# Racial difference in DNA mismatch repair deficiency associated with Lynch syndrome among colorectal cancer patients.

# Krysta Contino<sup>1</sup>, Robin Irons F<sup>2</sup>, Kathryn Behling C<sup>3</sup>, Tina Bocker Edmonston<sup>3</sup>, Yize Wang R<sup>1\*</sup>

<sup>1</sup>Division of Gastroenterology and Liver Diseases, Department of Medicine, Cooper Medical School of Rowan University, Camden, NJ, USA

<sup>2</sup>Department of Surgery, Cooper Medical School of Rowan University, Camden, NJ, USA

<sup>3</sup>Department of Pathology, Cooper Medical School of Rowan University, Camden, NJ, USA

#### Abstract

Introduction: Lynch syndrome accounts for approximately 3% of all colorectal cancers (CRC) in the United States. African American (AA) patients are at a higher risk for CRC and diagnosed at a younger age and more advanced stage. The prevalence of LS among AAs has not been well studied. We hypothesized that AAs differ from non-Hispanic Whites (NHWs) in the prevalence of CRC secondary to DNA mismatch repair (MMR) deficiency.

Methods: We retrospectively studied 91 CRC patients screened for MMR deficiency between 03/2014 and 03/2016 at our institution. Immunohistochemistry staining was used to examine expression of MLH1, MSH2, MSH6 and PMS2. The Student's t-test, chi-square test, and Fisher's exact test were used in statistical analysis.

Results: Compared to NHW patients (n=68), AA patients (n=23) trended toward younger age (mean  $\pm$  standard deviation [SD]: 54.0  $\pm$  13.6 vs. 59.3  $\pm$  10.7 years, p=0.06) and tumor location in the right colon (56.5 vs. 36.9%, p=0.10) and were similar in percentage of female patients, body mass index, and TNM stage. Among NHWs, 8 (11.7%) had loss of MLH1/PMS2, 1 (1.5%) had loss of MSH2/MSH6, and 1 (1.5%) had loss of PMS2 only. In contrast, all AAs had intact MMR protein expression. The difference in MMR deficiency between NHW (14.7%) and AA (0%) patients was statistically significant (p<0.05).

Conclusion: We found that the rate of MMR deficiency is lower in AA CRC patients compared to NHW patients. This finding warrants further study as it has significant implications for Lynch Syndrome screening in AA patients.

Keywords: Colorectal cancer, Lynch syndrome.

## Introduction

Identification of DNA mismatch repair (MMR) deficiency has become particularly important in the diagnosis and treatment of colorectal cancer and more recently an even broader spectrum of tumors [1-4]. Originally identified as an indicator of Lynch Syndrome, MMR status also has prognostic significance for treatment [5-7]. CRC patients with high microsatellite instability tumors, a molecular hallmark of MMR deficiency, have longer survival times than those without high microsatellite instability [8-11].

Several MMR proteins are involved, including MLH1, MSH2, MSH6 and PMS2 [12]. In CRC, MMR deficiency is seen in approximately 15% of patients, with most cases due to acquired loss of MLH1 expression caused by methylation of the MLH1 promotor. In about 3% of CRC patients, MMR deficiency is due to inherited mutations or Lynch Syndrome. Historically, patients were selected for screening for Lynch syndrome based on clinico-pathologic criteria, including the Amsterdam and Bethesda criteria [13-15]. Due to the poor sensitivity of these criteria and ready availability of immunohistochemical staining, many institutions have moved to universal or near universal screening protocols.

34

Accepted on March 28, 2018

In the United States, African Americans (AAs) have the highest rate of CRC followed by non-Hispanic whites (NHWs) and Hispanics [16]. AA patients are diagnosed at a younger age and more advanced stage, contributing to worse outcomes. The prevalence of MMR deficiency among AA CRC patients has not been well studied [17]. In this study, we aimed to compare the rates of MMR deficiency between AA and NHW patients diagnosed with CRC at our institution.

## **Research Methodology**

This study was approved by the Institutional Review Board at Cooper University Hospital in Camden, New Jersey, USA. We performed a retrospective chart review of 106 consecutive patients (none from the same family) who underwent CRC resection and were screened for MMR deficiency between March 2014 and March 2016 at our institution. Patients with familial adenomatous polyposis or inflammatory bowel disease were excluded. Indications for MMR deficiency testing at the time of the study were age  $\leq 70$  at the time of CRC diagnosis (with the primary goal of Lynch syndrome screening) or stage II CRC irrespective of age (with the intent of providing guidance for adjuvant treatment decisions). The 15 patients with other

*Citation:* Contino K, Irons FR, Behling CK, et al. Racial difference in DNA mismatch repair deficiency associated with Lynch syndrome among colorectal cancer patients. J Gastroenterol Dig Dis. 2018;3(2):38-36.

race/ethnicity (4 Asians, 11 Hispanics) were excluded from the final study sample because their number was too small for statistical analysis.

Immunohistochemical testing for MLH1, MSH2, MSH6, and PMS2 was performed by a reference laboratory and interpreted at Cooper University Hospital. In addition to patient race and MMR deficiency status, age, sex, body mass index, CRC location (right vs. left colon [including rectum]), and TNM stage were collected from the electronic medical record system. The Student's T-test, chi-square test, and Fisher's exact test were used in statistical analysis (SAS Version 9.4, Cary, NC).

#### Results

Compared to NHW patients (n=68), AA patients (n=23) trended toward younger age (mean  $\pm$  standard deviation [SD]: 54.0  $\pm$  13.6 vs. 59.3  $\pm$  10.7 years, p=0.06) and more right colon cancer (56.5 vs. 36.9%, p=0.10) and were similar in percentage of female patients, body mass index, and TNM stage (Table 1).

Among NHW patients, 8 (11.7%) had loss of MLH1/PMS2, 1 (1.5%) had loss of MSH2/MSH6, and 1 (1.5%) had loss of PMS2 only (Table 2). In contrast, all AAs had intact MMR protein expression. The difference in overall MMR deficiency between NHW (14.7%) and AA (0%) patients was statistically significant (p<0.05).

## Discussion

Comparing AA and NHW CRC patients at our institution, we found that the rate of MMR deficiency was significantly lower in AA patients. This finding is interesting considering that the AA patients were slightly younger and tended to have more right-sided CRCs. In fact, none of the 23 AA patients had MMR deficiencies, although we would expect 3 AA patients to test positive if their rate of MMR deficiency is similar to that of NHW patients (10 out of 68). In contrast, the NHW rate of MMR deficiency and the predominance of MLH1/PMS2 loss

Table 1.	Patient	characteristics	by race.
----------	---------	-----------------	----------

Non-Hispanic White (n=68)	African American (n=23)	P-value
59.3 (10.7)	54.0 (13.6)	0.06
48.5	47.8	0.95
29.7 (7.9)	28.8 (7.0)	0.66
36.9	56.5	0.10
72.1	73.9	0.86
	White (n=68)   59.3 (10.7)   48.5   29.7 (7.9)   36.9	White (n=68) American (n=23)   59.3 (10.7) 54.0 (13.6)   48.5 47.8   29.7 (7.9) 28.8 (7.0)   36.9 56.5

Table 2. DNA	mismatch	renair	(MMR)	deficiency by race.
1 4010 1. 1. 1.1.1	musmuuten	repair	(111111)	acjustency by race.

Variables	Non-Hispanic White (n=68)	African American (n=23)	P-value		
Loss of MLH1/PMS2, %	11.7	0	0.09		
Loss of MSH2/MSH6, %	1.5	0	0.75		
Loss of PMS2 only, %	1.5	0	0.75		
MMR deficiency, %	14.7	0	0.045		
Notes: The Fisher's exact test was used in the above analyses comparing NHW and AA patients.					

for NHW patients at our institution are similar to previous studies [1,10,17-19], confirming the compatibility and validity of our MMR deficiency test.

The current literature on racial difference in MMR deficiency is limited. The rate of MMR deficiency was reportedly similar in Latino patients compared to patients of European descent [17-19]. Different from our study, one study of 253 CRC patients showed that the rate of MMR deficiency was similar among AA, NHW and Hispanics in the Miami area [17], while another study of 25 young ( $\leq$  40 years) Jamaican CRC patients showed a higher rate of microsatellite instability and Lynch syndrome compared to previous studies [20]. It is possible that the genetic risk factors for CRC are different for AA patients at our institution in the Northeast compared to those in Miami (South) and Jamaica (Caribbean), or that most of the CRCs in AAs at our institution are due to non-genetic or environmental factors.

The major limitation of our study is the small sample size of AA and other minority patients, and the latter group was excluded from this study. The 10 patients tested positive for MMR deficiency were recommended to undergo genetic testing for Lynch Syndrome (either at our institution or locally), but their genetic testing results were not available to us. Our small sample size would preclude a comparison of Lynch Syndrome diagnosis between NHW and minority patients.

#### Conclusion

In conclusion, we found that the rate of MMR deficiency is lower in AA CRC patients compared to NHW patients at our institution. This finding warrants further study as it has significant implications for Lynch Syndrome screening in AA patients. We found that the rate of MMR deficiency is lower in AA CRC patients compared to NHW patients. This finding warrants further study as it has significant implications for Lynch Syndrome screening in AA patients.

## References

- 1. Hampel H, Frankel WL, Martin E, et al. Screening for the Lynch syndrome (hereditary nonpolyposis colorectal cancer). N Engl J Med. 2005;352(18):1851-60.
- 2. Koessler T, Oestergaard MZ, Song H, et al. Common variants in mismatch repair genes and risk of colorectal cancer. Gut. 2008;57(8):1097-101.
- 3. Palomaki GE, McClain MR, Melillo S, et al. EGAPP supplementary evidence review: DNA testing strategies aimed at reducing morbidity and mortality from Lynch syndrome. Genet Med. 2009;11(1):42-65.
- Le D, Durham JN, Smith KN, et al. Mismatch-repair deficiency predicts response of solid tumors to PD-1 blockade. Science. 2017;357:409-13.
- Parc Y, Gueroult S, Mourra N, et al. Prognostic significance of microsatellite instability determined by immunohistochemical staining of MSH2 and MLH1 in sporadic T3N0M0 colon cancer. Gut. 2004;53:371-5.
- 6. Sinicrope FA, Foster NR, Thibodeau SN, et al. DNA mismatch repair status and colon cancer recurrence and

survival in clinical trials of 5-flourouracil-based adjuvant therapy. J Natl Cancer Inst. 2011;103(11):863-5.

- 7. Win AK, Lindor NM, Young JP, et al. Risks of primary extracolonic cancers following colorectal cancer in Lynch syndrome. J Natl Cancer Inst. 2012;104(18):1363-72.
- 8. Fallik D, Borrini F, Boige A, et al. Microsatellite instability is a predictive factor of the tumor response to irinotecan in patients with advanced colorectal cancer. Cancer Res. 2003;63(18):5738-44.
- Bertagnolli M, Niedzwiecki D, Compton C, et al. Microsatellite instability predicts improved response to adjuvant therapy with irinotecan, fluorouracil, and leucovorin in stage III colon cancer: Cancer and Leukemia Group B Protocol 89803. J. Clin. Oncol. 2009;27:1814-21.
- 10. Boland CR, Goel A. Microsatellite instability in colorectal cancer. Gastroenterology 2010;138:2073-87.
- Li, Xiao Z, Braciak T, et al. Impact of age and mismatch repair status on survival in colorectal cancer. Cancer Med. 2017;6(5):975-81.
- Chen W, Swanson B, Frankel W. Molecular genetics of microsatellite- unstable colorectal cancer for pathologists. Diagn Pathol. 2017:12.
- Boland CR, Thibodeau SN, Hamilton SR, et al. A National Cancer Institute Workshop on Microsatellite Instability for cancer detection and familial predisposition: Development of international criteria for the determination of microsatellite instability in colorectal cancer. Cancer Res. 1998;58(22):5248-57.

- Vasen HFA, Watson P, Mecklin JP, et al. New clinical criteria for hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome) proposed by the International Collaborative Group on HNPCC. Gastroenterology. 1999;116:1453-6.
- 15. Umar A, Boland CR, Terdiman JP, et al. Revised Bethesda Guidelines for hereditary nonpolyposis colorectal cancer (Lynch syndrome) and microsatellite instability. J Natl Cancer Inst. 2004; 96(4), 261-8.
- Centers for Disease Control and Prevention. Colorectal cancer rates by race and ethnicity. https://www.cdc.gov/ cancer/colorectal/statistics/race.html. Accessed on January 28, 2018.
- 17. Berera S, Koru Senqul T, Miao F, et al. Colorectal tumors from different racial and ethnic minorities have similar rates of mismatch repair deficiency. Clin Gastroenterol Hepatol. 2016;14(8):1163-71.
- O'Kane GM, Ryan E, McVeigh TP, et al. Screening for mismatch repair deficiency in colorectal cancer: data from three academic medical centers. Cancer Med. 2017;6:1465-72.
- 19. Ricker CN, Hanna DL, Peng C, et al. DNA mismatch repair deficiency and hereditary syndromes in Latino patients with colorectal cancer. Cancer. 2017;123:3732-43.
- 20. Plummer JM, Chin SN, Aronson M, et al. Lynch syndrome in a predominantly Afrocentric population: A clinico-pathological and genetic study. Can J Surg. 2012; 55: 294-300.

# \*Correspondence to:

Yize R. Wang, MD, PhD Division of Gastroenterology and Liver Diseases Department of Medicine Cooper Medical School of Rowan University Cooper Digestive Health Institute 501 Fellowship Road, Suite 101 Mount Laurel, Camden, NJ-08054 USA Tel: (856) 642-2133 E-mail: wang-yize@cooperhealth.edu