Colorectal Tumors From Different Racial and Ethnic Minorities Have Similar Rates of Mismatch Repair Deficiency

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BACKGROUND & AIMS: **Microsatellite instability (MSI) in colorectal cancer cells results from deficient mismatch repair (MMR) protein function, either acquired or from germline alterations such as in patients with Lynch syndrome. Universal screening initiatives for Lynch syndrome have been encouraged. However, little is known about the true prevalence of MMR deficiency and MSI in colorectal tumors among individuals from different racial and ethnic subgroups or their clinical effects in these populations.**

METHODS: **We performed a retrospective analysis of 253 surgically resected, primary colorectal adenocarcinoma specimens identified from the University of Miami tumor registry from 2005 through 2010. We collected clinical data, including overall survival (OS), the proportion of patients alive at specific intervals, from non-Hispanic white, Hispanic, and black patients matched by stage. We performed immunohistochemical staining to detect MMR proteins in all specimens and polymerase chain reaction analysis of 51 tumors to detect MSI.**

RESULTS: **We detected MMR deficiency in 28 of 253 cases (11.1%), evenly distributed among blacks (9.6%), non-Hispanic whites (10.4%), and Hispanics (12.6%) ($P = .79$). Combined deficiencies in MLH1 and PMS2 were found in 23 of 28 MMR-deficient samples (82.1%); MSH2 and MSH6 were most frequently absent in tumor samples from Hispanics ($P = .03$). Eleven of 51 tumor samples (21.6%) had high levels of MSI, and we observed a high level of concordance between MMR and MSI (□ = .81). OS was significantly better in patients whose tumors had deficient MMR (hazard ratio for patients with MMR-deficient tumors vs MMR proteins intact = 0.37; 95% confidence interval, 0.15–0.91; $P = .03$). Race and ethnicity were not significant predictors of OS.**

CONCLUSIONS: **MMR deficiency in colorectal tumors occurs with similar rates among patients of different racial and ethnic groups, which is based on immunohistochemical analysis of 253 primary tumor specimens. This finding indicates the potential value of universal testing of colorectal cancer by immunohistochemistry in minority populations and confirms the benefit of MMR deficiency to OS.**

Keywords: DNA Mismatch Repair; Microsatellite Instability; Lynch Syndrome; Colorectal Cancer; Minority; Medically Underserved Populations.

Abbreviations used in this paper: **ADC, adenocarcinoma; AJCC, American Joint Committee on Cancer; black, black non-Hispanic; CI, confidence interval; CRC, colorectal cancer; FFPE, formalin-fixed paraffin-embedded; Hispanic, white Hispanic; HR, hazard ratio; IHC, immunohistochemical; JMH, Jackson Memorial Hospital; LS, Lynch syndrome; MMR, mismatch repair; MSI, microsatellite instability; MSI-H, high levels of microsatellite instability; MSS, microsatellite stable; NAACCR, North American Association of Central Cancer Registries; NHW, non-Hispanic white; OR, odds ratio; OS, overall survival; UM/SCCC, University of Miami/Sylvester Comprehensive Cancer Center.**

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Microsatellite instability (MSI) and DNA damage occur in colorectal cancers (CRCs) as a result of a defect in expression of functional mismatch repair (MMR) proteins. These defects are acquired from somatic mutations, epigenetic silencing, or germline mutations in MMR genes as part of Lynch syndrome (LS).[1–3] MSI impacts CRC phenotype; MSI CRCs have favorable survival compared with microsatellite stable (MSS) CRC and may have clinical implications with respect to chemotherapeutic response.[4,5] Since the recommendation supporting universal testing for MMR deficiency and/or MSI by several societies, many families of index cases with LS have benefitted from early identification of unsuspecting family members.[6–8]

Although the prevalence and availability of preventive measures for LS patients and their affected family members support universal screening initiatives, the true prevalence of MSI and LS in non-white patients is unclear. Studies in black patients have shown a high incidence of MSI, with CRCs occurring at a younger age and with more advanced staging when compared with the general population.[9–11] Studies in Hispanic patients of Central American origin have demonstrated MSI more frequently occurs in the context of LS. However, the study of MSI prevalence within the growing and diverse Hispanic population in the United States is extremely limited.[1,5] Establishing the prevalence of MSI among these racial and ethnic minority groups would clarify the value of universal testing in these populations. More importantly, others have posited differential rates of MSI between races may contribute to overall differences in survival between these groups.[12]

The aim of our study was to describe the prevalence and survival impact of MMR deficiency/MSI CRCs among an ethnically and racially diverse community. The simultaneous elucidation of MSI frequency among the 3 largest cohorts of the U.S. population, non-Hispanic white (NHW), white Hispanic (Hispanic), and black non-Hispanic patients (black), has not been reported to date. We also sought to determine the comparative utility of MMR and MSI testing for these populations.

Materials and Methods

Subject Selection and Clinical Data

Patient specimens were identified retrospectively from the tumor registry of the University of Miami/Sylvester Comprehensive Cancer Center (UM/SCCC), a tertiary care teaching hospital, and the oncology specialty clinic records from Jackson Memorial Hospital (JMH), the safety-net hospital for Miami-Dade County, between 2005 and 2010 inclusive. The institutional tumor registry from UM/SCCC and JMH has consistently met the North American Association of Central Cancer Registries (NAACCR) Gold Standard for Registry Certification.[13]

Vital Status

Cancer cases are added to the registry at the time of report, with annual updates to patient treatment and vital status obtained by review of institutional medical records, the Social Security Death Index, obituaries, and inquiry to patients, family members, and/or outpatient clinics. Patients were presumed to be alive until known otherwise. All CRC cases extracted from the registry and oncology clinics had confirmation of histologic diagnosis of CRC by review of pathology reports and clinical notes; the presence of tumor was also confirmed by a board-certified pathologist at the time of immunohistochemical (IHC) staining and before molecular studies. Consecutive cases of CRC were reviewed; included cases were surgically resected adenocarcinoma (ADC) of the colon or rectum with formalin-fixed paraffin-embedded (FFPE) tissue blocks available for processing. When available, normal tissue remote from the tumor site was selected; otherwise, matched colon tissue neighboring tumor was used as a control.

Ethnic and racial classifications were determined by the registry through chart review by using the portion of the medical record where patients are asked to self-identify to these groupings. Only those patients documented as Hispanic, NHW, and black were included; the patient population described herein is reflective of the racial/ethnic composition of the South Florida community. Our hospital systems service predominantly black and Hispanic populations, and accordingly, our cohort was limited in the availability of NHW patients. To diminish confounding from tumor stage, we permitted the American Joint Committee on Cancer (AJCC) stage distribution of our most limited group (NHWs) to drive the CRC stage proportions for the remaining racial/ethnic categories of black and Hispanic, with stratified stage matching in a 1:1:1 fashion.

Patients were excluded if the primary cancer was an alternative histology (ie, not a primary ADC of the colon or rectum) or if data were missing for major demographic/clinical end points. Tumor samples were excluded from analysis if tissue blocks were unavailable or insufficient or inadequate for processing and immunostaining. Patients were excluded from the MSI portion of the investigation if DNA quality or quantity was deemed insufficient for MSI analysis. In addition, we excluded 16 rectal cancer specimens that had received radiation before resection to avoid bias from tissue necrosis or DNA damage that may affect MSI results, although this exclusionary practice has been refuted since the initial design of our study.[14]

Additional data points obtained from pathology reports were tumor differentiation and grade, presence of synchronous cancers, and proximal, distal, or rectal location of tumor. Clinical data were obtained from the tumor registry database, including AJCC stage and vital status at the time of most recent query completed in