RESEARCH LETTER

Distinct Clinical Characteristics and Predictors of Sporadic Mismatch Repair-Deficient Colorectal Cancer

Colorectal cancer (CRC) is a heterogeneous disease.[1] The function of the DNA mismatch repair (MMR) system is a major determinant of CRC's clinical behavior and response to therapy. While most CRCs (~80%) are MMR proficient (pMMR), a minority (~20%) are mismatch repair deficient (dMMR); ~4–5% of this 20% are due to inherited germline pathogenic variants in MMR genes (Lynch syndrome) and the rest are primarily associated with acquired hypermethylation of the promoter of the *MLH1* gene, or very uncommonly, related to biallelic somatic MMR gene mutations.[1,2] To date, population-based data regarding clinical phenotypes and predictors of dMMR CRCs in comparison to pMMR CRCs remain very limited. A better understanding of such may inform effective preventive and therapeutic strategies for these tumors. In addition, while serrated polyps (SPs) are suggested as precursors to sporadic dMMR CRCs through the "serrated neoplasia pathway," the strength of association between SPs and dMMR CRCs remains incompletely understood.[1,2] To address these knowledge gaps, we compared the clinical characteristics of sporadic dMMR vs pMMR CRCs and investigated the clinical predictors of dMMR CRCs in a large, diverse, community-based population.

This retrospective cohort study included all members of KPNC who were diagnosed with CRC between 1/1/2009 and 12/31/2019, and whose CRC tumors underwent MMR immunohistochemistry (IHC) testing (Supplementary Methods). Patients with absent MLH1 (and without *BRAF V600E* mutation or *MLH1* promoter methylation), absent MSH2, MSH6, or PSH2 alone (with presence of MLH1) on MMR IHC had a high likelihood of Lynch syndrome based on previous studies and were excluded.[3] (Figure A1).

Among 7992 KPNC patients with incident CRC who underwent tumor MMR IHC, 7828 were sporadic CRCs, including 7067 pMMR CRCs and 761 dMMR CRCs. (Figure A1). Compared with pMMR CRCs, patients with dMMR CRC were more likely to be older (median age at diagnosis 78 years; 95% confidence interval [CI], 71–84 years vs 63 years; 95% CI, 53–73 years, $P < .0001$), female (70.4% vs 46.2%, $P < .0001$), being non-Hispanic White (75.4% vs 57.8%; $P < .0001$), have a smoking history (60.2% vs 48.4%, $P < .0001$), and have a history of SPs (35.0% vs 20.2%, $P < .0001$) (Table A1). Additionally, dMMR CRC tumors were more likely proximally located (88.8% vs 38.0%, $P < .0001$), had a higher histologic grade (23.9% vs 7.9% for grade 3, $P < .0001$), but had fewer distant metastasis (4.5% vs 17.3%, $P < .0001$). After adjustment of covariates, old age (adjusted odds ratio [aOR] 14.25 [95% CI, 9.67–21.01] for age >80 years vs 50–59 years), female sex (aOR 2.75 [2.31–3.27]), being non-Hispanic White (aOR for Asian 0.56 [0.42–0.75], Black (0.57 [0.39–0.81], and Hispanic 0.59 [0.44–0.79] individuals compared with non-Hispanic White individuals), history of smoking (aOR 1.36 [1.15–1.61]), and history of SPs (aOR 1.61 [1.29–2.02]) were independently associated with increased risk of dMMR CRCs (Table).

These substantial differences in clinical characteristics and phenotypic features between dMMR CRCs and pMMR CRCs support distinct carcinogenic pathways. Our findings suggested that dMMR CRCs primarily occurred at an older age with a female preponderance, consistent with prior reports in smaller series in different populations.[4,5] The increasing association with advanced age in dMMR CRCs may be related to the increased genomic methylation process associated with the aging process; in particular, hypermethylation of *MLH1* promoter may result in dMMR CRC as a later event.[6,7] The sex-related difference in dMMR CRCs is not entirely clear and warrants further investigation. Our findings also extend the current literature showing the predominant proximal location in dMMR CRCs and fewer distant metastasis compared with pMMR CRCs.[7] Furthermore, our study showed a history of SPs was associated with 60% higher odds of developing dMMR CRCs, which is concordant with SPs being precursors of dMMR CRCs in the serrated neoplasia pathway.[1]

The substantial differences noted in the risk of dMMR CRC between people of different races and ethnicities are poorly understood. Although equitable access to health care is associated with minimal differences in cancer incidence by race and ethnicity in our study population,[8] this apparent difference in pathologic type may indicate different environmental exposures or other variations in carcinogenesis that may have contributed to the pathogenesis of dMMR CRC. In a prior study within the KPNC population, Asian and Hispanic individuals had a significantly lower prevalence of sessile serrated polyps, a precursor of dMMR CRCs, compared with non-Hispanic White individuals.[9] This may at least partially explain the lower odds of developing dMMR CRCs in non-White individuals, although further studies are needed to confirm these findings as well as to delineate the underlying causes.

To our knowledge, this study represents the largest community-based evaluation comparing clinicopathologic differences between sporadic dMMR and pMMR CRCs. Additional strengths include evaluation of multiple patient-level variables, data completeness, and validated accuracy of data extraction from electronic databases. There are several limitations in this study. First, a small proportion (3.3%) of CRCs was diagnosed before 2011 when universal MMR IHC testing of CRC tumors was implemented. MMR IHC testing for these patients was likely on an opportunistic basis, but this is unlikely to impact the overall findings. Second, a small fraction (2.5%–3.9%) of sporadic dMMR CRCs are due to biallelic somatic MMR gene mutations.[10] These tumors could not be differentiated from dMMR CRCs due to *MLH1* promoter methylation based on MMR IHC screening

Table. Predictors of Sporadic CRC With dMMR

Variables	Adjusted odds ratio	95% confidence interval
Age at CRC diagnosis, years		
<50	**0.31**	**0.13–0.74**
50–59 (ref)	1.0	
60–69	**3.01**	**2.03–4.46**
70–79	**8.13**	**5.55–11.92**
80+	**14.25**	**9.67–21.01**
Sex		
Male (ref)		
Female	**2.75**	**2.31–3.27**
Race and ethnicity		
Asian	**0.56**	**0.42–0.75**
Black	**0.57**	**0.39–0.81**
Hispanic	**0.59**	**0.44–0.79**
Non-Hispanic White (ref)	1.0	
Other	0.79	0.54–1.18
Charlson comorbidity score		
0 (ref)		
1	0.87	0.67–1.13
2+	1.07	0.88–1.31
Family history of CRC (in first degree relatives)		
Yes (ref)		
No	1.21	0.95–1.54
History of smoking		
Ever	**1.36**	**1.15–1.61**
Never (ref)		
Unknown	2.31	0.51–10.43
Polyp history		
History of adenoma alone (ref)		
History of any SP (with or without a history of adenoma)	**1.61**	**1.29–2.02**
No polyp	0.85	0.66–1.10

Multivariable logistic regression analysis, adjusted for age, sex, race and ethnicity, Charlson comorbidity index, family history of CRC, and history of smoking. The results that were statistically significant were shown in bold numbers.
CRC, colorectal cancer; dMMR, mismatch repair deficiency; SP, serrated polyp.

alone; it is unknown if this small proportion differs in any of the evaluated characteristics.

In conclusion, in this large retrospective cohort study based on a diverse, community-based population, we found substantial clinicopathological differences between sporadic dMMR vs pMMR CRCs. Older age, female sex, being non-Hispanic White, history of smoking, and history of SPs were independently associated with a higher risk of dMMR CRCs. Older age at the diagnosis of dMMR CRC may suggest that *MLH1* promoter methylation-related carcinogenic mechanism occurs later in life. The association between a history of SPs and dMMR CRCs supports carcinogenesis through the serrated neoplasia pathway. The differences in dMMR CRC risk by race and ethnicity and smoking status remain poorly understood, but may result from varied environmental exposures, and warrant further evaluation.

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Supplementary Materials

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Abbreviations used in this paper: **CI, confidence interval; CRC, colorectal cancer; dMMR, mismatch repair deficiency; IHC, immunohistochemistry; KPNC, Kaiser Permanente Northern California; MMR, mismatch repair; pMMR, mismatch repair proficiency; SP, serrated polyp; aOR, adjusted odds ratio**

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Data Transparency Statement:
Data and study materials are available upon request. Certain computer programs and analytic codes or macros used in this study are specific to Kaiser Permanente Northern California (KPNC).

Reporting Guidelines:
STROBE.