Gene combination increases risk of lung cancer, particularly in light smokers, study finds

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Smokers with variations in two specific genes have a greater risk of smoking more cigarettes, becoming more dependent on nicotine and developing lung cancer, a new study from the Centre for Addiction and Mental Health (CAMH) shows.

The cancer risk from these two genes appears to be even higher in smokers who consume 20 or fewer cigarettes a day, according to the study published in the September issue of the Journal of the National Cancer Institute.

CAMH Scientist Dr. Rachel Tyndale and her team studied two genes: the nicotine metabolic gene (CYP2A6) and the nicotinic gene cluster (CHRNA5-A3-B3). These genes have been independently linked to smoking behaviours and lung cancer.

The new CAMH study looked at the effect of combined risks of both genes, possible gene interactions and the relative contribution of each gene on the number of cigarettes smoked, nicotine dependence and lung cancer risk in smokers.

"We found that the nicotine metabolic gene appears to have a larger influence on how many cigarettes people smoke each day, while the nicotinic gene cluster has a larger impact on the risk of lung cancer," said Dr. Tyndale. "The combined effect of having both high-risk gene

variations more than doubled the odds of developing lung cancer."

The CAMH study included 417 lung cancer patients and a comparison group of 443 individuals with no cancer – all current or former smokers. Each individual was classified as having a low, intermediate or high risk of heavier cigarette smoking or developing cancer, depending on which combination of gene variants they had. The genetic profiles of study participants were linked to reports of cigarette smoking, a standard test of nicotine dependence, and lung cancer presence.

The genetic risk of lung cancer due to these two genes was highest among lighter smokers with both high-risk gene variations, compared to those with one or none of the high-risk gene variations.

"While heavier smoking increases the overall risk for lung cancer (as well as other health problems), our study looked specifically at the effects of these two genes on cancer risk, said Dr. Tyndale, who is also head of CAMH's Pharmacogenetics Lab. "We found the genetic risk from these two genes made a larger contribution among lighter smokers."

This finding is significant because most people tend to smoke less than they used to – in Ontario, adult smokers use an average of 13 cigarettes per day, according to the 2009 CAMH Monitor. Lighter smokers tend to perceive their risk as being lower, but if they have high-risk variants of these two genes, the genetic risk for lung cancer is high.

The percentage of individuals with these two genetic variations depends on ethnic background. Together, these variations influence an individual's response to nicotine and nitrosamines – a substance in tobacco smoke that is carcinogenic to the lungs. Dr. Tyndale's previous research on the nicotine metabolic gene has shown that people who are "fast metabolizers" break nicotine down more quickly. They have a

harder time quitting and do not respond as well to nicotine replacement therapy as "slow metabolizers."

"This study indicates a significant risk for lung cancer is related to these two genes, and also suggests ways to intervene to reduce the risks," said Dr. Tyndale. "For instance, we are conducting a clinical trial to optimize cessation treatments based on genetic profiles, and fast metabolizers could be treated by using approaches that make them slow metabolizers."

Tobacco use is the primary cause of preventable disease and death in Canada and the USA. Smoking is the main cause of lung cancer, and also increases the risk of cancers of the colon, mouth, throat, pancreas, bladder and cervix.

Provided by Centre for Addiction and Mental Health