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Rates of TP53 Mutation are Significantly Elevated in African American Patients with Gastric Cancer

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Abstract

Background.—Gastric adenocarcinoma is a heterogenous disease that results from complex interactions between environmental and genetic factors, which may contribute to the disparate outcomes observed between different patient populations. This study aimed to determine whether genomic differences exist in a diverse population of patients by evaluating tumor mutational profiles stratified by race.

Methods.—All patients with gastric adenocarcinoma between 2012 and 2016 who underwent targeted next-generation sequencing of cancer genes by the Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets platform were identified. Patient race was categorized as Asian, African American, Hispanic, or Caucasian. Fisher's exact test was used to examine differences in mutation rates between racial designations for the most common mutations identified. The *p* values in this study were adjusted using the false discovery rate method.

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Results.—The study investigated 595 mutations in 119 patients. The DNA alterations identified included missense mutations (66%), frame-shift deletions (13%), and nonsense mutations (9%). Silent mutations were excluded. The most frequently mutated genes were ARID1A, CDH1, ERBB3, KRAS, PIK3CA, and TP53. Of these, TP53 was the most frequently mutated gene, affecting 50% of patients. The proportion of patients with TP53 mutations differed significantly between races ($p = 0.012$). The findings showed TP53 mutations for 89% (16/18) of the African American patients, 56% (10/18) of the Asian patients, 43% (9/21) of the Hispanic patients, and 40% (25/62) of the Caucasian patients.

Conclusions.—Significantly higher rates of TP53 mutations were identified among the African American patients with gastric adenocarcinoma. This is the first study to evaluate tumor genomic differences in a diverse population of patients with gastric adenocarcinoma.

Gastric adenocarcinoma is the third leading cause of cancer-related death worldwide, and the incidence and mortality rates differ greatly by geography and race/ethnicity.¹ For instance, gastric adenocarcinoma in Western (Europe and the United States) versus Asian populations is associated with differences in both presenting stage and overall survival.² The reported 5-year overall survival periods of patients in studies from Japan (54%), Korea (58%), and China (31%) are longer than those reported in studies from the United States (29%) and Canada (25%).³

The clinicopathologic presentation of gastric carcinoma also varies widely between Asian and Western countries. These variations include differences in histology (intestinal vs diffuse subtypes), location (distal vs proximal stomach), environmental exposures, dietary factors, and *Helicobacter pylori* status.^{4–6}

Of the many factors associated with long-term survival of gastric cancer patients, techniques of gastrectomy and systemic therapy have been studied considerably. Although less studied, biologic variations in gastric tumors among races may in part drive some of the observed survival disparities. Recent molecular characterizations of gastric adenocarcinomas demonstrate a significant molecular heterogeneity in this cancer.^{7,8}

Although gastric adenocarcinoma is less common in the United States than in the rest of the world, patterns of survival are confounded by the diverse racial and ethnic profile of the U.S. population.⁹ Data from the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute showed a worse disease-specific survival for African American patients with gastric cancer than for their Asian and Caucasian counterparts.¹⁰ Although this discrepancy could derive from access to care and socioeconomic status, it could also be related to differences in tumor biology.

We hypothesized that differences in tumor genomics may account for some of the discrepancy in outcomes between ethnic groups. Our primary aim was to evaluate tumor genomic differences in a diverse population of patients with gastric adenocarcinoma. Using single-institution data, we sought to identify alterations in the tumor genome among defined racial groups that may relate to differences in the biology of gastric cancer.

METHODS

All patients with gastric adenocarcinoma treated at the Memorial Sloan Kettering Cancer Center between 2012 and 2016 who had tumor evaluation by a targeted next-generation DNA sequencing assay were identified retrospectively. Patients were included in the study irrespective of race, stage of disease, prior treatment, or resection status. Tissue from primary tumors and metastasis, if no primary tumor sample was available, also were included in genomic evaluations.

Patients were excluded from the study if they had gastroesophageal (GE)-junction tumors or if the tumor could not be classified according to the Lauren classification (intestinal, diffuse, or mixed type). Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets (MSK-IMPACT) analysis and clinicopathologic data [sex, age, race, tumor-node-metastasis (TNM), survival] were collected from a prospectively maintained institutional database.

Genomic Evaluation

The MSK-IMPACT platform is a hybridization capture-based next-generation sequencing assay for targeted deep sequencing of all exons and selected introns of key cancer-associated genes. Initially MSK-IMPACT included full exon coverage of 341 genes. In a second iteration, this was expanded to a total of 410 genes. Instead of sequencing a tumor's whole genome or the entire part of the genome that codes for proteins, MSK-IMPACT analyzes the most important cancer genes, which are captured and sequenced on an illumina HiSeq platform. This targeted sequencing approach makes the analysis of tumor tissue more feasible and effective and increases the chance of finding clinically relevant genetic changes. The genes evaluated by MSK-IMPACT are those that have been shown to play a role in the development or phenotype of tumors.¹¹

Statistical Analyses

Descriptive clinical, pathologic, and mutation characteristics were presented using medians and ranges for continuous variables, and using frequencies and percentages for categorical variables. Race was categorized as Caucasian, African American, Asian, or Hispanic. Three patients had both a primary sample and metastatic samples available, but we included only the primary tumor sample for the analysis. All silent mutations were excluded.

Heat maps were used to assess the overall mutation pattern and the patterns by race. Any gene with a mutation present in at least 10 patients, irrespective of race, was included in the analyses.

Fisher's exact test was used to examine the differences in mutation rates between races. For adjustment of p values, the false discovery rate method was used. Adjusted p values lower than 0.05 and two-tailed were considered statistically significant. All analyses were performed using SAS 9.4 (The SAS Institute, Cary, NC, USA) and Cran R Version 3.3.0 (R Core Development Team, Vienna, Austria).

RESULTS

The analysis included 595 mutations in 119 patients. The study patients comprised 62 Caucasians (52.1%), 18 African Americans (15.1%), 18 Asians (15.1%), and 21 Hispanics (17.6%). Patient and pathologic characteristics as stratified by race are detailed in Tables 1 and 2. Of the 119 samples included, 87 (73%) were from the primary tumor, and the remaining samples were from the metastatic sites.

The following six genes were mutated in 10 or more patients: ARID1A, CDH1, ERBB3, KRAS, PIK3CA, and TP53. The most prevalent mutated gene was TP53, with 60 patients (50%) expressing a nonsynonymous gene alteration.

Although TP53 mutations were not associated with histopathologic subtype, tumor grade, or tumor location, we did identify an association with stage 4 disease (compared with stages 1–3). Of the six genes, only TP53 mutation rates differed significantly between the races ($p = 0.012$). A TP53 mutation was present in 89% (16/17) of the African American patients, 56% (10/18) of the Asian patients, 43% (9/21) of the Hispanic patients, and 40% (25/62) of the Caucasian patients (Table 3).

In the heat map for commonly mutated genes (Fig. 1), a discernable clustering for TP53 mutations was observed in the African American patients. This did not appear to be present among the other genes, either overall or by race. Only two of the African American patients analyzed had no TP53 mutation.

The majority of the gene mutations were missense mutations (66%, 390/595), followed by frame-shift deletions (13%, 77/595) and nonsense mutations (9%, 55/595) (data not shown). A breakdown of mutation classification by race for TP53 is outlined in Table 4, and the specific missense mutations are listed in Table 5.

DISCUSSION

We sought to evaluate genomic differences in gastric cancers among patients of different races. In doing so, we identified a significantly higher frequency of TP53 mutations in African American patients. This is the first study to suggest a difference in tumor genetics between African American patients with gastric cancer.

African Americans have the highest cancer-related death rate of any racial group in the United States for most cancers, with a lower 5-year overall survival rate than Caucasian patients (60 vs. 69%).¹² Recent data on racial disparities in cancer statistics demonstrated that gastric cancer had the largest discrepancy in survival rates between African Americans and Caucasians in the United States. For both male and female patients with gastric cancer, African Americans were 2.5 times more likely to die of their disease than Caucasians.¹³ These inequalities are thought to reflect social and economic disparities that may limit access to medical care, delay diagnosis, and postpone definitive treatment.^{12,13} However, some studies suggest that racial disparities persist even after accounting for differences in access to care and other socioeconomic factors.^{14,15} Our data suggest that the poor outcomes

reported for African American patients with gastric cancer also may be related to tumor biologic differences, and more specifically to frequency of TP53 mutation.

A study by The Cancer Genome Atlas (TCGA) defined the following four molecular subgroups of gastric cancer by profiling 295 primary gastric adenocarcinomas: Epstein-Bar virus-infected tumors, microsatellite instable tumors, genomically stable tumours, and chromosomally unstable tumors. In the latter, a significantly higher TP53 mutation was observed (71% of tumors). No difference was found in overall survival rates among these molecular subtypes, likely due to the small number of samples and relatively short follow-up period. Although not significant, an higher recurrence rate for the chromosomally unstable tumors was observed. It must be noted that African American patients were largely not included in these data.⁷

In a separate study, Cristescu et al.¹⁶ reported gene expression data of 300 primary gastric tumors to establish the following four molecular subtypes associated with distinct disease progression and prognosis: microsatellite instable (MSI) subtype, microsatellite stable/epithelial-to-mesenchymal transition (MSS/EMT) subtype, MSS/TP53⁺ (intact P53 activity) subtype, and MSS/TP53⁻ (functional loss of P53 gene) subtype. Interestingly, the subtype of MSS/TP53⁺ showed better prognosis than the MSS/TP53⁻ group.

In more than half of all human cancers, *TP53* gene alterations and dysfunction have been identified,^{17,18} and the presence of a mutation has been correlated with a shorter survival.¹⁹ The predictive value of TP53 mutations in breast cancer have been analyzed in multiple studies. The TP53 gene alterations in breast cancer have been associated with response to specific treatment regimens, and findings have shown these alterations to be useful in identifying patients at higher risk of disease recurrence and death.²⁰⁻²³

Mutations in TP53, found in the vast majority of triple-negative breast cancers, is associated with one of the worst prognoses among breast cancers and shown to be pre-dominant among African American patients.²⁴⁻²⁷ It should be noted that universal clinical use of TP53 mutation analysis has been difficult because the predictive significance is extremely variable according to tumor type, treatment, or both.²⁸

Missense TP53 mutations are the most common and represent about 72% of all mutations based on the UMD TP53 Mutations Database (<http://p53.fr>). Interestingly, we identified missense mutations in 41% of African American patients, and 65% of Caucasian patients. Missense mutations, while potentially preserving some wild-type function, generally act as dominant-negative and/or gain-of-function alterations occurring most commonly at corresponding amino acid residues 248, 273, and 175.¹⁷⁻²⁰ Intriguingly, these three “hotspot” mutations occurred in 47% of Caucasian patients and 14% of African American patients. Although the numbers are too small for a conclusion to be drawn, our results suggest that not only do the rates of TP53 mutations differ across racial groups in the United States, but the type of mutation may differ as well.

Several important limitations need to be considered when the results of this study are interpreted. First, the sample for all the patients was small, particularly for the non-Caucasian patients included in the study. Because our study involved a single tertiary cancer

center in the Northeast, our African American patients may not be representative of all African American patients in the United States. Second, the disease characteristics of these patients were heterogeneous and could not be controlled for in this small sample. The mutational status may have been related to an underlying disease factor more than to race. Additionally, we also included both primary and metastatic samples in our study, which may present different mutational profiles. Finally, race is a complex factor, and our study relied on patient-reported race designation, which can be complex in a diverse population such as that seen in the United States, and categorical delineations may be an oversimplification.

In conclusion, this is the first study to identify more mutations in the tumor-suppressor gene TP53 among African American patients with gastric adenocarcinoma than among other racial groups in the United States. In doing so, we have provided a potential biologic explanation for the poor survival associated with gastric cancer in African American patients. This study is particularly timely because drugs targeting TP53 mutations have entered early-phase clinical trials. Moreover, African American patients as a population have been difficult to accrue to clinical trials and may be ideal candidates for inclusion. Future larger studies are warranted to validate the results reported in this study.

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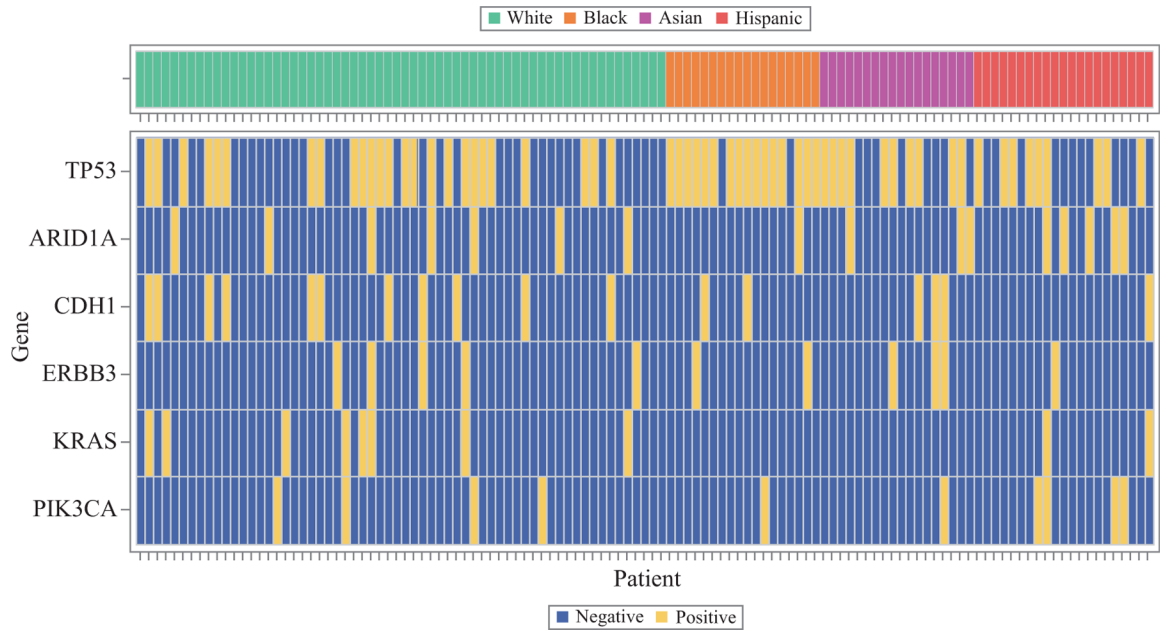


FIG. 1.
Heat map for the six genes

TABLE 1Patient characteristics ($n = 119$)

	<i>n</i> (%)
Gender	
Male	65 (55)
Female	54 (45)
Age	
Median	56
Range	23–84
Race	
Caucasian	62 (52)
African American	18 (15)
Asian	18 (15)
Hispanic	21 (18)
Stage	
1	11 (9)
2	16 (13)
3	18 (15)
4	74 (62)

Due to rounding, percentages may not add up exactly to 100%

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TABLE 2

Characteristics by race ($n = 119$)

	Caucasian ($n = 62$)	AA ($n = 18$)	Asian ($n = 18$)	Hispanic ($n = 21$)	All ($n = 119$)
	n (%)	n (%)	n (%)	n (%)	n (%)
Lauren classifications					
Diffuse	12 (19)	3 (17)	2 (11)	7 (33)	24 (20)
Intestinal	11 (18)	8 (44)	6 (33)	2 (10)	27 (23)
Mixed	9 (15)	1 (6)	4 (22)	2 (10)	16 (13)
Unknown	30 (48)	6 (33)	6 (33)	10 (48)	52 (44)
Tumor location					
Distal	19 (31)	5 (28)	7 (39)	5 (24)	36 (30)
Middle	17 (27)	7 (39)	10 (56)	7 (33)	41 (34)
Proximal	8 (13)	0 (0)	1 (6)	1 (5)	10 (8)
Whole	0 (0)	1 (6)	0 (0)	0 (0)	1 (1)
Unknown	18 (29)	5 (28)	0 (0)	8 (38)	31 (26)
Stage					
1	5 (8)	2 (11)	4 (22)	0 (0)	11 (9)
2	8 (13)	3 (17)	4 (22)	1 (5)	16 (13)
3	8 (13)	2 (11)	1 (6)	7 (33)	18 (15)
4	41 (66)	11 (61)	9 (50)	13 (62)	74 (62)
Grade					
Moderate	11 (18)	6 (33)	3 (17)	4 (19)	24 (20)
Moderate to poor	7 (11)	3 (17)	3 (17)	3 (14)	16 (13)
Poor	42 (68)	9 (50)	11 (61)	14 (67)	76 (64)
Unknown	2 (3)	0 (0)	1 (6)	0 (0)	3 (3)

Due to rounding, percentages may not add up exactly to 100%

AA African American

TABLE 3

Comparison of mutation rates between races (*n* = 119)

	Asian <i>N</i> (%)	AA <i>n</i> (%)	Hispanic <i>n</i> (%)	Caucasian <i>n</i> (%)	Adjusted <i>p</i> value
ARID1A					
Yes	3 (17)	1 (6)	5 (24)	7 (11)	0.54
No	15 (83)	17 (94)	16 (76)	55 (89)	
CDH1					
Yes	3 (17)	2 (11)	1 (5)	11 (18)	0.61
No	15 (83)	16 (89)	20 (95)	51 (82)	
ERBB3					
Yes	3 (17)	2 (11)	1 (5)	5 (8)	0.61
No	15 (83)	16 (89)	20 (95)	57 (92)	
KRAS					
Yes	0 (0)	0 (0)	2 (10)	8 (13)	0.54
No	18 (100)	18 (100)	19 (91)	54 (87)	
PIK3CA					
Yes	1 (6)	1 (6)	4 (19)	4 (7)	0.54
No	17 (94)	17 (94)	17 (81)	58 (94)	
TP53					
Yes	10 (56)	16 (89)	9 (43)	25 (40)	0.012
No	8 (44)	2 (11)	12 (57)	37 (60)	

Due to rounding, percentages may not add up exactly to 100%

AA African American

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TABLE 4

TP53 variant classification by race

	Caucasian	AA	Asian	Hispanic	All
	<i>n</i> (%)	<i>n</i> (%)	<i>n</i> (%)	<i>n</i> (%)	<i>n</i> (%)
Variant classification					
Missense mutation	17 (65)	7 (41)	4 (40)	4 (44)	32 (52)
Frame shift deletion	3 (12)	2 (12)	2 (20)	0 (0)	7 (11)
Nonsense mutation	4 (15)	6 (35)	2 (20)	1 (11)	13 (21)
Frame shift Insertion	1 (4)	1 (6)	0 (0)	0 (0)	2 (3)
Split site	1 (4)	1 (6)	1 (10)	3 (33)	6 (10)
In frame deletion	0 (0)	0 (0)	1 (10)	0 (0)	1 (2)
In frame insertion	0 (0)	0 (0)	0 (0)	1 (11)	1 (2)

Due to rounding, percentages may not add up exactly to 100%

AA African American

TABLE 5

Missense TP53 mutation variants by race^a

Codon	WT AA	Mutant AA	Caucasian (n = 17)	AA (n = 7)	Asian (n = 4)	Hispanic (n = 4)	All (n = 32)
			n (%)	n (%)	n (%)	n (%)	n (%)
175	Arg	His	3 (18)	0 (0)	0 (0)	2 (50)	5 (16)
266	Gly	Arg	1 (6)	2 (29)	0 (0)	0 (0)	3 (9)
273	Arg	His	2 (12)	0 (0)	1 (25)	0 (0)	3 (9)
237	Met	Ile	1 (6)	0 (0)	0 (0)	1 (25)	2 (6)
273	Arg	Cys	2 (12)	0 (0)	0 (0)	0 (0)	2 (6)
277	Cys	Phe	1 (6)	1 (14)	0 (0)	0 (0)	2 (6)
282	Arg	Trp	0 (0)	0 (0)	2 (50)	0 (0)	2 (6)
37	Ser	Cys	0 (0)	1 (14)	0 (0)	0 (0)	1 (3)
135	Cys	Phe	1 (6)	0 (0)	0 (0)	0 (0)	1 (3)
141	Cys	Tyr	1 (6)	0 (0)	0 (0)	0 (0)	1 (3)
145	Leu	Gln	1 (6)	0 (0)	0 (0)	0 (0)	1 (3)
173	Val	Leu	1 (6)	0 (0)	0 (0)	0 (0)	1 (3)
195	Ile	Thr	1 (6)	0 (0)	0 (0)	0 (0)	1 (3)
205	Tyr	Cys	0 (0)	1 (14)	0 (0)	0 (0)	1 (3)
244	Gly	Cys	0 (0)	1 (14)	0 (0)	0 (0)	1 (3)
245	Gly	Ser	0 (0)	0 (0)	0 (0)	1 (25)	1 (3)
248	Arg	Trp	1 (6)	0 (0)	0 (0)	0 (0)	1 (3)
248	Arg	Gln	0 (0)	1 (14)	0 (0)	0 (0)	1 (3)
274	Val	Gly	0 (0)	0 (0)	1 (25)	0 (0)	1 (3)
278	Pro	Ser	1 (6)	0 (0)	0 (0)	0 (0)	1 (3)

Due to rounding, percentages may not add up exactly to 100%

AA African American