Racial and ethnic patterns of variants of uncertain significance (VUS) among patients with early-onset colorectal cancer

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Background and Aim: Alongside the rising incidence of colorectal cancer among adults age younger than 50 (early-onset CRC; EOCRC), EOCRC disparities have grown more pronounced. We recently discovered racial/ethnic differences in germline pathogenic variants among EOCRC patients. However, patterns for variants of uncertain significance (VUSs) in a diverse EOCRC population remain uncharacterized. Consequently, we aimed to define the prevalence and spectrum of VUSs among patients with EOCRC by race and ethnicity.

Methods: We included individuals who identified as Ashkenazim, Asian, Black, Hispanic, or White, were diagnosed with a first primary CRC between ages 15-49, and underwent germline genetic testing of 14 CRC susceptibility genes—*APC, BMPR1A, CDH1, CHEK2, EPCAM, MLH1, MSH2, MSH6, MUTYH, PMS2, PTEN, SMAD4, STK11,* and *TP53*—performed by a nation-wide clinical testing laboratory. A five-tier classification system was applied to all genetic variations. We compared VUSs by race/ethnicity using chi-square tests and multivariable logistic regression adjusted for patient sex, age, CRC site, and number of primary CRCs.

Results: Among 3,980 patients with EOCRC (including 1,001 who identified as non-White), a total of 720 VUSs were identified in 634 individuals (15.9%). By race/ethnicity, 8.7% of Ashkenazim, 26.8% of Asian, 22.5% of Black, 17.7% of Hispanic, and 14.5% of White patients carried at least one VUS (P<0.0001). The proportion of patients with >1 VUS was also higher among Asian, Black and Hispanic (4.55%, 4.82%, and 3.20%; respectively) versus Ashkenazim and White patients (0% and 1.3%; respectively) (P<0.0001). The prevalence of VUSs in *APC, CDH1, CHEK2, MSH2, MUTYH, PMS2*, and *SMAD4* varied by race and ethnicity (all P<0.05). Overall, Asian (OR, 2.0; 95%CI 1.35-2.97) and Black (OR, 1.70; 95%CI 1.19-2.44) patients with EOCRC had significantly higher odds of presenting with any VUS versus White patients in adjusted models. Across individual genes, similar patterns were observed in adjusted models for VUSs in *MSH2* and *MUTYH* among Asian and Black patients, in *CDH1* for Asian patients, in *PMS2* and *SMAD4* for Black patients, and in *CHEK2* for Hispanic patients versus Whites.

Conclusions: Patterns of VUSs varied by race/ethnicity among young patients with CRC. A comprehensive assessment of VUSs across CRC susceptibility genes in diverse populations is warranted to guide efforts that will reduce uncertainty and will improve clinical care in this rising population.