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Study finds molecular 'signature' for rapidly increasing form of esophageal cancer

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During the past 30 years, the number of patients with cancers that originate near the junction of the esophagus and stomach has increased approximately 600 percent in the United States. The first extensive probe of the DNA of these esophageal adenocarcinomas (EACs) has revealed that many share a distinctive mix-up of letters of the genetic code, and found more than 20 mutated genes that had not previously been linked to the disease.

The research, led by scientists at Dana-Farber Cancer Institute, the Broad Institute, and other research centers, may offer clues to why EAC rates have risen so sharply. The findings, which are being released as an advanced online publication by *Nature Genetics*, point to an array of abnormal genes and proteins that may be lynchpins of EAC cell growth and therefore serve as targets for new therapies, according to the study's authors.

"Adenocarcinomas of the esophagus, particularly those that arise at the gastroesophageal junction, were extremely uncommon 40 years ago and now account for approximately 15,000 new cases in the United States each year," said Adam Bass, MD, of Dana-Farber and the Broad Institute, who is co-senior author of the paper with Gad Getz, PhD, of the Broad Institute and Massachusetts General Hospital. "Unfortunately, it's also a disease with a generally poor prognosis: five years after diagnosis, only about 15 percent of patients are still alive. Bass added that despite the increased incidence of EAC, there have been few new approaches to treatment. "The goal of our study was to identify

abnormalities within the genome of EAC cells to develop a foundation to better understand these tumors, diagnose them earlier, and develop better treatments," explained Bass.

EAC is thought to be associated with chronic gastroesophageal reflux, which sends stomach acid gurgling into the esophagus. This produces a condition known as Barrett's esophagus, in which cells at the lower end of the esophagus change to resemble cells in the intestine. Patients with Barrett's esophagus often go on to develop EAC.

Researchers don't know why EAC rates are increasing, but they speculate that it may be due to a rise in obesity, particularly in men: A heavier abdomen puts increased pressure on the stomach, causing acid to back up into the esophagus.

In the new study, researchers "sequenced" specific sections of DNA in cells from 149 EAC tissue samples, reading the individual letters of the genetic code within those areas. They focused on the one percent of the genome that holds the codes for making cell proteins. They also sequenced the entire genome – all the DNA within the cell nucleus – of cells from 15 of these EAC samples. Prior to this study, the largest sequencing study of EAC involved only a dozen tumor samples.

"We discovered a pattern of DNA changes that had not been seen before in any other cancer type," Getz remarked. The pattern involved a subtle swap in one of the four "nucleobases" that form the rungs of the DNA double helix, often designated by the letters C, T, G, and A. The investigators found that in many places where an A nucleobase was followed by another A nucleobase, the second "A" was replaced by a "C," a process known as transversion.

"We found this type of transversion throughout the genomes of the EAC cells we analyzed," Bass stated. "Overall, about one-third of all the

mutations we discovered within these cells involved this type of transversion. In some tumor samples, these transversions accounted for nearly half of all mutations," Getz added.

Although A-to-C changes are not commonly observed in cancer, there is some evidence that oxidative damage can produce these changes. (Oxidative damage occurs when cells cannot neutralize the potentially harmful products of oxygen's reactions with other molecules.) "Gastric reflux can produce this type of damage, suggesting that reflux may underlie this pattern of mutations," Bass commented.

In addition to the mutational "signature" of AA becoming AC, the research team identified 26 genes that were frequently mutated in the tumor samples.

Five of these were "classic cancer genes" that had previously been implicated in EAC, Bass said, and the others were involved in a variety of cell processes.

Among the genes not previously linked to EAC were ELMO1 and DOCK2, mutations that can switch on a gene called RAC1, which can cause cancer cells to invade surrounding tissue. "The discovery of mutated ELMO1 and DOCK2 in many of these tumors may indicate that this invasive process is particularly active in EAC, promoting metastasis," Bass related. "We know that EAC tumors tend to spread at an earlier stage than many other cancers, which may help explain why survival rates for EAC patients tend to be low."

The RAC1 pathway – the network of genes that control RAC1 activity – is being pursued for pharmaceutical development. The discovery of ELMO1 and DOCK2 mutations in EAC samples may spur testing of new agents targeting this pathway in EAC, said Bass.

"Identifying the mutated genes within these tumors will help us understand the underlying biology of the disease," said Bass. "It also presents us with a slate of known genetic abnormalities that can someday be used to diagnose the disease at an early stage, classify tumors by the particular mutations within EAC cells, and ultimately develop treatment geared to precisely those mutations."

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