Colorectal cancer patients with African ancestry have fewer clinically actionable alterations than white patients: Study

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Genomic profiling of patients who were treated for colorectal cancer at a major U.S. cancer center showed that patients with African ancestry had fewer actionable mutations than patients with European ancestry and were less likely to qualify for treatment with immunotherapy, according to data presented at the AACR Annual Meeting 2023, held April 14-19.

"African American patients are known to have worse clinical outcomes from colorectal cancer than patients from other racial backgrounds. The reasons for this are complex and likely reflect differences in risk factors, access to health care, and other socioeconomic variables," explained the study's first author, Henry Walch, MS, a computational biologist at the Marie-Josée and Henry R. Kravis Center for Molecular Oncology at Memorial Sloan Kettering Cancer Center (MSK). "However, the extent to which differences in germline or somatic genomic alterations influence outcomes remains unknown."

In order to assess these alterations in groups of different ancestries, Walch and colleagues analyzed targeted DNA sequencing data from 4,441 patients treated for colorectal cancer at MSK between 2014 and 2022. Tumors were sequenced using MSK-IMPACT, a gene sequencing panel that looks for mutations in up to 505 genes.

Genetic ancestry was estimated using reference populations from the 1000 Genomes Project. Patients were labeled European, African, East Asian, South Asian, or Native American when the predominant ancestry fraction was 80% or greater. Those with less than 80% of any one ancestry were considered admixed and were excluded from further

analysis. The study population comprised 3,265 patients of European ancestry, 263 East Asian, 245 African, 89 South Asian, and 15 Native American patients.

Among the study's key findings: The African ancestry group had a median overall survival of 45.7 months from time of diagnosis compared with 67.1 months for the European ancestry group.

The study also showed that 13.5% of patients of African ancestry qualified for immunotherapy based on U.S. Food and Drug Administration guidelines for certain biomarkers, including microsatellite instability and tumor mutational burden. This compared with 20.4% of patients of European ancestry.

Among microsatellite stable patients and those with a low tumor mutational burden, patients of African ancestry had lower rates of clinically actionable alterations than patients of European ancestry—5.6% compared with 11.2%.

The researchers also found that mutations in the adenomatous polyposis coli (APC) gene, a tumor suppressor, had different implications for patients in different groups. Walch explained that APC mutations are often the first step in the development of colorectal cancer. In this study, the researchers found that somatic alterations in this gene were associated with longer overall survival for patients of European, East Asian, and South Asian ancestry; however, for patients of African ancestry, APC alterations exhibited no prognostic value.

Walch said this study's findings suggest that somatic alterations could play a role in the persistent racial disparities in colorectal cancer but noted that this is a piece of a much larger puzzle.

"Even in a cohort where all patients were treated at the same institution,

patients of African ancestry had shorter overall survival from time of diagnosis than patients of other ancestries," he said.

The reduced rate of actionable mutations in patients of African ancestry may mean that these patients have fewer options of targeted therapies and immunotherapies that yield improved outcomes for many colorectal cancer patients, he continued.

"Patients who have an actionable mutation in their tumor can receive a targeted therapy that is precisely matched to that actionable change in their tumor. This can help to improve survival, particularly in microsatellite-stable patients who are resistant to first-line therapies," Walch explained.

"Our findings provide novel insights into the genomic basis of racial disparities in colorectal cancer and highlight the need of ancestry stratification for the analysis of associations between molecular profiles and clinical outcomes," Walch said. "This study is part of a larger effort where we aim to understand the reasons behind poor outcomes in African American patients with colorectal cancer. Our ultimate goal is to identify opportunities to intervene and improve outcomes in this underserved population."

One limitation of this study is that the data do not include information on environmental exposures, lifestyle, and socioeconomic factors, all of which play a role in colorectal cancer incidence and outcomes. Walch and colleagues are working to implement these factors in future models.

More information: Conference: www.aacr.org/meeting/aacr-annual-meeting-2023/