Mutations in Lung Cells Linked to Pack-Years of Smoking

People who never smoked were less likely to have cell mutations linked to lung cancer.

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People who smoke accumulate more mutations in their lung cells compared with those who never smoked, which could help explain their higher risk for lung cancer, according to findings published in the journal Nature Genetics.

Tobacco smoking is the leading cause of lung cancer, yet only a minority of smokers develop the malignancy. Lung cancer risk in smokers is known to be linked to their cumulative history of smoking. What is unknown is whether this is due to mutations accumulating at a higher rate in smokers' lung cells.

Jan Vijg, PhD, of Albert Einstein College of Medicine in New York City, and colleagues used a new genome sequencing technique to better understand the underlying genetics of smoking risk.

"This may prove to be an important step toward the prevention and early detection of lung cancer risk and away from the current herculean efforts needed to battle late-stage disease, where the majority of health expenditures and misery occur," study coauthor Simon Spivack, MD, MPH, said in a press release.

The researchers sequenced cells lining the lungs from 14 people between ages 11 and 86 who had never smoked in their lives. They also examined similar lung cells from 19 smokers between ages 44 and 81 who had a smoking history of at most 116 pack-years. A pack-year is the equivalent of smoking one pack containing 20 cigarettes every day for a year. The cells were collected from patients who were undergoing bronchoscopy for diagnostic tests unrelated to cancer.

Vijg's team found that people who had never smoked possessed a variety of lung cell mutations, including single-nucleotide substitutions, small insertions and deletions, with the frequency increasing with age. But the frequency of mutations was significantly higher in those who smoked.

"This experimentally confirms that smoking increases lung cancer risk by increasing the frequency of mutations, as previously hypothesized," Spivack said. "This is likely one reason why so few nonsmokers get lung cancer, while 10% to 20% of lifelong smokers do."

Moreover, lung cell mutations increased linearly with the number of pack-years. But after a smoking history of 23 pack-years, mutations stopped accumulating.

“The heaviest smokers did not have the highest mutation burden,” Spivack continued. “This leveling off of mutations could stem from these people having very proficient systems for repairing DNA damage or detoxifying cigarette smoke.”

Added Vijg, “We now wish to develop new assays that can measure someone’s capacity for DNA repair or detoxification, which could offer a new way to assess one’s risk for lung cancer.”

Click here to read the study abstract in the journal Nature Genetics.

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