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Racial Disparities in the Molecular Landscape of Cancer

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Abstract

Background/Aim: African Americans (AA) have the highest incidence and mortality of any racial/ethnic group in the US for most cancer types. Heterogeneity in the molecular biology of cancer, as a contributing factor to this disparity, is poorly understood. To address this gap in knowledge, we explored the molecular landscape of colorectal cancer (CRC), non-small cell lung cancer (NSCLC) and high-grade glioma (HGG) from 271 AA and 636 Caucasian (CC) cases.

Materials and Methods: DNA from formalin-fixed paraffin- embedded tumors was sequenced using next-generation sequencing. Additionally, we evaluated protein expression using immunohistochemistry. The Exome Aggregation Consortium Database was evaluated for known ethnicity associations.

Results: Considering only pathogenic or presumed pathogenic mutations, as determined by the American College of Medical Genetics and Genomics guidelines, and using Bonferroni and Benjamini-Hochberg corrections for multiple comparisons, we found that CRC tumors from AA patients harbored significantly more mutations of phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha (PIK3CA) than those from CC patients. CRC tumors in AA patients also appeared to harbor more mutations of mitogen-activated protein kinase kinase 1 (MAP2K1/MEK1), MPL proto-oncogene (MPL), thrombo-poietin receptor, and neurofibromin 1 (NF1) than those from CC patients. In contrast, CRCs from AA patients were likely to carry fewer mutations of ataxia-telangiectasia mutated (ATM), as well as of proto-oncogene B-Raf (BRAF), including

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the V600E variant, than those from CC patients. Rates of immunohistochemical positivity for epidermal growth factor receptor (EGFR) and DNA topoisomerase 2-alpha (TOP2A) tended to be higher in CRCs from AA patients than in CC patients. In NSCLC adenocarcinoma, BRAF variants appeared to be more frequent in the AA than in the CC cohort, whereas in squamous cell lung carcinoma, programmed death-ligand 1 (PD-L1) expression tended to be lower in the AA than in CC group. Moreover, HGG tumors from AA patients showed a trend toward harboring more mutations of protein tyrosine phosphatase non-receptor 11 (PTPN11), than HGG tumors from the CC cohort. In contrast, mutations of phosphatase and tensin homolog (PTEN) and tumor protein 53 (TP53) appeared to be higher in HGG tumors in CC patients than in their AA counterparts.

Conclusion: Our data revealed significant differences and trends in molecular signatures of the three cancer types in AA and CC cohorts. These findings imply that there may be differences in carcinogenesis between AA and CC patients and that race may be a factor that should be considered regarding cancer incidence and outcome.

Keywords

Cancer; mutational profiles; racial disparities

African Americans (AA) have the highest death rate and shortest survival of any racial/ethnic group in the US for most cancer types (1). Among males, in the period of 20082012, the age-adjusted incidence rates per 100,000 for all cancer combined were 592 and 529 for AA and Caucasians (CC), respectively. This represents a 12% increase in cancer cases among AA as compared to CC ($p<0.05$) for all cancer combined, and rates are also higher for the most common cancer types, including prostatic, lung, colorectal (CRC), kidney and pancreatic. Similarly, among males in the same period, the age-adjusted death rates per 100,000 for all cancers combined were 268 and 211 for AA and CC, respectively, representing a 27% increased risk of cancer death in AA as compared to CC ($p<0.05$) (1). A A females have a 14% higher risk of cancer death than CC women (1). Even in the absence of increased incidence, there may be a higher mortality among AA patients. For example, despite a lower incidence of breast cancer, AA women have higher breast cancer mortality rates than CC women, and this is unlikely to be due to lower access to care alone (2). One of the likely factors contributing to these differences is disparate tumor biology (3).

Molecular alterations that drive various types of cancer have been identified and have contributed to significant progress in the treatment of cancer (4, 5). Despite these advancements, the genetic landscape of cancer with respect to race is poorly understood. To address this gap in knowledge and provide a meaningful evaluation of the frequency of mutations, we characterized the mutational landscape in AA patients and compared it to CC patients with CRC, non-small cell lung cancer (NSCLC) and highgrade glioma (HGG).

Materials and Methods

Tissue samples.

Solid tumors were submitted to Caris Life Sciences, a Clinical Laboratory Improvement Amendments (CLIA), the College of American Pathologists (CAP) and the International Organization for Standardization (ISO)15189-certified/accredited laboratory (Phoenix, AZ,

USA) for molecular profiling aimed to provide molecular-guided treatment options. Race information was retrospectively collected from clinical records from the participating cancer institutions. Among the cases with race information available, the most frequent races were CC and AA. Therefore, these two races were investigated for comparative analysis. CRC, NSCLC, HGG and breast cancer were the most frequent cancer types among AA patients, and therefore were chosen for analysis. Breast cancer results were reported elsewhere (6). Because the study included only de-identified data, it was granted exemption by the Western Institutional Review Board. The molecular profiling included next-generation sequencing and immunohistochemistry.

Next-generation sequencing.

Direct sequencing was carried out on genomic DNA isolated from formalin-fixed paraffin-embedded tumor samples using the NextSeq platform (Illumina Inc., San Diego, CA, USA). A custom-designed SureSelectXT assay (Agilent Technologies, Santa Clara, CA, USA) was used for targeting 592 genes that were selected based on the COSMIC database (http://cancer.sanger.ac.uk/cosmic/browse/genome), representing the most well-described driver mutations in solid tumors. Prior to molecular testing, tumor enrichment was achieved by harvesting targeted tissue using manual microdissection techniques. Genetic variants were identified by board-certified molecular geneticists and categorized as ‘pathogenic’, ‘presumed pathogenic’, ‘variant of unknown significance’, ‘presumed benign’, or ‘benign’, according to the American College of Medical Genetics and Genomics standards (7). When assessing mutational frequencies of individual genes, ‘pathogenic’, and ‘presumed pathogenic’ were counted as mutations, while ‘benign’, ‘presumed benign’ variants and ‘variants of unknown significance’ were excluded. All variants were detected with greater than 99% confidence based on allelic frequency and amplicon coverage, with an average sequencing depth of coverage of greater than 500× and an analytical sensitivity of 5%.

Immunohistochemistry.

Immunohistochemistry was performed on formalin-fixed paraffin-embedded sections on glass slides. The following primary antibodies were used: rabbit polyclonal antiepidermal growth factor receptor (EGFR) (Santa Cruz Biotechnology, Dallas, TX, USA), rabbit monoclonal antiprogrammed death-ligand 1 (PD-L1) (clone SP142; Spring Bioscience, Pleasanton, CA, USA) and mouse monoclonal anti-DNA topoisomerase 2-alpha (TOP2A) (clone 3F6; Leica Biosystems, Buffalo Grove, IL, USA). Slides were stained using automated staining techniques, per the manufacturer’s instructions, and were optimized and validated per CLIA/CAP/ISO15189 requirements. Staining was scored for intensity (no staining: 0, weak staining: 1+, moderate staining: 2+, strong staining: 3+) and staining percentage (0–100%). Results were categorized as positive or negative by defined thresholds specific to each marker based on published clinical literature. A Board-certified pathologist evaluated all results independently. For PD-L1 immunohistochemistry, the staining was regarded as positive if its intensity on the membrane of the tumor cells was >2+ (on a semi-quantitative scale of 0–3: 0 for no staining, 1+ for weak staining, 2+ for moderate staining, or 3+ for strong staining) and the percentage of positively stained cells was >5%.

Bioinformatics analyses.

The Exome Aggregation Consortium Database (http://exac.broadinstitute.org/), as of May 2016, was evaluated for known ethnicity associations.

Statistical analyses.

In addition to using chi-square test, both Bonferroni and Benjamini-Hochberg methods were used to correct for multiple comparisons. A two-tailed *p*-value of less than 0.05 was considered statistically significant.

Results

Patient and tumor characteristics.

Of 907 tumors that were analyzed, 50.6% were CRC, 37.6% were NSCLC, and 11.8% were HGG (Table I). When all tumors are considered, 29.9% (271 out of 907) were collected from AA patients, and 70.1% (636 out of 907) were obtained from CC patients. The average patient age was 59 and 60 years for AA and CC, respectively. Patient gender was well balanced for both races. Primary *versus* metastatic composition was also well balanced for CRC and NSCLC, with 48.2% of all tumors taken from primary sites, and 51.8% from metastatic sites. For HGG, both newly diagnosed and recurrent tumors were included in the analysis. Of all HGG, 60.0% and 74.4% were glioblastoma multiforme in AA and CC, respectively, and the difference was not significant (data not shown). The average age was 47 and 56 years for AA and CC patients with HGG, respectively, with the AA cohort being younger (p=0.010; chi-square test; Table I).

CRC tumors from AA patients significantly more frequently harbored mutations of phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha (PIK3CA) than CRC tumors from CC patients.

Using next-generation sequencing and Bonferroni and Benjamini-Hochberg corrections for multiple comparisons, we found that significantly more CRC tumors from AA patients carried *PIK3CA* mutations than CRC tumors from CC patients (p=0.024). Specifically, *PIK3CA* mutations were detected in 26 out of 118 tumors from AA patients (22.0%), but in only 22 out of 243 from CC patients (9.1%; Table II). In both AA and CC, exon 9 mutations of *PIK3CA* were more prevalent than exon 20 mutations, with E542K and E545K variants as the most frequent. In addition to Bonferroni and Benjamini-Hochberg corrections for multiple comparisons, chi-square test also showed *PIK3CA* mutations in CRC to be significantly more frequent in AA than in CC patients (p=0.0009). Additional molecular alterations were observed that reached the level of significance by chi-square test, but not by Bonferroni and Benjamini-Hochberg corrections, and are described below as trends.

Other molecular alterations in CRC.

Next-generation sequencing data showed a trend toward fewer ataxia-telangiectasia mutated (*ATM*) mutations, as well as fewer proto-oncogene B-Raf (*BRAF*) mutations, including the V600E variant, in CRC tumors from AA than CC patients (p=0.022 and p=0.047, respectively; chi-square test; Table II). *ATM* mutations were mostly truncating and

frameshift mutations likely causing the loss of protein function. Mitogen-activated protein kinase kinase 1 (*MAP2K1/MEK1*), myeloproliferative leukemia (*MPL*) virus oncogene and neurofibromin 1 (*NF1*) mutations appeared to be more frequent in CRC in the AA than in the CC cohort. Specifically, two *MAP2K1/MEK1* mutations (D67N, K57N), two *MPL* mutations (Y252H), two *NF1* truncating mutations (R440X, R1769X), in addition to an *NF1* splice variant (c.6819+1G>A), were detected in tumors from AA patients but not in those from CC patients (p=0.035, p=0.039 and p=0.037, respectively; chi-square test; Table II). In addition, we found that adenomatous polyposis coli (APC), tumor protein 53 (*TP53*), and K-RAS proto-oncogene (*KRAS*) mutations were the most frequent variants in CRC tumors of both AA and CC patients without any significant difference between the two cohorts (data not shown). Furthermore, rates of immunohistochemical positivity for EGFR and TOP2A were high in both cohorts, but tended to be higher in CRCs from AA patients compared to CC patients (p=0.047 and p=0.005, respectively; chi-square test; Table III).

Molecular alterations in NSCLC.

When NSCLC adenocarcinomas were analyzed, only frequencies for *BRAF* mutations (V600E and non-V600E) appeared to be different between the two cohorts (p=0.020; chi-square test; Table IV). Notably, three out of seven *BRAF* mutations detected in adenocarcinomas from AA patients were V600E. In contrast, only one out of four *BRAF* variants in CC adenocarcinomas was V600E. In contrast, in squamous cell carcinomas, *BRAF* variants were absent from both AA and CC cohorts (data not shown). Interestingly, squamous cell carcinomas tested positively for PD-L1 expression by immunohistochemistry in seven out of 20 tumors from CC patients (35.0%), but in none of 11 tumors from AA patients (p=0.026; chi-square test). On the other hand, in adenocarcinomas there was no significant difference in PD-L1 immunohistochemical positivity between the two groups (data not shown).

Molecular alterations in HGG.

Next-generation sequencing data showed that protein tyrosine phosphatase non-receptor 11 (*PTPN11*) mutations (G503V and T507K) tended to be more frequent in HGGs in AA patients than in CC ones (p=0.011; chi-square test; Table V). In contrast, phosphatase and tensin homolog (*PTEN*) mutations were less frequent in the AA than in CC cohort (p=0.005; chi-square test; Table V). Similarly, deleterious *TP53* mutations appeared to be less frequent in AA than in CC patients (p=0.024; chi-square test; Table V).

Discussion

In the present study, we discovered 26 distinct pathogenic or presumed pathogenic *PIK3CA* variants (out of 118 tumors) in the AA cohort and they were more prevalent in the AA cohort than in the CC cohort (22.0% vs. 9.1%, respectively). Brim and Ashktorab reported two non-synonymous variants in *PIK3CA* gene in CRC in AA patients (8). In contrast, Phipps *et al.* reported no difference in *PIK3CA* by race (9).

Our findings are consistent with those of Yoon *et al.*, who reported a higher rate of *BRAF* mutations in CRC tumors among CC patients compared to AA patients (10). However, our

findings that the high frequencies of *TP53* variants in AA and CC CRC cohorts are similar (68.7 and 69.5%, respectively; data not shown) are not in accord with the data reported by Katkoori et al. (11). Our findings also differ from those reported elsewhere (10, 12, 13) supporting the notion that *KRAS* and *APC* mutation rates are higher in CRCs from AA patients. In addition, Heestand *et al.* showed that TOP2A amplification is associated with various solid tumors, including CRC (14). In the present study, we provide evidence supporting the view that CRC tumors from AA patients may have higher TOP2A expression than those from CC patients. Moreover, Theodoropoulos *et al.* reported race-associated EGFR overexpression in CRC (15). In the present report, we also showed evidence suggesting higher EGFR expression in CRC in AA patients than in CC ones.

A recent report by Campbell *et al.* provides evidence supporting the view that both lung adenocarcinomas and lung squamous cell carcinomas from AA and CC patients have similar mutational landscapes (16). In the present study, however, we report race-specificity for *BRAF* variants and PD-L1 immunohistochemical positivity. Overall, the differences between our data and other published evidence regarding racial disparities in the genomic landscape are not uncommon (17). These inconsistencies could be attributed to low numbers of AA patients with cancer compared to the numbers of CC patients in respective cohorts. This is a general trend (17) that contributes to wide intervals for mutational frequencies. Nevertheless, some of the observed differences may be representative of a difference in pathogenesis of cancer in AA as compared with CC patients. These differences could potentially help elucidate possible causes for increased mortality in AA patients, which currently remain unclear (18). Thus, additional research with larger cohorts should aid in further describing these differences. Moreover, new studies that include clinical outcomes are expected to provide important data linking molecular differences with disparate outcomes.

The incidence of HGG is higher in CC than in other races, including AA (19). Our novel data indicate that *PTEN, PTPN11* and *TP53* have potential race-specific molecular signatures associated with HGG tumors. Because genomic profiling has become a requirement for the proper clinical management of a number of tumor types, including gliomas (20), our race-specific genomic findings have the potential to advance precision cancer medicine. Furthermore, in both the AA and CC cohorts of the present study, a number of the detected oncogenic alterations (*e.g.* *APC*-, *KRAS*- and *PIK3CA*- associated) are actionable, *i.e.* possibly responsive to a targeted therapy (20–24). Thus, it is important to ensure that all cancer patients, regardless of race, undergo genomic profiling in order to be treated with appropriate targeted therapies (18).

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Table I.

Patient and tumor characteristics.

	CRC		NSCLC		HGG		All cancer types	
Tumors, n	459		341		107		907	
Race	AA	CC	AA	CC	AA	CC	AA	CC
Tumors, n	136	323	110	231	25	82	271	636
Patient age (mean)	61	58	63	66	47	56	59	60
Female, n	65	164	59	129	14	38	138	331
Male, n	71	159	51	102	11	44	133	305
Primary, n	68	145	52	106			120	251
Metastasis, n	67	168	50	114			117	282

AA, African American; CC, Caucasian; CRC, colorectal cancer; HGG, high-grade glioma; NSCLC, non-small cell lung cancer.

Table II.

Next-generation sequencing data for phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha (PIK3CA), ataxia-telangiectasia mutated (ATM), proto-oncogene B-Raf (BRAF), mitogen-activated protein kinase kinase 1 (MAP2K1/MEK1), myeloproliferative leukemia (MPL) virus oncogene and neurofibromin 1 (NF1) mutations in colorectal cancer (CRC) tumors from African Americans (AA) and Caucasians (CC) patients. Each variant is characterized by specific amino acid substitution at a given protein position, the specific DNA exon region, its pathogenicity, and the actual number of patients represented in each cohort (n). Standard one letter codes are used to indicate mutation-induced changes in amino acids. The most frequent mutations of PIK3CA are shown in bold.

Gene/variant	Exon	Function	AA (n)	CC (n)	*p*-Value
PIK3CA					
Total assayed			118	243	0.024*
R88Q	1	**P**	0	2	
E109del	1	**PP**	1	1	
N345K	4	**PP**	0	3	
E542K	**9**	**P**	**10**	**6**	
E545A	9	**P**	0	1	
E545G	9	**P**	1	0	
E545K	**9**	**P**	**6**	**4**	
Q546K	9	**P**	1	0	
Q546R	9	**P**	0	1	
Y1021C	20	**PP**	1	0	
M1043I	20	**P**	1	0	
G1049R	20	**P**	1	1	
H1047L	20	**P**	2	1	
H1047R	20	**P**	2	2	
ATM					
Total assayed			116	241	0.047‡
S49C	3	**PP**	0	4	
R337H	8	**PP**	0	1	
E632X	12	**P**	0	1	
L1238fs	25	**P**	0	1	
Y1241X	25	**P**	0	1	
L1449X	29	**P**	0	1	
F1774fs	35	**P**	0	1	
Q2108X	43	**P**	0	1	
R2443X	50	**P**	0	1	
W2638X	53	**P**	2	1	
F2799fs	57	**P**	0	1	
R3008C	63	**PP**	0	2	
R3008H	63	**P**	0	1	
BRAF					

Gene/variant	Exon	Function	AA (n)	CC (n)	*p*-Value
Total assayed			115	247	0.022[‡]
G464V	11	**P**	0	1	
G466V	11	**P**	0	1	
D594G	15	**PP**	2	0	
D594N	15	**PP**	0	1	
L597V	15	**PP**	0	1	
V600 K601delinsE	15	**PP**	0	1	
V600E	15	**P**	2	21	
MAP2K1/MEK1					
Total assayed			78	169	0.035[‡]
D67N	2	**PP**	1	0	
K57N	2	**PP**	1	0	
MPL					
Total assayed			115	244	0.039[‡]
Y252H	5	**PP**	2	0	
NF1					
Total assayed			78	169	0.037[‡]
R440X	12	**P**	1	0	
R1769X	38	**P**	1	0	
c.6819+1G>A	45	**P**	1	0	

C.6819+1G>A, splice variant showing the nucleotide change position; Del, deletion; Delins, double-deletion; Fs, frameshift; P, pathogenic; PP, presumed pathogenic; X, stop codon.

[*] Bonferroni and Benjamini-Hochberg correction

[‡] chi-square test.

Table III.

Rates of immunohistochemical positivity for epidermal growth factor receptor (EGFR) and topoisomerase 2-alpha (TOP2A) appear to be higher in colorectal (CRC) tumors from African Americans (AA) than in Caucasians (CC) patients.

Immunohistochemical positivity	EGFR		TOP2A	
	AA	CC	AA	CC
Total assayed, n	89	194	104	250
Positively stained, n	58	102	99	211
Percentage	65.2%	52.6%	95.2%	84.4%
p-Value[≠]	0.047		0.005	

[≠]Chi -square test.

Table IV.

Proto-oncogene B-Raf (BRAF) variants in lung adenocarcinomas and immunohistochemical positivity for programmed death-ligand 1 (PD-L1) in lung squamous cell carcinomas. Each variant is characterized by specific amino acid substitution at a given position in the protein, the specific DNA exon region, its pathogenicity, and the actual number represented in each cohort (n). Standard one letter codes indicate mutation-induced changes in amino acids.

Gene/variant	Exon	Function	AA (n)	CC (n)	*p*-Value
BRAF					0.020[≠]
Total assayed			51	108	
G469A	11	**P**	1	2	
D594N	15	**PP**	2	0	
G596R	15	**P**	0	1	
K601E	15	**PP**	1	0	
V600E	15	**P**	3	1	
Immunohistochemical positivity			AA	CC	*p*-Value
PD-L1					
Total assayed, n			11	20	0.022[≠]
Positively stained, n			0	7	
Percentage			0.0	35.0	

AA, African Americans; CC, Caucasians; P, pathogenic; PP, presumed pathogenic.

[≠]Chi-square test.

Table V.

Next-generation sequencing data for protein tyrosine phosphatase non-receptor 11 (PTPN11), phosphatase and tensin homolog (PTEN) and tumor protein 53 (TP53) variants in high-grade glioma (HGG) tumors tend to be race-specific. Each variant is characterized by specific amino acid substitution at a given protein position, the specific DNA exon region, its pathogenicity, and the actual number of patients represented in each cohort (n). Standard one letter codes are used to indicate mutation-induced changes in amino acids.

Gene/variant	Exon	Function	AA (n)	CC (n)	*p*-Value
PTPN11					
Total assayed			18	57	0.011‡
G503V	13	**PP**	2	0	
T507A	13	**PP**	1	0	
PTEN					
Total assayed			18	55	0.005‡
Q17X	1	**P**	0	1	
T26fs	1	**P**	0	2	
G129V	5	**PP**	0	1	
Q87X	5	**P**	0	1	
L193fs	6	**P**	0	1	
Q171X	6	**P**	0	1	
R173H	6	**P**	0	1	
Y176fs	6	**P**	0	1	
Y180X	6	**P**	0	1	
I253fs	7	**P**	0	2	
P246L	7	**P**	0	1	
S226fs	7	**P**	0	1	
R335X	8	**P**	0	1	
V317fs	8	**P**	0	1	
V315X	8	**P**	0	2	
TP53					
Total assayed			18	58	0.024‡
N29fs	3	**P**	0	1	
H115fs	4	**P**	0	1	
L130V	5	**PP**	0	1	
R175H	5	**P**	0	2	
R181H	5	**PP**	0	1	
V143A	5	**PP**	0	1	
H193P	6	**PP**	0	1	
I195T	6	**PP**	0	1	
Y205fs	6	**P**	0	1	
Y220C	6	**P**	0	1	
G244D	7	**PP**	0	1	

Gene/variant	Exon	Function	AA (n)	CC (n)	*p*-Value
R248Q	7	**P**	0	2	
Y234C	7	**PP**	0	1	
C275S	8	**PP**	1	0	
F270L	8	**PP**	1	0	
G266E	8	**PP**	0	1	
P278S	8	**PP**	0	1	
P301fs	8	**P**	0	2	
R267W	8	**PP**	0	1	
R273C	8	**5**	0	5	
R273H	8	**P**	1	1	
R306X	8	**P**	0	1	
R337C	10	**P**	0	1	
R342X	10	**P**	0	1	

AA, African Americans; CC, Caucasians; Fs, frameshift; P, pathogenic; PP, presumed pathogenic; X, stop codon.

$^{\neq}$Chi-square test.