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A counterintuitive finding that could benefit younger colorectal cancer patients

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Younger colon cancer patients appear to have more than three times as many mutations in their tumors as older patients, which could lead to more effective treatment decisions, say researchers at Georgetown Lombardi Comprehensive Cancer Center.

In the new study, they found that tumor mutation load, or TML, as well as gene mutations that play an important role in DNA repair, were more predominant in the younger patients.

The investigators undertook their analysis at a time when the rate of new colorectal cancers in patients ages 45 or younger is increasing. The abstract describing the work was released today. Additional details will be presented at the American Society of Clinical Oncology annual meeting next month in Chicago.

According to Mohamed E. Salem, M.D., assistant professor of medicine at Georgetown Lombardi, and senior investigator for the study, viewing high levels of mutations in tumors as a positive may seem counterintuitive, but it could be important to figuring out what therapies would work best. Importantly, he noted that immunotherapies work by taking the brakes off the immune system; the more mutations a cancer cell has, the more alien it appears to the immune-fighting cells hunting for cells that don't belong.

In one part of their study, the researchers looked at a biological mechanism known as mismatch repair, which occurs when a DNA

strand is replicated and the wrong base is inserted into a strand being copied. If there are mutations in the genes that direct the mismatch repair, then more tumors can arise.

In the other part of the study, the investigators looked at TML, which is a count of mutations in DNA. Tying the two factors together is the essence of their finding as a greater number of mismatch repair gene mutations can contribute to a high TML and high tumor mutation loads were seen in more young than old people in the study.

The investigators zeroed in on the biology of distal tumors found in the part of the colon closest to the rectum; distal tumors also include those found in the rectum. Distal tumors are on the rise in younger patients and typically convey better survival odds than proximal tumors, which occur further up the colon.

The researchers looked at advanced distal tumors from 229 colorectal cancer patients who were a median age of 40 and compared them with distal tumors from 503 patients who were a median age of 71. Most colorectal cancers appear after age 60.

Using advanced gene sequencing techniques, the researchers determined the TML for each tissue sample and catalogued which genes were most frequently mutated in those samples. While the researchers found a wide array of mutated genes, many of which play important roles in various types of cancer, there was no statistically significant difference in the rates of mutation in many cancer-causing genes in younger and older patients.

There were, however, a few genes were more frequently mutated in younger patients: HER2, NF1, and the DNA mismatch repair genes MSH6, MSH2, and POLE. They say the DNA mismatch repair mutations may explain the higher TML in younger patients.

Significantly, high TML was seen in 8.2 percent of young patients vs. 2.6 percent of older patients - over a three-fold difference.

"One of the leading theories for why rates of colorectal cancer are increasing in younger patients relates to lifestyle factors, including diet and exercise," says the study's principal investigator, Benjamin Weinberg, MD, chief hematology/oncology fellow at Georgetown Lombardi. "There is also increasing evidence that bacteria and local inflammation of the colon can drive cancer growth. We can now add tumor mutation load to the list of factors and begin exploring if there is a link between TML and these lifestyle factors."

More information: Abstract #192404:
Impact of patient age on molecular alterations in left-sided colorectal tumors.
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