Prostate Cancer

Variation in Molecularly Defined Prostate Tumor Subtypes by Self-identified Race

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Abstract

Background: Socioeconomic and health care utilization factors are major drivers of prostate cancer (PC) mortality disparities in the USA; however, tumor molecular heterogeneity may also contribute to the higher mortality among Black men.

Objective: To compare differences in PC subtype frequency and genomic aggressiveness by self-identified race.

Design, setting, and participants: Five molecular subtype classifiers were applied for 426 Black and 762 White PC patients in the Decipher Genomics Resource Information Database (GRID).

Outcome measurements and statistical analysis: Differences in subtype frequency and tumor genomic risk (Decipher score >0.6) by race were evaluated using $\chi^2$ tests and multivariable-adjusted logistic regression models.

Results and limitations: Subtype frequencies differed by race for four classifiers. Subtypes characterized by the presence of SPOP mutations, SPINK1 overexpression, and neuroendocrine differentiation were more common among Black men. ERG and ETS fusion-positive subtypes were more frequent among White men, with no clear differences for subtypes reflecting luminal versus basal lineage. The hypothesized low-risk Kamoun S2 subtype was associated with a lower Decipher score among White men only ($p = 0.01$ for heterogeneity), while the aggressive You PCS1...
1. Introduction

Prostate cancer (PC) mortality is more than twofold higher among Black men than among White men in the USA [1]. Socioeconomic and health care–related factors are major drivers of PC mortality disparity [2], but genomic and biological features may also be associated with this disparity [3]. Prostate tumors are phenotypically and molecularly heterogeneous [4,5]. The prevalence of prostate tumor mutations, copy number alterations, gene fusions, and splicing variants differs by self-identified race [6–12]. Although clinical and pathological attributes convey prognostic information, they are insufficient to fully characterize prognosis and guide treatment. Prognostic stratification of tumors is needed to optimally intercept progression of aggressive tumors and minimize overtreatment of indolent tumors.

Numerous classification schema have been developed to define biologically and clinically relevant prostate tumor subtypes [4,5,13–18]. The majority of these prostate tumor subtyping schemes have been developed in predominantly White populations and have not been well studied in Black men. Consequently, it remains unclear whether the prevalence of these subtypes and their prognostic value differ by race. Widespread implementation of precision medicine approaches that fail to consider tumor heterogeneity associated with race may widen existing PC disparities [19]. We applied five transcriptomic subtype classifiers to tumors obtained after radical prostatectomy and assessed their distributions and associations with the Decipher genomic risk score by self-identified race.

2. Patients and methods

2.1. Study population

Data used in this study were retrieved from the Decipher Genomics Resource Information Database (GRID) registry (NCT02609269) of PC patients who underwent clinical testing or participated in research studies with the Decipher genomic classifier assay. The registry consists of patient-level deidentified, anonymized demographic and clinicopathological data, including self-identified race, and gene expression profiles from tumor specimens [20]. This study was approved by the Dana-Farber Cancer Institute institutional review board.

We identified 429 self-identified Black men who underwent radical prostatectomy at Cleveland Clinic, Durham Veterans Affairs Medical Center, Johns Hopkins University, Thomas Jefferson University, the University of Pennsylvania, and the Urology Group in the Decipher GRID [6,8,21–23]. For comparison, 780 self-identified White men from the Mayo Clinic were selected from the Decipher GRID. Three Black and 18 White men had incomplete clinicopathological data and were excluded, leaving a population of 426 Black and 762 White men for analysis. Details of the gene expression profiling methods are provided in the Supplementary material.

2.2. Identification and classification of subtypes

Five previously reported transcriptomically defined subtyping approaches developed specifically for PC and for which sufficient methodological detail was available for implementation were considered (Table 1). These approaches were selected to reflect a range of subtype classifiers proposed for PC, including approaches defined by the presence of specific genomic alterations [14], tumor histology [15], or tumor lineage [16], as well as completely agnostic clustering approaches to define subtypes [17,18]. Methods for subtype classifier implementation are outlined in the Supplementary material.

2.3. Statistical analyses

Subtype distributions were compared by self-identified race using Pearson’s $\chi^2$ test. Agglomerative hierarchical clustering using Cramer’s V as the clustering metric was applied to assess the associations between the subtype classifiers. The Wilcoxon rank-sum test was used to assess differences in median Decipher score by race for subtypes. Logistic regression models were also used to estimate the odds ratio (OR) and 95% confidence interval (95% CI) for a high Decipher score (>0.6) across subtypes. As mortality outcomes were unavailable, we used the Decipher score, a validated genomic risk score that is predictive of metastasis and PC-specific mortality, as a marker of tumor genomic risk of progression [24]. The heterogeneity of these associations by race was evaluated using a likelihood ratio test of subtype $\times$ race product terms. Sensitivity analyses using a propensity score–matched subcohort and normalization of the Decipher score across study sites are described in the Supplementary material. All statistical tests were two-sided with $p < 0.05$ considered statistically significant. All statistical analyses were performed in R version 3.6.0 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

The distributions of age and clinical and pathological characteristics for 426 Black and 762 White PC patients are shown in Table 2. White patients had a greater mean
age of diagnosis (64.6 yr) relative to Black patients (61.2 yr).

Pretreatment prostate-specific antigen (PSA) levels were higher among White patients, with 46.6% of White patients having PSA >10 ng/ml, versus 29.6% of Black patients. Some 39.8% of White patients had Gleason score ≥8 tumors versus 13.6% of Black patients. Extraprostatic extension (48.2% among White vs 32.6% among Black patients), seminal vesicle invasion (33.1% vs 13.6%), and lymph node invasion (13.9% vs 1.2%) were more frequent among White patients.

Five subtype classifiers were applied to the cohort (Table 1). To examine whether subtype assignment was correlated across classifiers, pairwise χ² tests were performed to compare subtype distributions across the five classifiers. Subtype assignments were associated (p < 0.01) across classifiers in the total population for all pairwise comparisons except Kamoun/Zhang and Alshalalfa/Kamoun. To examine which classifiers grouped samples most similarly, hierarchical clustering was performed using Cramer’s V. Clustering analyses identified two subtype clusters that grouped samples similarly: (1) You, Zhang, and Alshalalfa; and (2) Tomlins and Kamoun (Supplementary Fig. 1). The You, Zhang, and Alshalalfa classifiers all reflect AR activity and luminal/basal lineage. The Tomlins and Kamoun subtypes reflect the presence of ERG or ETS fusions. These two clusters of classifiers were observed for both Black and White men.

Table 3 shows the distribution of subtypes by race. The distributions differed by race in crude frequency and after adjustment for tumor clinicopathological characteristics for four of the five classifiers. The You PCS1 subtype was more prevalent among Black men (25.1%) than White men (18.2%; multivariable-adjusted p = 0.01). The Kamoun S3 subtype was more frequent among Black men (73.7%) than White men (33.2%), while White men had higher frequencies of the S1 (36.7% White vs 13.8% Black) and S2 subtypes (30.1% White vs 12.4% Black; p = 0.01). Using the Tomlins classifier, the ERG+ subtype was most common among White men (43.8%), while the triple negative (ERG−ETS−SPINK1−) subtype was most common among Black men (56.1%; p < 0.01). The SPINK1+ subtype was also more common among Black men (17.6% vs 8.9% among White patients).
For PCS1 was higher among White men than Black men. For the You subtypes, the median Decipher score Zhang classifier did not significantly differ between Black and White men (p = 0.04, Wilcoxon rank-sum test). The median Decipher score for the Tomlins subtypes was higher among Black men than White men (p < 0.001). Finally, the subtype associations with the Decipher score by race observed in the unmatched full cohort were consistent in the matched subcohort, with suggestively heterogeneous associations for the Kamoun and You subtype classifiers (Supplementary Fig. 2, Supplementary Table 3).}

The distributions of the Decipher genomic risk classifier by subtype and race are shown in Fig. 1. The median Decipher genomic risk score was modestly higher among Black than White men (0.45 vs 0.41; p = 0.04, Wilcoxon rank-sum test). The median Decipher score for the Tomlins subtypes was higher among Black men than White men (p < 0.001), with no differences for the other Tomlins subtypes. For the You subtypes, the median Decipher score for PCS1 was higher among White men than Black men (p < 0.001), while the reverse pattern was observed for the PCS3 subtype (p < 0.001). The Kamoun S2 subtype had a lower median Decipher score among White men than among Black men (p < 0.001). Finally, the Zhang and Alshalaifa subtype classifiers did not show strong evidence of differences in the distribution of the Decipher score by race across subtypes.

After adjustment for tumor clinicopathological characteristics, the Zhang basal, Tomlins ERG+, You PCS1, Kamoun S1, and Alshalaifa neuroendocrine subtypes were associated with higher Decipher scores (>0.6; Table 4). Differential associations between subtypes and the Decipher score were observed by race for three of the five classifiers. For the You subtypes, the PCS3 subtype was associated with a lower Decipher score among White men in comparison to the PCS1 subtype (OR 0.29, 95% CI 0.18–0.45), but there was no association among Black men (OR 1.05, 95% CI 0.58–1.92; p for heterogeneity [p_{het}] = 0.001). Similarly, the Kamoun S2 subtype was associated with a lower Decipher score in comparison to S1 tumors among White men (OR 0.39, 95% CI 0.23–0.62), but not among Black men (OR 0.98, 95% CI 0.39–2.45; [p_{het}] = 0.01). For the Tomlins subtypes, among Black men, the ETS+, SPINK1+, and triple negative subtypes were all significantly associated with lower Decipher score in comparison to the ERG+ subtype (all ORs <1). By contrast, none of the Tomlins subtypes were associated with the Decipher score compared to the ERG+ subtype among White men ([p_{het}] = 0.007). The Zhang ([p_{het}] = 0.20) and Alshalaifa ([p_{het}] = 0.96) subtypes were not differentially associated with the Decipher score by race, with the basal and neuroendocrine subtypes were associated with a higher Decipher score among both Black and White men.

Differences in tumor clinical and pathological characteristics by race (Table 1) raised concerns about residual confounding. Thus, we assembled a propensity score–matched subset of our cohort consisting of 356 Black and 356 White men. The matched subcohort showed balance by race in age and tumor clinicopathological characteristics (Supplementary Table 1). A high Decipher score was found in 27.5% and 18.0% of the Black and White men, respectively. Similar patterns in the subtype distributions by race were observed in the matched subcohort as in the full cohort (Supplementary Table 2). The Tomlins SPINK1+ and triple negative, You PCS1, and Kamoun S3 subtypes were enriched among Black men, while the Tomlins ERG+, You PCS2, and Kamoun S1 and S2 subtypes were more frequent among White men. Finally, the subtype associations with the Decipher score by race observed in the full cohort were consistent in the matched subcohort, with suggestively heterogeneous associations for the Kamoun and You subtype classifiers (Supplementary Fig. 2, Supplementary Table 3).

The difference for the Tomlins subtypes observed in the unmatched full cohort was attenuated and was not statistically significant in the matched subcohort.

Since the distribution of the Decipher genomic risk classifiers differed by race and data source, we evaluated whether batch effects and variability in patient populations across sites might explain differences in the associations between subtype and Decipher score by calculating source-specific Z-score–normalized Decipher scores. In multivariable-adjusted linear models, similar associations were observed between the subtypes and the crude and normalized Decipher scores by race to those that were observed in the primary analyses (Supplementary Table 4). These results suggest that the differential associations between subtypes and the Decipher genomic risk score by race were probably not caused by bias introduced by batch effects across data sources.

4. Discussion

We investigated variation in the distribution and prognostic value of molecularly defined PC transcriptomic subtype classifiers by race in the Decipher GRID. Five subtyping schemas were identified and implemented, representing a spectrum of the subtyping approaches that have been proposed in PC. Four of the five classifiers yielded significant differences in subtype distributions by race. Moreover, in three of the five classifiers the association between sub-
Fig. 1 – Distribution of scores for the Decipher genomic risk classifier for Black and White patients with prostate cancer in the total population and by subtypes. The p values are from Wilcoxon rank-sum tests.
Table 4 – Odds of a high Decipher score (>0.6) by tumor molecular subtype in the total population and stratified by patient self-identified race

| Subtype classification           | Odds ratio (95% confidence interval)* | Probability (p) |
|---------------------------------|--------------------------------------|-----------------|
|                                 | Total population                     | Black           | White          |
| Zhang subtypes                  |                                      |                 |                |
| Luminal                         | Reference                            | Reference       | Reference      | 0.20            |
| Basal                           | 1.44 (1.07–1.94)                     | 1.86 (1.14–3.03) | 1.24 (0.85–1.81) |
| Tomlins subtypes                |                                      |                 |                |
| ERG+                            | Reference                            | Reference       | Reference      | 0.007           |
| ETS+                            | 0.61 (0.40–0.92)                     | 0.13 (0.03–0.64) | 0.82 (0.52–1.28) |
| SPINK1+                         | 0.52 (0.29–0.90)                     | 0.28 (0.12–0.69) | 0.70 (0.26–1.70) |
| Triple negative                 | 0.63 (0.45–0.88)                     | 0.32 (0.16–0.62) | 0.86 (0.57–1.30) |
| You subtypes                    |                                      |                 |                |
| PCS1                            | Reference                            | Reference       | Reference      | 0.001           |
| PCS2                            | 0.40 (0.26–0.60)                     | 0.69 (0.29–1.65) | 0.27 (0.16–0.45) |
| PCS3                            | 0.49 (0.35–0.69)                     | 1.05 (0.58–1.92) | 0.29 (0.18–0.45) |
| Kamoun subtypes                 |                                      |                 |                |
| S1                              | Reference                            | Reference       | Reference      | 0.01            |
| S2                              | 0.50 (0.33–0.75)                     | 0.98 (0.39–2.45) | 0.39 (0.23–0.62) |
| S3                              | 0.56 (0.40–0.78)                     | 0.46 (0.23–0.92) | 0.66 (0.44–0.98) |
| Alshalalfa subtypes             |                                      |                 |                |
| Adenocarcinoma                  | Reference                            | Reference       | Reference      | 0.96            |

*p value for heterogeneity from a likelihood ratio test of race × subtype product terms.

*Odds ratios and 95% confidence intervals were estimated from logistic regression models including race, subtype, age, Gleason group, prostate-specific antigen level, extraprostatic extension, seminal vesicle invasion, and lymph node invasion.

types and a genomic risk score differed by race, suggesting that some subtypes may have differential prognostic value across racial groups independent of tumor clinicopathological characteristics.

PCs are clinically and molecularly heterogeneous, but unlike for other cancer sites, consensus subtypes have yet to emerge. Identification of relevant subtypes can potentially enhance prognostic stratification, guide clinical decision-making, and yield insights into disease etiology. Numerous PC subtyping schema have been proposed, including subtypes defined according to specific genomic alterations, tumor histology, and tumor lineages, as well as purely agnostic clustering [4,5,13–18]. However, PC subtyping approaches, including those assessed in the present study, have generally not considered tumor molecular heterogeneity by race or ethnicity in identifying subtypes. The Kamoun S1 and S2 subtypes and You PCS2 subtype were identified through agnostic clustering analyses and found to have frequent ERG fusions [17,18]. These subtypes were less prevalent among tumors from Black men. Moreover, the prognostic value of the ERG fusion–enriched Kamoun S2 subtype differed by race, with this subtype associated with lower Decipher score among White men but not among Black men. These findings align with those for the Tomlins classifier, which uses gene expression data to infer the presence or absence of three mutually exclusive genomic alterations: ERG fusions, ETS fusions, and SPINK1 overexpression [14]. Although the Tomlins ERG subtype was less common among Black men, it was associated with the highest genomic risk across subtypes for Black men. Our findings also confirmed prior reports that the SPINK1+ and triple negative subtypes are more common among Black men [11]. Interestingly, luminal and basal subtypes identified via the You and Zhang classifiers were associated with similar Decipher scores among Black men [16,18]. This finding among Black men contrasts with the initial publications of both classifiers, which were largely based on White men. You et al [18] reported that the PCS1 luminal subtype represents an aggressive tumor phenotype, while Zhang et al [16] reported that the basal subtype was enriched in advanced disease. Similarly, the AR activity–related classifiers (Alshalalfa, You, and Zhang) did not show strong differences in subtype distribution or prognostic value among Black men relative to White men [15,16,18]. Thus, our results validate the original prognostication of these subtypes for White men, but suggests that different associations may be seen in Black men.

The disparity in PC mortality by race or ethnicity is among the largest across cancer sites and has been persistent over time, reflecting both higher incidence and worse survival among Black men [25]. The survival disparity is largely driven by socioeconomic and contextual factors that influence health care utilization [2,3]. Population studies in equal access settings such as the Veterans Affairs medical system and randomized clinical trials have shown no differences in PC survival by race or ethnicity [26,27]. However, differences in tumor genomic heterogeneity by race may also contribute to the mortality disparity [2,3]. Somatic mutation profiles differ between Black and White men, with mutations at ERF, ESR1, SPOP, and ZFXH3 enriched in primary tumors in Black men, while mutations at TP53 are enriched in tumors in White men [28–31]. ERG rearrangements and deletions at PTEN are more frequent in primary tumors in White men, whereas amplifications at MYC are more common in metastatic tumors in Black men [9,28,31,32]. In addition, gene expression analyses have consistently revealed dysregulation of immune response pathways in tumors in Black men [7,28,33–35]. Creed et al. [36] reported that nearly half of the genes included in commercial gene expression prognostic signatures such as Oncotype Dx Prostate, Prolaris, and Decipher are differentially expressed between Black and White men, although
there were negligible prognostic differences between Black and White men for the Prolaris and Decipher scores [23,36].

Our study has some limitations. The study used the construct of self-identified race and we are unable to distinguish between variation in tumor phenotype that arises as a result of differences in social and environmental context and lifestyle factors, and variation associated with genetic ancestry. In addition, while we implemented five subtyping classifiers that were representative of the spectrum of subtyping approaches in PC, our work is not a comprehensive analysis of all subtyping approaches that been proposed for PC. The subtypes included in our analyses were developed specifically for prostate tumors and thus we did not evaluate classifiers developed for other cancer sites such as PAM50, which has been demonstrated to have prognostic relevance when applied to PCs [13]. An additional limitation of this work is that clinical endpoint data were unavailable for a majority of the study population and therefore the Decipher genomic risk score was used as a measure of the tumor risk of progression. Although the Decipher test is a validated predictor of the risk of high-grade disease, risk of metastasis, and PC-specific mortality, it is an imperfect surrogate [37–39]. Thus, though we report that certain subtypes had higher (or lower) Decipher scores among Black men, we cannot infer that this definitively implies differential prognosis. Importantly, Howard et al. [23] reported no difference in the prognostic value of the Decipher score among Black men. The Decipher GRID is generated through clinical and research use of the Decipher score and thus, owing to referral patterns, the registry population may not be wholly generalizable to the broader US population. Because the data studied here were pooled from multiple contributing institutions and differences in the clinical and pathological tumor characteristics by race existed, confounding is a concern. Attempts to account for confounding using traditional regression methods and the formation of a matched cohort yielded highly similar results. Nevertheless, residual confounding by social and contextual factors could still have influenced the results observed. Finally, the pooling of data from multiple sources raises concerns about batch effects. However, subtype classifiers were applied before pooling data, and the associations observed with the Decipher genomic risk score were robust in a sensitivity analysis that normalized the distribution of the score across sources.

5. Conclusions

We report that several previously proposed molecular subtyping classifiers for PC showed different subtype distributions and associations with a genomic risk score by race. The molecular heterogeneity observed in existing tumor subtypes suggests that differences in subtype frequency may influence racial disparities in PC. Additional research is needed to validate these findings and investigate possible differences in subtype prognosis by race. As molecular subtyping approaches in PC have largely been developed in Eurocentric populations, greater inclusivity of under-represented populations in PC genomics research may yield important insights into biologically or clinically relevant PC molecular subtypes for translation to diverse patient populations.

Author contributions: Kevin H. Kensler had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Kensler, Awasthi, Alshalalfa, Yamoah, Rebbeck.

Acquisition of data: Awasthi, Alshalalfa, Trock, Freedland, Freeman, You, Den, Dicker, Karnes, Klein, Lal, Liu, Davicioni, Rayford, Yamoah, Rebbeck.

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Data sharing statement: Gene expression data are freely available from the Decipher GRID on request from Decipher Biosciences Inc.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euros.2022.03.014.

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