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Risk Factors for Prostate Cancer Recurrence in African American Patients: VA versus Non-VA Healthcare Recipients

THESIS

Submitted in partial satisfaction of the requirements for the degree of

MASTER OF SCIENCE

in Biomedical and Translational Science

by

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DEDICATION

This work is dedicated to my family for their endless support and the sacrifices they have been making for my education and future. Also, to my peers for motivating and inspiring me daily.

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ABSTRACT of THESIS

Comparing Health Outcomes of African American Prostate Cancer Patients: VA versus Non-VA Healthcare Recipients.

By
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Master of Science in Biomedical and Translational Science
University of California, Irvine, 2021

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Biochemical recurrence (BCR) has been a cause of concern for patients and medical professionals. Although several studies have reported that only half the patients with BCR eventually progress to metastatic disease at 10 years, there is a substantial need for developing a predictive pattern or algorithm to efficiently identify and categorize prostate cancer patients based on their risk of recurrence. Currently non-Hispanic African American adults experience the highest incidence and mortality rates for cancers, with prostate cancer being one of the most prevalent. These statistics could be significantly reduced by introducing an appropriate predictive mechanism by which patients with higher risk of recurrence and tumor progression could be identified and recommended for more aggressive treatments during initial diagnosis, preventing possible progression to metastasis. Recurrence and oncologic outcomes may be dependent on sociodemographic factors and certain other factors contributing to comorbidities. We selected the patients from Veterans Affairs medical facilities for a comparison group, primarily due to reports suggesting that VA patients provide a diverse group of individuals with different socioeconomic, educational, and medical backgrounds. VA patients are generally expected to present with clinically worse comorbidities. Ultimately, the aim was to demonstrate a significant association between higher SES and lowered risk of BCR in African American prostate cancer patients, adjusted for the site of care. We used ‘complexity’, Gleason, and Decipher scores to compare the differences in African American and White patients adjusting for site of care. Our results suggest that African American patients have higher complexity scores, which we defined as a dynamic state in which the personal, social, and clinical aspects of the patient's experience operate as complicating factors. African American patients also had higher Decipher scores regardless of site of care, suggesting a higher risk of BCR. Our findings indicate that complexity scores and Decipher scores can be simultaneously employed to assist in identifying patients with high risk of BCR, allowing for recommendations for intensive treatments.

INTRODUCTION

Non-Hispanic Black adults are the second largest minority group and 13 percent of the total population of the United States and only an insignificant portion of the total population has regular access to healthcare, which justifies their lowered life expectancy despite the recent advances in the medical field and newly introduced inclusion programs (1). African American adults experience higher incidence and mortality rates for cancers, in which early detection and appropriate care could lead to improved outcomes (2). In a recent study, DeSantis et al. (3) projected approximately 98,020 new cancer cases in Black men in 2019. It is important to realize that health status for every prostate cancer patient may vary tremendously, and results could possibly be influenced by factors such as race/ethnicity and socioeconomic status (SES). It is uncertain whether the Non-Hispanic Black race naturally demonstrates a stage-for-stage increased risk of prostate cancer specific mortality (PCSM) or whether the current disparities are caused by racial complexes constructed by society (3,4) that might lead, through epigenetic mechanisms, to more severe illnesses. For instance, Black Americans have a higher prevalence of trigger events and lower socioeconomic characteristics which directly correlate with greater insurance loss and difficulty in insurance gain (5,6), which through epigenetic mechanisms would lead to greater disease severity. Similar population-based estimates also demonstrate a positive correlation between being of African American racial/ethnical background and a higher likelihood of being diagnosed with metastatic prostate cancer (7). Annually, the Surveillance, Epidemiology, and End Results (SEER) database release data regarding age adjusted PCSM rates and one distinguishable limitation is the evident lack of diversity in research as well as limited data comparing African Americans with different socioeconomic backgrounds which has created a gap in understanding the association of risk factors and recurrence rates for various illnesses within this population (8,9).

The malignant transformation of the prostate entails a step-by-step process, beginning with prostatic intraepithelial neoplasia (PIN), followed by localized prostate cancer, then advanced prostate adenocarcinoma with local invasion, which ultimately leads to metastatic prostate cancer (10). Prostate cancer can spread quickly – metastasize – or more commonly grow at a slow and

asymptomatic manner. Autopsy reviews have shown that many cancer patients that succumbed to other fatal causes also had prostate cancer, which remained dormant and asymptomatic throughout their lives (11). The American Cancer Society (11) states that prostate neoplasm may start out as a pre-cancerous condition categorized into Prostatic intraepithelial neoplasia (PIN) and Proliferative inflammatory atrophy (PIA). In PIA, cells appear smaller than the standard size and signs of inflammation exists. PIA may lead to high-grade PIN or directly to cancer. Men over 50 years are susceptible to developing prostate cancer presenting with lower urinary tract symptoms, visible hematuria, or sexual dysfunctions (12).

Oncologic outcomes may differ based on various factors such as race, income, age, quality of care, or the stage in which the disease was first diagnosed. There is little information on how African American prostate cancer patients respond to treatment and how effective is the treatment process in preventing biochemical recurrence (BCR). The difference in sociodemographic, environmental, and behavioral factors within the African American race might help determine the risk factors responsible for more aggressive tumors and BCR. Due to such variability in prostate cancer progression, it is vital to identify predictive patterns which might influence progression as well as BCR regardless of active surveillance or even radical prostatectomy. After studies confirmed that one of prostate cancer's central features was its genomic features and hormone responsiveness (13), the Gleason score and other diagnosis tools such as genomic classifiers (GC) have helped medical professionals assess and assign appropriate therapeutic methods to patients depending on the aggressiveness and progression of their disease. The Decipher Prostate Cancer Test is a genomic classifier that stratifies patients by risk of prostate cancer progression and is usually utilized in determining the intensity of treatment.

More in-depth analysis of differences in scores (GC, complexity, and Gleason scores) may allow us to identify clinically significant correlations between race and the BCR likelihood when adjusting for confounding factors such as socioeconomic status, environmental and cultural influences on epigenetic mechanisms, as well as source of care. To assess the significance of SES on overall health status, site of care is a valid primary point of comparison, therefore, we have chosen to compare the African American prostate cancer patients who receive care at a

Veterans Affair (VA) hospital to those patients of non-VA medical facilities. According to a Veteran Affair's Office of Health Equity report African Americans make up around 12 percent of the total veteran population (14). This population offers great diversity in terms of socioeconomic and overall health status. Ultimately, the aim is to demonstrate a significant association between higher SES and lowered risk of BCR in African American prostate cancer patients, adjusted for their medical background and socioeconomic status. Hypothetically it is expected that patients who receive care at VA medical facilities are more likely to have low standards of living, relatively lower resilience, and clinically worse overall health status. In this study we aim to test the hypothesis that sociodemographic factors, site of care, overall health status of African American prostate cancer patients can impact the risk of BCR and eventually metastasis. In this study, we will use Decipher score (GC) for its ability to predict BCR and eventually metastasis.

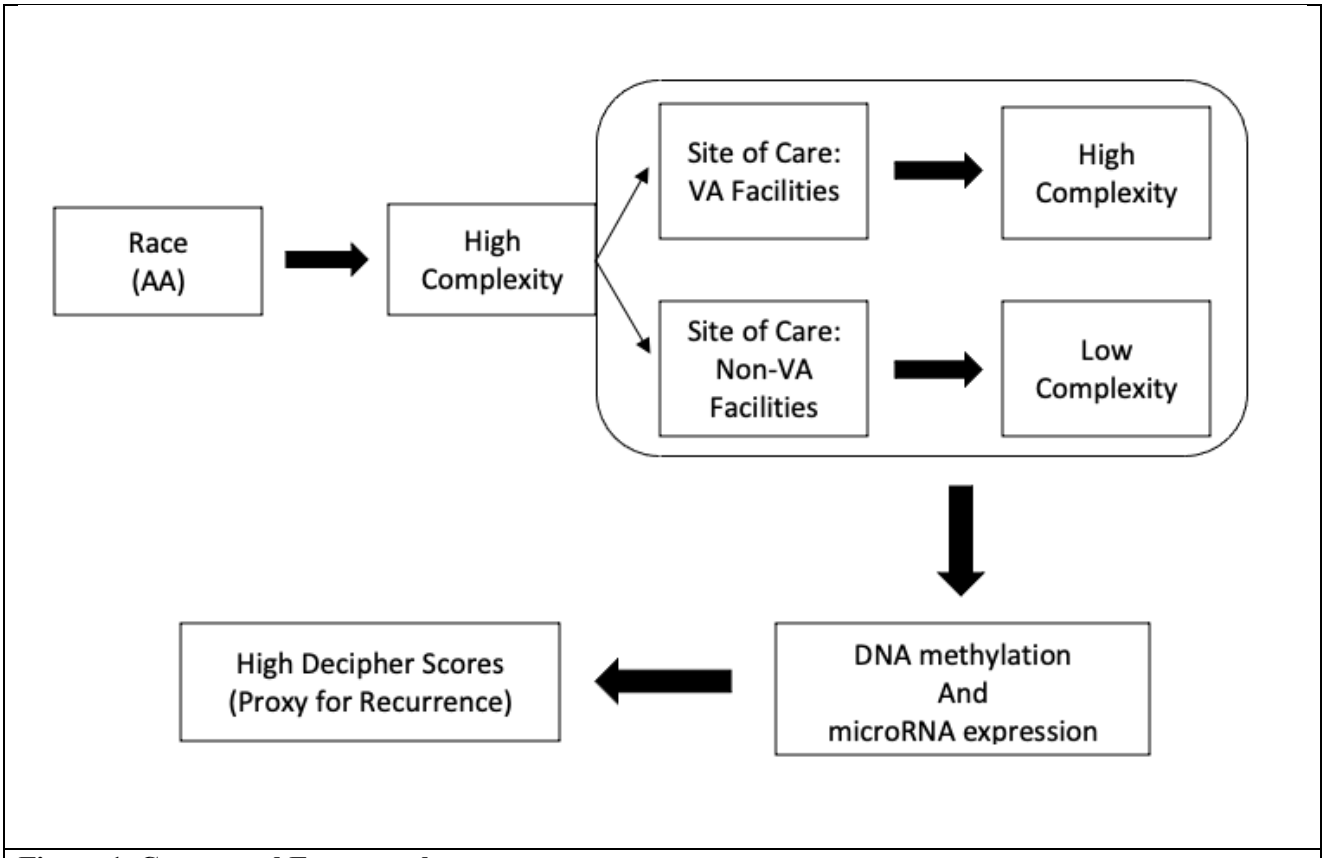

Figure 1. Conceptual Framework

BACKGROUND

Ranking among the top five cancers for both mortality and incidence, the global burden of prostate cancer is substantial (15). Studies from 2016 reported prostate cancer to be the most diagnosed cancer in men, with an estimated 1.6 million incident cases globally (16). Contrary to belief, prostate cancer is more common in developed countries with the odds of diagnosis being one in six among nations with a high sociodemographic index, compared to one in forty-seven among countries with low-middle sociodemographic index (16). While being the leading cause of incident cancer in the United States, prostate cancer incidence is known for its clinically significant global variation (17). After adjusting for age, men of African descent have the highest incidence rate globally, meanwhile, Asian natives rank among the lowest recorded (17). Incidence rates are relatively highest in more developed parts of the world, largely reflecting the ease of access to healthcare, screening, and early detection, meanwhile prostate cancer mortality rates are highest in regions inhabitant by men of African descent (18). Family history can also influence prognosis and the risk of recurrence. Studies have revealed that familial aggregation of prostate cancer may significantly be due to genetic factors and lifestyle patterns (19). Multiple investigations, such as epidemiological studies, large scale GWASs, and twin studies have highlighted a genomic component to prostate cancer etiology. As discussed earlier, epidemiological studies on family history indicate a strong correlation between history of prostate cancer in immediate family members and increased risk of illness (20). GWASs have observed and identified many prostate cancer susceptibility loci (21, 22), for example, risk associated single-nucleotide polymorphism (SNP) rs339331 increases expression of the cancer-promoting RFX6 gene which occurs through a functional interaction with the prostate cancer susceptibility gene HOXB13 (23). Studies also suggest that African American patients are 2.4 times more likely to succumb to prostate related cancer compared to white men (24). These observations signify a strong correlation between prostate carcinogenesis and factors such as SES, genetics, race, lifestyle, access to healthcare, and healthcare disparities (25).

Environmental and Behavioral Factors

Social determinants of health and racial disparities have been studied to determine whether sociodemographic factors, social status, and access to healthcare contribute to an increased risk of cancer recurrence or metastasis. Most studies have established an association between

socioeconomic status and prostate cancer aggressiveness and recurrence. Socioeconomic factors such as poverty, income inequality, and lack of education have been recognized as social determinants of health and are hypothesized to influence the risk of prostate cancer (26). Although low socioeconomic status has been associated with lowered survival rates and poor health outcomes, it is important to determine whether the impact of sociodemographic factors can be used as a predictor of recurrence so that the course of treatment can be modified at earlier stages. Nicolau et al. studied the socioeconomic position over the life course of men, and they concluded that socioeconomic position during childhood stages impacted the risk of prostate cancer in later stages of life (27,28), suggesting that environmental factors and behavior could impact the risk of incidence, aggressiveness, and possibly recurrence. Therefore, it is important to use valid scales to categorize the risks associated with recurrence and metastasis in order to develop appropriate treatment courses at earlier stages of illness. In this study, a comparison between African Americans with different socioeconomic backgrounds will be useful in determining possible correlation between SES (race related) and recurrence rates (therapy related).

There are several theories regarding both biological and sociodemographic risks that are unique to African American men compared to Caucasian American men. Patients with relatively low income, those residing in disadvantageous neighborhoods, as well as those with limited social support have always been victims of disparate prostate cancer specific care such as lack of frequent screening, diagnosis at later stages, and lack of appropriate therapy (29,30). Lack of access to preventative healthcare due to lack of health insurance and financial freedom of African American men in lower income class and socioeconomic status could explain this enhanced prostate cancer burden. Other non-financial obstacles such as poor health consciousness, fear of diagnosis, or treatment non-adherence also play a significant role in the advancement of diseases in uneducated African American men. Contrary to expectations, there is evidence that men with higher socioeconomic status or men who live in higher-SES neighborhoods have a higher incidence of prostate cancer (31). However, the tumors of such individuals are generally localized and low grade at diagnosis (32). The main interpretation of the association between sociodemographic and prostate cancer and these recent findings is that access to healthcare, higher income, better lifestyle, nutrient rich diets, less comorbidities, lower

depression scores, and higher resilience that men with higher socioeconomic status possess will more likely lead to a lowered risk of recurrence, early detection, as well as lower morbidity and mortality (33).

Despite the biological explanations for some of the prostate cancer risk presentation and outcomes in African American men, certain additional underlying factors such as diet, neighborhood, and education can play a clinically meaningful role in exacerbating these risks and disparities. Through the years, prostate cancer studies have examined dietary factors as a significant modulator for prostate cancer risk. Western dietary regimens of high consumption of fat, red meat, processed meats, alcohol, dairy products, and lower fish intake may contribute to more aggressive prostate cancer (34-35). Such dietary patterns are generally observed within low-SES households and neighborhoods where access to organic and fresh food is limited. Obesity is another factor which is a well-established risk factor for various health conditions, including prostate cancer. African Americans have a higher prevalence of obesity that other races (36). Obesity has also been associated with higher grade prostate cancer as well as recurrence rates (37,38). A study by Chu and Freedland can confirm that prostate cancer risk has been significantly associated with various metabolic factors. Their investigation concluded that individuals at risk of prostate cancer may benefit from healthy eating, weight loss, and physical activity (39).

Sociodemographic factors are a foundation of structural inequalities that might create health inequalities, which may trigger health disparities (40). These differences are integrated into the societal structure that are reflected by living conditions, income status, lack of access to quality food, healthcare, housing, and education. Such factors can indirectly and negatively influence prostate cancer risks through biological and behavioral pathways (41). Higher income and education may impact health through a cascade effect on the ability to acquire resources such as access to healthcare (42), meanwhile residing in food oasis area can provide access to healthier and nutritious dietary regimens (43), which in turn can lead to lowered cancer risks. Unfavorable neighborhood environments can also indirectly impact prostate cancer risk through chronic stress mechanisms. Individuals living in low-SES neighborhoods are typically more exposed to higher degree of emotional stress caused by insecurities, lack of safety, and discomfort which can result

in initiation of carcinogenesis (44). Such trends are usually observed in predominately African American communities or neighborhoods (34).

Lifestyle

The concept of lifestyle includes but is not limited to factors such as diet, stress, behavior, physical activity, career decisions, smoking, alcohol consumption, and income. Every individual's genetic background, lifestyle and environmental factors are responsible in determining their overall health status (45). Previous studies have demonstrated that carcinogenesis is the result of genetic and epigenetic changes to protein-coding oncogenes as well as tumor suppressor genes. Malignancies such prostate cancer typically result from somatic genetic events. Further research has revealed that in addition to somatic genetic alterations, prostate cancer could demonstrate dysfunctional tumor repressor genes caused by epigenetic changes in expression (46). Epigenetic mechanisms include DNA methylation, biochemical modifications of histones, and expression of non-coding RNAs, such as micro-RNAs. Such alterations have been identified to contribute to higher grade tumors in African American patients (47-49). Epigenetic mechanisms are defined as flexible genomic parameters capable of altering genome function under exogenous influence as well as providing mechanisms for stable propagation of gene activity states (50). Exogenous influences are defined as environmental and behavioral factors. Therefore, alterations in epigenetics influenced by environmental and behavioral factors have been associated with a variety of diseases, including prostate cancer (51). Overall, African Americans diagnosed with prostate cancer are generally diagnosed at a younger age, have higher Gleason scores, incidence of palpable disease, and higher PSA levels (52). According to reports, African American patients are more susceptible to the process of hyper-methylation of genes in pre-cancerous prostate tissue which may promote malignancy (53). We will briefly discuss how hyper-methylation of tumor suppressor genes may be a causal factor in the racial differences between African American and White patients (54).

DNA Methylation

DNA methylation is an epigenetic regulator of gene expression, which has been associated with prostate cancer (55). Any significant disruption of DNA methylation pattern is characterized by genome-wide loss of methylation, in parallel with hypermethylation of certain gene promotor

regions (56). Gene silencing may be associated with increased methylation in promotor regions, specifically within cytosine guanine dinucleotides (CpGs) islands. For instance, frequent dysregulation of the GSTP1 gene in prostate tumor tissue is a good example of how gene silencing and hypermethylation may increase risk or impact prostate cancer progression. Another example includes the hypomethylation of gene regions responsible for gene instability (57). Alterations in methylation patterns may occur during early carcinogenesis stages and certain methylation events might influence disease outcomes, suggesting that methylation biomarkers may be utilized for predicting disease progression and guiding treatment decision for both providers and patients (58). DNA methylation is ultimately responsible for gene silencing through blocking transcriptional factors or activators from accessing the target sites (59). Few studies have examined DNA methylation in African American prostate cancer patients, reporting differences in methylation patterns among African American and European American patients (54). For example, a study by Tang et al. indicated that hypermethylation of RARB had a clinically meaningful association with higher risk of aggressive prostate cancer in African American men only (60). Another study by Woodson et al. reported that hypermethylation of CD44 in tumor tissue of patients was positively correlated with tumor grade and disease aggressiveness (61). Investigations also found that several genes including SNRPN, ABCG5, and MST1R were hypermethylated in African American patients only (62). Extensive and detailed investigation is necessary to determine whether such methylation patterns can be associated with certain lifestyle and environmental factors in African American men with different SES, or whether these epigenetic alterations may simply be a uniform and race-specific occurrence in all African American prostate cancer patients.

MicroRNA Expression: miR-24 and miR-34b

Factors impacting epigenetics also alter microRNA expressions. A miR-24 precursor is a small non-coding RNA which regulates gene expression. Recent studies on miR-24 suggest that this specific mircoRNA suppresses the expression of two significant cell cycle control genes (63), which may play a clinically meaningful role in the development of aggressive prostate tumors, especially in African American patients. Hashimoto et al. suggest that miRNAs may play a significant role in abnormal gene regulation in African American prostate cancer patients. Studies have shown that miR-24 is a potent tumor suppressor in African American prostate

cancer cell line (53). Reports have stated that miR-24 expression is decreased in African American prostate cancer patient due to promoter hyper-methylation. Therefore, hyper-methylation of CpG (DNA) islands may suppress miR-24-1 expression, which in turn creates a difference in the expression of this specific microRNA, which might be a key difference between African American and White prostate cancer patients (53). Down-regulation of miR-24 correlates with racial variation and aggressiveness of tumors. In other words, dysregulation of tumor suppressor miR-24 results in low levels in MDA-PCa-2b (African American cell line), compared to DU-145 (Caucasian cell line). Since cancer-related pathways are suppressed after miR-24 over-expression, this microRNA may in fact be a central regulator of major events, which directly and indirectly correlates to race-related prostate carcinogenesis and aggressiveness. Much like the miR-24, the miR-34b plays an important role in tumor suppression in many cancer types. In a published study, Shiina et al. reported that miR-34b expression is lower in African American prostate tumor samples compared to white patients (64). Due to the allelic deletions and loss of heterozygosity that frequently occur at 11q23, the expression of miR-24b and c is low in all prostate tumors. This microRNA can be epigenetically regulated through promoter hypermethylation in certain prostate cancer cell lines and tumor specimens. A recent study reported lower miR-34b chromosome in MDA-PCa-2b, however, this was not observed in DU-145 cells (64). This observation therefore, explains the lack of tumor suppressors in African American prostate cancer patients, resulting in more aggressive tumors. Lower miR-34b expression in African American is inversely correlated with high androgen receptor (AR) level which leads to cell proliferation and cancer progression. These findings may play a revolutionary role in the prediction and treatment of aggressive African American prostate cancers. For instance, such findings can be useful for identifying individuals at risk of metastasis even after radical prostatectomy (RP).

BCR Predictability

Approximately half of men diagnosed with prostate cancer undergo local therapy with radical prostatectomy, and among these patients, it is estimated that a third will eventually have a raising serum PSA which is a proxy for recurrence (65,66). Rising levels of PSA as precursors for disease recurrence pose certain management risks for patients as well as providers. This is due to the unpredictable outcomes for men presenting with BCR. In some scenarios, BCR will only

have local recurrences, however, some recurrences progress to clinical metastasis (67). Therefore, a 'one-size fits all' treatment such as systemic or salvage local therapy would only result in over-treatment and adverse sexual and cardiovascular effects (67). Regardless of these high-risk treatment outcomes, many studies indicate that early treatment of patients with BCR with an appropriate therapy may improve progression-free survival (68).

By developing a reliable prediction algorithm, identification and categorization of high-risk patients will be possible, therefore, allowing providers and patients to decide on a treatment course with appropriate aggressiveness within an adequate timeframe. As mentioned earlier, molecular characteristics such as DNA methylation and altered microRNA expression can dictate tumor progression. Since exogenous influences on molecular characteristics correlates with disease aggressiveness, we reason that quantifying potential mortality and morbidity into a universal scale (Complexity Score) will allow us to determine whether sociodemographic and overall health status of a patient is a predictor of BCR or even metastasis. We assume the validity of this algorithm by acknowledging that factors such as sociodemographic (exogenous influencer) and overall health status of an individual most accurately represents their mortality and morbidity potential.

In addition, the activity of genes in the tumor that are known to be involved in prostate cancer progression can be evaluated using the Decipher test. The Decipher test can predict the 5-year risk of clinical metastases after RP by measuring the expression levels of 22 RNA features within various biological pathways across the genome (69,70). Decipher scores may positively impact the decision-making process for patients and providers regarding the adjuvant treatment of patients with aggressive pathology or salvage treatment of patients with rising PSA levels. A recent study has reported decreased decisional conflicts in patients and providers when Decipher scores were utilized to determine an appropriate treatment course (71). In a study by Freedland et al. (72) with the objective to test the predictive capabilities of the genomic classifier (GC), it was observed that on a multivariable analysis, for each 0.1 unit increase in the Decipher score, which is scaled from 0 to 1, the hazard ratio for metastasis was 1.58 with a p value of 0.002. The results also suggested that the 5-yr cumulative incidence of metastasis post salvage radiation therapy in patients with low, intermediate, and high Decipher scores was 2.7%, 8.4%, and 33.1%, respectively ($p<0.001$). So, their data concluded that genomic classifier might be a strong predictor of metastases among men receiving treatment for recurrent prostate cancer even after

radical prostatectomy, identifying men who are excellent candidates for systemic therapy due to their very high-risk of metastases.

Site of Care: VA vs. Non-VA

The veterans Affairs (VA) healthcare system is designed with the aim to provide quality medical care to veterans in the United States, however, the quality of care at VA hospitals have been a cause of concern for Congress (73). Multiple studies have been published on the reportedly inferior access to care and quality of care in VA settings compared to non-VA settings, and this study aims to compare and contrast the health outcomes of African American prostate cancer (VA and non-VA) patients. A recent study by O'Hanlon et al. stated that VA systems were more adherent to recommended care processes and guidelines compared to other systems of care. However, these processes did not necessarily grant better outcomes, for instance, mortality (73). Since veterans are subject to worse baseline health status than the general population, VA patients may be a justified selection of participants to collect and compare their health outcomes when evaluating health outcomes of prostate patients. Some VA patients are also more likely ranked lower on the sociodemographic index. Based on available data, VA and non-VA facilities had almost similar and comparable healthcare quality, however, rates of complications and availability of services were the least favorable in this comparison (73). In another study of case-mix adjusted patient experience measures by Anhang Price et al., results suggested that in addition to adherence to guidelines and recommended processes, VA hospitals were the same or better compared to the quality of non-VA inpatient and outpatient care (74). However, risk-adjusted readmission rates were significantly worse in VA hospitals. Reports indicate a fluctuating quality measure performance across VA settings, which might suggest that Veterans in some areas are not receiving adequate or similar quality of care as other VA facilities are offering. Moreover, veterans might differ from non-VA patients in terms of clinical and demographic characteristics. Cooperberg et al. studied the sociodemographic and risk characteristics of prostate cancer patients in VA systems, and found out VA patients with prostate cancer had lower income and education levels, were more likely be African American and present with multiple comorbidities. VA patients generally had higher PSA levels and biopsy Gleason scores even when adjusted for ethnicity and socioeconomic status (75). Despite the lack of a biological explanations for higher Gleason scores in VA patients, certain features unique to

this population such as body mass index, dietary parameters, smoking habits, various lifestyle factors and exposure to potential carcinogens during military service are usually not accounted for while studying this population (76,77).

METHODS

Total of 631 patients, with 514 Caucasian Americans and 117 African Americans were included in this project, Data from the California Initiative to Advance Precision Medicine in Early Prostate Cancer will be used. Data was collected from patients seen at five medical centers namely: University of California Irvine Medical Center, University of California Los Angeles Medical Center, Cedars Sinai Hospital, the West Los Angeles Veteran's Administration Hospital, and the Long Beach Veteran's Administration Hospital.

Hypothesis and Aims:

We hypothesize that recurrence is associated with race and site of care and African American prostate cancer patients receiving care in VA facilities are at a higher risk of recurrence, this could correlate with factors encouraging patients to select VA facilities to receive care or simply due to how VA patients are treated for specific illnesses. Reports and data suggest that patients who select VA facilities are at an economic disadvantage compared to non-VA patients, therefore, our aim is to test whether race and site of care can impact the risk of biochemical recurrence through analysis of complexity scores and a genomic classifier. In this study we aim to identify the significance of our two primary variables (race and site of care) as well as the social, cultural, and medical components of these variables to determine the usefulness of genomic classifier and complexity scores as predictive tools or algorithms in identifying patients at higher risks.

Statistical analysis –

We calculated the complexity scores for each study group with mean differences and 95% confidence intervals. Differences were measured by adjusting for site of care and race. We also compared percentage of patients treated versus on active surveillance in total as well as adjusting for site of care. Decipher scores were also calculated and presented as a percentage of the total population with high-risk Decipher scores. Decipher scores were adjusted for complexity as well as site of care.

Gleason Scores:

One important component of staging cancer is the grade of the cancer. Traditionally, prostate cancer grades are described according to the **Gleason Score.** Biopsy samples will be assigned one Gleason grade to the most predominant pattern in a patient's biopsy and a second Gleason grade to the second most predominant pattern. For example: 3 + 4. The two grades will then be added together to determine the Gleason score. A Gleason score of 6 is low grade, 7 is intermediate, and a score of 8 to 10 is high grade cancer.

Complexity scores:

The concept of complexity is difficult to define, but for this project, we functionally define complexity as a dynamic state in which the personal, social, and clinical aspects of the patient's experience operate as complicating factors. Clinical experiences have identified several components of patient complexity, including clinical complications such as chronicity and comorbidity, burdensome treatment and self-care regimens or environmental and social factors that influence access and overall health. Patients exist at the intersection of these circumstances meaning that they eventually will face multiple complicating factors at once. Current conceptual literature on complexity factors emphasizes on their clinical, socioeconomic, or cultural factors and their functions in complicating care, which is a descriptive approach, which provides significant analytic guidance for PCPs. Since complexity emphasizes on factors that directly complicate clinical management, we have selected several factors, for instance, age, resilience, Total Illness Burden Index, comorbidities, and other factors that are usually deemed by experts to increase complexity because they increase the need for resources or expertise for successful management. We combined them into a single "complexity" variable to determine its association with race and site of care through further analysis. Patients with higher scores are associated with more complications. By finding an association between the factors generated in our complexity model and real-world constructs such as immigration status, sociodemographic features, and medical comorbidities we may be able to correctly identify high-risk patients.

RESULTS

This study categorized patients by race and site of care at the time of diagnosis. After excluding patients with incomplete data or unmatched descriptions, the study consisted of 631 patients, including 117 African American (19%) patients (Table 1). Mean age was 65 years and approximately 66% were retired or unemployed. Interestingly, most African American patients had clinically worse health assessment ratings including lower overall health ratings, Total Illness Burden Index scores (TIBI), resilience, and worse healthy habits compared to white patients (Table 1). African Americans also had higher PSA levels (8.4).

	Race		
	White	African American	**p-value**
Age (mean, SD)	65.8 (7.5)	64.7 (6.1)	0.083
Education (% some college)	92.1	78.0	<0.001
Employment Status			
Working (PT or FT)	51.6	34.0	0.003
Retired	45.3	52.6	0.243
Unemployed	3.0	13.4	<0.001
Married (%)	71.0	35.1	<0.001
Total Illness Burden Index (mean, SD)	8.0 (3.1)	11.2 (3.2)	<0.001
Overall Health Rating (mean, SD)	70.8 (22.2)	55.3 (24.3)	<0.001
SF-36 PFI10(mean, SD)	86.8 (19.8)	71.1 (29.9)	<0.001
SF-36 Pain (mean, SD)	20.5 (21.8)	35.4 (28.3)	<0.001
SF-36 Energy (mean, SD)	67.6 (19.6)	62.0 (23.7)	0.032
CESD (mean, SD)	39.3 (15.6)	45.8 (19.6)	0.003
Resilience (mean, SD)	75.3 (15.3)	67.4 (24.6)	0.004
Stress (mean, SD)	39.3 (18.9)	42.4 (21.8)	0.189
Fatigue (mean, SD)	18.8 (20.5)	29.8 (26.1)	<0.001
Physical Activity (mean, SD)	54.2 (16.0)	47.5 (19.6)	0.002
Healthy Habits (mean, SD)	64.3 (17.3)	55.3 (20.9)	<0.001
Participatory decision-making style (mean, SD)	76.0 (20.9)	81.9 (19.6)	0.015
Passivity	22.8 (18.1)	25.2 (19.1)	0.268
PSA (mean, SD)	7.0 (16.6)	8.4 (11.9)	0.295
Gleason Score (%)			
3 + 3	39.3	37.6	0.854
3 + 4	32.4	36.6	0.507
4 + 3	13.1	13.9	0.975
	15.2	11.9	0.506

Table 1. Patient Characteristics table.

Complexity scores were used to assess the factors which complicate and contribute to BCR. In total, white patients (0.42) were less complex compared to African Americans (0.54). Results suggested that the generally lower health scores of African American patients (Table 1) are a valid predictor and contributing factor when identifying more complex patients. When adjusted for site of care, Non-VA African American patients had higher complexity scores, however, VA patients had similarly high scores regardless of race (Table 2). Understanding that higher social and medical comorbidities presented by VA patients, higher scores are expected, and in addition, the African Americans patients displayed such results regardless of site of care.

"Complexity Scores"	**White (n = 514)**	**African American (n = 117)**	**Mean Difference (95% CI)**
Total (mean, SD)	0.42 (0.28)	0.54 (0.31)	- 0.12 (-.06, -.18)*
Non-VA patients (mean, SD)	0.40 (0.28)	0.54 (0.30)	- 0.16 (-.08, -.2)*
VA patients (mean, SD)	0.55 (0.30)	0.53 (0.31)	0.02 (-.04, 0.08)

Table 2. Complexity scores by race and site of care (VA or non-VA).
p < .05

To investigate the distribution of treatment among patients, table 3 displays the results from analyzing the proportion of patients treated with more extensive therapies compared to active surveillance. In the African American group, 53.3% of patients were treated with more aggressive therapies compared to the active surveillance. This could partially reflect the need for African American patients to be treated more aggressively, considering the known mortality and recurrence rates due to racial differences. Interestingly, based on Gleason scores (Table 1), 70 % of both races were categorized with low (3 + 3) or intermediate (3 + 4) graded tumors, indicating they are eligible for active surveillance. However, when adjusted for complexity scores, only 70% of African Americans were on active surveillance. This might suggest hidden treatment biases or other factors responsible for lack of decision making between providers and patients of the African American race. When adjusted for site of care, more African American patients at non-VA facilities were treated, meanwhile, white patients at VA sites were more likely to be recommended for aggressive therapy (Table 3).

Percent treated (vs. on active surveillance)	White (n = 514)	African American (n = 117)	Mean difference (95% CI)
All patients (% treated)	49.8	53.3	- 3.5 (-13.5, 6.5)
Adjusted for complexity (% treated)	46.6	31.8	14.8(5.3, 24.3)*
Seen at non-VA sites (% treated)	40.8	55.3	- 12.5 (-24.5, -1.5)*
Seen at VA sites (% treated)	67.4	51.9	15.5 (-36.7, -28.6)**

Table 3. Percent treated vs active surveillance by race. Unadjusted and adjusted for complexity.
p < .05
****p < .005***

Based on the expression pattern of 22 RNA markers from the tumor or specimen, we used the Decipher Prostate Cancer Test as a genomic test that serves as a prognostic marker of cancer control outcomes in patients. Unexpectedly, results suggest that more African American patients (37.1%) presented with high-risk Decipher scores (Table 4). When adjusting for complexity, the difference between races were insignificant with a mean difference of 2.3%. Approximately 55.2% of African American prostate cancer patients on treatment had high-risk decipher scores, which might indicate that decipher scores might be capable of serving as a predictor when used in parallel with complexity and Gleason scores.

High-risk Decipher Scores	White (n = 514)	African American (n = 117)	Mean Difference (95% CI)
Unadjusted for complexity (% high-risk)	28.6	37.1	- 8.5 (-18.1, 1.1)
Adjusted for complexity (% high-risk)	32.3	30.0	2.3 (-6.9, 11.5)
On treatment (% high-risk)	34.4	55.2	- 20.8 (-30.7, -10.9)**

Table 4. Decipher scores by race, unadjusted and adjusted for complexity.
****p < .005***

DISCUSSION

Biochemical recurrence following radical prostatectomy has been a cause of concern for patients and physicians, although studies have reported that only half of the patients with BCR ultimately progress to metastatic disease at 10 years (67). Nonetheless, there is a need to efficiently evaluate and categorize patients based on the risk of recurrence and metastasis. Current diagnostic models involve standard imaging modalities incapable of distinguishing local from distant metastasis during BCR and rising PSA levels (78). In such instances, there is a need for 'supplementary assessment' of a patient's risk of recurrence and clinical metastasis, therefore, the use of a genomic classifier in congruence with "complexity scores" may enable providers to identify candidates for intensive therapy more effectively while sparing those not at risk for BCR. Studies have reported that treatment recommendations align appropriately with Decipher risk categories: low-risk patients typically receive recommendation for active surveillance, whereas high-risk patients are more likely to receive recommendations for more aggressive treatment (71).

In this study, we relied on the ability of a GC and 'Complexity Scores' to assess the risk of recurrence among African American (VA vs. Non-VA) patients. In addition, identifying and analyzing the effect of exogenous factors on molecular characteristics of the primary tumor might also assist in better predicting BCR and metastatic progression (79,80). Our data analyses showed few significant findings, corresponding with established studies. First, the Gleason scores for African American patients demonstrated that more than 70 percent had well differentiated (3 + 3) and moderately differentiated (3 + 4) cells, which places them in the low-intermediate categories. These patients are generally the best candidates for active surveillance. Caucasian American and African American patients had very similar Gleason score distributions, with most patients having relatively low scores. However, when adjusted for complexity, only half of African American patients were on active surveillance regardless of site of care. This might indicate that African Americans had greater than expected BCR rates, therefore, more patients were recommended for intensive treatment.

Second, the 'Complexity' data revealed that within this study population, African Americans had higher complexity scores in total compared to Caucasian patients. This signifies a theoretically

higher mortality and morbidity potentials in African American patients. Although previous investigations have reported that African American men have higher incidence and mortality rates (2,7,17), nonetheless, we can correlate our findings and established study results by viewing this analysis from an alternative perspective: if complexity scores are determined by mortality and morbidity factors, then we can assume that complexity scores are close representations of the effects of exogenous factors such as socioeconomic and behavioral factors on the human molecular characteristics. This might be true since molecular characteristics such as DNA hypermethylation and microRNA expression can alter BCR and metastasis progression, hence, influencing morbidity and mortality. Data analysis revealed that BCR risk was not associated with site of care in African American patients, hence, suggesting that African Americans had higher mortality and comorbidities regardless. Overall, VA patients had relatively high complexity scores, possibly indicating higher risk of BCR or metastasis progression. This observation obeys the clinically established correlation between high-risk patients and exposure to risk factors such as low income, healthcare disparities, low educational levels, and exposure to carcinogens (veterans during war) (75).

Next, we manage to demonstrate that the use of GC added incremental prognosis value in identifying patients with high risk of BCR following PR. Decipher test results suggest that race and race-induced variations are prominent risk factors in prostate cancer patients. Prior studies have combined Decipher with another valid model for identifying prostate cancer patients at risk with noticeable success (70). Using the Decipher test in congruence with complexity scores, we may develop a set of indicators capable of predicting which prostate cancer patients are at a higher risk of BCR and metastasis progress. Therefore, we can reason that African Americans with low to intermediate Gleason scores but high complexity and Decipher scores should receive recommendations for more aggressive therapy. Based on our analysis of most African Americans, despite having low or intermediate Gleason scores, most patients contribute to higher complexity and Decipher scores, suggesting an increased risk of BCR and metastasis progression. Results from our study displayed uniformly high scores for African American patients regardless of site of care. Besides genetics, we may assume that such similarities across groups could be associated with the developmental stages of African American patients. This suggests that more affluent African American patients must not have necessarily had similar SES

and access to healthcare as they do now. For instance, most African American athletes with high income levels, did not possess the same SES, lifestyle, and behavioral patterns growing up. Studies have shown that changes caused by environmental and epigenetic factors do during childhood and developmental stages and persist through adulthood (27,28).

An unmet clinical requirement for patients with a risk of BCR after RP is a predictor capable of accurately identifying only those patients who will ultimately develop metastatic disease. The GC appears to be an optimistic predictor of clinical metastasis as this study has demonstrated. Although more in-depth studies in larger and more diverse patient populations are required, our findings suggest that Decipher test and complexity scores can be used to identify men requiring intense treatment at the time of BCR.

Limitations –

This was a retrospective cross-sectional study, suggesting that causality often cannot demonstrated reliability from our results. Possible correlations between our variables could be due to confounding and moderator components within this study parameters. Decipher scores did not adjust for site of care, a primary variable in this study, suggesting there no direct links between Decipher scores and site of care. Performing an actual genetic analysis is costly and time consuming, therefore Complexity scores and GC were used as replacements, which might not accurately account for alterations in epigenetic mechanisms. Also, this study requires a larger and more diverse study population to generate enough power for more meaningful associations.

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