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## African American race is not associated with risk of reclassification during active surveillance: Results from the Canary Prostate Cancer Active Surveillance Study (PASS)

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### Abstract

**OBJECTIVE**—To evaluate whether African American (AA) men are at higher risk of reclassification in a large, prospective multi-institutional active surveillance (AS) cohort.

**METHODS**—The Canary Prostate Active Surveillance Study (PASS) is a protocol-driven active surveillance cohort with pre-specified prostate-specific antigen (PSA) and surveillance biopsies regimen. Men included in this study had Gleason Grade Group 1 or 2 at diagnosis, < 5 years between diagnosis and enrollment, and had undergone 1 surveillance biopsy. Risk of reclassification, defined as an increase in Gleason score on subsequent biopsy, was compared between AA and CA using cox proportional hazards models. For the subset of men undergoing delayed prostatectomy, rates of adverse pathology, defined as pT3a or greater or Gleason Grade Group 3 or greater, were compared for AA and CA.

**RESULTS**—Of 1,315 men, there were 89 (7%) AA and 1,226 (93%) CA. There were no differences in the rate of treatment for AA and CA. In multivariate models, AA race was not associated with the risk of reclassification (HR=1.16, 95% CI: 0.78 – 1.72). Among 441 men who had a prostatectomy after a period of AS, rate of adverse pathology was similar for AA and CA (46% vs 47%, p=0.99).

**CONCLUSIONS**—Among men on AS who follow a standardized protocol of regular PSA and biopsy, AA men were not at increased risk of pathologic reclassification on AS or adverse pathology at prostatectomy. AS appears to be an appropriate management strategy for AA men with favorable risk prostate cancer.

### Keywords

prostate cancer; reclassification; active surveillance; race; African-American

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## INTRODUCTION

Over the last decade, the utilization of active surveillance (AS) has increased among men with low-risk prostate cancer (PCa) in the US.<sup>1, 2</sup> There is strong evidence from many studies supporting the use of AS as an alternative to immediate radiation or radical prostatectomy for favorable-risk PCa<sup>3-6</sup>; However, there remains uncertainty about the utilization of AS among some high-risk groups, and although rates of AS among AA have increased over time, they remain far lower than rates among Caucasian (CA) men.<sup>7</sup> African-American (AA) men have a higher incidence of PCa and increased potential for underlying aggressive disease compared to whites.<sup>8</sup> Recent studies also suggest that the underlying biology of PCa among AA men may be distinct.<sup>9</sup> Given this knowledge and the underrepresentation AA men in patient cohorts demonstrating favorable active surveillance outcomes for men with low-risk PCa, the appropriateness of AS for AA men is unclear.<sup>10</sup>

Several studies have evaluated the influence of AA race on PCa outcomes among AS-eligible, low-risk men who underwent radical prostatectomy (RP). The results of these studies are inconsistent, with the majority reporting a significant positive association between AA race and adverse outcomes after prostatectomy, and several reporting no differences in outcomes between AA and Caucasian (CA) men.<sup>10</sup> The comparability of these studies to AS patient populations is limited as all men underwent surgery and there may be racial disparities in referral patterns, patient selection, and treatment preferences and recommendations.<sup>7, 11, 12</sup> Few studies to date have evaluated the association of AA race with risk of progression among AS patients<sup>13-17</sup>, many of which are based on single-institution practices with small numbers of AA men. Here we evaluate the association of AA race with risk of disease reclassification and adverse pathology among men managed by AS in the multicenter Canary Prostate Active Surveillance Study (PASS).<sup>18</sup>

## METHODS

The Canary PASS cohort utilizes a standardized active surveillance protocol ([clinicaltrials.gov NCT000756665](https://clinicaltrials.gov/NCT000756665)). The PASS protocol includes PSA measured every 3 months and clinic visits occurring every 6 months. The protocol also includes ultrasound-

guided prostate biopsies with the first surveillance (confirmatory) biopsy between 6 and 12 months after diagnosis followed by a biopsy at 24 months after diagnosis and at 2-year intervals thereafter. Other tests, including genomic testing and multiparametric magnetic resonance imaging (mpMRI), may be performed at the discretion of participating clinicians. Data collected include Gleason score, number of cores at each biopsy, number of cores positive for cancer at each biopsy, prostate volume, and the corresponding PSA values for diagnostic and any follow-up biopsies prior to enrollment. At enrollment in PASS, patients provided self-reported race/ethnicity, family history of PCa, and smoking status, and clinic staff measured height and weight to calculate body mass index (BMI). All men provided written informed consent prior to enrollment in PASS, and study procedures were approved by the local institutional review board for each study site.

Men included in this analysis were enrolled as of February 2018, had a prostate cancer diagnosis within 5 years of enrollment, had Gleason Grade Group 2 (3+4) cancer, and had at least one surveillance biopsy after diagnostic biopsy (1,434 participants). For this analysis, the cohort was limited to AA and CA men, leaving 1,351 participants for analysis.

### Outcomes

The primary outcome for these analyses was time to disease reclassification while on AS. Reclassification was defined as any increase in primary or secondary Gleason grade at re-biopsy. As a secondary outcome, rates of adverse pathology at RP, defined as Gleason Grade Group 3, pT3a disease, or pN1, were evaluated between AA and CA men.

### Statistical Methods

Descriptive statistics were used to characterize the study sample. Differences between AA and CA were evaluated using Wilcoxon sign rank tests for continuous variables and Fisher's tests for categorical variables.

Kaplan Meier curves were plotted to examine differences in reclassification- and treatment-free probability by race (AA vs CA). Participants without reclassification were censored at date of last study contact, treatment, or 2 years after their last biopsy, whichever came first. For treatment-free survival, participants without treatment were censored at date of last study contact. Cox proportional hazards models (PH) were used to estimate the unadjusted and covariate-adjusted hazards ratios for the association between AA race and risk of reclassification. Covariate adjusted models considered the following variables: diagnostic Gleason Grade Group (1 vs 2), BMI, percentage of cores positive for cancer (calculated as the number of cores positive for cancer divided by the total number of cores collected), prostate size, diagnostic age, diagnostic PSA, family history of PCa, and smoking status (current/former vs never). The baseline hazard for each Cox PH model was stratified by study site to account for site-by-site differences in reclassification rates. Tests of proportionality confirmed that PH assumptions were met. Sensitivity analyses were performed among the subset of men with Gleason Grade Group 1 PCa.

To evaluate whether bias related to compliance with the surveillance protocol may have impacted results, exploratory analyses compared the rates of loss to follow up, number of surveillance biopsies, annual number of PSA values, timing and rates of treatment, and

compliance to the protocol-directed biopsy schedule between AA and CA participants. All analyses were 2-tailed with alpha set at 0.05 and were performed using SAS version 9.4 and R version 3.3.0.

## RESULTS

Of the 1,315 men in this study, 89 (7%) self-identified as AA. The median age of men overall was 63 years (95% CI: 58 – 67). AA and CA men were comparable with respect to Gleason Grade Group at diagnosis, the percentage of total cores positive for prostate cancer, prostate size, family history of prostate cancer and smoking status. Compared to CA, AA had significantly higher median PSA and PSA density at diagnosis and body mass index at study entry (Table 1).

Median length of follow-up among men with no reclassification was 3.9 years (IQR 2.2 to 5.9) overall, with AA having approximately 1 year less follow-up compared to CA (Table 2), which is consistent with the relatively recent addition of PASS clinical sites serving racially diverse populations. The median number of surveillance biopsies on study, number of PSA per year and use of mpMRI were similar for AA and CA men. Overall treatment rates were comparable for AA and CA men, though AA men were more likely to undergo radiation and less likely to undergo radical prostatectomy than CA men (Table 2).

Overall, there was no difference in reclassification-free survival between AA and CA men ( $p=0.39$ ; Figure 1). Table 3 gives the unadjusted and multivariable adjusted hazards of pathologic reclassification at biopsy among AA men relative to CA men on AS. On unadjusted analysis, AA men had a similar risk of reclassification as CA men. In multivariate models adjusted for diagnostic biopsy and clinical variables, AA race was not significantly associated with the risk of reclassification (HR=1.16, 95% CI: 0.78 – 1.72). Results were nearly identical for a sensitivity analysis limited to men with Grade Group 1 PCa at diagnosis (data not shown). Among the subset of men treated via RP ( $n=13$  AA,  $n=223$  CA), rates of adverse pathology at RP were similar for AA and CA men (46% vs 47%;  $p=0.99$ ).

We conducted several analyses to explore possible bias related to biopsy timing and compliance with the active surveillance protocol. There were no differences between AA and CA men in the number of surveillance biopsies or annual number of PSA screenings. Overall treatment rates (35% vs 34%;  $p=0.99$ ) and timing of treatment were similar for AA and CA men (Figure 2). In addition, the proportions of surveillance biopsies conducted according to the protocol-directed schedule was similar between AA and CA men (data not shown).

## DISCUSSION

Limited data exist on the safety and efficacy of AS as a management strategy for AA men with favorable risk PCa at diagnosis. Concerns about the use of AS for AA men are driven by the significant disparities in PCa incidence and mortality, which have remained consistent even in the era of PSA screening.<sup>19</sup> In this analysis from a large, prospective multi-institutional cohort, we found similar rates of disease reclassification among AA and CA

men with favorable-risk prostate cancer managed by a standardized AS protocol. In addition, among the small subset of men who ultimately underwent surgical treatment after a period of AS, rates of adverse pathology at prostatectomy were similar between AA and CA men.

Numerous studies have reported conflicting outcomes for AA men diagnosed with low-risk prostate cancer, the majority of which are based on populations of AS-eligible men who underwent RP. Many of these studies report significant increases in risks of adverse pathologic findings, recurrence, and cancer-specific mortality among AA compared to men of other racial groups.<sup>10</sup> In contrast several studies reported no differences in stage-for-stage PCa outcomes by race<sup>20–23</sup>, which is consistent with our finding of similar rates of adverse pathology at RP between AA and CA men in PASS. Studies limited to men who were surgically treated may be biased by factors associated with the selection of treatment. AA men are less likely to undergo primary RP and are therefore underrepresented in these studies.<sup>7, 11, 12</sup> In addition, reported racial disparities in prostate cancer outcomes among RP patients may be related to differences in access to care.<sup>24</sup> In fact, studies conducted in populations with similar access to care have reported no differences in stage-for-stage prostate cancer outcomes for AA and CA.<sup>20–22</sup>

Few studies to date have evaluated the association of race with PCa outcomes among AS populations.<sup>13–17</sup> Of the five prior studies, four reported a significant positive association between AA ethnicity and risk of reclassification<sup>13</sup>, or disease progression on AS<sup>14, 15, 17</sup>. Most studies were based on retrospectively collected data from a single-institution with smaller numbers of AA men and are limited by short follow-up. Comparisons between our study and those reported in the literature are further complicated by the use of different definitions of disease progression, the majority of which used an aggregate of changes in disease volume/grade or an increase in PSA.<sup>14, 15, 17</sup> Only one prior study among men with very low-risk PCa assessed reclassification by grade, and found a 3-fold increased risk of grade reclassification among AA compared to CA.<sup>13</sup> Of note, this cohort had a substantially lower rate of grade reclassification among CA patients at three years (16%) compared to PASS and other AS cohorts.<sup>25</sup> To evaluate whether variations in the underlying risk of upgrading could account for the difference between our results and this prior study, we conducted an additional analysis restricted to PASS patients diagnosed with very low risk PCa (T1c, Gleason score ≤6/grade group 1, PSA <10 ng/mL, < 3 prostate biopsy cores positive, ≥50% cancer in each core, and PSA density <0.15 ng/mL/g). Within the subset of men who met the criteria for very low risk PCa at diagnosis (n=593), there remained no association of AA race with risk of grade reclassification (multivariate HR=0.75, 95% CI: 0.32 – 1.75; p=0.51).

It is important to note several potential sources of bias that may be impacting associations of AA race and outcomes in studies of active surveillance. Racial disparity in the intensity of surveillance (i.e., the frequency of PSA/digital rectal exam (DRE) or biopsy) or conduct of surveillance (e.g. biopsy compliance, the method of biopsy (e.g. use of mpMRI), or differences in pathologic review<sup>13</sup>), could impact the likelihood of detecting progression events on AS. In particular, retrospective studies of active surveillance, in which the conduct of surveillance activities was not protocol-directed, may be subject to these biases, although few studies present data to allow evaluation of their potential presence.

There are several elements of the PASS cohort that serve as strengths for this study. First is the use of a standardized active surveillance protocol across all clinical sites. PSA/DRE tests and surveillance biopsies are collected at pre-specified, protocol-directed time-points in PASS<sup>18</sup>, allowing for a similar opportunity to detect reclassification among all men on PASS and minimizing the potential for screening-related ascertainment bias. Additional strengths for this study include the intentionally broad eligibility criteria of the PASS cohort, which includes diagnostic Gleason Grade Group 1 and 2 with no limitations on PSA/PSA density or tumor burden, increases the generalizability of these results to the current population of men eligible for and electing to undergo AS. In addition, the large multicenter design of PASS includes 10 clinical sites throughout North America; thus, these results are less likely to be impacted by the judgement of an individual or small group of providers.

Some limitations also deserve mention. Although the number of African Americans in this study is the largest to date (n=89), it is still modest, and the number of AA men who underwent surgery is small; thus, the findings reported here should be interpreted cautiously. Recent efforts to improve diversity in PASS include the addition clinical sites serving more diverse populations. It is also notable that the length of overall follow-up in PASS is modest (median = 3.9 years), although longer than previous studies<sup>14-17</sup>, which limits the evaluation of intermediate/long-term oncologic outcomes of interest. In addition, the length of follow-up time is somewhat shorter for AA than for CA men (2.9 vs. 3.9 years). Given that drop-out rates and the time to treatment and reclassification were similar between AA and CA men in PASS, this difference is most likely due to the relatively recent addition of PASS clinical sites serving racially diverse populations, which have accrued less follow-up time. Continued enrollment of patients from these sites is ongoing in PASS, and it will be important to confirm these findings once more follow-up time has accrued.

In conclusion, in this prospective cohort of men on AS who follow a standardized protocol of regular PSA and biopsy, AA men did not demonstrate a higher risk of adverse pathologic reclassification while on AS. Furthermore, those who eventually underwent RP did not have a higher risk of adverse pathology by delaying their therapy. The results from Canary PASS support the use of a standardized AS protocol among AA men with favorable risk PCa.

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**Key of Definitions: African American race and risk of reclassification in PASS**

|            |                     |
|------------|---------------------|
| <b>AA</b>  | African American    |
| <b>AS</b>  | Active Surveillance |
| <b>CA</b>  | Caucasian           |
| <b>DRE</b> | Digital Rectal Exam |

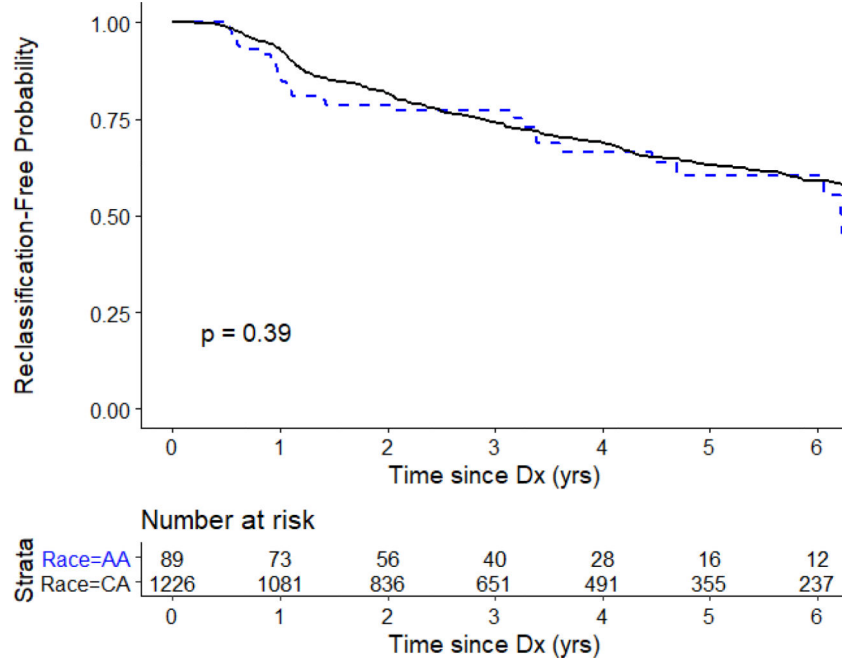
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|-------------|---|
| <b>mpMR</b> | multiparametric magnetic resonance        |
| <b>PASS</b> | Prostate Cancer Active Surveillance Study |
| <b>PCa</b>  | Prostate Cancer                           |
| <b>PH</b>   | Proportional Hazards                      |
| <b>PSA</b>  | Prostate Specific Antigen                 |
| <b>RP</b>   | Radical Prostatectomy                     |

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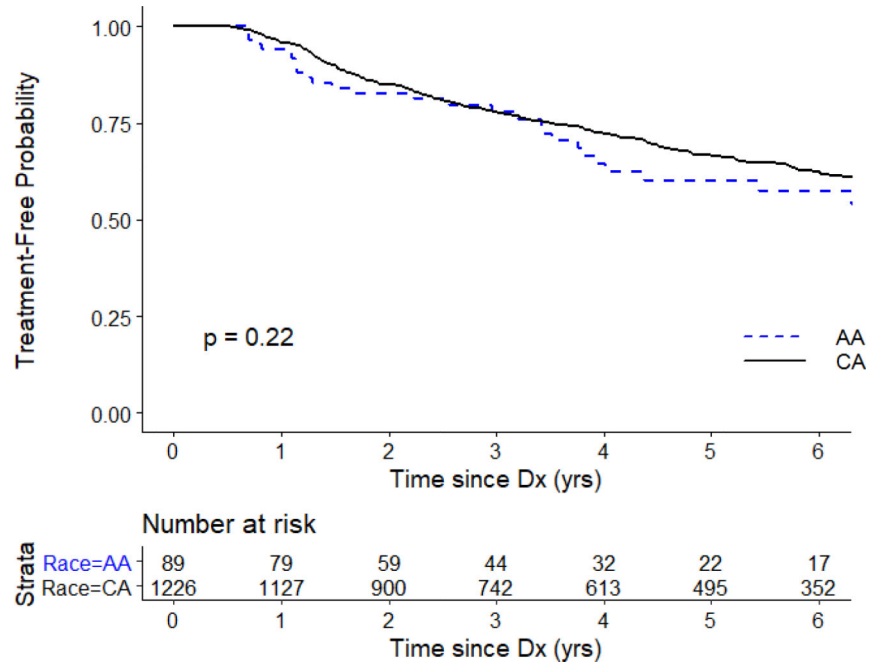
**Figure 1.** Kaplan-Meier curve of reclassification-free survival by race.

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**Figure 2.**  
Kaplan-Meier curve of treatment-free survival by race.

**Table 1.**

PASS participant characteristics by race

| Variable                                      | AA only (n=89)        | CA only (n=1226)      | P-value <sup>4</sup> |
|---|-----------------------|-----------------------|----------------------|
|   | n (%) or median [IQR] | n (%) or median [IQR] |                      |
| Age (years) <sup>1</sup>                      | 63 [55, 67]           | 63 [58, 67]           | 0.30                 |
| Gleason <sup>1</sup>                          |                       |                       | 0.42                 |
| Grade group 1                                 | 80 (90)               | 1129 (92)             |                      |
| Grade group 2                                 | 9 (10)                | 97 (8)                |                      |
| Very low Risk                                 | 35 (39.3)             | 558 (45.5)            |                      |
| % Positive cores <sup>1,2</sup>               | 8 [8, 17]             | 10 [8, 17]            | 0.26                 |
| Prostate size (cm <sup>3</sup> ) <sup>3</sup> | 42 [32, 64]           | 42 [31, 57]           | 0.14                 |
| PSA (ng/ml) <sup>1</sup>                      | 5.6 [4.4, 7.8]        | 4.9 [3.8, 6.4]        | <.001                |
| PSA density <sup>1</sup>                      | 0.14 [0.09, 0.18]     | 0.11 [0.08, 0.16]     | 0.01                 |
| BMI (kg/m <sup>2</sup> ) <sup>3</sup>         | 28 [26, 32]           | 27 [25, 30]           | 0.04                 |
| Family history of PCa <sup>3</sup>            | 28 (32)               | 342 (28)              | 0.47                 |
| Smoking Status <sup>3</sup>                   |                       |                       | 0.10                 |
| Current/Former                                | 45 (51)               | 507 (41)              |                      |
| Never   | 44 (49)               | 719 (59)              |                      |

<sup>1</sup>Corresponds to the value at prostate cancer diagnosis<sup>2</sup>% Positive cores is defined as # cores positive for cancer/total # cores collected<sup>3</sup>Corresponds to the value at enrollment in PASS<sup>4</sup>P-value from Wilcoxon rank sum test for continuous variables, and Fisher's exact test for categorical variables.

**Table 2.**

Clinical, surveillance and treatment characteristics of AA and CA men in PASS.

| Variable                                | AA only (n=89)        | CA only (n=1226)      |
|---|-----------------------|-----------------------|
|   | n (%) or median [IQR] | n (%) or median [IQR] |
| Length of Follow-up, years <sup>I</sup> | 2.9 [2.0, 4.6]        | 3.9 [2.2, 6.0]        |
| Number surveillance biopsies            | 2 [1, 2]              | 2 [1,3]               |
| Number PSA/year                         | 3 [2, 4]              | 3 [3, 4]              |
| mpMRI use                               | 23 (26)               | 365 (30)              |
| Grade reclassification                  | 30 (34)               | 419 (34)              |
| Treatment (any)                         | 30 (34)               | 411 (34)              |
| <i>RP</i>                               | 13 (43)               | 233 (57)              |
| <i>RAD</i>                              | 17 (57)               | 155 (38)              |
| <i>ADT/Other</i>                        | 0                     | 23 (5)                |
| Adverse Pathology at RP*                | 6/13 (46)             | 109/233 (47)          |

<sup>I</sup> Among men who did not reclassify

**Table 3.**

Predictors of grade reclassification on surveillance biopsy in PASS.

| Variable                         | Unadjusted               |                      | Adjusted                 |                      |
|----------------------------------|--------------------------|----------------------|--------------------------|----------------------|
|                                  | HR (95% CI) <sup>^</sup> | P-value <sup>^</sup> | HR (95% CI) <sup>^</sup> | P-value <sup>^</sup> |
| AA race                          | 1.17 (0.79 – 1.72)       | 0.44                 | 1.16 (0.78 – 1.72)       | 0.46                 |
| Age <sup>1</sup>                 | 1.02 (1.00 – 1.03)       | 0.01                 | 1.03 (1.01 – 1.04)       | <0.001               |
| Gleason Grade Group <sup>1</sup> | 0.97 (0.66 – 1.41)       | 0.86                 | 0.66 (0.45 – 0.98)       | 0.04                 |
| % Positive cores <sup>1</sup>    | 1.37 (1.26 – 1.47)       | <0.001               | 1.34 (1.24 – 1.45)       | <0.001               |
| Prostate size                    | 0.56 (0.46 – 0.69)       | <0.001               | 0.40 (0.32 – 0.50)       | <0.001               |
| PSA <sup>1</sup>                 | 1.37 (1.17 – 1.61)       | <0.001               | 1.67 (1.41 – 1.97)       | <0.001               |
| BMI <sup>2</sup>                 | 1.03 (1.01 – 1.05)       | 0.01                 | 1.05 (1.02 – 1.07)       | <0.001               |
| Family history <sup>2</sup>      | 0.94 (0.85 – 1.25)       | 0.56                 | 0.96 (0.77 – 1.19)       | 0.71                 |

<sup>1</sup> At diagnosis<sup>2</sup> At enrollment<sup>^</sup> Hazard ratios, 95% confidence intervals and p-values from Cox proportional hazard models