Medical Xpress

Early-onset colorectal cancer germline genetic differences identified by race, ethnicity

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The first investigation to delve into genetic predisposition for early-onset colorectal cancer by race and ethnicity has identified differing germline risk variants.

The study, which was published June 15th in the *Journal of Clinical Oncology*, suggests that current multi-gene panel tests may not be representative of early-onset colorectal cancer risk in diverse populations. It found that racial and ethnic patterns exist for variants in susceptibility genes APC, CHEK2, MLH1, PTEN and monoallelic MUTYH. However, no differences in overall prevalence were identified for young Black and white patients, even though pronounced early-onset colorectal cancer disparities exist between the two groups, which raises the possibility that ancestry-specific risk variants have yet to be identified.

"As the incidence rates of early-onset colorectal cancer continue to rise and yield a disproportionate impact across diverse populations, our findings draw timely attention to the need for health equity considerations in multi-gene panel testing development," said the study's corresponding author, Andreana Holowatyj, Ph.D., MSCI, assistant professor of Medicine at Vanderbilt University Medical Center and Vanderbilt-Ingram Cancer Center.

The investigators looked for germline cancer susceptibility gene variants in 14 genes across five different populations: individuals who self-identified as Ashkenazi Jewish, Asian, Black, Hispanic, and white and were diagnosed with early-onset colorectal cancer between the ages of

15 and 49.

They found that one in every eight carried at least one pathogenic or likely pathogenic variant in a colorectal cancer susceptibility gene. Among the groups, deleterious variants were found in 12.7% of Ashkenazi Jews, 9.5% of Asians, 10.3% of Blacks, 14% of Hispanics and 12.4% of whites. The clinical-grade germline testing by Ambry Genetics was conducted on a total of 3,980 patients. Over 1,000 of the patients identified as non-white, providing the investigators with a first-of-its-kind opportunity for direct comparisons of germline genetic variants across diverse population groups.

Racial and ethnic patterns were defined for APC, CHEK2, MLH1, monoallelic MUTYH and PTEN. The investigators also evaluated estimates for Lynch syndrome, an inherited disorder that increases colorectal cancer risk. The prevalence sharply varied, ranging from 3.2% among Ashkenazi Jewish patients to 9.9% for Hispanic patients.

The investigators noted in the article that no differences in the overall prevalence of germline genetic features were observed between young Black patients and white patients despite well-established outcome disparities.

"This observation raises several questions for us about what factors may be driving the pronounced disparities in early-onset colorectal cancer outcomes between young Black and white patients. If germline genetics contribute to racial differences in colorectal carcinogenesis and outcomes, then it is possible we have not yet identified ancestry-specific variants associated with disease. It is known that beyond genetics, the interplay between biology, social determinants of health, and behaviors underlies distinct early-onset colorectal cancer patterns across populations," Holowatyj said.

"Thus, this work is an important first step toward a deeper dive into paired germline and tumor genome-wide sequencing across diverse populations to drive the discovery of potential genomic drivers and biomarkers for disease management."

More information: Hannah M. Seagle et al, Clinical Multigene Panel Testing Identifies Racial and Ethnic Differences in Germline Pathogenic Variants Among Patients With Early-Onset Colorectal Cancer, *Journal of Clinical Oncology* (2023). DOI: 10.1200/JCO.22.02378

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