiation therapy or prostatectomy.

[d] Prostate cancer spread to lymph nodes outside the pelvis or metastases in bones or other organs.

[e] Hazard ratio (95% CI).

Furthermore, African American men were not more likely to experience metastases that Non-Hispanic White men (10-year cumulative incidence 1.5% vs 1.4%, P = .49) or to die from their disease 10-year cumulative incidence 1.1% vs 1.0%, P = .82) (figure 2). Note that the curves on the graph are somewhat difficult to see because the event rates are very low.

Figure 2



Major Task 3, Subtask 2 (To identify specific triggers for definitive therapy in men undergoing active surveillance) is currently in progress. We are working to identify optimal triggers for repeat biopsy or definitive treatment. Progress will be reported in the next annual report.

Major Task 4

Major Task 4 was to develop and validate natural language processing (NLP) tools to extract structured data from unstructured text. We have made significant progress and believe NLP can be used to interpret biopsy and prostatectomy pathology reports. At this time we need to

perform a formal validation to quantify the efficacy of this NLP. This will likely be completed during the next reporting period. We have also had some success developing NLP algorithms for metastases though these will take more time to develop.

c. What opportunity for training and professional development has the project provided? This project has provided immense opportunities for professional development. Dr. Rose has closely collaborated with the mentors of the grant who are international leaders in the fields of prostate cancer and health disparities. They have been collaborating in both informal work and mentoring sessions as well as formal departmental and Health System-wide research presentations.

d. How were the results disseminated? The results of this work have been published in one of the most important medical journals, *The Journal of the American Medical Association (JAMA).* JAMA has an impact factor of 47.7. JAMA is also the most widely circulated medical journal in the world according to JAMA's website. The paper was also published with an accompanying editorial (Shen JAMA 2020). The work has also been covered extensively in the lay press.

e. What do you plan to do during the next reporting period to accomplish additional goals? During the next reporting period we will plan to complete the remainder of Major Task 3 and to continue working on Major Task 4. We will also focus on developing next steps

f. Impact:

a. What was the impact on the development of the principle discipline? Our publication in JAMA showed that active surveillance in safe and effective in African American men. This

finding is critically important for the African American community for several reasons. First, low risk prostate cancer is extremely common in Black men. Prior to our work, the prevailing opinion was that active surveillance was not safe for Black men. This led to aggressive treatment and the associated side effects including erectile dysfunction, urinary incontinence and bowel problems. Due to our work many men will be able to safely undergo active surveillance and avoid these side effects. Additionally, the availability of active surveillance makes PSA screening more palatable since it reduces the main harm of screening which is overdiagnosis and overtreatment of indolent disease.

b. What was the impact on other disciplines? These findings have clear and important implications for urologists, medical oncologists, and radiation oncologists. However, these results are also very important for primary care providers as they can substantially reduce the risk of PSA screening by reducing overtreatment of indolent disease. Finally, these results are very important for those who care about the role of access to medical care as a determinant of health care outcomes. We believe that one of the strengths of the study and the reason outcomes were similar is that the Veterans Health Administration reduces barrier to receipt of medical care which helps to reduce racial disparities.

c. What was the impact on technology transfer? Nothing to report

d. What was the impact to society beyond science and technology? The impact on society from this project is substantial. We believe that one of the strengths of the study and the reason outcomes were similar is that the Veterans Health Administration reduces barrier to receipt of medical care which helps to reduce racial disparities. This project is part of a line of research in our lab that is actively attempting to clarify whether poorer outcomes for African Americans is do to differences in biology or rather the result of barriers to receiving optimal medical care. On balance, we have found that when receiving care in an equal access

medical system like the Veterans Health Administration outcomes for African American men are equal to similar Non-Hispanic White men. These results have critical implications for health policy and social justice.

g. **Changes/Problems:** Nothing to report

h. **Products:** See attached publication and accompanying editorial.

i. Participants and other Collaborating Organizations:

Participating individuals

Name:	Brent S. Rose, MD
Project Role:	PI
Researcher Identifier (e.g. ORCID ID):	None
Nearest person month worked:	6
Contribution to Project:	Dr. Rose has performed and overseen the entire analysis including IRB approval, data preparation, and analysis.
Funding Support:	-DOD grant PC171106 (present award) -Department of Radiation Medicine at the University of California, San Diego
Name:	Rishi Deka
Project Role:	Post-doc
Researcher Identifier (e.g. ORCID ID):	none
Nearest person month worked:	6
Contribution to Project:	Dr. Deka has performed work processing and analyzing data for this project
Funding Support:	-DOD grant PC171106 (present award) -Department of Radiation Medicine at the University of California, San Diego

Active other support: Nothing to report

j. **Special reporting Requirements:** Nothing to report

k. **Appendices:** Nothing to report

JAMA | Original Investigation

Association Between African American Race and Clinical Outcomes in Men Treated for Low-Risk Prostate Cancer With Active Surveillance

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IMPORTANCE There is concern that African American men with low-risk prostate cancer may harbor more aggressive disease than non-Hispanic White men. Therefore, it is unclear whether active surveillance is a safe option for African American men.

OBJECTIVE To compare clinical outcomes of African American and non-Hispanic White men with low-risk prostate cancer managed with active surveillance.

DESIGN, SETTING, AND PARTICIPANTS Retrospective cohort study in the US Veterans Health Administration Health Care System of African American and non-Hispanic White men diagnosed with low-risk prostate cancer between January 1, 2001, and December 31, 2015, and managed with active surveillance. The date of final follow-up was March 31, 2020.

EXPOSURES Active surveillance was defined as no definitive treatment within the first year of diagnosis and at least 1 additional surveillance biopsy.

MAIN OUTCOMES AND MEASURES Progression to at least intermediate-risk, definitive treatment, metastasis, prostate cancer–specific mortality, and all-cause mortality.

RESULTS The cohort included 8726 men, including 2280 African American men (26.1%) (median age, 63.2 years) and 6446 non-Hispanic White men (73.9%) (median age, 65.5 years), and the median follow-up was 7.6 years (interquartile range, 5.7-9.9; range, 0.2-19.2). Among African American men and non-Hispanic White men, respectively, the 10-year cumulative incidence of disease progression was 59.9% vs 48.3% (difference, 11.6% [95% CI, 9.2% to 13.9%); $P < .001$); of receipt of definitive treatment, 54.8% vs 41.4% (difference, 13.4% [95% CI, 11.0% to 15.7%]; $P < .001$); of metastasis, 1.5% vs 1.4% (difference, 0.1% [95% CI, −0.4% to 0.6%]; $P = .49$); of prostate cancer–specific mortality, 1.1% vs 1.0% (difference, 0.1% [95% CI, −0.4% to 0.6%]; $P = .82$); and of all-cause mortality, 22.4% vs 23.5% (difference, 1.1% [95% CI, −0.9% to 3.1%]; $P = 0.09$).

CONCLUSIONS AND RELEVANCE In this retrospective cohort study of men with low-risk prostate cancer followed up for a median of 7.6 years, African American men, compared with non-Hispanic White men, had a statistically significant increased 10-year cumulative incidence of disease progression and definitive treatment, but not metastasis or prostate cancer–specific mortality. Longer-term follow-up is needed to better assess the mortality risk.

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Active surveillance is the preferred treatment option for many men with low-risk prostate cancer to avoid or delay the adverse effects of definitive treatments. However, there is concern that African American men with early-stage cancer may harbor more aggressive disease than non-Hispanic White men and may not be good candidates for active surveillance.[1-3] Consequently, there has been lower uptake of active surveillance in African American men,[4] potentially leading to an increased burden of treatment-related adverse effects, including urinary incontinence, erectile dysfunction, and rectal bleeding.

There have been sparse data on clinical outcomes in African American men treated with active surveillance. Published studies have generally shown that African American individuals have significantly higher rates of pathologic upgrading and treatment progression.[5-9] However, these studies have been limited by small sample size, short follow-up, and lack of important clinical outcomes such as metastasis, prostate cancer-specific mortality, and all-cause mortality.

The US Veterans Health Administration (VHA) Health Care System is an equal-access medical care system with a high proportion of African American men and an integrated medical record system. This study sought to test the hypothesis that African American men undergoing active surveillance are at a significantly higher risk of disease progression, metastases, and death from prostate cancer compared with non-Hispanic White men.

Key Points

Question Is active surveillance a safe and effective option for African American men with low-risk prostate cancer?

Findings In this retrospective cohort study that included 8726 men with low-risk prostate cancer followed up for a median of 7.6 years, African American men, compared with non-Hispanic White men, had a statistically significant increased 10-year cumulative incidence of disease progression (59.9% vs 48.3%) and definitive treatment (54.8% vs 41.4%), but not metastasis (1.5% vs 1.4%) or prostate cancer–specific mortality (1.1% vs 1.0%).

Meaning Among African American men with low-risk prostate cancer, active surveillance was associated with increased risk of disease progression and definitive treatment compared with non-Hispanic White men, but not increased mortality; however, longer-term follow-up is needed to better understand mortality risk.

Methods

Study Design

This was a retrospective cohort study of African American and non-Hispanic White men (hereafter, White men) with pathologically confirmed low-risk prostate cancer diagnosed between January 1, 2001, and December 31, 2015, who underwent active surveillance in the US VHA. The last follow-up was the date of the event of interest, the last VHA encounter, or March 31, 2020, whichever occurred first. Active surveillance was defined as no definitive treatment within the first year of prostate cancer diagnosis and at least 1 additional biopsy after the first diagnostic biopsy. Low-risk prostate cancer was defined as a Gleason score of 6 or less, clinical tumor stage of 2A or less, and prostate-specific antigen (PSA) level less than 10 ng/dL.[10] Patients with prior pelvic radiation, those with missing covariates (defined below), and men who were neither African American nor White were excluded. Race/ethnicity was self-reported by each veteran and based on fixed categories.

Data

All study data were extracted from the VHA's Corporate Data Warehouse and accessed through the VHA Informatics and Computing Infrastructure.[11] The VHA Corporate Data Warehouse contains electronic health records of more than 9 million veterans from the years 2000 to 2020 who receive care at approximately 1244 health care facilities, including 170 medical centers and 1074 outpatient clinics throughout the US.[11] This study was reviewed and approved by the VHA San Diego Health Care System (Institutional Review Board Protocol No. 150169). This approval included a waiver of informed consent.

Outcomes

The end points of interest were disease progression, definitive treatment, metastasis, prostate cancer–specific mortality, nonprostate cancer–specific mortality, and all-cause mortality. Disease progression was defined as an increase of PSA level to 10 ng/dL or greater, a pathologic Gleason score greater than 6 (Gleason Grade Group >1), or the development of metastases. Pathologic Gleason score was identified through natural language processing of all biopsy and prostatectomy reports. A validation analysis of the natural language processing algorithm in 100 randomly selected patients with manual medical record review revealed 95% concordance with no significant difference in accuracy between African American and White men.

Definitive treatment was identified through analysis of diagnosis and procedural codes and augmented by manual medical record review. *International Classification of Diseases, Ninth Revision* (*ICD-9*) and *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* (*ICD-10*) diagnosis codes; *ICD-9* and *ICD-10* procedure codes; and *Current Procedural Terminology* codes were first searched in the VHA Corporate Data Warehouse to determine receipt of radiotherapy or prostatectomy. To identify care received outside of the VHA, diagnosis and procedure codes were searched in outpatient and inpatient files in Centers for Medicare and Medicaid Services Data and Non-VHA Care Coordination Data linked to the VHA Corporate Data Warehouse. Furthermore, manual medical record review was conducted for patients with a PSA level decline of at least 50% at any time after prostate cancer diagnosis to screen for receipt of definitive treatment not identified with the previously described methods.

Identification of metastatic prostate cancer was identified through targeted medical record review. Manual review of electronic medical records was performed for patients who met any of the following criteria:

1. *ICD-9* or *ICD-10* codes for metastasis of the bone (198.5, C79.51, and C79.52) or malignant neoplasm of nonpelvic lymph nodes (196.0, 196.1, 196.2, 196.3, 196.5, 196.8, 196.9, C77.0, C77.1, C77.2, C77.3, C77.4, C77.8, and C77.9);

2. PSA level greater than 20 ng/dL;
3. Receipt of androgen deprivation therapy.

Manual review of the medical records of 100 patients who did not fulfill these criteria did not find any cases of missed metastases. Prostate cancer–specific mortality, nonprostate cancer–specific mortality, and all-cause mortality were identified through the National Death Index and manual medical record review. Because National Death Index data extended only through 2015, manual medical record review of patients recorded as deceased after 2015 in the VHA Corporate Data Warehouse was performed to determine cause of death.

Clinical outcomes were modeled as a function of African American race, age, baseline PSA level, clinical tumor stage, Charlson Comorbidity Index score,[12] statin use, antiplatelet use, antihypertensive use, alcohol use disorder, substance use disorder, smoking status, region, zip code–level median household income and education, and year of diagnosis. Median household income and education were assigned to an individual's zip code based on census variables from the American Community Survey.[13] Clinical tumor stage was categorized as 1 and 2; median household income as less than $30 000, $30 000 to less than $60 000, $60 000 to less than $100 000, and $100 000 or more; percentage with a bachelor's degree as less than 10%, 10% to less than 20%, 20% to less than 30%, and 30% or more; region as West, Midwest, South, and Northeast; and race as African American and White. Age and PSA levels were continuous variables. Alcohol use disorder, substance use disorder, and smoking status were ascertained through the following *ICD-9* and *ICD-10* codes within the year prior to prostate cancer diagnosis: alcohol use disorder: 305.0, 305.00-305.03, F10.10, and F10.11; substance use disorder: 305.2-305.9, 305.20-305.23, 305.30-305.33, 305.40-305.43, 305.50-305.53, 305.60-305.63, 305.70-305.73, 305.80-305.83, 305.90-305.93, F11.10, F11.11, F12.10, F12.11, F13.10, F13.11, F14.10, F14.11, F15.10, F15.11, F16.10, F16.11, F18.10, F18.11, F19.10, F19.11, 304.0-304.9, 304.00-304.03, 304.10-304.13, 304.20-304.23, 304.30-304.33, 304.40-304.43, 304.50-304.53, 304.60-304.63, 304.70-304.73, 304.80-304.83, 304.90-304.93, F11.20, F11.21, F12.20, F12.21, F13.20, F13.21, F14.20, F14.21, F15.20, F15.21, F16.20, F16.21, F19.20, and F19.21; and tobacco use disorder: 305.1 and F17.200.

Statistical Analysis

All statistical analyses were performed using SAS version 9.2 (SAS Institute), R Studio version 3.5.1 (The R Foundation), and Stata version 13 (StataCorp), assuming a 2-sided α of .05. Because there was no a priori designation of a primary outcome, the study design may predispose to type I error due to multiple comparisons. Therefore, a sensitivity analysis using a post hoc Bonferroni correction was performed for all clinical outcomes. There were 6 outcomes and the corrected significance threshold was 0.008. All conclusions were the same without Bonferroni correction, and the analyses reported in the article are uncorrected. The Gray test was used to evaluate differences in the cumulative incidences of clinical outcomes between African American and White men. Differences in categorical variables were assessed with χ^2 tests, and differences in continuous variables were assessed with Wilcoxon tests.

Disease progression, definitive treatment, metastasis, prostate cancer–specific mortality, and nonprostate cancer–specific mortality were assessed using Fine-Gray competing risks regression. For disease progression, definitive treatment, and metastasis, death from any cause was a competing event; for prostate cancer–specific mortality, nonprostate cancer death was a competing event; and for nonprostate cancer–specific mortality, prostate cancer death was a competing event. All-cause mortality was assessed with Cox proportional hazards regression. The assumption of proportional hazards was tested using graphical inspection of Schoenfeld residuals and no violation was seen.

Among those who met inclusion criteria, 37 participants (0.4% of the total cohort) were excluded for missing data on zip code–level income or education. No other patients who met inclusion criteria were excluded for missing data.

Results

Study Population

The cohort included 8726 men with low-risk prostate cancer managed with active surveillance, of which 2280 (26.1%) were African American and 6446 (73.9%) were White (**Figure 1**). **Table 1** describes the characteristics of the cohort. African American men had a significantly lower median age at diagnosis compared with White men (63.2 vs 65.5 years) and were significantly more likely to present with a lower clinical tumor stage. Additionally, African American men were significantly more likely to use antihypertensive and antiplatelet medications, and had significantly higher rates of alcohol, substance, and tobacco use disorders. Compared with White men, African American men were significantly more likely to live in the South and in areas with lower zip code–level median household income and education levels.

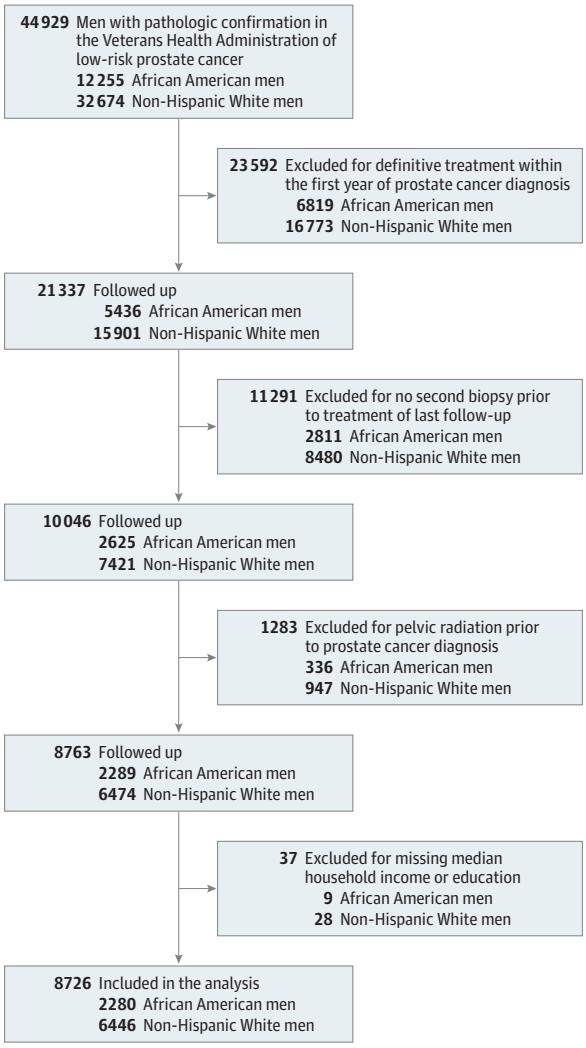
The median number of PSA tests was 12 (interquartile range [IQR], 8-17) among African American participants, and 12 (IQR, 8-17) among White participants (P = .34). The median number of biopsies was 2 (IQR, 2-3) among African American participants and 2 (IQR, 2-3) among White participants; this difference was statistically significant (P = .02). The median time to second biopsy was not significantly different between African American and White men (both 3.5 years, P = .87).

The median follow-up time for the entire cohort was 7.6 years (IQR, 5.7-9.9; range, 0.2-19.2), with no significant difference in the length of follow-up between African American men (7.4 years; IQR, 5.7-9.6; range, 0.2-18.2) and White men (7.6 years; IQR, 5.7-9.9; range, 0.2-19.2) (P = .14) (Table 1). A total of 2081 patients were followed up for at least 10 years (499 African American men [21.9%] and 1582 White men [24.5%]).

Disease Progression

During the study follow-up, 3766 patients experienced disease progression (1156 African American and 2610 White men). The cumulative incidence of disease progression at 10 years

Figure 1. Active Surveillance Cohort Flow Chart



was 59.9% for African American and 48.3% for White men (**Table 2** and **Figure 2**A; difference, 11.6% [95% CI, 9.2%-13.9%); Gray $P < .001$). In the multivariable competing risks regression, African American men were significantly more likely to experience disease progression (subdistribution hazard ratio [SHR], 1.3 [95% CI, 1.2-1.4]; $P < .001$). African American men were significantly more likely to experience a PSA level of 10 ng/dL or greater (SHR, 1.3 [95% CI, 1.1-1.5]; $P < .001$) and significantly more likely to experience a Gleason score greater than 6 (SHR, 1.4 [95% CI, 1.2-1.5]; $P < .001$) after diagnosis.

Definitive Treatment

A total of 3575 patients received definitive treatment (1137 African American and 2438 White men). The cumulative incidence of definitive treatment at 10 years was 54.8% for African American men and 41.4% for White men (Table 2 and Figure 2B; difference, 13.4% [95% CI, 11.0%-15.7%]; Gray $P < .001$). In the multivariable competing risks regression, African American men were significantly more likely to receive definitive treatment (SHR, 1.3 [95% CI, 1.2-1.4]; $P < .001$).

Metastasis

During the study follow-up, 109 men experienced metastatic prostate cancer, including 30 African American and 79 White men. The cumulative incidence of metastasis at 10 years was 1.5% for African American men and 1.4% for White men (Table 2 and Figure 2C; difference, 0.1% [95% CI, -0.4% to 0.6%]; Gray $P = .49$). In the multivariable competing risks regression, African American men were not significantly more likely to experience metastasis (SHR, 1.2 [95% CI, 0.8-1.9]; $P = .48$).

Mortality

A total of 87 patients experienced death from prostate cancer, including 22 African American and 65 White men. The cumulative incidence of prostate cancer-specific mortality at 10 years was 1.1% for African American men and 1.0% for White men (Table 2 and Figure 2D; difference, 0.1% [95% CI, -0.4% to 0.6%]; Gray $P = .82$). In the multivariable competing risks regression, African American men were not significantly more likely to experience prostate cancer-specific mortality (SHR, 1.2 [95% CI, 0.7-2.1]; $P = .82$). During the study follow-up, a total of 1652 men experienced nonprostate cancer death, including 387 African American men and 1265 White men. The cumulative incidence of nonprostate cancer death at 10 years was 21.2% for African American men and 22.4% for White men (Table 2; difference, 1.2% [95% CI, -0.7% to 3.2%]; Gray $P = .14$).

In the multivariable competing risks regression, African American men were not significantly more likely to experience nonprostate cancer mortality (SHR, 1.0 [95% CI, 0.9-1.1]; $P = .70$). A total of 1739 patients experienced death from any cause, including 409 African American men and 1330 White men. The cumulative incidence of all-cause mortality at 10 years was 22.4% for African American men and 23.5% for White men (Table 2 and Figure 2E; difference, 1.1% [95% CI, -0.9% to 3.1%]; Gray $P = .09$). In the multivariable Cox proportional hazards regression, African American men were not significantly more likely to experience all-cause mortality (SHR, 1.0 [95% CI, 0.9-1.1]; $P = .85$).

Discussion

In this retrospective cohort study of 8726 men with low-risk prostate cancer managed with active surveillance and followed up for a median of 7.6 years, African American men, compared with White men, had a statistically significant increased 10-year cumulative incidence of disease progression and definitive treatment, but not metastasis or prostate cancer-specific mortality. Longer-term follow-up is needed to better assess the mortality risk.

Active surveillance is the preferred treatment option for many men with low-risk prostate cancer to avoid or delay the adverse effects of definitive treatments.[14] Major surveillance cohort studies have consistently shown favorable mortality outcomes with 10-year cancer-specific survival ranging from 97% to 100%.[15-21] However, these studies included very few African American men. There are several reasons to question the generalizability of previously published studies performed in predominantly White patients to the

Table 1. Demographics and Baseline Characteristics of African American and Non-Hispanic White Men Undergoing Prostate Cancer Active Surveillance

Variable	No. (%)		Absolute difference, % (95% CI)
	African American men[a]	Non-Hispanic White men[a]	
Patients, No.	2280	6446	
Time to follow-up, median (IQR), y	7.4 (5.7 to 9.6)	7.6 (5.7 to 9.9)	0.2 (0.1 to 0.3)
Age, median (IQR), y	63.2 (58.3 to 67.1)	65.5 (62.3 to 69.5)	2.4 (2.1 to 2.7)
Prostate-specific antigen level, median (IQR), ng/dL[b]	5.2 (4.2 to 6.6)	5.2 (4.2 to 6.6)	0 (-0.09 to 0.09)
Year of prostate cancer diagnosis			
2001-2005	137 (6.0)	499 (7.7)	1.7 (0.5 to 2.8)
2006-2010	739 (32.4)	2301 (35.7)	3.3 (1.0 to 5.5)
2011-2015	1404 (61.5)	3646 (56.5)	5.0 (2.6 to 7.3)
Clinical tumor stage[c]			
1	2073 (90.9)	5471 (84.8)	6.1 (4.6 to 7.5)
2	207 (9.0)	975 (15.1)	6.1 (4.6 to 7.5)
Charlson Comorbidity Index score[d]			
0	1815 (79.6)	4968 (77.0)	2.6 (0.6 to 4.5)
1	367 (16.1)	1242 (19.2)	3.1 (1.3 to 4.8)
≥2	98 (4.3)	236 (3.6)	0.7 (-0.2 to 1.6)
Region[e]			
South	1161 (50.9)	2136 (33.1)	17.8 (15.4 to 20.1)
Midwest	379 (16.6)	1556 (24.1)	7.5 (5.6 to 9.4)
West	269 (11.8)	1596 (24.7)	12.9 (11.2 to 14.5)
Northeast	471 (20.6)	1158 (17.9)	2.7 (0.8 to 4.6)
Proportion of zip code with at least a bachelor's degree, %[f]			
<10	677 (29.6)	1353 (20.9)	8.7 (6.5 to 10.8)
10 to <20	1071 (46.9)	3177 (49.2)	2.3 (-0.08 to 4.6)
20 to <30	415 (18.2)	1484 (23.0)	4.8 (2.9 to 6.6)
≥30	117 (5.1)	432 (6.7)	1.6 (0.5 to 2.6)
Median household income, $[g]			
<30 000	394 (17.2)	228 (3.5)	13.7 (12.1 to 15.3)
30 000 to <60 000	1436 (62.9)	4271 (66.2)	3.3 (1.0 to 5.6)
60 000 to <100 000	420 (18.4)	1757 (27.2)	8.8 (6.8 to 10.7)
≥100 000	30 (1.3)	190 (2.9)	1.6 (0.9 to 2.2)
Statin use within prior year	1,110 (48.6)	3315 (51.4)	2.8 (0.4 to 5.2)
Antiplatelet use within prior year	517 (22.6)	925 (14.3)	8.3 (6.4 to 10.2)
Antihypertensive use within prior year	1707 (74.8)	4091 (63.4)	11.4 (9.2 to 13.5)
Cigarette use within prior year[h]	498 (21.8)	1157 (17.9)	3.9 (1.9 to 5.8)
Alcohol use disorder within prior year[h]	132 (5.7)	277 (4.3)	1.4 (0.3 to 2.5)
Substance use disorder within prior year[h]	603 (26.4)	1225 (19.0)	7.4 (5.3 to 9.4)

Abbreviation: IQR, interquartile range.

[a] Self-reported race.

[b] Prostate-specific antigen level less than 10 ng/dL is required to be considered low risk.

[c] Clinical tumor stage 1: cancer is nonpalpable and does not extend beyond prostate; and stage 2: cancer is palpable and does not extend beyond prostate.

[d] The Charlson Comorbidity Index measures the burden of comorbid conditions. It is calculated based on diagnoses present in the year prior to prostate cancer diagnosis. Each condition is assigned a score of 1, 2, 3, or 6. A score of 0 indicates that a patient did not have any medical comorbidities in the year prior to prostate cancer diagnosis, 1 indicates 1 mild comorbid condition, and 2 or greater indicates that the patient had at least 1 severe comorbid condition or multiple mild conditions. The range for all patients in the study was 0 to 10 (non-Hispanic White men: 0-7; African American men: 0-10).

[e] Based on US Census Bureau regions.

[f] Percentage of zip code with an educational attainment level of at least a bachelor's degree.

[g] Median household income of the zip code of residence.

[h] Ascertained through *International Classification of Diseases, Ninth Revision* and *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* codes.

Table 2. Outcomes for African American and Non-Hispanic White Men Undergoing Prostate Cancer Active Surveillance

End point	10-y Cumulative incidence No. (%)		Absolute difference, % (95% CI)	Subdistribution hazard ratio (95% CI)
	African American men[a] (n = 2280)	Non-Hispanic White men[a] (n = 6446)		
Disease progression[b]	1156 (59.9)	2610 (48.3)	11.6 (9.2 to 13.9)	1.3 (1.2 to 1.4)
Definitive treatment[c]	1137 (54.8)	2438 (41.4)	13.4 (11.0 to 15.7)	1.3 (1.2 to 1.4)
Metastasis[d]	30 (1.5)	79 (1.4)	0.1 (-0.4 to 0.6)	1.2 (0.8 to 1.9)
Prostate cancer-specific mortality	22 (1.1)	65 (1.0)	0.1 (-0.4 to 0.6)	1.2 (0.7 to 2.1)
Nonprostate cancer-specific mortality	387 (21.2)	1265 (22.4)	1.2 (-0.7 to 3.2)	1.0 (0.9 to 1.1)
All-cause mortality	409 (22.4)	1330 (23.5)	1.1 (-0.9 to 3.1)	1.0 (0.9 to 1.1)[e]

[a] Self-reported race.

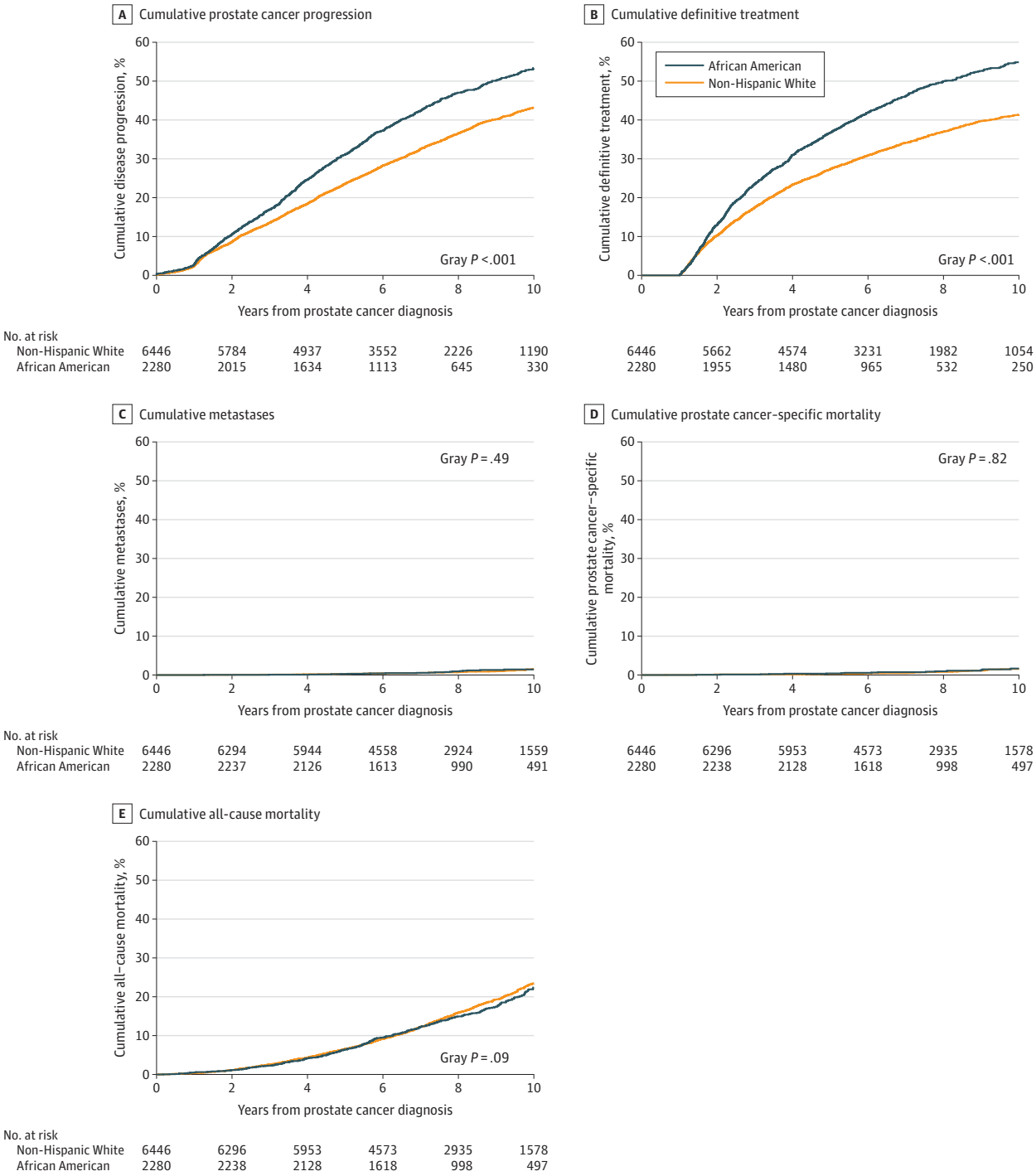
[b] Disease progression was defined as an increase in prostate-specific antigen level greater than 10 ng/dL, pathologic Gleason score greater than 6 (Gleason Grade Group >1), or development of metastases at any point during follow-up.

[c] Receipt of radiation therapy or prostatectomy.

[d] Prostate cancer spread to lymph nodes outside the pelvis or metastases in bones or other organs.

[e] Hazard ratio (95% CI).

Figure 2. Cumulative Incidences of Selected Outcomes



A, The median years of follow-up were 5.82 (interquartile range [IQR], 3.66-8.47) for African American men and 6.50 (IQR, 4.22-9.08) for non-Hispanic White men (Wilcoxon $P < .001$). B, The median years of follow-up were 5.37 (IQR, 2.85-7.32) for African American men and 6.02 (IQR, 3.48-8.62) for non-Hispanic White men (Wilcoxon $P < .001$). C, The median years of follow-up were 7.45 (IQR, 5.66-9.58) for African American men and 7.62 (IQR, 5.67-9.91) for non-Hispanic White men (Wilcoxon $P = .11$). D, The median years of follow-up were 7.48 (IQR, 5.67-9.62) for African American men and 7.62 (IQR, 5.69-9.95) for non-Hispanic White men (Wilcoxon $P = .14$). E, The median years of follow-up were 7.48 (IQR, 5.67-9.62) for African American men and 7.62 (IQR, 5.69-9.95) for non-Hispanic White men (Wilcoxon $P = .12$).

African American population.[22] First, population-based studies indicate that African American men are 2.4 times as likely to die from prostate cancer, compared with White men, due to increased incidence and poorer survival after diagnosis.[23-26]

Second, multiple studies of African American men undergoing immediate radical prostatectomy have shown significantly higher rates of upgrading and adverse pathology.[1,27,28] Third, most published studies on clinical outcomes in African American men have generally shown significantly increased progression and need for treatment.[5-9,29] Consequently, there has been slower uptake of active surveillance in African American men compared with White men.[4,30]

This study included 2280 African American men from VHA medical centers across the US; to our knowledge, this represents the largest sample of African American participants in an active surveillance study. The results are consistent with most studies that show significantly increased rates of definitive treatment and disease progression in African American men compared with White men. These findings may have important implications. First, several recent studies have suggested equal outcomes for African American and White men when managed in equal-access settings.[23,31] While improving access to care is undoubtedly beneficial, the results of this study suggest that only improving access is unlikely to completely ameliorate the disparity in pathologic outcomes. These data, in conjunction with the lower age at diagnosis and higher overall incidence of prostate cancer in African American men, continue to point to some underlying difference in the biology of the disease. Second, because African American men are significantly more likely to experience disease progression, improved patient selection and close follow-up are critical to maintaining favorable outcomes. Whether protocols developed in predominantly White cohorts are appropriate for African American men remain to be evaluated.

In contrast to the pathologic end points, the present study did not find any significantly increased risk of metastases, prostate cancer–specific mortality, or all-cause mortality in African American men. Furthermore, the estimates of metastases and prostate cancer–specific mortality for African American men in this cohort are broadly in line with results from prospective cohort studies composed of predominantly White men,[32-34] suggesting that African American men should not be excluded from active surveillance protocols.

The discrepancy between pathologic outcomes and longer-term end points merits further consideration. Most progression events were either upgrading to Gleason score 7 disease or to a PSA level greater than 10 ng/dL where metastases are relatively rare and active surveillance could still be considered.[11,14] It is possible that when carefully observed and promptly treated, the small increased risk of local disease progression may not substantially affect the risk of metastases. However, a median follow-up of 7.6 years is still a relatively short interval for the development of metastases and death from low-risk prostate cancer. The duration of follow-up may not be sufficient to detect differences in metastases and mortality. Point estimates for metastasis and prostate cancer–specific mortality were in the direction of worse outcomes for African American men. Longer-term follow-up is needed to better assess the metastasis and mortality risk.

Limitations

This study has several limitations. First, as a retrospective cohort study of active surveillance practiced in the VHA community, there was no specific follow-up protocol for active surveillance. To differentiate between active surveillance and watchful waiting, patients were required to have at least 1 repeat biopsy. However, subsequent PSA, biopsy, and treatment decisions were made at the discretion of the treating physicians and their patients. There were no substantial differences in the frequency of PSA or repeat biopsy that would affect results, but differential management by race cannot be ruled out.

Second, there was no prespecified method or timing of clinical ascertainment of metastases.

Third, manual medical record review was used to determine patients who developed metastases. It is possible that some patients with metastases were not identified. However, there was no evidence these errors would have varied by African American status. The similarity in long-term outcomes is also corroborated by prostate cancer–specific mortality, although cause of death ascertainment has limitations as well.[35]

Fourth, all patients received their care through the VHA, which may limit the generalizability of these findings. This health care setting may reduce barriers to care that still exist for African American men in other health care settings.

Fifth, there were several end points in this study, which raises some concern for type I error due to multiple comparisons. Further research should seek to validate these findings.

Conclusions

In this retrospective cohort study of men with low-risk prostate cancer followed up for a median of 7.6 years, African American men, compared with non-Hispanic White men, had a statistically significant increased 10-year cumulative incidence of disease progression and definitive treatment, but not metastasis or prostate cancer–specific mortality. Longer-term follow-up is needed to better assess the mortality risk.

ARTICLE INFORMATION

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REFERENCES

1. Sundi D, Ross AE, Humphreys EB, et al. African American men with very low-risk prostate cancer exhibit adverse oncologic outcomes after radical prostatectomy. *J Clin Oncol*. 2013;31(24):2991-2997.

2. Mahal BA, Alshalalfa M, Spratt DE, Davicioni E, Zhao SG, Feng FY, et al. Prostate cancer genomic-risk differences between African American and White men across Gleason Scores. *Eur Urol*. 2019;75(6):1038-1040.

3. Mahal BA, Berman RA, Taplin ME, Huang FW. Prostate cancer-specific mortality across Gleason scores in black vs nonblack men. *JAMA*. 2018;320(23):2479-2481.

4. Mahal BA, Butler S, Franco I, et al. Use of active surveillance or watchful waiting for low-risk prostate cancer and management trends across risk groups in the United States, 2010-2015. *JAMA*. 2019;321(7):704-706.

5. Odom BD, Mir MC, Hughes S, et al. Active surveillance for low-risk prostate cancer in African American men. *Urology*. 2014;83(2):364-368.

6. Iremashvili V, Soloway MS, Rosenberg DL, Manoharan M. Clinical and demographic characteristics associated with prostate cancer progression in patients on active surveillance. *J Urol*. 2012;187(5):1594-1599.

7. Abern MR, Bassett MR, Tsivian M, et al. Race is associated with discontinuation of active surveillance of low-risk prostate cancer. *Prostate Cancer Prostatic Dis*. 2013;16(1):85-90.

8. Sundi D, Faisal FA, Trock BJ, et al. Reclassification rates are higher among African American men than Caucasians on active surveillance. *Urology*. 2015;85(1):155-160.

9. Davis JW, Ward JF III, Pettaway CA, et al. Disease reclassification risk with stringent criteria and frequent monitoring in men with favourable-risk prostate cancer undergoing active surveillance. *BJU Int*. 2016;118(1):68-76.

10. National Comprehensive Cancer Network. Clinical practice guidelines in oncology. Accessed January 7, 2020. https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf

11. Department of Veterans Affairs. About VHA. Accessed January 7, 2020. https://www.va.gov/health/aboutvha.asp

12. Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. *J Clin Epidemiol*. 1994;47(11):1245-1251.

13. Coogan PF, Castro-Webb N, Yu J, O'Connor GT, Palmer JR, Rosenberg L. Neighborhood and individual socioeconomic status and asthma incidence in African American women. *Ethn Dis*. 2016;26(1):113-122.

14. National Comprehensive Cancer Network. NCCN guidelines for patients: prostate cancer. Accessed January 10, 2020. https://www.nccn.org/patients/guidelines/prostate/files/assets/common/downloads/files/prostate.pdf

15. Carter HB, Kettermann A, Warlick C, et al. Expectant management of prostate cancer with curative intent. *J Urol*. 2007;178(6):2359-2364.

16. Tosoian JJ, Trock BJ, Landis P, et al. Active surveillance program for prostate cancer. *J Clin Oncol*. 2011;29(16):2185-2190.

17. Klotz L, Zhang L, Lam A, Nam R, Mamedov A, Loblaw A. Clinical results of long-term follow-up of a large, active surveillance cohort with localized prostate cancer. *J Clin Oncol*. 2010;28(1):126-131.

18. van As NJ, Norman AR, Thomas K, et al. Predicting the probability of deferred radical treatment for localised prostate cancer managed by active surveillance. *Eur Urol*. 2008;54(6):1297-1305.

19. Berglund RK, Masterson TA, Vora KC, Eggener SE, Eastham JA, Guillonneau BD. Pathological upgrading and up staging with immediate repeat biopsy in patients eligible for active surveillance. *J Urol*. 2008;180(5):1964-1967.

20. Soloway MS, Soloway CT, Williams S, Ayyathurai R, Kava B, Manoharan M. Active surveillance: a reasonable management alternative for patients with prostate cancer: the Miami experience. *BJU Int*. 2008;101(2):165-169.

21. Soloway MS, Soloway CT, Eldefrawy A, Acosta K, Kava B, Manoharan M. Careful selection and close monitoring of low-risk prostate cancer patients on active surveillance minimizes the need for treatment. *Eur Urol*. 2010;58(6):831-835.

22. McClelland S III, Mitin T. The danger of applying the ProtecT Trial to minority populations. *JAMA Oncol*. 2018;4(3):291.

23. Dess RT, Hartman HE, Mahal BA, et al. Association of black race with prostate cancer-specific and other-cause mortality. *JAMA Oncol*. 2019;5(7):975-983.

24. DeSantis CE, Siegel RL, Sauer AG, et al. Cancer statistics for African Americans, 2016. *CA Cancer J Clin*. 2016;66(4):290-308.

25. Steele CB, Li J, Huang B, Weir HK. Prostate cancer survival in the United States by race and stage (2001-2009). *Cancer*. 2017;123(suppl 24):5160-5177.

26. Noone AM, Howlader N, Krapcho M, et al. SEER Cancer Statistics Review (CSR) 1975-2015. Accessed January 15, 2020. https://seer.cancer.gov/archive/csr/1975_2015/

27. Katz JE, Chinea FM, Patel VN, et al. Disparities in Hispanic/Latino and non-Hispanic Black men with low-risk prostate cancer and eligible for active surveillance. *Prostate Cancer Prostatic Dis*. 2018;21(4):533-538.

28. Maurice MJ, Sundi D, Schaeffer EM, Abouassaly R. Risk of pathological upgrading and up staging among men with low risk prostate cancer varies by race. *J Urol*. 2017;197(3, pt 1):627-631.

29. Gökce MI, Sundi D, Schaeffer E, Pettaway C. Is active surveillance a suitable option for African American men with prostate cancer? a systemic literature review. *Prostate Cancer Prostatic Dis*. 2017;20(2):127-136.

30. Butler S, Muralidhar V, Chavez J, et al. Active surveillance for low-risk prostate cancer in Black patients. *N Engl J Med*. 2019;380(21):2070-2072.

31. Riviere P, Luterstein E, Kumar A, et al. Racial equity among African American and non-Hispanic White men diagnosed with prostate cancer in the Veterans Affairs Healthcare System. *Int J Radiat Oncol Biol Phys*. 2019;105(1):E305.

32. Tosoian JJ, Mamawala M, Epstein JI, et al. Intermediate and longer-term outcomes from a prospective active-surveillance program for favorable-risk prostate cancer. *J Clin Oncol*. 2015;33(30):3379-3385.

33. Klotz L, Vesprini D, Sethukavalan P, et al. Long-term follow-up of a large active surveillance cohort of patients with prostate cancer. *J Clin Oncol*. 2015;33(3):272-277.

34. Hamdy FC, Donovan JL, Lane JA, et al; ProtecT Study Group. 10-Year outcomes after monitoring, surgery, or radiotherapy for localized prostate cancer. *N Engl J Med*. 2016;375(15):1415-1424.

35. Moghanaki D, Howard LE, De Hoedt A, et al. Validity of the National Death Index to ascertain the date and cause of death in men having undergone prostatectomy for prostate cancer. *Prostate Cancer Prostatic Dis*. 2019;22(4):633-635.

EDITORIAL

Active Surveillance for Black Men With Low-Risk Prostate Cancer

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Overtreatment of patients with early-stage prostate cancer is a widely recognized clinical problem.[1,2] Most patients with low-risk prostate cancer (defined as prostate-specific antigen [PSA] level ≤10 ng/mL, biopsy Gleason score 6, and clinical stage T1c or T2a by the National Comprehensive Cancer Network guidelines) do not benefit from immediate aggressive treatment in terms of lengthening survival.[3] Patients may be harmed by surgical or radiation treatments that lead to negative short-term and long-term effects on quality of life.[4] Overtreatment of early-stage prostate cancer is associated with an estimated more than $300 million in avoidable annual Medicare spending.[5]

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Active surveillance is a management approach in which low-risk patients with prostate cancer undergo routine monitoring most commonly using PSA testing, prostate biopsy, and increasingly with magnetic resonance imaging. Definitive treatment is offered to patients who demonstrate cancer progression during surveillance.

Multiple studies have shown that active surveillance can spare about 50% of low-risk patients from treatment, with little risk of developing metastatic disease (ie, missing the opportunity for cure).[6,7] Based on these results, active surveillance is now recommended for patients with low-risk prostate cancer by many guideline panels including the National Comprehensive Cancer Network,[3,8,9] and its use is increasing. An area of controversy is whether active surveillance is equally safe for Black patients. Current guidelines describe Black race as an important risk factor when considering active surveillance for low-risk patients.[3,8,9] This is because prior studies have shown that among Black patients, compared with White patients, the onset of prostate cancer is earlier and tumor volumes are greater even among men with low-risk disease.[10] Further, existing data show that Black patients with low-risk prostate cancer who underwent radical prostatectomy were more likely to harbor more aggressive disease on surgical pathology compared with White patients.[10] Among several studies to date that evaluated active surveillance in Black patients and White patients, the Black cohort exhibited higher rates of cancer progression (odds ratio, 1.97-4.60) and remained on active surveillance for relatively shorter periods (31.2 months vs not reached, respectively).[10]

These prior studies have established that Black patients diagnosed with apparent "low-risk" prostate cancer may have more biologically aggressive disease compared with White patients. Together with a 2-fold higher prostate cancer mortality among Black patients, compared with White patients, even for Gleason score 6 cancer (mortality rates of 0.22% vs 0.40%, respectively),[11] a relative underutilization of active surveillance in Black patients has been noted.[12] It is unknown whether this underutilization of active surveillance among Black men is appropriate or represents another form of care disparity given the potential benefits of active surveillance in reducing harms from overtreatment.

In this issue of *JAMA*, Deka et al[13] report a retrospective cohort analysis of 2280 Black patients and 6446 White patients with low-risk prostate cancer who underwent active surveillance in the Veterans Health Administration (VHA) Health Care System. In this study, at 10 years, higher rates of disease progression (59.9% vs 48.3%) and definitive treatment (54.8% vs 41.4%) were observed among Black patients compared with White patients, but there were no significant differences in development of metastases (1.5% vs 1.4%), prostate cancer–specific mortality (1.1% vs 1.0%), or all-cause mortality (22.4% vs 23.5%).

The study excluded patients who did not receive a surveillance prostate biopsy, and analyzed Black and White patients who received similar surveillance rigor with PSA testing (median of 12 tests per patient in both groups) and biopsy (median of 2 biopsies per patient in both groups). Data from this study are consistent with prior research that demonstrated higher rates of progression among Black patients with "low-risk" prostate cancer and higher rates of definitive therapy. Nevertheless, in the equal-access VHA health care setting in the study by Deka et al,[13] low and similar rates of metastasis and mortality among Black and White men were achieved. Further, active surveillance allowed more than 40% of Black men with low-risk prostate cancer to avoid treatment within 10 years.

While these findings suggest that active surveillance can be safe and effective for Black men, a cautionary note must be raised regarding generalizing results from the equal-access VHA medical centers to more common care contexts. Because Black patients have more biologically aggressive prostate cancer and higher progression rates during active surveillance compared with White men, there is a greater need for Black men in the general population to have access to high-quality and timely care to avoid delays in diagnosing cancer progression and receiving definitive treatment. However, existing literature has repeatedly demonstrated widespread inequities whereby Black patients with prostate cancer, compared with White patients, are less likely to receive radical prostatectomy and radiotherapy, and are more likely to experience treatment delays.[14-16]

Moreover, the rigor of implementation of active surveillance care processes in routine clinical practice is largely unknown. Using data from a prospective population-based active surveillance cohort, Peterson et al[17] analyzed 346 patients (including 82 Black patients, 258 White patients, and 6 patients of Asian, American Indian, or unknown race) enrolled from across North Carolina in collaboration with the state cancer registry. Only 58% of patients received routine surveillance

PSA tests within the first 2 years and only 45% received a surveillance biopsy; overall, only 32% received guideline-recommended surveillance monitoring. Many of these patients (ie, the 55% who did not receive a surveillance biopsy) would have been excluded from the study by Deka et al[13] and are not represented in published prospective studies[6] that ensured patients had rigorous and timely monitoring.

Another recent study provides complementary evidence that racial disparities in prostate cancer outcomes can be reduced by improved access to care. Dess et al[18] analyzed data from the Surveillance, Epidemiology, and End Results registries, which represent care and outcomes in clinical practice, VHA Health Care System; and National Cancer Institute-sponsored clinical trials. Compared with White patients, Black patients with prostate cancer in the Surveillance, Epidemiology, and End Results registries had higher rates of prostate cancer-specific mortality, although this difference was not observed in the VHA or clinical trial cohorts.[18] Together, the findings of Dess et al[18] and from the study by Deka et al[13] suggest that racial disparities in prostate cancer outcomes are addressable, and any biologic differences between the cancers of Black vs White patients can be overcome.

For active surveillance to become a safer reality for most patients with low-risk prostate cancer, Black and White alike, who are not treated in clinical trials or equal-access health care settings, active surveillance research must move into population-based settings. For example, additional studies are needed to examine the rigor of surveillance monitoring in population-based cohorts, to evaluate the timeliness of cancer progression diagnosis and treatment, and to test interventions to mitigate care disparities. Whether Black men and White men with low-risk prostate cancer receiving active surveillance have similarly good outcomes in the general population remains unknown. Additional research to examine whether the use of genomic tests at the time of diagnosis can mitigate the biologic differences, so that "low-risk" cancer for Black patients and White patients are more similar, may provide additional useful information.

Findings from the study by Deka et al[13] in this issue of *JAMA* suggest that for patients being treated in equitable care delivery systems such as the VHA, active surveillance appears comparably safe for Black men as for White men. Further reassurance would be gained from research showing similar outcomes in broader general population settings outside of the VHA context. Until such evidence is available, concerns about biologic differences in prostate cancer between Black and White men and potential disparities in receiving timely surveillance monitoring and treatment on cancer progression may continue to drive lower rates of active surveillance use among Black patients.

ARTICLE INFORMATION

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REFERENCES

1. Fenton JJ, Weyrich MS, Durbin S, Liu Y, Bang H, Melnikow J. Prostate-specific antigen-based screening for prostate cancer: evidence report and systematic review for the US Preventive Services Task Force. *JAMA*. 2018;319(18):1914-1931. doi:10.1001/jama.2018.3712

2. Thompson IM. Overdiagnosis and overtreatment of prostate cancer. *Am Soc Clin Oncol Educ Book*. 2012;e35-e39. doi:10.14694/EdBook_AM.2012.32.98

3. National Comprehensive Cancer Network. Prostate cancer (version 2.2020). Accessed July 13, 2020. https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf

4. Hoffman KE, Penson DF, Zhao Z, et al. Patient-reported outcomes through 5 years for active surveillance, surgery, brachytherapy, or external beam radiation with or without androgen deprivation therapy for localized prostate cancer. *JAMA*. 2020;323(2):149-163. doi:10.1001/jama.2019.20675

5. Trogdon JG, Falchook AD, Basak R, Carpenter WR, Chen RC. Total Medicare costs associated with diagnosis and treatment of prostate cancer in elderly men. *JAMA Oncol*. 2019;5(1):60-66. doi:10.1001/jamaoncol.2018.3701

6. Klotz L, Zhang L, Lam A, Nam R, Mamedov A, Loblaw A. Clinical results of long-term follow-up of a large, active surveillance cohort with localized prostate cancer. *J Clin Oncol*. 2010;28(1):126-131. doi:10.1200/JCO.2009.24.2180

7. Tosoian JJ, Mamawala M, Epstein JI, et al. Active surveillance of grade group 1 prostate cancer: long-term outcomes from a large prospective cohort. *Eur Urol*. 2020;77(6):675-682. doi:10.1016/j.eururo.2019.12.017

8. Chen RC, Rumble RB, Loblaw DA, et al. Active surveillance for the management of localized prostate cancer (Cancer Care Ontario Guideline): American Society of Clinical Oncology clinical practice guideline endorsement. *J Clin Oncol*. 2016;34(18):2182-2190. doi:10.1200/JCO.2015.65.7759

9. Sanda MG, Cadeddu JA, Kirkby E, et al. Clinically localized prostate cancer: AUA/ASTRO/SUO guideline. part i: risk stratification, shared decision making, and care options. *J Urol*. 2018;199(3):683-690. doi:10.1016/j.juro.2017.11.095

10. Gökce MI, Sundi D, Schaeffer E, Pettaway C. Is active surveillance a suitable option for African American men with prostate cancer? a systemic literature review. *Prostate Cancer Prostatic Dis*. 2017;20(2):127-136. doi:10.1038/pcan.2016.56

11. Mahal BA, Berman RA, Taplin M-E, Huang FW. Prostate cancer-specific mortality across Gleason scores in black vs nonblack men. *JAMA*. 2018;320(23):2479-2481. doi:10.1001/jama.2018.11716

12. Butler S, Muralidhar V, Chavez J, et al. Active surveillance for low-risk prostate cancer in black patients. *N Engl J Med*. 2019;380(21):2070-2072. doi:10.1056/NEJMc1900333

13. Deka R, Courtney PT, Parsons JK, et al. Association between African American race and clinical outcomes in men treated for low-risk prostate cancer with active surveillance. *JAMA*. Published November 3, 2020. doi:10.1001/jama.2020.17020

14. Weiner AB, Matulewicz RS, Schaeffer EM, Liauw SL, Feinglass JM, Eggener SE. Contemporary management of men with high-risk localized prostate cancer in the United States. *Prostate Cancer Prostatic Dis*. 2017;20(4):442. doi:10.1038/pcan.2017.35

15. Stokes WA, Hendrix LH, Royce TJ, et al. Racial differences in time from prostate cancer diagnosis to treatment initiation: a population-based study. *Cancer*. 2013;119(13):2486-2493. doi:10.1002/cncr.27975

16. Friedlander DF, Trinh QD, Krasnova A, et al. Racial disparity in delivering definitive therapy for intermediate/high-risk localized prostate cancer: the impact of facility features and socioeconomic characteristics. *Eur Urol*. 2018;73(3):445-451. doi:10.1016/j.eururo.2017.07.023

17. Peterson S, Basak R, Moon DH, et al. Population-based cohort of prostate cancer patients on active surveillance (AS): guideline adherence, conversion to treatment and decisional regret. *J Clin Oncol*. 2019;37(15 suppl):6512. doi:10.1200/JCO.2019.37.15_suppl.6512

18. Dess RT, Hartman HE, Mahal BA, et al. Association of Black race with prostate cancer-specific and other-cause mortality. *JAMA Oncol*. 2019;5(7):975-983. doi:10.1001/jamaoncol.2019.0826