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When cancer of unknown origin strikes, patient's family members face increased risk

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Cancer usually begins in one location and then spreads, but in 3 percent to 5 percent of cancer patients, the tissue where a cancer begins is unknown. In these individuals a cancer diagnosis is made because it has metastasized to other sites. Patients with these so-called "cancers of unknown primary," or CUP, have a very poor prognosis, with a median survival of three months. A new study in the *JAMA Oncology* finds that family members of CUP patients are at higher risk of developing CUP themselves, as well as cancers of the lung, pancreas, colon and some cancers of the blood.

Jewel Samadder, M.D., is the lead researcher on the University of Utah and Huntsman Cancer Institute (HCI) study. He said he was motivated to do the study when he had a patient that presented with abnormal fluid accumulation in his abdomen. They removed the fluid and found cancer cells, but could never find the primary source of the cancer, even after an extensive search involving imaging and endoscopy.

"The relatives were very distraught and we had very little that we could tell them about where the cancer started from in their loved one and whether they, as family members, were at increased risk for cancer," he said.

Also upsetting to CUP patients and family members, according to Samadder, is the difficulty physicians have in determining the best course of therapy to recommend. "Because we are not able to identify the primary tumor site, we are not able to select a type of chemotherapy

or radiotherapy that the cancer would respond to best."

He adds that the inability to select the best therapy and the advanced nature of these cancers are likely responsible for the poor outcomes.

To understand the familial risk associated with CUP and to determine where these cancers may have originated in the body, the researchers decided to do a retrospective study where they looked at CUP patients and their families between 1980 and 2010.

The study was possible because of a unique resource at HCI called the Utah Population Database (UPDB), which links genealogy information of Utah families with demographic and medical information, including the Utah Cancer Registry, a statewide cancer archive that collects all incidents of cancer diagnoses in the state.

Using these databases, researchers were able to identify 4,160 patients diagnosed with CUP over a 30-year span and to identify which of these patients had family members that were also diagnosed with cancer. These data were used to calculate the cancer risk by site for first-degree (parents, siblings, children), second-degree (uncles, aunts, grandparents, nephews, nieces), and first cousin relatives compared to randomly selected matched population controls who were cancer free.

According to Samadder, "The study could have gone two ways. One way is that relatives are not at increased risk of any one cancer, that cancer of unknown primary is some sort of bad luck event. But we didn't find that. We found that there are certain cancers that seem to be of increased risk in close, and even distant family members. In first-degree relatives, the most important ones we identified are lung, pancreatic, and colon cancer."

The researchers found that first-degree relatives of a CUP patient have a

35 percent increased risk for CUP, 37 percent increased risk for lung cancer, 28 percent increased risk for pancreatic cancer, and 20 percent increased risk for colorectal cancer when compared to relevant control populations.

Samadder said he can now give some important information to relatives of CUP patients about their cancer risk and ways in which they may try to moderate this risk. "What is important about lung, pancreas, and colon cancer is that two of these, lung and pancreas, are smoking-related cancers. So we can advocate to family members to avoid smoking. For colon cancer we can recommend screening guidelines, such as regular colonoscopies, to try to mitigate against the risk."

Samadder added, "This paper also suggests that these tissues, such as lung, pancreas, and colon may be the primary sites for at least a portion of these cancers of unknown primary."

He said in the future this study may give guidance to physicians on which tissues to look at more closely when they have a CUP patient and possible therapies that might work better in these patients. "It opens up a new avenue of research, a new way of looking at the biology of cancers of unknown primary to see if it looks like they are really coming from one of these sites, and if so, should chemotherapy be tailored to one of these sites because that may be better than giving a chemotherapy that has no tailoring at all."

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