Genetic region linked to a 5 times higher lung cancer risk

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A narrow region on chromosome 15 contains genetic variations strongly associated with familial lung cancer, says a study conducted by scientists at Washington University School of Medicine in St. Louis and other institutions in the United States and the United Kingdom.

The researchers found a more than five times higher risk of lung cancer for people who have both a family history of the disease and these genetic variations. The risk was not affected by whether the study participants smoked or didn't smoke.

Published in the Sept. 13 issue of the *Journal of the National Cancer Institute*, this study is the fourth since April 2008 to implicate this genetic region in the development of lung cancer, and it strengthens the possibility that testing for variations in this region could become a valuable way to warn individuals of their higher risk.

"Many smokers don't get lung cancer, which suggests there is a genetic difference in smokers who do get the disease," says senior author Ming You, M.D., Ph.D., a researcher in cancer chemoprevention at the Siteman Cancer Center at Washington University School of Medicine and Barnes-Jewish Hospital. "We also know that some families have a high incidence of lung cancer. If we can identify the genetic factors linked to lung cancer in such people before they get the disease, we can take steps to help prevent it. This genetic region might be part of the answer."

Lung cancer, the leading cancer killer in the United States, will likely cause 162,000 deaths in 2008 in men and women combined, according to projections. The National Cancer Institute indicates that cigarette smoking is linked to 87 percent of these deaths.

Among research groups studying lung cancer susceptibility, many other genetic markers of increased risk have been identified, but the area identified in this study on chromosome 15 is the only genetic region that is consistent across many studies, You says.

The three other recent studies that identified these specific genetic variations focused on sporadic lung cancer, but the current study established a strong risk factor in this chromosomal region for the kind of lung cancer that is inherited. Sporadic lung cancer occurs in individuals without a family history of lung cancer, while familial lung cancer, as defined for this study, is lung cancer that occurs in three or more direct blood relatives.

The three recent studies on sporadic lung cancer cited an approximately 30 percent greater risk for individuals with specific genetic variations in this region of chromosome 15, a much lower risk than found in the current study, You notes.

One of these studies indicated that smoking increases the risk when people have the genetic variations on chromosome 15, but two of the studies indicated that smoking adds no increased risk in such people. The increase in risk identified in the current study also was not dependent on whether a person smoked.

"If these genetic variations are associated with a five-fold increased risk, regardless of whether you smoke, that's very important information," says You, professor of surgery at the School of Medicine. "It would suggest that specific genes in this region and smoking are independent

risk factors for lung cancer, and together they might cause an even greater increase in lung cancer risk."

The researchers looked at 194 people with familial lung cancer and compared their genetic profiles to 219 people over age 60 with no history of lung cancer. To make their study population as uniform as possible, only Caucasian subjects were included. DNA samples from blood or cheek swabs from each participant were screened for more than 300,000 known human genetic variations, or SNPs (pronounced "snips," these are points on chromosomes where people's DNA commonly differs by just one unit, or nucleotide).

The research group found several genetic variants, or SNPs, with a strong association to familial lung cancer on chromosomes 1, 3, 6, 9, 12 and 20, but a cluster of SNPs on the long arm of chromosome 15 had the strongest link to the disease. These genetic variants were found much more often in the study subjects with lung cancer. The statistical analysis of the data suggests that people with a family history of lung cancer and the variants on both copies of chromosome 15 have a 5.7- to 7.2-fold higher risk for developing lung cancer compared to the control group.

The chromosomal region that contains the high-risk-associated variations is the site of several known genes, including three that code for proteins implicated in nicotine addiction. That connection ties the genes to lung cancer associated with smoking, but some evidence also exists that the genes are directly involved in lung cancer development.

"These genes play roles in cellular proliferation and cell death," You says. "And they are active in lung cancer tumors. More research will be needed to fully delineate the part they play in lung cancer and whether they will be good targets for cancer therapies in the future."

Source: Washington University School of Medicine