Four genetic variants linked to esophageal cancer and Barrett's esophagus

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An international consortium co-led by researchers at Fred Hutchinson Cancer Research Center and the QIMR Berghofer Medical Research Institute in Australia has identified four genetic variants associated with an increased risk of esophageal cancer and its precursor, a condition called Barrett's esophagus.

The findings, by corresponding author Thomas L. Vaughan, M.D., M.P.H., a member of the Epidemiology Program in the Public Health Sciences Division at Fred Hutch, are published online ahead of the December print issue of *Nature Genetics*. Vaughan co-led the project with co-author David Whiteman, Ph.D., head of the Cancer Control Group at QIMR (formerly known as the Queensland Institute for Medical Research).

Both are members of the international Barrett's and Esophageal Adenocarcinoma Consortium, or BEACON, an open scientific forum for research into the causes and prevention of esophageal cancer and Barrett's esophagus that involves more than 40 scientists in North America, Europe and Australia.

"Epidemiologic findings, largely based on the work of BEACON investigators, clearly demonstrate that environmental factors such as obesity, gastroesophageal reflux , smoking and diet are largely responsible for the rapidly increasing incidence and mortality from esophageal adenocarconima," said Vaughan, who serves as BEACON's chair and is also a professor of epidemiology at the University of

Washington School of Public Health. "However, a growing body of evidence also suggests an important role for inherited susceptibility."

To better understand the role of genetics in Barrett's and esophageal cancer, Vaughan and his BEACON colleagues pooled data and DNA specimens from 15 international studies conducted in the past 20 years to estimate the heritability of these conditions and identify genetic variants associated with increased risk. Altogether they gathered DNA samples and lifestyle risk-exposure data from more than 8,000 study participants, including about 5,500 with esophageal cancer or Barrett's esophagus and about 3,200 participants without these conditions who served as a comparison group.

The DNA samples were genotyped at Fred Hutch using a high-density array that allowed for the simultaneous and accurate assessment of more than 1 million genetic variants. To increase the statistical power of the study and its ability to identify potential causal genetic mutations, information on control subjects gleaned from public data repositories was added to the mix. The data analysis was conducted at the University of Washington in collaboration with the QIMR research group in Queensland.

After combing through all of the data, the researchers identified genetic variants at three locations – on chromosomes 3, 9 and 19 – as being significantly associated with esophageal adenocarcinoma and Barrett's esophagus. In addition, they found that a genetic variant on chromosome 16 that had been previously linked to Barrett's esophagus was also associated with an increased risk of esophageal adenocarcinoma.

Vaughan and colleagues also found that the role of inherited susceptibility to this cancer appears to be much stronger in the early stages of disease – that is, the development of Barrett's esophagus – rather than the progression of Barrett's to cancer.

"These findings establish strong starting points for further epidemiologic studies to pin down the causal variants, and laboratory studies to identify the mechanisms by which the causal variants might affect the development of Barrett's esophagus and esophageal adenocarcinoma," Vaughan said. "The fact that all four of the new loci are in or near genes associated with early development of the esophagus or already associated with oncogenic activity is particularly exciting, as it implies that we may be close to finding some important pathways in the development of this highly fatal disease."

Ultimately, the researchers believe these findings will contribute to the development of new screening tools to identify those at highest risk of esophageal adenocarcinoma and its precursor, particularly when combined with established risk factors such as obesity and gastric reflux. "Down the line we anticipate that a better understanding of the pathophysiology of these diseases will lead to better and earlier treatments," Vaughan said.

Barrett's is associated with chronic heartburn and affects an estimated 1 million to 2 million Americans. While the risk of developing esophageal cancer in a person with Barrett's is only about 0.5 percent per year, the outlook is grim if the disease is not diagnosed early. The majority of patients with invasive esophageal cancer die within a year of diagnosis.

This year, esophageal cancer will strike nearly 18,000 Americans and kill more than 15,000. Esophageal adenocarcinoma, which accounts for more than 60 percent of esophageal-cancer cases, is seven times more common in men than women.

More information: "A genome-wide association study identifies new susceptibility loci for esophageal adenocarcinoma and Barrett's esophagus," dx.doi.org/10.1038/ng.2796

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