Most Lung Cancer Patients Who Never Smoked Have Targetable Mutations

Targeted therapies are available for eight tumor mutations, highlighting the importance of genomic testing.

October 29, 2021 By Liz Highleyman

Most never smokers who develop lung cancer have tumor mutations that may make them eligible for targeted therapies, according to a recent study published in the Journal of Clinical Oncology. This finding underscores the importance of tumor genomic testing to help guide treatment.

Lung cancer is the second most common type of cancer in the United States (after breast cancer among women and prostate cancer among men), and it is by far the leading cause of cancer death. Smoking is the leading risk factor for lung cancer, but at least 10% to 20% of people who develop lung cancer never smoked. Most never smokers develop non-small-cell lung cancer; small-cell lung cancer is very rare among people who never smoked.

Lung cancer in never smokers appears to be a distinct disease from smoking-related cancer. One difference is that it occurs more often among women and younger people. Another is that it is more likely to be treatable with precision medicine. While lung tumors in smokers have more mutations overall, tumors in never smokers are more likely to have so-called driver mutations that spur uncontrolled cell growth.

“There appears to be something unique about lung cancer in people who have never smoked,” Ramaswamy Govindan, MD, of Siteman Cancer Center and Washington University School of Medicine in St. Louis, said in a press release. “About 60% of these tumors are found in females and 40% in males. Cancer in general is more common among men, but lung cancer in never smokers, for some unexplained reasons, is more common among women.”

Govindan and his team performed whole-exome or RNA sequencing on 157 adenocarcinoma lung tumor samples from people with no history of smoking to identify clinically actionable genetic alterations. They compared these results with data from 76 tumor samples from never smokers and 299 samples from smokers sequenced by the Cancer Genome Atlas and the National Cancer Institute’s Clinical Proteomic Tumor Analysis Consortium.

The researchers found that 78% to 92% of tumors from never smokers had potentially treatable driver mutations, compared with 50% of tumors from smokers. A subset of never-smoker samples

(5.9%) showed mutation signatures that were more similar to those of smokers, suggesting exposure to secondhand smoke.

“We found that the vast majority of these patients have genetic alterations that physicians can treat today with drugs already approved for use,” Govindan said. “Our study highlights the need to obtain high-quality tumor biopsies for clinical genomic testing in these patients so we can identify the best targeted therapies for their individual tumors.”

There are now approved medications that target ALK, BRAF, EGFR, KRAS, MET, NTRK, RET and ROS1 tumor mutations in people with lung cancer.

The researchers also found that smaller and similar proportions of nonsmokers and smokers (6.4% and 6.9%) had germline, or inherited, mutations in DNA repair genes, which are known to predispose people to develop cancer. But, Govindan noted, “It is possible additional genes are involved with predispositions to cancers [in never smokers] and we just don’t know what those are yet.”

While several targetable mutations are more common in never smokers, current and former smokers have some advantages too. A recently approved drug targets KRAS mutations, which are more common among smokers. People who smoke are also more likely to benefit from checkpoint inhibitor immunotherapy because their tumors have more mutations overall, making it easier for the immune system to recognize them as abnormal. Govindan’s team found that tumors from never smokers were less likely to express immune checkpoint proteins (such as PD-L1) and less likely to contain cancer-fighting immune cells.

The study also raises the question of whether lung cancer screening, now recommended for current and former heavy smokers, may also be appropriate for never smokers too.

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