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Comparison of germline mutations in African American and Caucasian men with metastatic prostate cancer

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Abstract

Background: The goal of this study is to evaluate germline genetic variants in African American men with metastatic prostate cancer as compared to those in Caucasian men with metastatic prostate cancer in an effort to understand the role of genetic factors in these populations.

Methods: African American and Caucasian men with metastatic prostate cancer who had germline testing using multigene panels were used to generate comparisons. Germline genetic results, clinical parameters, and family histories between the two populations were analyzed.

Results: A total of 867 patients were included in this retrospective study, including 188 African American and 669 Caucasian patients. There was no significant difference in the likelihood of a pathogenic or likely-pathogenic variants (PV/LPVs) between African American and Caucasian patients ($p = .09$). African American patients were more likely to have a variant of unknown significance than Caucasians (odds ratio [OR] = 1.95; $p < .0001$). BRCA1 PV/LPVs were higher in African Americans (OR = 4.86; $p = .04$). African American patients were less likely to have a PV/LPV in non-BRCA DNA repair genes (OR = 0.30; $p = .008$). Family history of breast (OR = 2.09; $p = .002$) or ovarian cancer (OR = 2.33; $p = .04$) predicted PV/LPVs in Caucasians but not African-Americans. This underscores the limitations of family history in AA men and the importance of personal history to guide germline testing in AA men.

Conclusions: In metastatic prostate cancer patients, PV/LPVs of tested genes did not vary by race, BRCA1 PV/LPVs were more common in the African American subset. However, PV/LPVs in non-BRCA DNA repair genes were less likely to be encountered in African Americans. Family history associated with genetic testing results in Caucasians only.

KEYWORDS

African American, genetics, germline, metastatic prostate cancer, pathogenic variants, racial disparity

1 | INTRODUCTION

Racial disparity has been a persistent and challenging problem in prostate cancer research despite ongoing efforts. African American men are at higher risk of prostate cancer and approximately twofold higher risk of dying from prostate cancer compared to other racial or ethnic groups (1, 2). For African Americans there are significant differences in screening and treatment patterns, enrollment in clinical trials, outcomes, limited understanding of tumor biology and biomarker utility specific to African American patients.[1–8] Similar to race, family history is also a potent risk factor for prostate cancer. The inherited risk of prostate cancer is estimated to be as high as 60% and men with a first degree relative (FDR) with prostate cancer have been reported to be twice as likely to develop this disease.[9] While risk factors such as family history and race have been well characterized, much remains unknown about how genetic factors influence risk in African Americans with prostate cancer. To date, African American men have been underrepresented in germline genetic studies of prostate cancer.[8,10]

Studies in advanced prostate cancer have been conducted primarily on Caucasian/European cohorts, and these studies have highlighted the prevalence and clinical significance of germline alterations. For example, Pritchard, et al.[11] showed that pathogenic/likely pathogenic germline variants (PV/LPV) in DNA repair genes were present in 11.8% of patients with metastatic prostate cancer. Patients with selected DNA repair germline PV/LPV not only have an increased risk of developing cancer, but a number of mutations are associated with a poor prognosis. Importantly, patients with germline *BRCA1* and *BRCA2* pathogenic mutations and metastatic prostate cancer may respond better to PARP inhibitors and platinum-based chemotherapy.[12–14] Specifically, patients with mCRPC and *BRCA1* or *BRCA2* alterations had significantly longer progression free and overall survival with olaparib, compared to those treated with abiraterone or enzalutamide. The benefit of PARP inhibitors may be extended to patients with selected alterations detected in other homologous recombination repair genes.[15] Both olaparib and rucaparib are now Food and Drug Administration (FDA) approved for treatment of mCRPC and both approvals specifically note germline *BRCA1/2* mutations. Studies have shown that mismatch repair gene status in tumors predicts for a positive therapeutic response to PD-1 inhibitors[16] and pembrolizumab was FDA-approved in 2018.

In a cross-sectional study of 3607 men with prostate cancer, 17.2% ($n = 620$) were found to have pathogenic or likely pathogenic germline variants. Age, race, and family history did not correlate with positive test results though these clinical data were quite limited. Only 227 (~6%) of the men tested were African American. African Americans had lower rates of positive variants compared to other ethnic groups (odds ratio [OR] = 0.527; $p = .006$).[17] In a study focusing on a subset of well characterized genes, African American patients with prostate cancer had significantly fewer germline alterations compared to Caucasians (7.5% vs. 13.9%, respectively).[18] This study was problematic because clinical data were limited. Kwon et al.[19] had a variety of ethnic groups in a large analysis but only 41 patients were of African ancestry. Taken together studies of germline PV/LPV in African American men remain suboptimal.

ELAC/HPC2,[20] *MSR1*,[21] *CHEK2*[22], and *EPHB2*[23] have been reported in association with prostate cancer risk in African American men but await confirmatory studies. Multiple linkage and GWAS studies have linked the 8q24 region with prostate cancer; these risk SNPs are

relatively small in magnitude of effect and the underlying etiology of noncoding changes remains under study.[24–26] Though these associations have been identified in African American patients with prostate cancer, reproducible causal or risk genes have not been identified and current gene panels used for germline genetic testing are primarily derived from variants identified in other ethnicities. Given the underrepresentation in clinical genetic testing and research, and the clinical importance, for patients and their families, it is especially critical to better understand racial disparity with respect to germline PV/LPV data.

Given the notable paucity of germline data on African American men, especially those with advanced prostate cancer, the goal of the present study is to evaluate germline alterations in African American men, all of whom had documented metastatic prostate cancer. Ultimately, understanding the landscape of germline variants in African Americans, with concomitant clinical cofactors and family history, is critical for understanding and reducing health care disparities.

2 | MATERIALS AND METHODS

2.1 | Patient cohort

African American and Caucasian men with metastatic prostate cancer were recruited from seven sites including Tulane University Cancer Center, Levine Cancer Institute/Carolinas Medical Center, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, University of Washington, Mayo Clinic, and Atlantic Urology Clinics. All patients in this cohort had distant metastatic disease, confirmed by radiographic imaging, and all had germline genetic testing. In addition to germline testing results, clinical data including self-reported race, Gleason score, age at diagnosis, clinical staging, and self-reported cancer family history were retrospectively compiled from medical records. All clinical data were deidentified before analyses under Tulane University IRB protocol number 2019-329 which waived the requirement to obtain written patient informed consent.

2.2 | Germline panel composition and testing

Patients in this cohort had prior germline testing with a commercially available clinical panel between 2015 and 2020. Institutions used a variety of germline panels evaluating germline alterations in 12–86 cancer-associated genes. The panels utilized included: Invitae Multi-Cancer panel ($N = 645$) (Invitae), Color Hereditary Cancer panel ($N = 183$) (Color Genomics), Myriad MyRisk panel ($N = 7$) (Myriad Genetics), BROCA panel ($N = 6$) (UW Medical Center), and other commercial panels ($N = 16$). Variants were evaluated and subjected to clinical interpretation using American College of Medical Genetics and Genomics criteria.[27] According to the results reported by each commercial panel, variants interpreted as pathogenic (PV) or likely-pathogenic (LPV) were considered positive and have previously been established to have pathogenic consequences. Variants of unknown significance (VUS) were also identified using standard classification procedures.

TABLE 1 Demographics of the metastatic prostate cancer population tested

	African American	Caucasian
Median age of diagnosis	60 (40–82)	63 (42–93)
Median age at time of germline testing	68 (40–89)	69 (43–93)
Gleason score		
<7	6% ($n = 9$)	6% ($n = 26$)
=7	34% ($n = 50$)	28% ($n = 125$)
>7	58% ($n = 87$)	67% ($n = 301$)
Metastatic at diagnosis	44% ($n = 65$)	37% ($n = 136$)

2.3 | Statistical analysis

The χ^2 test and confidence intervals were calculated using SAS 9.7 (SAS). To compare proportions between groups when the number of occurrences in a cell were fewer than 5, the Fisher exact test was used. The p values less than .05 were considered significant. These tests were used to assess associations between genetic alterations and clinical variables including race and family history. To accommodate the diversity of genetic panels and institutions, for individual gene analyses, patients were excluded if the panel used for germline testing did not include the given gene of interest.

3 | RESULTS

3.1 | Study population

A total of 867 patients were included in this retrospective study. This included 188 African American patients and 669 Caucasian patients (see Table 1 and Table S1); all patients had radiographic positive metastatic prostate cancer. The median age at diagnosis was 60 years (range = 40–82) for African Americans and 63 years (range = 42–93) for Caucasians. At the time of germline testing, the median age for African Americans was 68 years (range = 40–89) and 69 years (range = 43–93) for Caucasians. In African Americans, 6% ($n = 9$) had a Gleason score of less than 7, 34% ($n = 50$) had a Gleason score of 7, and 58% ($n = 87$) had a Gleason score more than 7. In Caucasians, 6% ($n = 26$) had a Gleason score of less than 7, 28% ($n = 125$) had a Gleason score of 7, and 67% ($n = 301$) had a Gleason score of more than 7. 44% of African Americans ($n = 65$) were metastatic at diagnosis compared to 37% of Caucasians ($n = 136$). No statistically significant differences between the African American and Caucasian groups were seen in terms of age at diagnosis, age at testing, Gleason scores, or metastatic disease at diagnosis.

TABLE 2 Germline variants detected

	Negative	PV/LPV	PV/LPV + VUS	VUS	Total
African American	35.1% (*n* = 66)	5.3% (*n* = 10)	4.3% (*n* = 8)	55.3% (*n* = 104)	188
Caucasian	48.9% (*n* = 327)	8.1% (*n* = 54)	6.4% (*n* = 43)	36.6% (*n* = 245)	669
Unknown	50% (*n* = 5)	30% (*n* = 3)	0% (*n* = 0)	20% (*n* = 20)	10
Grand total	44.4% (*n* = 385)	9.2% (*n* = 80)	5.8% (*n* = 51)	40.5% (*n* = 351)	867

Abbreviations: LPV, likely-pathogenic variants; PV, pathogenic variants.

3.2 | Pathogenic, likely-pathogenic, and VUS

In the African American patients, 6% of patients (*n* = 11) had a PV/LPV, 55% of patients (*n* = 104) had a VUS, 4% of patients (*n* = 8) had both a PV/LPV and VUS, and 35% of patients had no PV/LPV or VUS reported (*n* = 65) (Table 2). For Caucasians, 10% of patients (*n* = 66) had a PV/LPV germline alteration, 37% of patients (*n* = 245) had a VUS, 6% of patients (*n* = 43) had both a PV/LPV and VUS, and 47% of patients had no germline alterations (*n* = 315). Overall, there was no significant difference in the likelihood of a PV/LPV between African American and Caucasian patients (*p* = .09). African American patients were more likely to have a VUS than Caucasians (OR = 1.95; 95% confidence interval [CI [1.40, 2.71]; *p* < .0001).

Each gene represented on a germline panel was compared between African American and Caucasian patients with metastatic prostate cancer (Table S2). Of the genes evaluated, African Americans were more likely to have a *BRCA1* PV/LPV (OR = 4.86; 95% CI [1.08, 21.93]; *p* = .04), however, we note the small number of cases as a limitation. There were no other PV/LPVs detected which were significantly different between African American and Caucasian patients. Among VUSs, VUS in *BRCA2* (*p* = .04), *PALB2* (*p* = .0007), and *PTCH1* (*p* = .03) were more frequent in African Americans compared to Caucasians. There were no other gene specific VUSs which were significantly different between African Americans and Caucasians (Table S3).

Next, functionally related genes were evaluated as a group (Tables 3–5). African American patients were substantially less likely to have a PV/LPV in any non-*BRCA* gene (OR = 0.27; 95% CI [0.12, 0.64]; *p* = .0008). Additionally, African American patients were less likely to have a PV/LPV in a non-BRCA DNA repair gene (*MSH2*, *MSH6*, *PMS2*, *MLH1*, *ATM*, *RAD50*, *RAD51D*, *NBN*, *CHEK2*, *BRIP1*, *PALB2*, *RAD51C*, *ATM*, *BLM*, and *TP53*) (OR = 0.30; 95% CI [0.11, 0.85]; *p* = .008). Among all DNA repair genes analyzed herein (including *BRCA1* and *BRCA2)* there was no significant difference between African American and Caucasian patients (*p* = .29).

3.3 | Family history

Cancer family history was collected from patient charts (see Tables S4, S5, S6, and S7). Among these prostate cancer patients, PV/LPV findings were more likely in Caucasians with at least one FDR with ovarian cancer (OR = 2.33; 95% CI [1.05, 5.17]; *p* = .04). However, there was no significant difference in the frequency of PV/LPV alterations in African Americans with FDR with ovarian cancer (OR = 6.33; 95% CI [0.98, 40.76]; *p* = .08). There was no significant difference in the frequency of PV/LPVs in African Americans (*p* = .12) or Caucasians (*p* = .33) with at least one FDR with prostate cancer. In Caucasians, PV/LPV germline alterations were more likely with at least one FDR with breast cancer (OR = 2.09; 95% CI [1.31, 3.32]; *p* = .002). However, there were no significant difference in the frequency of PV/LPV alterations in African Americans with at least one FDR with breast cancer (OR = 2.15; 95% CI [0.75, 6.19]; *p* = .21). There was no significant difference in the frequency of PV/LPV alterations in Caucasians (*p* = .80) with at least one FDR with pancreatic cancer. None of the African American patients reported a family history of pancreatic cancer.

4 | DISCUSSION

These findings highlight the importance of testing and expanding access to testing especially for African American patients with metastatic prostate cancer. We did not find any overall differences in the frequency of PV/LPVs between African Americans and Caucasians in this population of men with metastatic prostate cancer. However, African American patients were less likely to have a PV/

TABLE 3 PV/LPV in any non-BRCA gene

PV/LPV non-BRCA gene	African American	Caucasian	OR	*p* Value	95% CI
Yes	3% (*n* = 6)	11% (*n* = 72)	0.2749	.0008	0.1176, 0.6426
No	97% (*n* = 181)	89% (*n* = 597)			

Abbreviations: CI, confidence interval; LPV, likely-pathogenic variants; OR, odds ratio; PV, pathogenic variants.

TABLE 4 PV/LPV in DNA-repair genes (*BRCA1*, *BRCA2*, *MSH2*, *MSH6*, *PMS2*, *MLH1*, *ATM*, *RAD50*, *RAD51D*, *NBN*, *CHEK2*, *BRIP1*, *PALB2*, *RAD51C*, *ATM*, *BLM*, and *TP53*)

PV/LPV DNA repair genes	African American	Caucasian	OR	*p* Value	95% CI
Yes	9% (*n* = 16)	12% (*n* = 77)	0.7152	.2887	0.4066, 1.2579
No	91% (*n* = 172)	88% (*n* = 592)			

Abbreviations: CI, confidence interval; LPV, likely-pathogenic variants; OR, odds ratio; PV, pathogenic variants.

TABLE 5 PV/LPV in non-BRCA DNA repair genes (*MSH2*, *MSH6*, *PMS2*, *MLH1*, *ATM*, *RAD50*, *RAD51D*, *NBN*, *CHEK2*, *BRIP1*, *PALB2*, *RAD51C*, *ATM*, *BLM*, and *TP53*)

PV/LPV non-BRCA DNA repair gene	African American	Caucasian	OR	*p* Value	95% CI
Yes	2% (*n* = 4)	7% (*n* = 45)	0.3014	.00836	0.107, 0.8493
No	98% (*n* = 184)	93% (*n* = 624)			

Abbreviations: CI, confidence interval; LPV, likely-pathogenic variants; OR, odds ratio; PV, pathogenic variants.

LPV in any non-*BRCA* genes and in non-*BRCA* DNA repair genes. African Americans were more likely to have a PV/LPV *BRCA1* compared to their Caucasian counterparts.

African Americans in this study had a significantly higher overall incidence of germline VUSs. In a gene specific analysis, VUS alterations in *BRCA2*, *PALB2*, and *PTCH1* were more frequently detected in African Americans compared to Caucasians. Unlike PV/LPV, for any given VUS, by definition, there is insufficient evidence to determine whether or not a mutation is detrimental or contributes to cancer risk. In African Americans, the significantly increased detection of VUSs likely reflects a bias in variant classification of genes, which relies on patient data primarily assembled and validated from Caucasian cohorts. Importantly, this bias may also extend to PV/LPVs and may account for the overall lower frequency of pathogenic variants in this African American cohort. Regardless of the pathogenicity of individual VUSs, the higher frequency of VUSs in African Americans indicates that this population may be underrepresented in population data utilized in identifying variants. This underrepresentation may be especially critical for germline variants in prostate cancer given the high significantly higher incidence of prostate cancer in African Americans. More data are necessary to further classify these VUS into pathogenic or non-pathogenic categories.

The higher frequency of *BRCA1* in African Americans with metastatic prostate cancer is notable given the recent FDA approvals of olaparib and rucaparib for patients with germline *BRCA1* or *BRCA2*. These data emphasize the importance of improving access to genetic counseling and germline genetic testing for inherited cancer risk for African American men with advanced prostate cancer. Similarly, when comparing somatic tumor DNA from metastatic prostate cancer in African Americans and Caucasians, there were more tumoral *BRCA1* mutations in African Americans (4%) compared to Caucasians (1%).[28] We are cautious to note that conclusions need replication in larger data sets before they can be considered definitive.

Guidelines reliant on family history have a number of shortcomings and current National Comprehensive Cancer Network guidelines are not reliant on family history alone. It is well known that family history is incomplete for many, and even important genes have incomplete penetrance. Herein, however, family history was associated with PV/LPV in several selected Caucasian populations but not in African Americans. Caucasians but not African Americans with a FDR with breast or ovarian cancer (but not prostate cancer) were more likely to have a PV/LPV. This may or may not reflect differences in recall, family structure, health communication, and genetic dependency, as well a smaller sample sizes resulting in a relatively under-powered assessment in the African American dataset.

While this study included a large number of metastatic prostate cancer patients there were significant limitations. A larger sample size is needed to optimally assess the germline landscape in this population. Additionally, it is possible that the current gene panels are incomplete when it comes to important genes associated with prostate cancer, especially in African Americans. This was a retrospective study of metastatic prostate cancer patients and testing biases are possible. We have not tracked how many patients refused to undergo testing. Clinical practices at different institutions may have varied in unknown manners. Though most of the genes tested, especially DNA-repair genes, were the same across panels, there were clear variations in other cancer related genes in accordance with what panel was used. This is a limitation of the study. Similarly, the number of genes included on the panels varied. While this was taken in to account for the present analyses for individual genes, optimally all patients should have been tested with a standardized gene panel. This study was also limited to self-reported data for both race and family history. Similarly, since this is a multi-institutional study, genetic variability attributable to geographic factors may also be a limitation.

More access to clinical genetic testing and more research opportunities are needed to address disparities and underrepresentation of African American prostate cancer patients. Further studies are critical for understanding the germline genetic components contributing to disparities in prostate cancer risk and prostate cancer outcomes.

CONFLICT OF INTERESTS

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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