スタディによりいくつかの新たながんとLynch症候群が関連付けられた(Abstract LBA1509)

ゲノム研究の結果、Lynch症候群は高MSI腫瘍を有する人々に多いことが示された

Genomic study finds Lynch syndrome is common among people with MSI-high tumors

2018 ASCO Annual Meetingで発表された15,000を超える腫瘍検体のゲノム研究の結果、マイクロサテライト不安定性が高い（MSI-H）腫瘍を有する人々はLynch 症候群を有する確率が高いことが示された。MSI-H腫瘍を有する人々のうち、16%はその後Lynch症候群を有することが明らかになった。予想通り、1,025のMSI-H/MSI-I腫瘍の約25%は、大腸がんまたは子宮内膜がんであった。しかし、Lynch症候群を有することが同定されたMSI-H/MSI-Iを有する患者の50% 近くが、これまでこの症候群と関連がないとされていたかまたはまれであったタイプのがん（中皮腫、肉腫、副腎皮質がん、悪性黒色腫、前立腺および卵巣胚細胞がんなど）を有していた。

Full Text

A genomic study of more than 15,000 tumor samples shows that people with tumors that have high microsatellite instability (MSI-H) - a genomic marker associated with a large number of genetic mutations in the tumor - are more likely to have Lynch syndrome, a hereditary condition that increases a person's risk of developing many different types of cancer. Among people with MSI-H tumors, 16% were subsequently found to have Lynch syndrome. Researchers also found that Lynch syndrome is linked to more types of cancer than previously thought.

The study was presented at the 2018 American Society of Clinical Oncology (ASCO) Annual Meeting.

"Our findings suggest that all patients with MSI-H tumors should be tested for Lynch syndrome, regardless of cancer type or family or personal history of cancer," said senior study author Zsofia Kinga Stadler, MD, Clinic Director of the Clinical Genetics Service and a medical oncologist at Memorial Sloan Kettering Cancer Center in New York. "Diagnosing Lynch syndrome gives us the unique opportunity of helping not only our cancer patients, but also at-risk family members, as their cancer risk can be lowered through increased cancer surveillance and, in some cases, preventive surgery."

It is estimated that about 1 in 300 (0.3%) people in the general population has Lynch syndrome, which increases a person's risk of developing several cancers. The most common cancers associated with Lynch syndrome are colorectal and endometrial, but people with Lynch syndrome also have a higher risk of developing other gastrointestinal (beyond colorectal), ovarian, brain, and skin cancers. The hallmark of Lynch syndrome-associated tumors is MSI-H.

MSI is a genomic marker that indicates a defect in a cell's ability to repair damaged DNA, resulting in the accumulation of mutations. Traditionally, MSI testing has been performed on colorectal and endometrial cancers as an initial screening test to identify those patients who may be at risk for having Lynch syndrome.

Researchers analyzed more than 15,000 tumor samples collected from patients with more than 50 different types of advanced cancer using a comprehensive genomic test called MSK-IMPACT. All study participants were part of a prospective study of MSK-IMPACT and received cancer treatment at the Memorial Sloan Kettering Cancer Center in New York.

Researchers also tested blood samples from study participants for inherited mutations in genes involved in DNA repair: MLH1, MSH2, MSH6, PMS2, and EPCAM. Mutations in these genes cause Lynch syndrome. Tumors caused by Lynch syndrome have mismatch repair deficiency (MMR-D) and are MSI-H.

Based on the results of the genomic analysis, the tumor samples were classified into three groups: MSI-stable (MSS, no MSI instability found), MSI-indeterminate (MSI-I, moderate level of MSI), and MSI-H. The vast majority (93.2%) of tumors were found to be MSS; 4.6% were MSI-I; and 2.2% were MSI-H.

Inherited mutations in Lynch syndrome-associated genes were found in 16% of people with MSI-H tumors, compared to 1.9% of those with MSI-I tumors and only 0.3% of those with MSS tumors.

As expected, about 25% of the 1,025 MSI-H/MSI-I tumors were colorectal or endometrial cancers. These are the most common cancers linked to Lynch syndrome, and MSI testing is routinely performed on such tumors. However, nearly 50% of patients with MSI-H/MSI-I tumors who were identified as having Lynch syndrome had cancer types not previously, or rarely, linked to the syndrome, including: mesothelioma, sarcoma, adrenocortical cancer, melanoma, prostate, and ovarian germ cell cancer. Of these patients, 45% did not meet Lynch syndrome genetic testing criteria based on family or personal cancer history. According to the authors, this suggests that Lynch syndrome is linked to a broader spectrum of cancers than previously thought and that MSI-H/MMR-D is predictive of Lynch syndrome, regardless of cancer type.

In the final step of the study, 57 MSI-I/MSI-H tumor samples were also tested for abnormal DNA repair proteins - and MMR-D was found in nearly all (98.3%) of those tumors. These findings suggest that if either MSI-H or MMR-D is found in the tumor, hereditary genetic testing for Lynch syndrome should be performed.

"This study enhances our ability to catch Lynch syndrome where it may have been previously overlooked, thanks in large part to advances in precision medicine. This gives us a valuable opening to preempt future cancers in our patients through better, earlier, and more accurate diagnosis of Lynch syndrome," said ASCO Expert Shannon Westin, MD.

The chance of developing certain cancers linked to Lynch syndrome can be lowered through frequent screening (e.g., yearly colonoscopy and endoscopy for gastrointestinal cancers) and preventive surgery (e.g., removal of the uterus and ovaries for gynecologic cancers). More research is needed to develop screening and preventive strategies for other cancers linked to Lynch syndrome.

This study received funding from the Romeo Milio Lynch Syndrome Foundation, the Marie-Josée and Henry R. Kravis Center for Molecular Oncology, the Robert and Kate Niehaus Center for Inherited Cancer Genomics, the Fieldstone Family Fund, a Stand Up to Cancer Colorectal Cancer Dream Team Translational Research Grant, and the NIH/NCI Cancer Center Support Grant.

ASCO2018特集