Lung tumors in never-smokers show greater genomic instability than those in smokers

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Lung adenocarcinomas in people who have never smoked show greater genome instability than those in smokers, supporting the theory that lung cancer in never smokers arises through different pathways, according to research presented at the 14th World Conference on Lung Cancer in Amsterdam, hosted by the International Association for the Study of Lung Cancer (IASLC).

"We identified several genomic regions that were differentially altered in the lung tumor genomes of smokers and never smokers," said principal investigator Kelsie Thu, a researcher at the BC Cancer Agency Research Centre in Vancouver, Canada. "We also found that a greater fraction of lung tumor DNA harbored genetic alterations in never smokers compared to smokers. The discovery that there are different patterns of genetic alterations in smokers and never smokers suggests that lung cancers in these cohorts are likely distinct diseases driven by different molecular mechanisms, and thus, may require different treatments."

Up to 25% of lung cancer cases worldwide occur in people who have never smoked, and never smokers with lung cancer typically exhibit traits different from those of smokers. They are more often women, Asian, have a higher incidence of epidermal growth factor receptor (EGFR) mutations, better responses to EGFR-targeting drugs and are more commonly diagnosed with adenocarcinoma.

"There are a few known differences between lung cancers in smokers

and never smokers. However, the differences discovered thus far are clinical features or genetic alterations at only a few specific genes," Thu said. "For our study, we wanted to use an unbiased, whole-genome approach that would allow us to investigate all of the genes in the genome simultaneously. This enables us to identify genome-wide patterns of genetic alterations in lung tumors from smokers and never smokers. Our study was a comparative study, meaning that we compared the lung tumor genomes from smokers to those from never smokers to identify genetic (DNA level) alterations specific to one group or the other. The genetic alterations specific to the never smoker group may have important roles in driving the development of lung cancer in never smokers."

In the study, researchers extracted DNA from lung adenocarcinomas and matched non-malignant tissues for 30 never smokers, 14 former smokers and 39 current smokers. The DNA was assessed for EGFR and KRAS mutations. Copy number profiles were generated for each tumor using matched non-malignant lung tissue as a baseline for the identification of somatic copy number alterations. Two independent, publicly available datasets composed of lung adenocarcinomas from never smokers and smokers were used as validation datasets.

On average, never smokers' lung tumors showed higher frequencies of copy number alterations and greater proportions of altered genomes compared with those of smokers. This difference was more pronounced when former smokers were excluded and never smokers were compared with current smokers only.

Provided by International Association for the Study of Lung Cancer

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