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Patients with family history of colorectal cancer may be at risk for aggressive form of the disease

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BOSTON—When people with a family history of colorectal cancer develop the disease, their tumors often carry a molecular sign that the cancer could be life-threatening and may require aggressive treatment, Dana-Farber Cancer Institute scientists report in a new study.

The finding, reported in the *Journal of the* National Cancer Institute, draws on data from studies that have tracked the health of tens of thousands of people over several decades. It suggests that colorectal cancer patients could one day have their tumor tissue tested for the molecular sign, and, if necessary, receive more powerful therapies and a familial cancer-risk assessment for their relatives. It further suggests that such patients' relatives could be eligible for more frequent colonoscopies to catch the disease at the earliest possible stage.

When people with a family history of colorectal cancer develop the disease, their tumors often carry a molecular sign that the cancer could be life-threatening, report Dana-Farber Cancer Institute scientists. The finding suggests it may be possible to identify colorectal cancer patients who should receive more aggressive therapies and whose relatives may be at increased risk for the aggressive form of the disease.

Unlike other abnormalities that raise the risk of colon cancer in some families, the newly discovered sign is not linked to a gene mutation that can be inherited from one's parents or grandparents. It appears in DNA

segments that are thought to have entered the human genome millennia ago, possibly through infection by retroviruses. These sections, known as long interspersed nucleotide element 1 (LINE-1), are sprinkled throughout the human genome and make up about 17 percent of our DNA. Normally, LINE-1 doesn't cause much trouble, because it's blanketed by methyl groups (packets of one carbon atom bound to three hydrogen atoms).

In the current study, researchers led by Dana-Farber's Shuji Ogino, MD, PhD, MS, and Charles Fuchs, MD, MPH, found that for many colorectal cancer patients with a family history of the disease, the LINE-1 in their tumor cells was nearly bare of methyl groups (a condition known as hypomethylation).

"Previous studies have suggested that some colorectal cancers exhibit an instability of the epigenome, the cell's system for controlling when genes are active," says Ogino, the paper's first author. "One of the signs of this deficiency, it was proposed, is hypomethylation of LINE-1. We wanted to find whether a family history of colorectal cancer creates a higher risk of such hypomethylation."

Fuchs is the paper's senior author.

In contrast to a small, previous study, which suggested that LINE-1 hypomethylated colorectal cancers cluster in certain families, the new study took a large-scale "prospective" approach to gain more definitive insights. Investigators used data from the Nurses' Health Study and the Health Professionals Follow-up Study—which follow the health of tens of thousands of people for decades—to see if participants who had a family history of colorectal cancer tended to develop colorectal cancer with low-level methylation of LINE-1.

"We found that, compared to individuals without a family history of

colorectal cancer, people who had first-degree relatives affected with the disease indeed had a higher risk of developing colorectal cancer with hypomethylated LINE-1," Ogino says. "Because this variety of colorectal cancer can quickly become dangerous, testing colorectal cancer patients for tumor LINE-1 hypomethylation may offer a valuable way of identifying those in greatest need of aggressive treatment. Such testing could also help identify patients whose relatives may be at increased risk for the aggressive form of the disease. Further study is needed to determine how this type of testing can be used in a clinical setting."

Provided by Dana-Farber Cancer Institute