

Researchers find common gene disorder doubles risk of lung cancer, even among nonsmokers

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Mayo Clinic researchers have found that carrying a common genetic disorder doubles the risk of developing lung cancer in smokers and nonsmokers. The study is published in the May 26 issue of the *Archives of Internal Medicine*, a journal published by the American Medical Association.

Researchers found that the genetic disorder, alpha-1 antitrypsin deficiency (alpha1ATD), could explain up to about 12 percent of lung cancer patients in this study and likely represents the same widespread risk in the general population. "This is a seriously underdiagnosed disorder and suggests that people who have lung cancer and chronic obstructive pulmonary diseases (COPD) in their families should be screened for these gene carriers," says Ping Yang, M.D., Ph.D., a Mayo Clinic epidemiologist and lead investigator on the study.

The current standard diagnostic test measures protein produced by the gene. Because of the cost and limited availability of the test, it's not suitable for general screenings. A less expensive DNA-based gene panel test is being developed.

The World Health Organization estimates that at least 10 million Americans and 120 million people worldwide are alpha1ATD carriers. According to Dr. Yang, this study shows that the disorder "is among the highest for major gene effects on the risk of a common cancer."

A normal alpha1AT gene produces a protein that stops enzymes from breaking down elastin, which keeps lung tissue elastic for normal function. Carriers of alpha1ATD commonly develop emphysema and/or chronic obstructive pulmonary disease (COPD). Prior to this study, the connection between alpha1ATD, COPD and lung cancer risk had not been established.

"It has been suspected that alpha1ATD increased susceptibility to lung cancer," says Dr. Yang, "but this is the first solid evidence that supports and quantifies this risk.

"Importantly, our results support the hypothesis that the excess risk of lung cancer among patients with COPD may be a result of lung tissue damage from emphysema, or chronic infection or inflammation of the lungs, or both," she says.

Individuals who are alpha1ATD carriers should have lung function checked on a routine basis and should avoid potential lung carcinogens. "We found people who carry these genes are more vulnerable to carcinogen-containing tobacco smoke, even secondhand smoke, than noncarriers," says Dr. Yang.

In this study, a team of 12 researchers looked at three different groups: 1,443 patients with lung cancer treated at Mayo Clinic from 1997 to 2003; a control group of 797 residents in the community; and a second control group of 902 siblings of the lung cancer patients.

They found that:

- The alpha1ATD carrier rate among 1,443 genotyped patients with lung cancer was 13.4 percent, compared to 7.8 percent among unrelated control participants.

- All alpha1ATD gene carriers were at a similarly greater risk of

developing lung cancer, regardless of smoking status. Those who had never smoked were at a 2.2-fold higher risk; light smokers had a twofold greater risk; and moderate to heavy smokers had a 2.3-fold increased risk. Although there's no absolute definition, less than 20 pack-years of smoking cigarettes is defined as light; more than 40 pack-years as heavy. A pack-year is the number of packs of cigarettes smoked per day multiplied by the number of years the person has smoked.

-- A history of COPD increased lung cancer risk significantly for light, moderate and heavy smokers, but affected those who had never smoked the most; an almost sixfold increased risk.

-- Increased lung cancer risk among alpha1ATD carriers is independent of a family history of lung or other cancers.

The estimated attributable risk for alpha1ATD carriers in this study among those who never smoked and among heavy smokers was 11 percent to 12 percent, suggesting that the genetic disorder might explain a significant proportion of lung cancer in the general population. The majority of study participants were of European descent, the population in which this genetic disorder is common.

Although the study helps explain why people who have never smoked can develop lung cancer, it doesn't mean that people who don't have the gene won't develop lung cancer, says Dr. Yang. "Smoking remains the overwhelming risk factor for lung cancer development."

Source: Mayo Clinic

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