Introduction

For a number of cancers, African Americans (AA) have the highest rates of mortality and shortest survival of any racial or ethnic group, bearing a disproportionate share of the cancer burden in the United States. Using the Surveillance, Epidemiology, and End Results (SEER) and the North American Association of Central Cancer Registries (NAACCR) databases, DeSantis et al. projected 189,910 new cancer cases expected to be diagnosed among blacks in 2016 (1). Among men, prostate cancer continues to be the malignancy with the highest incidence and ranks third in cancer death per the American Cancer Society’s latest data. Widely accepted risk factors for prostate cancer include age, family history, and race, with AA men and Caribbean men of African ancestry being more susceptible than other groups. The lifetime probability of developing the disease has recently been reported to be 13.3% in non-Hispanic whites compared to 18.2% in AA men, with incidence rates of 123.0 and 208.7 per 100,000 persons in non-Hispanic whites and AAs, respectively. Similarly, black men have the highest mortality rate for prostate cancer of any ethnic group in the United States, some 2.4 times higher than the rate in white men. While prostate cancer mortality has declined since 1996 for all ethnicities, significant racial disparities continue to exist at all stages of prostate cancer management, from...
diagnosis to treatment (2,3).

**Socioeconomic and cultural factors impacting access to care**

While the causes of disparities in outcomes for AA men with prostate cancer are many and complex, certainly socioeconomic and cultural factors play a role. In general, socioeconomic status is inversely correlated with health outcomes (2,4). In the case of prostate cancer, the Selenium and Vitamin E Cancer Prevention Trial (which included 4,674 AA and 27,566 CA men) is one of numerous studies that report an earlier average age at prostate cancer diagnosis in AAs, who also were less likely to have a college degree. In addition, in this study AA men had a higher prevalence of diabetes, smoking, and obesity, all of which may have contributed to the higher incidence of prostate cancer in AA men and resulting in poorer health outcomes overall (5,6). Others have further observed that household median income and advanced-stage diagnosis were inversely correlated, contributing to the finding that advanced-stage diagnosis was more common in AA men (6).

Among patients within the same socioeconomic strata, however, racial disparities in health outcomes continue to persist. After accounting for socioeconomic status, Kinlock et al. found that cancer screening was more common in Caucasian-American (CA) than in AA men (3). Furthermore, the risk of death from prostate cancer in AAs was consistently higher than in CAs regardless of socioeconomic status, suggesting other factors influencing this outcome. For example, a higher proportion of AA men than white men reported medical mistrust and dissatisfaction with the healthcare system, highlighting pervasive cultural barriers that must also be overcome to improve health disparities (3).

Although comparable outcomes have been reported between active surveillance (AS), radiation therapy, and surgical management in low-risk cohorts, treatment decisions are ideally made on an individualized basis following an informed discussion and shared decision making between the patient and the physician. Not surprisingly, racial biases continue to impact such decisions, with reports showing that historically, black men undergo less aggressive treatment and more watchful waiting (WW), even after adjusting for socioeconomic status. Within the context of high-risk disease, numerous studies have shown a clear racial variation in the primary treatment of prostate cancer, including more use of WW and lower use of radical prostatectomy (RP) among minorities compared to their white counterparts (7,8). Further studies have shown that white men were less likely to select WW/AS as cancer risk increased, while risk level was unrelated to black men undergoing WW/AS, highlighting the increased likelihood of undertreatment of some AA men with localized prostate cancer (9,10).

Current guidelines including the National Comprehensive Cancer Network suggest observation be considered for select men with low risk prostate cancer, or those with more significant disease, but a limited life expectancy. Although current guidelines are driven in large part by landmark prospective randomized trials that legitimized observational management as a safe alternative to surgical management of some men with prostate cancer, such studies were conducted in relatively racially homogenous Scandinavian cohorts (11-13). Results from the Prostate Intervention Versus Observation Trial (PIVOT) addressed some of the concerns regarding generalizability of the original Swedish cohorts. This study population included black men in 33% of the observation arm and in 30.5% of the prostatectomy arm and demonstrated similar findings that RP did not significantly reduce overall mortality at 10 years as compared to observation (14) suggesting again that for many men with limited life expectancy observation is a reasonable approach regardless of race or ethnicity. The safety of observation for men with significantly longer life expectancies however, is less clear as both PIVOT and the Scandinavian trials showed significantly higher rates of disease progression among the men in the observation arms.

**The role of biologic factors in prostate cancer outcomes**

Although some of the racial disparities in prostate cancer outcomes may be attributed to socioeconomic and cultural factors, emerging evidence suggests significant biological differences may also play a role in determining health outcomes. It is the biological differences between the prostate cancers that arise in AA men as opposed to CA men among other differences that bring into question the safety of AS for AA men. One potential compensatory response is to increase the intensity and frequency of surveillance in these men, though whether such an approach would detect disease within the window of curability remains to be seen. It is known that prostate cancer is diagnosed at a younger age in AA compared to CA men, with a reported propensity for higher grade disease at diagnosis (15,16).
In an assessment of 2,874 men aged 39 to 77 years who underwent RP between 1991 and 2007 at Karmanos Cancer Institute in Detroit, MI., it was found that prostate cancer volume after RP was greater in black than in white men. The same study also found that prostate cancer became distant disease at a ratio of 4 black men to 1 white man in the Detroit SEER population (17). Such findings support the concept that inherent biologic differences may exist between prostate cancer in AA compared to CA men, with perhaps a more aggressive disease progression and earlier transformation to higher stages of disease (17).

To gain further insight into the molecular basis of such findings, recent genome-wide association studies (GWAS) in prostate cancer have continued to open new avenues of investigation into prostate cancer biology (18). For example, single nucleotide polymorphisms (SNPs) in a number of genes were reported to be associated with prostate cancer in AA, but not in CA men. Promising targets include members of the cytochrome P450 family, the phagocytic receptor CD14, calcium sensing receptor, androgen receptor, and variations around region 8q24 and 7q21, products of which are likely involved in androgen metabolism, making them rational links to prostate cancer growth and progression (19-24).

In addition to intrinsic molecular differences in prostate biology, several systemic biochemical differences that are positively correlated with AA race are also likely to play a role in the increased incidence and worse prostate cancer prognosis in AA men. Suboptimal levels of vitamin D, for example, have been linked to prostate cancer, among many other non-skeletal chronic diseases, and it has been shown that lower serum vitamin D levels occur in darker-skinned individuals (25). Similarly, many studies have suggested an association of the IGF axis with an increased likelihood of aggressive prostate cancer. Given the increased prevalence of type II Diabetes in AA individuals, serum concentrations of IGF-1 and IGFBP3 are actively being investigated as providing a biochemical milieu conducive to harboring proliferation of prostatic neoplasms (26-28).

Other ongoing areas of investigation include studies concerning the metabolic and nutrient profile of AA men as possible contributors to their higher prostate cancer risk. One such study observed that increased serum LDL was associated with an increased likelihood of prostate cancer diagnosis in black men, but not in non-black men. Another study noted that serum lycopene levels were inversely correlated with prostate cancer risk, and that AA men in particular are shown to harbor lower lycopene levels compared to other races (29,30). While such studies have failed to generate a definitive consensus on the molecular drivers of prostate cancer in AA men, they do point to a multitude of ways in which the racial disparities in prostate cancer may at least in part be secondary to true biological differences apart from the existing issues of health care access.

**AS in AA men**

The role of AS in the management of prostate cancer is well established for low risk disease, and there is evidence to suggest it is underutilized (31). Several studies have demonstrated excellent outcomes for well selected men with low risk disease. A systematic review looking at seven large AS series found that prostate cancer-specific mortality was low (0–1%), with the longest median follow-up among included trials being 6.8 years (32). Nearly a third of patients ultimately undergo further treatment after a median of 2.5 years on AS, with most doing so due to disease reclassification. None of the seven included series, however, specified the racial backgrounds of included participants (32), leaving open the question of the safety of AS in AA men. Such concerns are promulgated by many in the urology community who point to studies such as one by Mahal et al, which conclude that AA race was associated with a higher risk of prostate cancer-specific mortality compared to CA race among men with low risk disease (33). Such differences in outcomes and rates of curative therapy were found to be independent of socioeconomic factors. Additionally, these findings are corroborated by earlier reports of advanced pathological features at prostatectomy found in AA men with otherwise low-risk disease, in addition to the higher likelihood of positive surgical margins compared with CA men (34).

Another consideration for AA men considering AS is the increased potential of missing clinically significant disease at biopsy due to the location of the tumor. Most contemporary transrectal ultrasound guided biopsy schemes oversample the peripheral zone as most prostate cancers arise in this location. However, Sundi et al. noted that AA men with very low risk prostate cancer at diagnosis have a significantly higher prevalence of anterior cancer foci that are of higher grade and larger volume (35). Tumors in this region may at least in part be secondary to true biological differences apart from the existing issues of health care access.

Recent retrospective studies however, have challenged
the assertion that AA men have worse pathologic outcomes than CA men with similar disease characteristics on biopsy. Using the Shared Equal Access Regional Cancer Hospital (SEARCH) database, Leapman et al. have suggested that AA race was not significantly associated with pathological upgrading, major upgrading, up-staging, or positive surgical margins, and that AA and CA men who underwent RP for low-risk disease (36) had comparable 5-year recurrence free survival rates. Additionally, investigators using the SEER database found no statistically significant differences between CA and AA men regarding adverse pathologic features (37). Thus data remain conflicting regarding pathologic outcomes for AA men treated for prostate cancer, thus further complicating the decision of whether to consider AS in these men.

**Biomarkers in the context of AS**

The effectiveness of observational management may also be enhanced by new innovations such as novel biomarkers in men considering AS. Novel tests such as Prolaris (Myriad Genetics, Inc., Salt Lake City, UT, USA), Oncotype DX Prostate (Genomic Health, Inc., Redwood City, CA, USA), and Decipher Biopsy (GenomeDx Biosciences, Inc., San Diego, CA, USA) analyze genomic patterns in biopsy specimens and can aid in decision making when considering AS versus definitive treatment. However, the underlying data that validates many of these novel biomarkers involve relatively few men of African descent relative to the general population (38). While there is no evidence to date to suggest that these tests perform differently in AA men compared to CA men, the fact that there may be biologic differences in the cancers in AA compared to CA men, maintains the possibility that these tests may be affected, though this remains to be seen. It is currently an area of increasing research. While these tests can be helpful in AA men, it is important physicians understand their strengths and limitations, and discuss these with their patients.

More is now also known about specific molecular aberrations in prostate cancer, with several new discoveries over the past decade. Under current investigation are a number of androgen regulated genes, including tumor suppressor PTEN deletion, SPINK1 overexpression, SPOP mutations, and ERG rearrangements that may prove fruitful in not only understanding prostate cancer biology, but also in developing non-invasive tools that can be used to identify higher risk patients. Unfortunately, much of the investigations surrounding these potential new biomarkers have also failed to incorporate significant numbers of AA men in their studies. In one recent study, however, Yamoah and colleagues compared the prevalence of numerous prostate cancer biomarkers between AA and CA men, and identified a subset of such markers that predicted the risk of clinicopathological outcomes in an ethnicity-dependent manner (39). Utilizing another approach, Sanchez et al. used immunoseroproteomics to profile anti-tumor autoantibody responses in men with prostate cancer, comparing European Americans (EA) and AAs, and found that tumor-specific antibody responses differed between AA and EA men, with sera from AA men exhibiting increased responses to the tumor antigen alpha enolase (ENO-1) (40). Such approaches may one day allow for new noninvasive testing that could enhance the use of observational management in AA men.

**Special considerations in AS for AA men**

Given the inherent limitations of current technology to determine the potential aggressiveness of a man's prostate cancer at diagnosis, the decision to pursue AS is one that should be entered into after an informed discussion and shared decision making between patient and physician. Given the generally worse outcomes for AA men with prostate cancer, this is even more important for AA men. As outlined in this review, there are likely a myriad of reasons contributing to this disparity including socioeconomic, cultural, as well as possible biologic factors all playing a role. Therefore, while there is no consistent evidence to suggest that AS in AA men is unsafe, it is clear that special considerations with perhaps enhanced surveillance techniques be considered in the management of these men. For instance, since it has been shown that low grade prostate cancer may exhibit lower PSA values in black men, one could consider using lower PSA thresholds and PSA density values to trigger repeat biopsies in addition to simply more frequent monitoring (41,42). In addition, given the increased prevalence of anterior zone cancers, AA men may be better served with surveillance strategies involving the incorporation of multiparametric MRI and targeted biopsy sampling of the anterior zone (35), or even consideration of transperineal prostate biopsies to enable adequate anterior zone sampling when MRI is not possible. Further, as outlined above, while the available genomic risk stratification tools have not been evaluated to the same extent in AA men as they have in CA men, these tests can still be helpful, particularly if they identify a cancer as being
more aggressive than clinical variables alone would suggest.

In addition to the possible biologic factors that may directly influence prostate cancer aggressiveness, racial disparities in prostate cancer outcomes are also in no small part influenced by socioeconomic and cultural barriers to healthcare access and patient compliance, which have certainly played a significant role in the treatment of prostate cancer in AA patients in the past and are of particular importance when considering AS. Since a significant fraction of men who initiate AS will go on to demonstrate disease progression and require curative intervention, poor compliance and failure to follow up can have lethal consequences in the context of unrecognized disease progression. Krishna et al. found that CA men on observation were more likely to adhere to an AS schedule compared to AA men, who had significantly lower odds of staying within a regimented AS protocol and had a greater likelihood of transitioning to WW by default (43). Thus poorly compliant men in general (whether due to socioeconomic circumstances, access to healthcare, or personal choice), and poorly compliant AA men in particular, given their increased risk of poorer outcomes from prostate cancer overall, may make poor candidates for AS and should consider definitive therapy. Lastly, it is prudent to have a low threshold for conversion from surveillance to definitive therapy in AA men at the earliest signs of disease progression to minimize the risk of missing the window of opportunity for cure in these men who at baseline are at increased risk of poorer outcomes from prostate cancer.

Conclusions

AS for the management of low-risk prostate cancer has been increasing and in the general population appears safe, allowing for a reduction in the harms of prostate cancer screening, such as overtreatment. AA men have overall worse outcomes from prostate cancer, compared to CA men for a variety of socioeconomic, cultural and possibly biologic reasons, thus complicating the use of AS in this population. Data including outcomes for patients on AS as well as validation studies of genomic risk assessment tools and biomarkers have included relatively few AA men, limiting the interpretation of their use in this population. There exists no direct data at this time to suggest that AS cannot be safely carried out in AA men following an informed discussion and after engaging in shared decision making. Strategies for optimizing care and mitigating risk include pursuing close surveillance strategies with steadfast patient compliance, the use of multiparametric MRI with targeted biopsies including the anterior prostate to reduce the risk of undersampling, as well as a judicious and thoughtful incorporation of novel molecular biomarkers for risk stratification. In addition, physicians should have a low threshold for consideration of definitive therapy. Finally, thought leaders who design and conduct clinical trials in this area should focus additional efforts in increasing the engagement of minority participants in their trials, to gain an improved representation of underserved populations in future studies.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Jiang S, Narayan V, Warlick C. Racial disparities and considerations for active surveillance of prostate cancer. Transl Androl Urol 2018;7(2):214-220. doi: 10.21037/tau.2017.09.11