Abnormal DNA repair genes may predict pancreatic cancer risk

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Abnormalities in genes that repair mistakes in DNA replication may help identify people who are at high risk of developing pancreatic cancer, a research team from The University of Texas M. D. Anderson Cancer Center reports in the Jan. 15 issue of Clinical Cancer Research.

Defects in these critical DNA repair genes may act alone or in combination with traditional risk factors known to increase an individual's likelihood of being diagnosed with this very aggressive type of cancer.

"We consider DNA repair to be the guardian of the genome," said lead author Donghui Li, Ph.D., professor in the Department of Gastrointestinal Medical Oncology at M. D. Anderson. "If something is wrong with the guard, the genes are more readily attacked by tobacco carcinogens and other damaging agents."

With this in mind, Li and her colleagues set out to identify DNA repair genes that could act as susceptibility markers to predict pancreatic cancer risk. In a case-control study of 734 patients with pancreatic cancer and 780 healthy individuals, they examined nine variants of seven DNA repair genes. The repair genes under investigation were: LIG3, LIG4, OGG1, ATM, POLB, RAD54L and RECQL.

The researchers looked for direct effects of the gene variants (also called single nucleotide polymorphisms) on pancreatic cancer risk as well as potential interactions between the gene variants and known risk factors

for the disease, including family history of cancer, diabetes, heavy smoking, heavy alcohol consumption and being overweight.

The M. D. Anderson team found that the risk of developing pancreatic cancer was 77 percent lower among individuals with the variant form of the LIG3 gene (LIG3 G-39A AA). In contrast, people who carried the variant form of the ATM gene (ATM D1853N AA) were more than twice as likely to develop the disease as those without the genetic variation.

When the investigators examined possible interactions between gene variants and known risk factors, they found no significant interplay between the abnormal DNA repair genes and smoking, heavy alcohol consumption or excess body weight. However, two of the gene variants (ATM D1853N and LIG4 C54T) did interact with diabetes to affect pancreatic cancer risk.

For example, compared to non-diabetics with the ATM D1853N GG genotype, diabetics carrying the ATM D1853N GA/AA genotypes had more than triple the risk of developing pancreatic cancer. Similarly, compared to non-diabetics with the LIG4 CC genotype, diabetics with the LIG4 CT/TT genotype had more than double the risk of developing the disease.

Li noted that the ultimate goal of this research is to identify high-risk individuals for closer scrutiny and follow up.

"We know that people with diabetes have a higher risk of developing pancreatic cancer, but we don't know who will actually develop the disease and who will not," Li said. "The same is true for smokers. But we can't do CT scans on every diabetic or every smoker.

"We need to develop biomarkers that will enable us to do a quick genetic

test on a diabetic patient, heavy smoker or someone with a family history of pancreatic cancer," she continued. "We could then do a screening test, identify those with the highest risk, and monitor them more closely." U

nderstanding the role of variant DNA repair genes in the development and prognosis of pancreatic cancer would also give researchers more insight into their functional significance. This increased knowledge should promote the development of new therapeutic strategies to target these abnormal genes.

Source: University of Texas M. D. Anderson Cancer Center