First prospective analysis links breast and pancreatic cancer risk with Lynch syndrome

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A new prospective study of patients with Lynch syndrome – an inherited disorder of cancer susceptibility caused by mutations in specific DNA repair genes – provides the first strong evidence that people with Lynch syndrome face significantly increased risks of breast and pancreatic cancers. The study also provided new, clearer estimates of the risks of cancers already recognized to be associated with Lynch syndrome, including those of the colon, uterus, ovary, kidney, stomach and bladder. The findings – published February 13 in the *Journal of Clinical Oncology* – may have implications for screening and early detection of cancers in patients with the condition. Additionally, the study showed that relatives of individuals with Lynch syndrome who do not carry a genetic mutation associated with the condition have no increased risk of developing cancer, compared to the general population.

While the risk of pancreatic cancer had been suggested in prior research on Lynch syndrome, the elevated risk of breast cancer was an unexpected finding in this study. "Our study is the first prospective analysis to find a strong association between breast cancer and Lynch syndrome," explained Mark A. Jenkins, PhD, senior author and Associate Professor at The University of Melbourne in Australia. "Further clarification of the risk of breast cancer for women at various ages is needed to determine the recommended age for mammography for each patient, and to determine whether additional tests such as MRI are warranted for women with Lynch syndrome."

DNA errors are a common occurrence within cells. Under normal

circumstances, cells are able to correct these errors – for example, by using a set of genes called "mismatch repair genes," which correct a specific type of DNA errors called mismatches. When these errors are not repaired, due to the failure of the mismatch repair genes, additional gene mutations can occur, which can lead to cancer development.

Lynch syndrome is an inherited condition characterized by a mutation in one of the four key mismatch repair genes, and carriers are known to be at high risk for developing cancer, particularly colon cancer. In fact, researchers estimate that three to five of every 100 colon cancers are caused by Lynch syndrome. Individuals with Lynch syndrome are also at greater risk of developing multiple cancers during their lifetime, and tend to be diagnosed with cancer at a younger age than people in the general population. According to the National Cancer Institute, one to three percent of the population may have Lynch syndrome.

In this study, researchers followed a group of 446 carriers of one of four mismatch repair mutations related to Lynch Syndrome, as well as 1,029 of their relatives who did not carry these mutations ("non-carriers"). Participants were evaluated every five years at recruitment centers affiliated with the Colon Cancer Family Registry in Australia, New Zealand, Canada and the United States. The analysis was conducted by Aung Win, MPH, MBBS, Research Fellow at The University of Melbourne.

After a median follow-up of five years, the researchers found that, compared to the general population, carriers had a 20-fold greater risk of colorectal cancer; a 30-fold greater risk of endometrial (uterine) cancer; a 19-fold higher risk of ovarian cancer; an 11-fold greater risk of renal (kidney) cancer; a 10-fold greater risk of pancreatic, stomach, and bladder cancers; and a four-fold greater risk of breast cancer. They confirmed that carriers who developed cancer also tended to be diagnosed at an earlier age than the general population. The researchers

did not find evidence that family members who were non-carriers had any increased risk of cancer, suggesting that they do not need more intense cancer screening than the general population.

"Eventually, we expect that the management of cancer risk, including the choice and timing of screening, will be able to be tailored to the specific underlying gene mutation in a person with Lynch syndrome," said Jenkins.

"Currently, individuals with the syndrome are typically advised to undergo colonoscopy at an earlier age and more frequently than the general population. However, there is no data demonstrating that screening for these other cancers is beneficial, in part due to the absence of effective screening tests."

The researchers are continuing to follow this cohort. Since much larger numbers of carriers are needed to determine cancer risks specific to each of the four genes for Lynch syndrome, they are establishing the International Mismatch Repair Consortium to pool data from 51 clinical research centers in Africa, Asia, Australia, Europe, and North and South America. Collectively, these centers treat more than 7,500 families with Lynch syndrome and over 13,000 mismatch mutation carriers.

Robert Sticca, MD, ASCO Cancer Communications Committee member, executive editor of CancerProgress.Net and surgical oncologist said: "This study adds to growing evidence linking specific inherited genetic mutations to certain cancers. Additional follow-up will lead to even more accurate estimates of cancer risk for individuals with Lynch syndrome. Such data may help us refine screening guidelines and could ultimately lead to early detection of the cancers these patients are at risk for, preventing the long-term consequences of cancer development. In addition, these data may indicate that some patients with Lynch syndrome are eligible for prophylactic treatments to prevent the

development of these cancers."

More information: Lynch Syndrome (www.cancer.net/patient/Cancer+Types/Lynch+Syndrome)
Genetics (www.cancer.net/patient/All+About+Cancer/Genetics)
Cancer.Net Guides to Cancer (www.cancer.net/patient/Cancer+Types)

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