Genomic Study Finds Lynch Syndrome Is Common Among People With MSI-High Tumors

Study links several new cancers to Lynch syndrome

ASCO Perspective

“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.

CHICAGO – 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 will be featured in a press briefing today and 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.”

About Lynch Syndrome and MSI

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. Since the FDA approved the immunotherapy pembrolizumab (Keytruda®) in 2017 for use in all MSI-H tumors, regardless of tumor type, MSI testing of tumors has become broadly used to identify patients who may benefit from pembrolizumab.

About the Study
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. The test uses next-generation sequencing (NGS) to look for mutations in hundreds of cancer-related genes, as well as other molecular changes, including MSI.

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.

Key Findings
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.

Next Steps
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 (SU2C-AACR-DT22-17), and the NIH/NCI Cancer Center Support Grant (P30 CA008748).

**Study at a Glance**

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<th>Disease</th>
<th>Multiple Cancers</th>
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<td><strong>Trial Phase, Type</strong></td>
<td>Genomic Study</td>
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<td><strong>Patients on Trial</strong></td>
<td>15,000+</td>
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<td><strong>Primary Finding</strong></td>
<td>16% of patients with MSI-H tumors have Lynch syndrome</td>
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<td><strong>Secondary Finding(s)</strong></td>
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View the disclosures for the 2018 ASCO Annual Meeting News Planning Team.

ATTRIBUTION TO THE AMERICAN SOCIETY OF CLINICAL ONCOLOGY ANNUAL MEETING IS REQUESTED IN ALL COVERAGE.

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**2018 ASCO Annual Meeting: Presentation Information**

Tumor Testing in Precision Oncology: From Heredity to Counseling to Implementation Clinical Science Symposium  
Zsofia Kinga Stadler, MD  
Memorial Sloan Kettering Cancer Center  
Monday, June 4, 2018: 8:00-8:10 a.m. CT  
McCormick Place, S102

Background: The success of immunotherapy in microsatellite unstable (MSI-H) and/or DNA mismatch repair deficient (MMR-D) tumors has resulted in routine MSI-H/MMR-D testing in advanced solid tumors. Unlike colorectal (CRC) and endometrial cancer (EC), where this has long been undertaken, the characterization of Lynch syndrome (LS) across heterogeneous MSI-H/MMR-D tumors is unknown. Methods: Through a targeted NGS panel, MSI status was determined via MSIsensor. Scores of < 3, ≥3 to < 10, or ≥10 designated Microsatellite stable (MSS), MSI-Indeterminate (MSI-I) or MSI-H status, respectively. Germline mutations were assessed in MLH1, MSH2, MSH6, PMS2, EPCAM. Immunohistochemical staining (IHC) for MMR-D and tumor signatures in LS patients were assessed. Clinical variables were correlated with MSI and compared via Chi square or T-test. Results: Of 15,045 tumors spanning > 50 cancers, 93.2% were MSS, 4.6% MSI-I, and 2.2% MSI-H. Germline mutations were identified in 0.3% (37/14,020), 1.9% (13/699), and 16.3% (53/326) in the MSS, MSI-I, and MSI-H groups, respectively (p-value < 0.001). 25% of 1,025 MSI-H/MSI-I tumors were CRC/EC, but 50% (33/66) of LS patients had MSI-H/MSI-I tumors less commonly or not previously associated with LS (mesothelioma, sarcoma, adrenocortical, melanoma, ovarian germ cell). LS pts with MSI-H/MSI-I non-CRC/EC tumors only met testing criteria in 63.6% of cases, had lower MSIsensor scores, and were more likely to be MSI-I (MSI-I: non-CRC/EC, 30.3% (10/33) vs CRC/EC 9.1% (3/33); p-value = 0.03). IHC was completed in 86.4% (57/66) of LS MSI-H/MSI-I tumors, with 98.3% MMR-D-concordance. Of LS pts with MSS tumors, 78% had MSH6/PMS2 mutations, but 71% of LS pts with MSI-H/MSI-I tumors had MLH1/MSH2/EPCAM mutations(p-value < 0.001). 89% (33/37) of MSS tumors of LS pts had non-MMR-D signatures. Conclusions: MSI-H/MMR-D is predictive of LS across tumor types and suggests a more heterogeneous spectrum of LS-associated cancers than previously appreciated. Nearly 40% of LS pts with MSI-H/MMR-D non-CRC/EC tumors did not meet clinical criteria for genetic testing, suggesting that MSI-H/MMR-D tumors, regardless of cancer type or family history, should prompt germline testing for the evaluation of LS.

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