Evidence mounts for endometrial cancer tumor testing to identify women with Lynch syndrome

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A recent article by Norris Cotton Cancer Center researchers published in the January 2014 issue of the journal *Clinical Chemistry* reviews the scientific evidence that warrants screening all endometrial cancers for Lynch syndrome. Next to colorectal cancer, endometrial cancer is the most common form of cancer in women with Lynch syndrome. Currently at Dartmouth-Hitchcock Medical Center, every colon cancer specimen is screened for Lynch syndrome via specialized tumor testing. There is mounting evidence that this special tumor testing should also be done on every endometrial cancer specimen. This tumor testing, known as immunohistochemistry (IHC) and microsatellite instability (MSI), gives clinicians some preliminary information to see if Lynch syndrome played a role in the development of their patient's cancer.

Lynch syndrome, also known as hereditary nonpolyposis colorectal cancer (HNPCC) syndrome, is an inherited disorder that increases the risk for many types of cancers, but in particular colon and endometrial cancer. Lynch syndrome is passed down to a child from a parent who has the disease. The inherited gene is abnormal, or mutated, which leads to increased cancer risk. Variation occurs in one of four mismatch repair (MMR) genes (i.e., MLH1, MSH2 including EPCAM, MSH6, or PMS2). This mutation leads to instability in the DNA's ability to repair mismatches and ultimately increases an individual's risk for certain cancers. However, it is important to keep in mind that not all people who inherit the genetic mutation will develop cancer.

"While not all women with endometrial cancer have Lynch syndrome, endometrial cancer is the second most common type of cancer that women with Lynch syndrome develop. The importance of screening women with endometrial cancer for Lynch syndrome is based on their risk of developing other forms of cancer for which screening and early detection can have an enormous impact on the patient and their family," said Gregory J. Tsongalis, PhD, professor of Pathology at Geisel School of Medicine at Dartmouth and Director of Molecular Pathology.

The genetic mutations of Lynch syndrome are associated with a 40-80 percent risk of colon cancer, 25-60 percent risk of endometrial cancers, and 10-12 percent risk of ovarian cancer. Depending on the specific gene altered, the risks can be even greater. For example, mutations in the MSH6 gene translate into a lifetime risk of 70 percent for endometrial cancer. A smaller, but still elevated risk of urinary tract, small bowel, stomach, pancreas, biliary tract, and brain tumors also exists.

"In 40-60% of women with Lynch syndrome, endometrial cancer is their first malignancy and up to 14 percent of women with Lynch syndrome presenting with cancer have both a gynecologic and colonic cancer simultaneously. Raising awareness of endometrial cancer's association with Lynch syndrome will lead to identification of more patients and families who may benefit from screening. Screening tumors with IHC and MSI helps identify tumors that may be associated with Lynch syndrome and also guides subsequent genetic testing for specific MMR gene sequencing," said Laura J. Tafe, MD, assistant professor of Pathology Geisel School of Medicine at Dartmouth and assistant director of Molecular Pathology.

For individuals at high risk for Lynch syndrome, DNA sequencing effectively tests for the condition by examining a DNA sample for genetic mutations within the MMR genes. In women who have been identified to have Lynch syndrome, screening for endometrial cancer

can be considered. This often involves a transvaginal ultrasound and/or endometrial biopsy. The early signs of endometrial can include abnormal vaginal bleeding, so women with Lynch syndrome should be educated about these symptoms and seek prompt medical attention if they present. For colorectal cancer screening, frequent colonoscopy screening is the recommended surveillance method.

"Genetic testing for Lynch syndrome can be a powerful tool for families. Genetic testing can tell us who in a family are at an increased risk for cancer and who are not, allowing for more personalized screening and prevention recommendations. Those individuals with a mutation can increase cancer surveillance to manage their elevated risks; those individuals who test negative for a familial mutation are considered to have the general population's risks for cancer and do not need a special screening protocol," said Eleanor Riggs, MS, CGC, certified genetic counselor in Norris Cotton Cancer Center's Familial Cancer Program.

Provided by The Geisel School of Medicine at Dartmouth

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