RUSSELL COBB

AETIOLOGY

Crucial clues

Studies in never-smokers have revealed key lung-cancer mutations — but the cause of the disease is still a mystery.

BY SARAH DEWEERDT

The lung-cancer patients that thoracic oncologist Sébastien Couraud remembers most are those who have never smoked cigarettes. He recalls one woman who tried for years to get her husband to stop his heavy habit, but in the end it was her, not him, who developed lung cancer — perhaps from breathing second-hand smoke. Another patient, the wife of a smoker, developed lung cancer long after her husband died of the disease. Couraud also remembers a group of colleagues who had been exposed to the same workplace carcinogen and who attended chemotherapy treatments together — until one day one of them didn't. "It's these patients you keep in your mind," says Couraud, who works at Hospices Civils de Lyon in France.

About one quarter of lung-cancer cases worldwide occur in people who have smoked fewer than 100 cigarettes in their life. In Europe and the United States, people who have never smoked account for 10–15% of lung cancers. In southeast Asia, half of all the women who develop lung cancer have never smoked. In fact, if lung cancer in never-smokers were considered a distinct disease, it would be the seventh leading cancer killer worldwide[1] (see 'Killing without smoke).

It makes sense to consider lung cancer in never-smokers separately. "It is almost like a different disease," says Joan Schiller, a lung-cancer specialist at the University of Texas Southwestern Medical Center in Dallas. Lung cancer in people who have never smoked is almost always a subtype of non-small-cell lung cancer called adenocarcinoma. By contrast, smokers get not only adenocarcinoma but also squamous cell carcinoma and small-cell lung cancer. Tumours in never-smokers tend to be less aggressive than in smokers, although they are frequently diagnosed at a more advanced stage because never-smokers, and their doctors, regard lung cancer as an exceedingly unlikely prospect and so often miss the early signs.

Tumours in never-smokers also tend to carry a distinctive set of genetic changes called driver mutations that are involved in turning cells malignant. Classifying patients according to their history of smoking has helped to understand lung cancer's gene mutations over the past decade, but researchers have found that this is not the best strategy for treating individual patients. That is because the most effective treatment often depends on the molecular characteristics of the tumour, not the characteristics of the patient. "Smoking status is sort of a surrogate for that, but it's an imperfect surrogate," says thoracic oncologist Charles Rudin at Memorial Sloan Kettering Cancer Center in New York City. So the task now is not only to continue to work out the patterns and consequences of tumour mutations, but also to delve into some of the mysterious aspects of lung cancer in never-smokers — especially the genetic and environmental causes and how to mitigate them.

GENETIC VARIATIONS

Studying the mechanisms of lung cancer is easier in never-smokers because they have not been exposed to the onslaught of DNA-altering chemicals in cigarette smoke. This has helped researchers to sort out which changes in a lung-cancer cell are driver mutations and which are passenger mutations — those that are simply along for the ride. "The lung cancers that occur in never-smokers are genetically simpler," says Rudin. "They have fewer mutations, but they may have the key mutations that are really important drivers."

The first clues that studying lung cancer in never-smokers might be particularly helpful in understanding the mechanisms of the disease emerged in the early 2000s. Clinical trials analysing a class of cancer medication called small-molecule tyrosine kinase inhibitors, which targets a family of proteins that

are mutated in many types of cancer, showed that never-smokers, individuals with adenocarcinoma, women and people with east Asian ancestry were more likely to respond well to the drugs than people with a history of smoking[2].

In 2004, three independent groups published studies that uncovered the molecular basis behind these observations. This class of tyrosine kinase inhibitors is effective against lung cancers that carry mutations in the epidermal growth factor receptor (*EGFR*) gene[3-5]. These mutations are more common in lung cancers that occur in the groups that responded well to the drugs in clinical trials. *EGFR* mutations are seen in 28% of never-smokers with lung cancer in the United States and in 68% of Asian people. By contrast, such mutations occur in only 5% of current smokers and in 11% of former smokers with lung cancer in the United States.

Since then, researchers have identified additional lung-cancer driver mutations that are more common in never-smokers than smokers[1]. "Many of the discovery efforts have been focused on never-smokers as a way of finding these driver mutations," says Geoffrey Oxnard, a thoracic oncologist at Dana-Farber Cancer Institute in Boston, Massachusetts. Researchers have identified therapies that target some of these tumour mutations, and the search is on for others.

FATAL RESISTANCE

The relationship between the types of lung-cancer mutations and whether someone smokes are not absolute. For example, although *EGFR* mutations are more common in never-smokers, one-third of lung cancers with *EGFR* mutations occur in smokers — therefore, knowledge of driver mutations and corresponding treatments gleaned from studies of never-smokers may benefit smokers with the disease. Testing for mutations in genes such as *EGFR* is gaining popularity as a tool for lung-cancer management in smokers and never-smokers.

Half to three-quarters of lung-cancer patients who have never smoked carry at least one mutation that will respond to targeted therapies such as tyrosine kinase inhibitors. This might seem encouraging news for never-smokers with lung cancer — but only to a point. "Their cancer is more treatable than cancer in smokers and they live longer as a result of having these targetable mutations, but we're not curing them," says Barbara Gitlitz, a lung-cancer specialist at the University of Southern California in Los Angeles. "It's still an extremely deadly disease." In part, this is because of the lower lung scrutiny that never-smokers get. "We're diagnosing these people at stages where they're not curable," Gitlitz explains.

But there is more negative news: the targeted therapies that benefit many never-smokers with lung cancer eventually stop working because the tumours develop drug resistance. Tackling drug resistance, suggests Rudin, will require better versions of targeted therapies — or better ways to use them (see page S8).

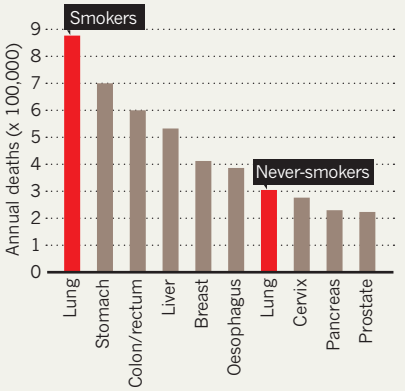
TROUBLESOME RISKS

Perhaps an even bigger mystery is what causes lung cancer in never-smokers, and how risk factors produce different driver mutations in lung tumours. "Lung cancer in never-smokers is a very interesting tool to focus on risk factors for lung cancer other than smoking," explains Couraud, who is working on a comprehensive study of tumour mutations among 384 never-smokers in France who have lung cancer.

Some risk factors are well known — breathing in second-hand cigarette smoke, for example, which is responsible for 20–50% of lung-cancer deaths in never-smokers in the United States. Studies have shown[1] that the more second-hand smoke a person is exposed to, the less likely he or she is to have *EGFR*-mutant lung cancer — in other words, breathing in a lot of second-hand smoke is likely to cause the same form of lung cancer as that seen in smokers. Curiously, however, data from the French cohort of never-smokers does not show this pattern — in fact, Couraud reports, those data show no relationship between second-hand smoke exposure and any driver mutation.

KILLING WITHOUT SMOKE

If considered as a separate disease, lung cancer in people who have never smoked would rank seventh in global cancer mortality.



SOURCE: REF. 2.

And tobacco smoke is not the whole story. In east Asia, never-smokers who develop lung cancer are disproportionately women, in part because of exposure to coal smoke in unventilated homes (see page S16). And in 2013, the International Agency for Research on Cancer confirmed outdoor air pollution as carcinogenic (see page S14). As the number of people smoking cigarettes continues to decline throughout the world, risk factors for lung cancer will change. "Lung cancer is not going to entirely go away because we convince people to stop smoking," Oxnard says.

Before cigarette smoking became widespread, lung cancer was rare, leading to just 0.7% of cancer deaths in the United States in 1914, versus an estimated 27% in 2014. Respiratory cancers — a category that includes not only lung cancer but also mesothelioma — are the most common cancers acquired as a result of exposures on the job to carcinogens such as asbestos or silica, for example.

> ***"Lung cancer is not going to entirely go away because we convince people to stop smoking."***

Connecting what is known about lung-cancer risk factors to individual patients remains difficult. "We don't have a clear understanding of why the majority of never-smokers develop lung cancer," Rudin says.

Some lung-cancer risk probably also comes from inherited genetic factors. Until five years ago, most studies investigating familial lung cancer have focused on families who smoked. As a result, there has been no good way to distinguish whether it is exposure to second-hand smoke or genes that have caused lung cancer. Researchers are just beginning to puzzle out the inherited factors that increase lung-cancer risk in the absence of exposure to tobacco smoke. A few studies have identified individuals with an inherited mutation in *EGFR*. This mutation, working through a mechanism that is not yet understood, seems to produce resistance to targeted therapies and also increase susceptibility to developing lung cancer[6,7].

The population of people who have never smoked but have lung cancer has become a model for studying other subgroups of people with the disease. Oxnard and Gitlitz, for example, are co-leading a study of genomic changes in patients who were diagnosed with lung cancer before the age of 40. Lung cancer is rare in this age group, and researchers say that studying this population may help to uncover additional driver mutations and therapeutic approaches — just as studies of never-smokers have done. "We as clinicians have the responsibility to keep our eyes open for such clinical outliers," Oxnard says, "because they may provide unique insights on a more deep biological level." ■

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