Uncovering Molecular Differences in Pancreatic Ductal Adenocarcinoma Tissues from Black and White Patients in the US

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Introduction

Pancreatic cancer is the 3rd leading cause of cancer related deaths in the US, with 62,210 new cases estimated in 2022 (NCI). The occurrence of new cases in the US has continued to rise in the last two decades, particularly in the Black population. To uncover biological pathways driving higher incidences of pancreatic malignancy in the Black population, one critical step is to determine the molecular differences in pancreatic tumors between Black and White patients. However, publicly available pancreatic tumor data include disproportionately low numbers of Black patients, making it challenging to perform proper analyses and identify molecular features associated with race. In this study, we analyzed molecular profiles of 4249 patients (White = 3797, Black = 452) with pancreatic ductal adenocarcinoma (PDAC, the most common subtype of pancreatic cancer) and compared driver mutation frequencies, tumor mutational burden (TMB), PD-L1 expression and other features between racial groups.

Methods

We analyzed de-identified patient records with a primary diagnosis of PDAC from the Tempus multimodal database. All patients underwent somatic NGS testing via a commercially available 595-648 gene DNA panel (Tempus xT) that assesses somatic mutations (including SNVs, Indels, CNVs, and select SVs), microsatellite instability (MSI), and tumor mutational burden (TMB). Samples included in this study also had whole transcriptome RNA-seq performed. Clinical and demographic information (including race) was abstracted from clinical records (*e.g.*, order forms, patient records, *etc.*). The age range of patients in our study spanned from 22 to 90 years, with a median age of 68 for White patients and 66 for Black patients. In cases where smoking status was documented, approximately 52% of White patients and 55% of Black patients were either current or former smokers. For patients with available disease stage information, the majority of both White (76%) and Black (73%) patients were stage IV within 60 days of sample collection. Statistical comparisons between White and Black samples were made with either the Chi-squared or Fisher's Exact tests. False discovery rate (FDR) corrections were applied to pairwise comparisons. All statistical analyses were performed in R version 4.2.

Results

Somatic Mutation Frequencies Stratified by Race

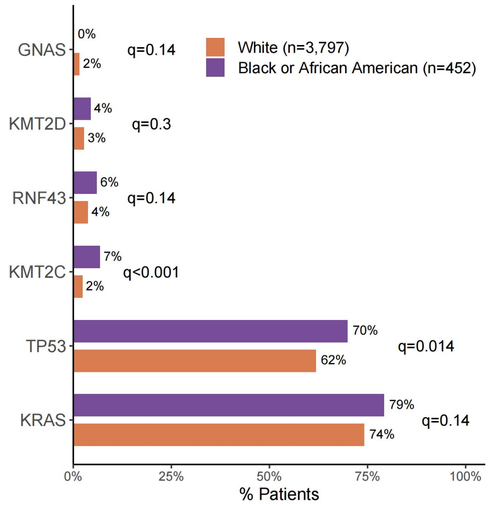

Figure 1. Mutational frequencies for the indicated genes in Black and White patients with PDAC. Q-values report statistical significance after accounting for multiple comparisons.

KRAS

Characteristic	Overall, N = 4,249[1]	White, N = 3,797[1]	Black or African American, N = 452[1]	p-value[2]	q-value[3]
G12R	447 (11%)	382 (10%)	65 (14%)	0.005	0.037
Q61H	130 (3.1%)	120 (3.2%)	10 (2.2%)	0.3	0.8
G12V	983 (23%)	871 (23%)	112 (25%)	0.4	0.8
G12C	44 (1.0%)	38 (1.0%)	6 (1.3%)	0.5	0.8
G13D	8 (0.2%)	7 (0.2%)	1 (0.2%)	0.6	0.8
Q61R	57 (1.3%)	50 (1.3%)	7 (1.5%)	0.7	0.8
G12D	1,441 (34%)	1,291 (34%)	150 (33%)	0.7	0.8
A146T	3 (<0.1%)	3 (<0.1%)	0 (0%)	>0.9	>0.9

[1] n (%)
[2] Pearson's Chi-squared test; Fisher's exact test
[3] False discovery rate correction for multiple testing

TP53

Characteristic	Overall, N = 4,249[1]	White, N = 3,797[1]	Black or African American, N = 452[1]	p-value[2]	q-value[3]
R273H	92 (2.2%)	77 (2.0%)	15 (3.3%)	0.075	0.2
R175H	196 (4.6%)	181 (4.8%)	15 (3.3%)	0.2	0.2
R213	71 (1.7%)	60 (1.6%)	11 (2.4%)	0.2	0.2
R248Q	72 (1.7%)	62 (1.6%)	10 (2.2%)	0.4	0.4

[1] n (%)
[2] Pearson's Chi-squared test
[3] False discovery rate correction for multiple testing

GNAS

Characteristic	Overall, N = 4,249[1]	White, N = 3,797[1]	Black or African American, N = 452[1]	p-value[2]	q-value[3]
R201H	36 (0.8%)	36 (0.9%)	0 (0%)	0.028	0.056
R201C	24 (0.6%)	23 (0.6%)	1 (0.2%)	0.5	0.5

[1] n (%)
[2] Fisher's exact test
[3] False discovery rate correction for multiple testing

Table 1. For each of the indicated genes — KRAS (top), TP53 (middle) and GNAS (bottom) — we assessed differences in specific mutation frequencies for select pathogenic or likely pathogenic missense mutations.

Tumor Mutational Burden and PD-L1 Positivity are Higher in Black Patients

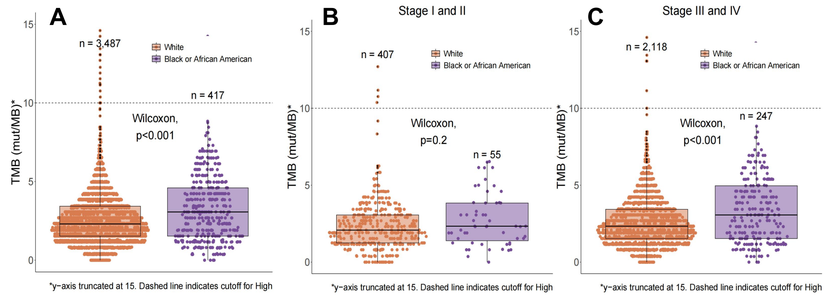

Figure 2. TMB differences by race for **(A)** all patients (note not all patients had stage info). **(B)** Early stage and **(C)** Late stage. Significant differences according to race are driven by late-stage (III and IV) patients.

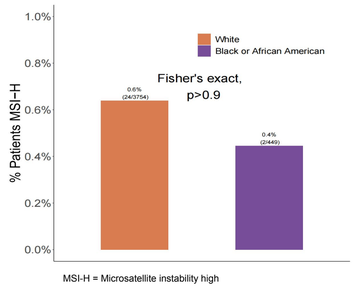

Figure 3 Frequency of patients classified as MSI-H. In this study no differences in prevalence were observed between the two racial groups assessed. Most patients in this cohort of PDAC patients were microsatellite stable (MSS).

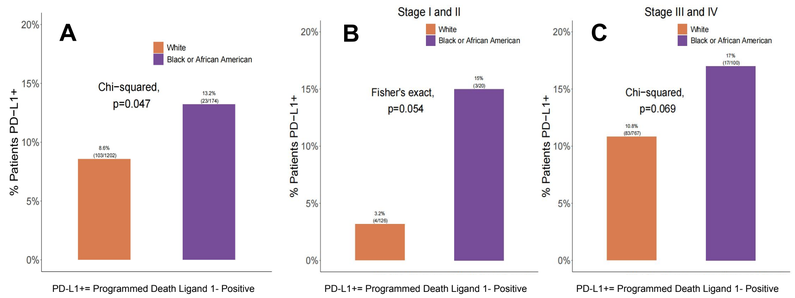

Figure 4 **(A)** Frequency of PD-L1+ patients. PD-L1+ patients for early **(B)** and late-stage **(C)** patients are shown separately and have similar trends.

Summary

In one of the most racially diverse cohorts of PDAC patients reported to date, we evaluated the association between molecular features and patients' racial backgrounds. Our findings reveal that **Black patients exhibit significantly elevated levels of tumor mutational burden (TMB), increased PD-L1 expression, and more frequent alterations in *KMT2C***. These results suggest that both tumor intrinsic and extrinsic factors may contribute to the higher incidence of PDAC in the Black population—either promoting increased tumor mutations or selecting for cancer cells with a higher mutational burden as the disease progresses—underscoring the need for further investigation into the relevant biological pathways.