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Early-onset Colorectal Cancers from Patients of Different Races May Exhibit Distinct Genetic Features

PHILADELPHIA – Racial differences in genetic mutations were observed among early-onset colorectal cancers (CRC), according to data presented during Week 1 of the virtual AACR Annual Meeting 2021, held April 10-15.

The incidence of early-onset CRC, defined as CRC diagnosed in adults younger than 50 years, has risen dramatically in recent decades, explained presenting author Andreana N. Holowatyj, PhD, MS, an assistant professor of medicine and cancer biology at the Vanderbilt University Medical Center and Vanderbilt-Ingram Cancer Center.

"It's quite striking that there has been, on average, a 1.5 percent increase in early-onset CRC incidence each year over the last 25 years or so," she said. "It has burgeoned into a public health crisis and highlighted the need to understand the factors that may be contributing to the rise in cases."

Holowatyj previously observed that Black patients, but not Hispanic patients, with early-onset CRC had a greater risk of death compared with white patients. Since Hispanic and Black populations often have similar socioeconomic situations, Holowatyj and colleagues hypothesized that underlying biological factors, together with other complex factors, may contribute to the observed disparities in early-onset CRC.

In the latest study, Holowatyj and colleagues utilized the AACR Project GENIE database, which is a publicly accessible international cancer registry of real-world data, to examine genetic data from the tumors of 6,120 patients with CRC, of whom 1,761 had early-onset CRC. Six hundred forty-five tumors with microsatellite instability were excluded from the analysis since this phenotype may be associated with inherited genetic mutations that could confound the results. The final sample included 133 non-Hispanic Black, 144 Asian or Pacific Islander, and 1,315 non-Hispanic white patients with early-onset CRC and 3,883 patients with late-onset CRC.

Holowatyj and colleagues examined tumor mutations by race in patients with early-onset CRC. While they found no differences in tumor mutational burden between white and Asian/Pacific Islander patients with early-onset CRC, their analysis revealed that Black patients with early-onset CRC had significantly higher tumor mutational burden than white patients. Furthermore, distinct genetic mutations were observed among patients of different races.

Compared with the tumors of white patients with late-onset CRC, tumors from those with early-onset CRC were more likely to have non-silent mutations (which lead to alterations in the protein product) in LRP1B, TP53, TCF7L2, DOCK8, SMAD2, and SMAD3, and less likely to have non-silent KDR and FLT4 mutations after adjusting for sex, site and histology, sequencing assay, sample type, and tumor mutational burden. Among Black patients, early-onset CRC tumors were four times more likely to have non-silent mutations in CREBBP and also more likely to have non-silent mutations in TGFBR2 than tumors from late-onset CRC. Tumors from Asian patients with early-onset CRC were 48 percent and 66 percent less likely to present with non-silent mutations in APC and PIK3CA, and were 4.7 times more likely to have non-silent mutations in FAT1 compared with those of Asian patients with late-onset CRC.

Moreover, different mutation frequencies in CRCs among young patients across racial groups were observed for LRP1B, TGFBR2, APC, and PIK3CA.

Future research from Holowatyj and colleagues will explore how these differentially mutated genes may uniquely contribute to early-onset colorectal carcinogenesis. Using preclinical models, the researchers plan to study the molecular pathways that are affected by these different mutations to understand how tumor formation, progression, and treatment response may differ by race.

“This first-of-its-kind study revealed molecular differences in early-onset CRC by race,” said Holowatyj. “Although validation is needed, these findings may help us understand if molecular features of the tumor contribute to disparities in disease burden. In the long term, our findings could also help develop diagnostic and/or therapeutic biomarkers for early-onset CRC and could facilitate precision medicine for young patients.

“The unique consortium of information found within the AACR Project GENIE database—including clinical-grade sequencing data, demographics, and other clinical data from around the world—provided us with sufficient cases to study this disease across diverse populations in a way that we would not be able to at individual institutions,” she added.

“While this study revealed potential biological determinants of disparities in early-onset CRC, it is important to acknowledge that race is a social construct and this is just one piece of the puzzle,” Holowatyj noted. “Several complex and related factors, including genetic ancestry and systemic racism, also may contribute to such disparities.”

Limitations of the study include the lack of data on patient outcomes, genetic ancestry, and the tumors’ clinical features, such as stage and grade, as well as the small population of Hispanic individuals in the database, which precluded their inclusion in the analysis. An additional limitation was that age was defined as age at tumor sequencing in the database, rather than age at diagnosis. However, this would not be expected to alter the results of the study, according to Holowatyj. “Tumor sequencing occurs after diagnosis, so those who were under 50 years old at the time of sequencing and classified as having early-onset CRC would also have been younger than 50 years at diagnosis,” she explained.

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Abstract

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Abstract Body:	Colorectal cancer incidence among individuals age younger than 50 (early-onset CRC) continues to rise with etiologies unknown. Synchronously, early-onset CRC disparities have grown more pronounced. Molecular characteristics underlying CRC disparities among young adults remain

uncharacterized. In a study of 5,292 patients (1,483 early-onset; 28.0%) with CRC and clinical-grade targeted sequencing data from AACR Project GENIE, we explored tumor mutational burden (TMB) and genomic patterns of early-onset CRC by race/ethnicity using multivariable regression models adjusted for sex, histology, sequencing assay, primary sample type and TMB. In total, 9.4% of CRCs (n=500) were hypermutated (>17.77 mutations/Mb). Excluding the hypermutated cancers, early-onset CRCs had 5.6 mutations/Mb versus 6.2 mutations/Mb among CRCs from late-onset cases. Moreover, among young patients, Blacks (n=115), but not Asians (n=122), had significantly higher TMB compared with Whites (n=1,245) with non-hypermutated CRC (*P*=0.02 and 0.38, respectively). Overall, young patients with non-hypermutated CRCs had significantly higher odds of presenting with nonsilent mutations in *TP53* (Odds Ratio [OR]=1.26, 95%CI: 1.08-1.47, *P*=0.003) and *SMAD2* (OR=1.69, 95%CI: 1.19-2.40, *P*=0.003) versus late-onset cases after adjustment for sex, race, histology, sequencing assay, sample type and TMB. In contrast, young patients had a 40% and 44% decreased odds of presenting with *KDR* and *FLT4* nonsilent mutations, respectively, compared with patients with late-onset non-hypermutated CRC (*KDR*: OR=0.60, 95%CI: 0.38-0.95, *P*=0.03; *FLT4*: OR=0.56, 95%CI: 0.33-0.94, *P*=0.03). Mutation heterogeneity in *TGFBR2* (Cochran's Q test: *P*=0.003) and *NOTCH1* (*P*=0.02) was also observed between early-onset and late-onset cases. By race, distinct genomic patterns of early-onset CRC emerged. Young Whites with non-hypermutated CRC had higher odds of presenting with *SMAD2* and *TP53* mutations (*SMAD2*: OR=1.88, 95%CI:1.28-2.78, P=0.001; *TP53*: OR=1.25, 95%CI:1.06-1.48, P=0.007), and decreased odds of presenting with *FLT4* mutations (OR=0.56, 95%CI: 0.32-0.99, *P*=0.04) versus late-onset non-hypermutated CRC cases. Among Black individuals, early-onset non-hypermutated CRC cases had significantly higher odds of presenting with *TGFBR2* nonsilent mutations versus late-onset cases (OR=61.37, 95%CI:2.24-1680.45, *P*=0.01). Young Asians had 6-fold increased odds of presenting with nonsilent mutations in *NOTCH1* versus Asians with non-hypermutated late-onset CRC (OR=6.26, 95%CI:1.32-29.68, P=0.02). By race, distinct *TGFBR2* (*P*=0.0001) and *NOTCH1* (*P*=0.02) mutation frequencies were observed in non-hypermutated CRCs among young patients. Together, this study provides initial evidence that molecular features of early-onset CRC may differ by race/ethnicity, which could provide insight into biological mechanisms underlying early-onset CRC disparities.

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