Study revises colorectal cancer risk down and other cancer risks up for women with Lynch Syndrome

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Lynch Syndrome is a heritable genetic mutation that causes colorectal, endometrial and other cancers. A cooperative study that included the University of Colorado Cancer Center, published in this month's issue of the *Journal of the National Cancer Institute*, revises the risk of colorectal cancer down but other cancers up for women with Lynch Syndrome who have had endometrial cancer.

"This new information helps patient care in two important ways. First, it helps us counsel women with Lynch Syndrome who have had endometrial cancer about the magnitude of their future cancer risk, which turns out to be about 55 percent over the 20 years after diagnosis of their endometrial cancer. Second, it helps fill in the picture of the spectrum of cancers that are associated with Lynch Syndrome, which includes not only colorectal and endometrial cancers, but kidney, ureter, renal, pelvic, urinary, bladder and breast cancers in that order as well," says Dennis J. Ahnen, MD, CU Cancer Center investigator and professor of gastroenterology at the Denver VA Medical Center, one of the paper's co-authors.

The research group, which includes member from six centers, used data from 127 women included in the Colon Cancer Family Registry (CCFR). Ahnen notes that the CCFR is unique among cancer registries in that it not only collects information on patients with colorectal cancer and their treatment outcomes, but also routinely performs molecular

characterization of these tumors, which can show which of these cancers are associated with Lynch Syndrome or other genetic abnormalities. Importantly, this molecular categorization allows researchers to discover which of the three possible pathways led to a patient's cancer – the traditional chromosomal instability pathway accounts for about 80 percent of all colorectal cancers, and Lynch Syndrome combines with an epigenetic pathway to account for the remaining 20 percent.

"Knowing a cancer's genetic makeup allows us to ask questions not only about colorectal cancer in general, but about its molecular subtypes separately. These three types are included under the umbrella of colorectal cancer but have different prognoses and react differently to therapies. Effectively, they're quite different diseases," Ahnen says.

One of the study's important findings was an 11 percent lifetime risk for breast cancer after Lynch-associated endometrial cancer, 2.51 times the risk of women outside this population. Also elevated with Lynch Syndrome were lifetime risks of bladder (9 percent) and kidney (11 percent) cancers. But while the current study expands the spectrum of cancers associated with Lynch Syndrome, it also provides estimates of risk of colorectal cancer that are lower than previous estimates.

"When you think about it," Ahnen says, "most of the prior data on Lynch-associated colorectal cancer risk was from people referred to a high-risk clinic usually because of a strong family history of cancer. Of course, these people are likely to have higher cancer risk than the general population. The registry data minimizes this selection bias and allows us to look at a more representative cross-section of the colorectal cancer population. This cross-section shows a 50-60 percent lifetime risk of developing colorectal cancer in people with Lynch Syndrome, as opposed to earlier estimates of 70-80 percent risk."

"There are many remaining questions we can ask using the CCFR data,"

Ahnen says. "For example, what's the best way to screen people for Lynch Syndrome? Based on the risks the registry shows, should we screen all colorectal cancers for Lynch and then all family members of Lynch patients for the mutation or should we focus on some clinical subset of the population such as those with CRC at a young age? Likewise we can determine if colorectal cancers that arise from different molecular pathways are associated with different risk factor profiles, different prognoses or have different responses to available treatments."

To Ahnen, this specific study's findings are important but even more essential is the approach taken by the Colon Cancer Family Registry to collect and molecularly characterize these cancers. As cancer becomes an ever-longer list of related but distinctly different diseases, each perhaps with a molecular Achilles heel, the Colon Cancer Family Registry allows researchers like Ahnen to ask questions about treatment of these molecular subtypes that are rarely possible with cancer registries that treat, say, breast or prostate cancers as monolithic diseases.

Cancer is becoming seen as "cancers" and in many ways, the Colon Cancer Family Registry allows researchers in this field to lead the way.

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