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Many Lung Cancers Are Now in Nonsmokers. Scientists Want to Know Why.

The face of lung cancer — once older men with a history of smoking — has changed.



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By Nina Agrawal and Allison Jiang

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Annie Chen first noticed she was unusually short of breath in 2017, while running to catch the bus home to New Jersey from her job in Manhattan. She told her primary care doctor, thinking of her father, who died of lung cancer at 71. But her doctor told her not to worry — her father was a heavy smoker, and Ms. Chen had never smoked.

She continued to have difficulty breathing, but it wasn't until two years later that a doctor ordered an X-ray, and Ms. Chen was diagnosed with Stage 4 lung cancer. "My whole world crashed," she said. She was just 48, with an 11-year-old daughter, a husband who also had health issues and a mortgage to pay off.

"My family needs me," she recalled thinking.

Ms. Chen's case represents a confounding reality for doctors who study and treat lung cancer, the deadliest cancer in the United States. The disease's incidence and death rates have dropped over the last few decades, thanks largely to a decline in cigarette use, but lung cancers unrelated to smoking have persisted.

The thinking used to be that smoking was "almost the only cause of lung cancer," said Dr. Maria Teresa Landi, a senior investigator at the National Cancer Institute, which is part of the National Institutes of Health. But worldwide, roughly 10 to 25 percent of lung cancers now occur in people who have never smoked. Among certain groups of Asian and Asian American women, that share is estimated to be 50 percent or more.

These cancers are increasingly drawing the attention of researchers like Dr. Landi, who are studying the role that environmental exposures, genetic mutations or other risk factors might play. They have already found some early hints, including a clear link to air pollution.

Physicians are also testing new approaches to better detect lung cancer in nonsmokers, and trying to understand why it is more prevalent in people of Asian ancestry and women and why it is being seen among younger people.

"We all still think about the Marlboro man as what lung cancer looks like," said Dr. Heather Wakelee, chief of oncology at the Stanford University School of Medicine. In many cases, though, that's no longer true. "We're just baffled as to why," she said.

Looking for Clues

Many lung cancers in nonsmokers have no known cause and are discovered only by chance.

That was the case for Sandra Liu, 59, who lives in New Jersey. Ms. Liu was diagnosed this year with adenocarcinoma, the most common type of lung cancer among nonsmokers. Doctors found the mass after she had a full-body checkup

during a visit to China — a process popular with some Chinese expatriates visiting the country that includes a chest scan.

"I would have never thought to go for a CT," she said, noting she had no major symptoms and never smoked.

Scientists are starting to see that the biology of cancer in nonsmokers like Ms. Liu differs from cancers seen in people with a smoking history — and may require different strategies for prevention and detection.

One large study, called "Sherlock Lung" and led by Dr. Landi and colleagues at the University of California, San Diego, is looking at the mutational signatures, or patterns of mutations across the cancer genomes, of 871 nonsmokers with lung cancer from around the world.

Their latest findings, published in Nature this month, showed that certain mutations, or changes to DNA, were much more common in people who lived in areas with high amounts of air pollution — for example, Hong Kong, Taiwan and Uzbekistan. More pollution was linked to more mutations. (The study did not include data from India, considered to have the highest levels of outdoor pollution.)



Leah Phillips, who never smoked but was diagnosed with lung cancer at age 43, at her home in Pewee Valley, Ky. Jon Cherry for The New York Times

The researchers didn't just find that pollution may directly damage DNA. They also saw signs that pollution causes cells to divide more rapidly, which further increases the likelihood of cancer.

Studies have also shown that people who don't smoke but have a family history of lung cancer, such as Ms. Chen and Ms. Liu — both of Ms. Liu's grandfathers had the disease — are at increased risk. This could be because of shared genetics, a common environment or both, said Dr. Jae Kim, chief of thoracic surgery at City of Hope in Duarte, Calif.

And scientists know that nonsmokers with lung cancer are more likely than people who smoked to have certain kinds of "driver" mutations, changes to the genome that can cause cancer and drive its spread, Dr. Kim said. In contrast, people who

smoke tend to accumulate many mutations over time that can eventually lead to cancer. This difference in the type of mutations may be one reason lung cancer among people under 50 is more prevalent among nonsmokers than smokers.

There are probably other factors, too, including exposure to radon, asbestos and possibly aristolochic acid, a compound once common in traditional Chinese medicine. Dr. Landi's research linked the compound to lung cancer mutations among Taiwanese patients. (Taiwan banned products containing it in 2003.)

Studies from Asia have also suggested secondhand smoke, fumes from cooking oils and a history of tuberculosis or other lung disease as possible culprits. However, these potential contributors are less common in the United States, where Asian American women who don't smoke are still nearly twice as likely as other women to be diagnosed with the disease, said Scarlett Gomez, a professor of epidemiology and biostatistics at the University of California, San Francisco.

To understand what's driving the disparity in the United States, Dr. Gomez, Dr. Wakelee and colleagues at other Northern California institutions are now studying the relationships among genes, environmental contaminants and lung cancer in Asian American nonsmoking women.

"Ultimately, we want to be able to come up with actionable risk factors, just like we do for breast cancer and colorectal cancer," Dr. Gomez said.



When Ms. Chen was diagnosed, her cancer was already advanced. It has since spread, and she is now receiving targeted therapy. Shuran Huang for The New York Times

Revisiting Screening Guidance

Studies like Dr. Gomez's may help address the question of who should be screened for lung cancer. In the United States, routine screening is recommended only for people ages 50 to 80 who smoked at least the equivalent of one pack of cigarettes per day for 20 years.

Because of that, lung cancer in nonsmokers is often not caught until it's advanced, said Dr. Elaine Shum, an oncologist at NYU Langone Health. That can have devastating consequences for patients like Ms. Chen, who is still undergoing treatment after a third metastasis of her cancer.

Dr. Shum and others are now exploring whether screening should be expanded. In Taiwan, a nationwide trial tested the effectiveness of CT scans in people ages 55 to 75 who never smoked but had one other risk factor. Doctors detected cancer in 2.6 percent of patients — enough that Taiwan now offers routine screening for nonsmokers with a family history of lung cancer.

Dr. Shum and colleagues recently ran a similar pilot study among women of Asian ancestry who were 40 to 74 years old and had never smoked. In preliminary results from about 200 patients, they found invasive cancer at comparable rates to the Taiwan study. Data from the full set of 1,000 patients who were screened are forthcoming.

Still, it would take far more research to determine who in the United States, if anyone, would benefit from broader screening and whether it could meaningfully reduce lung cancer deaths. Screening more people can lead to more false positives, which may mean patients get biopsies and other interventions they don't need. And some cancers doctors find are so slow-growing that they may never cause harm, said Dr. Natalie Lui, a thoracic surgeon at the Stanford University School of Medicine.

"What if we're taking out all these tiny lung cancers that would not have been lifethreatening?" Dr. Lui said.

On the flip side, she thinks of the patients she regularly sees who have aggressive or advanced lung cancers but never smoked. "If there was screening, we could save their life," Dr. Lui said.

The good news is that survival with advanced cancers has improved with newer therapies that effectively keep the disease at bay for years in many patients.



Ms. Phillips has five ribbon tattoos, one for each year she has survived lung cancer. Jon Cherry for The New York Times

Such treatments have benefited Leah Phillips, of Pewee Valley, Ky. Doctors first mistakenly diagnosed her with asthma and then anxiety. Later, they said she had pneumonia. When an oncologist finally told her in 2019 that she had metastatic lung cancer, he gave her six to 12 months to live. "Go home and get your affairs in order," Ms. Phillips remembered him saying. She was 43, and her children were 9, 13 and 14.

"I'm not leaving my kids," Ms. Phillips thought. After getting a second opinion, she started taking a drug that targets one of the driver mutations in lung cancer. She prayed to make it to her eldest child's graduation. "I cried through his entire senior year," she said.

In June, she watched her middle child graduate. "Now I need to make it to the next one," she said.

Ms. Phillips, who co-founded a nonprofit called the Young Lung Cancer Initiative to increase awareness of the condition, said people look at her askance when she tells them she has lung cancer but never smoked. They didn't know it was possible.

It's not your grandfather's lung cancer anymore, she tells them.

Nina Agrawal is a Times health reporter.