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Genetic cause of 15 percent of colorectal cancer diagnoses identified

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Up to 15 percent of colorectal cancers show a genetic mutation known as DNA mismatch repair deficiency, or dMMR. Until now, little has been known about how the mutation behaves in rectal cancer patients, what causes dMMR, and which treatments may be most effective.

A study at The University of Texas MD Anderson Cancer Center uncovered new data about dMMR's hereditary basis in rectal cancer which may guide physicians in diagnoses, treatment and preventive measures, and in exploring of potential new therapy options. Results from the study, which examined 62 patient records from 1992 to 2012, were reported in the July 18 online issue of the *Journal of Clinical Oncology*.

The retrospective study provided a benchmark for current treatment approaches including chemotherapy and surgery and confirmed dMMR patients likely are to have a good prognosis. The study also highlighted the need to pay attention to long-term care after surviving rectal cancer.

DNA mismatch repair is the body's method for repairing mutations or gene defects that occur during cell division. Sometimes things go awry with this vital tool, resulting in increased mutations and cancer. Four genes - MLH1, MSH2, MSH6 and PMS2 - previously have been associated with DNA mismatch repair. Until now, researchers believed MLH1 and MSH2 were the main culprits causing the DNA repair machinery to break down. The MD Anderson study found MSH2 and MSH6 to be most commonly found among dMMR rectal cancer patients.

The paper's author believes such genetic information allows for a more tailored approach to diagnosis and treatment known as precision medicine, which is the focus of President Obama's Precision Medicine Initiative that launched in 2015. Precision medicine encourages therapeutic options tailored to specific characteristics, such as a person's genetic makeup, or the genetic profile of an individual's tumor.

"Our paper provides a perfect illustration of how the power of precision medicine can be realized," said Y. Nancy You, M.D., associate professor of Surgical Oncology. "This new genetic understanding of dMMR provides immediate implications for telling patients how well they will do long term and for choosing the best surgical and chemotherapy options."

You said identifying MSH2 and MSH6 as genes with mutations that patients can potentially pass on to family members is key to offering improved identification and surveillance for patients and family members at risk for dMMR.

"If we know a patient carries this mutation, then we can enroll them in our Familial High-Risk GI Cancer Clinic, where we follow them and their at-risk family members and conduct cancer surveillance tests to detect pre-cancerous lesions and remove them as early as we can," said You. "We also emphasize following a healthy lifestyle as there is some evidence lifestyle choices still matter even in this genetic disease."

You added that having a better understanding of the genetic underpinnings of dMMR rectal cancers and a more thorough assessment of how patients respond to standard treatments, will allow physicians to make more informed decisions when it comes to offering new therapies that become available.

"There is the potential for improved care with novel immunotherapeutic

approaches, but the prognostic and predictive implications of dMMR have not been specifically established to date in rectal cancer," she said. "By bridging the previous knowledge gaps, the efficacy of new therapies and preventive efforts can be more accurately assessed and improved."

Provided by University of Texas M. D. Anderson Cancer Center