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Study sheds light on esophageal cancer, offers insight into increasingly common disease

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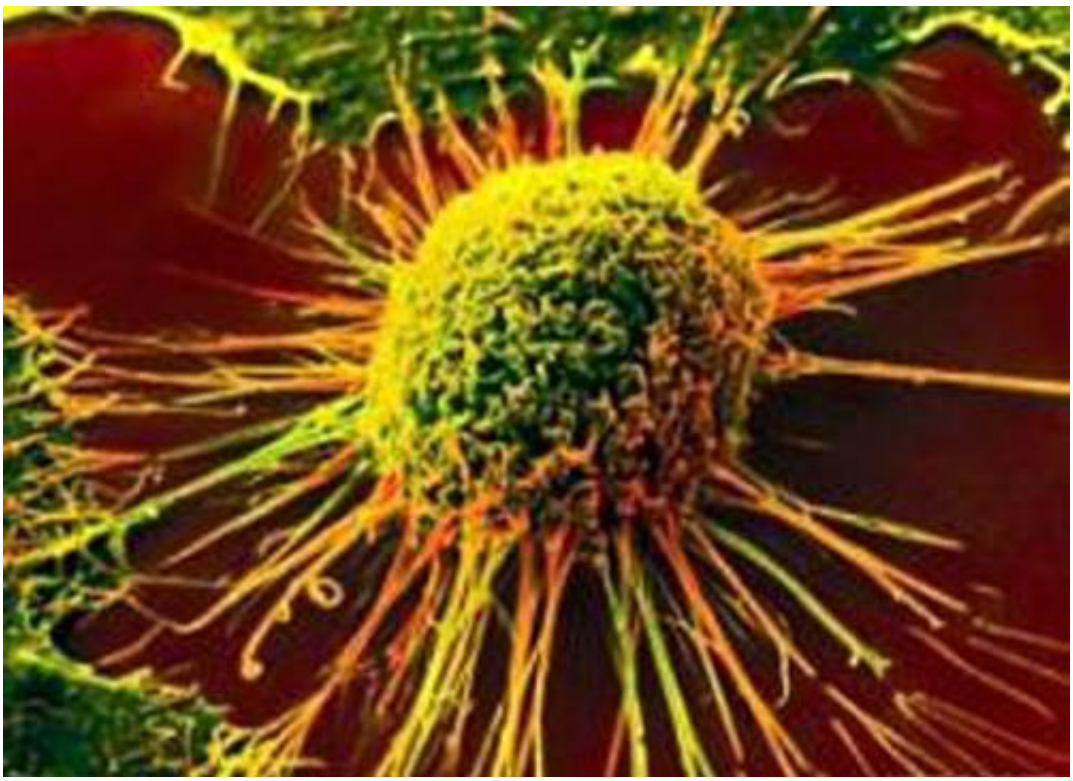

A comprehensive analysis of 559 esophageal and gastric cancer samples, collected from patients around the world, suggests the two main types of esophageal cancer differ markedly in their molecular characteristics and should be considered separate diseases.

The study, published today in *Nature* from The Cancer Genome Atlas (TCGA) Research Network, includes two key takeaways. First, upper esophageal cancers more closely resemble cancers of the head and neck, while tumors further down in the esophagus are virtually indistinguishable from a subtype of stomach cancer. Second, cancer clinical trials should group patients according to molecular subtype—in general, grouping lower esophageal tumors with stomach cancers, while evaluating upper esophageal cancers separately.

"These findings add several layers of depth and sophistication to our current understanding of esophageal cancer genomics," said Adam Bass, M.D., co-leader of TCGA's esophageal cancer study and physician-scientist at Dana-Farber Cancer Institute. "Our hope is this work settles several long-standing uncertainties in the esophageal cancer field and will serve as the definitive reference manual for researchers and drug developers seeking more effective clinical trials and new treatment approaches."

Physicians have known for decades that esophageal cancers, when looked at under the microscope, fall into one of two categories—adenocarcinomas, which resemble stomach or colorectal cancers, and squamous cell carcinomas, which are similar to some lung, skin, and head and neck cancers. What remained unknown was the extent to which adenocarcinomas and squamous esophageal cancers differ molecularly and the relationship between esophageal adenocarcinoma and stomach adenocarcinoma.

"We have shown that these clinical subtypes differ profoundly at the molecular level," said Peter W. Laird, Ph.D., a principal investigator in the international TCGA Research Network and a professor at Van Andel Research Institute. "These findings suggest that whether the tumor originates in the esophagus or the stomach is less relevant than the molecular characteristics of the individual tumors."

Esophageal cancer represents just 1 percent of new cancer diagnoses in the U.S. However, it kills 4-in-5 patients within five years of diagnosis, and current treatment approaches often fail to help. Additionally, cases of esophageal adenocarcinoma have skyrocketed over the last four decades, increasing seven-fold since the mid-1970s. Within the field, there has been great uncertainty regarding the relationship between this growing burden of esophageal adenocarcinoma and adenocarcinomas that occur in the stomach.

Results from this new report argue against the need to continue to debate the demarcations of esophageal and gastric adenocarcinoma and instead view gastroesophageal adenocarcinoma as a more singular entity, analogous to colorectal cancer. Specifically, this study revealed that esophageal adenocarcinomas have striking molecular similarity to a class of stomach cancers called chromosomally unstable tumors, the hallmark of which are significant structural chromosomal aberrations.

Oncologists say this nuanced view of the disease, including the detailed molecular taxonomy of esophageal adenocarcinomas, will likely change their approach to studies and treatment.

"It is clear from the TCGA data that esophageal squamous and esophageal adenocarcinomas are completely different diseases and should never be included in the same therapeutic trial," said Yelena Y. Janjigian, M.D., a gastrointestinal oncologist from Memorial Sloan Kettering Cancer Center who was not involved in the study. "In esophageal adenocarcinoma, it is likely a combination of pathways and therapeutic strategies that will be successful. The therapeutic significance of these alterations will be explored in follow-up studies."

Members of the TCGA Research Network team say these studies represent the work of dedicated collaborators, who seek to maximize results in search of new ways to battle cancer.

"Studies from TCGA transcend the work of any one institution or individual," said Ilya Shmulevich, Ph.D., a principal investigator in the international TCGA Research Network and a professor at the Institute for Systems Biology. "These are massive undertakings that are possible only through contributions from hundreds of specialists and scientists around the world—people dedicate years of their lives to these projects in the hope of finding new treatments for people who are very sick."

More information: Integrated genomic characterization of oesophageal carcinoma, *Nature*, nature.com/articles/doi:10.1038/nature20805

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