



Carcinogenic emissions from burning smoky coal in poorly ventilated homes present grave health risks.

tease out the molecular signature of its mutations and flag genetic variants that make some people unusually prone to developing lung cancer.

INHERITANCE MATTERS

Lung cancer kills about 1.6 million people around the world every year, and is responsible for the largest number of cancer deaths worldwide. In the past decade, researchers have recognized that as many as 25% of lung cancers occur in people who have never smoked. Studying the issue closer, they've come to recognize that lung cancer in smokers has a distinct genetic signature from the disease seen in smokers (see page S12).

The incidence of lung cancer among non-smoking women also varies with geographical location, epidemiological studies have shown. It has been estimated that non-smoking women in east Asia are four times as likely to develop lung cancer than women in Europe or Africa (see 'Women's risk').

Seow's own research has focused mainly on lung cancer in urban Singaporeans. She has found that since the 1960s, cancer rates among Chinese immigrants (including smokers and non-smokers) are higher than among Malays and Indians, the other major ethnic groups in Singapore.

But the reported increase in incidence of lung cancer is not exclusive to the Chinese. In the past few years, several studies¹ have shown that people with Japanese and Korean ancestry also carry heritable genetic variants that put them at risk. To further study this phenomenon and consolidate data from across the region, cancer epidemiologists Qing Lan and Nathan Rothman at the United States National Cancer Institute (NCI) established the Female Lung Cancer Consortium in Asia in 2009.

Just five years later, the consortium has borne fruit, with implications that extend well beyond the tiny island-nation of Singapore. In 2012, Lan, Rothman, Seow and a dozen other researchers published the results of a genetic study involving more than 14,000 women — 6,600 of whom had never smoked but had lung cancer, and 7,500 controls — from 6 countries in east Asia. In an analysis known as a genome-wide association study — in which researchers look for genetic variations that occur more frequently in people with a disease — the team compared genome markers found in people with lung cancer to genome markers in the cancer-free control group. They found² three new DNA sites associated with the disease — one on chromosome 10 and two on chromosome 6 — and confirmed the relationship between three other variants previously flagged on chromosomes 3, 5 and 17.

Such a study would have been very difficult without the concentration in east Asia of non-smokers with lung cancer. "To get the numbers to look for genetic causes, conducting studies in Asia has a big advantage," says

PUBLIC HEALTH

A burning issue

An unusually high number of women from east Asia develop lung cancer. Few smoke, but that's only part of the mystery.

BY NIDHI SUBBARAMAN

Lung cancer snuck into the lives of Angela Tan (not her real name) and those she loved. When she died her family and friends were stunned. The Chinese schoolteacher who lived in Singapore was in her early 40s and had never smoked a cigarette in her life.

Tan's death seemed to challenge the prevailing assumption that lung cancer is a smoker's disease. In fact, she had plenty of company: non-smoking east Asian women have been diagnosed with the disease in high numbers. "There is a striking disconnect between smoking rates and lung cancer incidence, particularly in Chinese women," says Adeline Seow, a cancer epidemiologist from the Saw Swee Hock School of Public Health at the National University of Singapore.

Seow has another connection to this story:

she is Tan's niece. She was a medical student when her aunt died, and it left an indelible mark on her. "At the time, there was no explanation that we were aware of," she recalls. So she set out to find that explanation and answer the question: what makes east Asian women particularly susceptible to lung cancer?

Cancer researchers have called this phenomenon a natural experiment. It's a chance to study the aetiology of lung cancer that arises independently of its most notorious causative agent: tobacco smoking, says Dean Hosgood, who studies cancer and population health at the Albert Einstein College of Medicine in New York City. "As tobacco smoking is decreasing, other factors are going to become a larger proportion of lung cancer cases," he says. That shift makes investigating this group all the more valuable — and researchers are racing to identify the pathways involved in the disease,

SOURCE: REF. 6.

Neil Caporaso, a specialist in the genetics and epidemiology of lung cancer at NCI and a co-author of the study.

The evidence also allowed the researchers to rule out the influence of another gene variant, on chromosome 15, that had been a suspected player in non-smokers' lung cancer. Its absence in this large cohort confirmed other data that suggested that people with the variant at a particular location on this chromosome, known as 15.25q, are more likely to develop cancer if they smoke tobacco.

It is also clear that the genes do not act alone. Variation at two particular regions on chromosomes 10 and 6 are associated with a 30% and 15% increase in the risk of developing lung cancer, respectively. (By contrast, smoking increases risk by 2,500%.) It is likely that genes work alongside an environmental factor, perhaps something in the air, says Hosgood, who was a postdoctoral researcher with Lan and Rothman, and a co-author on the study.

FANNING THE FLAMES

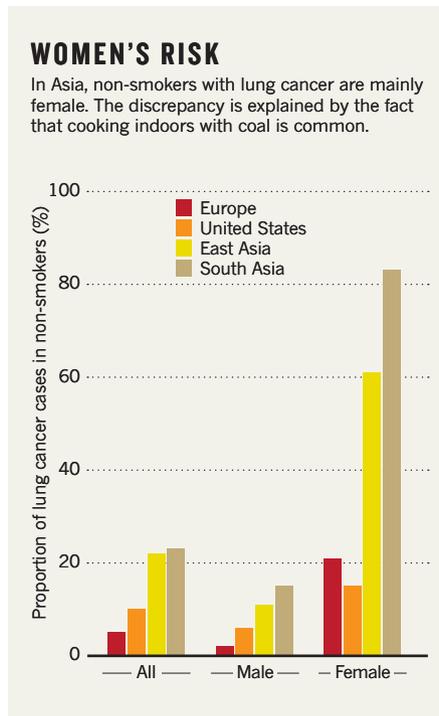
For many years, Xuanwei, a farming town in western China, had one of the highest rates of lung-cancer incidence anywhere in the world. As early as the 1970s, researchers noticed that women in the community were developing lung cancer at equal or higher rates as men, despite being less likely to smoke. In the mid-1980s, a handful of teams investigated the cause, and quickly found a suspect: coal.

Judy Mumford, a researcher with the US Environmental Protection Agency, was among the first investigators on the ground. Mumford and her colleagues explained that although women in Xuanwei rarely smoked tobacco, at home they cooked food over open fire pits that burned smoky coal³. Families also used coal to heat their houses and closed the shutters on their windows to keep the cold out, which trapped smoke and particulate matter inside. Chimneys were uncommon and many homes were poorly ventilated.

Ten years before Mumford's 1987 paper was published, Chinese authorities suspected that the mortality rate for women in Xuanwei from lung cancer was higher than anywhere else in the country. In fact, the death rate was 8 times higher than the national average and 17 times higher than the rest of the province³. But change was taking root. In 1976, alert to the unusually high death rates in Xuanwei, the Chinese government offered 10 yuan (US\$5) to families to spend on building chimneys.

Lan was a graduate student when she first travelled to Xuanwei in the 1990s. Looking for a clear link between coal and cancer, Lan investigated the effect of the change in stove

“What component of coal causes lung cancer? That’s an important area that needs to be studied.”



ventilation. She interviewed farmers who had lived in the area since 1976, and studied hospital records for the incidence of lung cancer. Her results were dramatic: in families that stopped cooking over an open fire indoors and heating their homes with smoky coal, lung cancer rates decreased by 41% in men and 46% in women⁴.

“That was a key study that really showed pretty convincingly that coal was related to lung cancer,” says Rothman. In a follow-up study, Hosgood and colleagues showed that when families switched to a portable stove that could be used outside, men reduced their risk of dying from lung cancer by 39% and women by 59%⁵. Subsequent research on mice showed that indoor smoky coal emissions can be 1,000 times more carcinogenic than cigarette smoke⁶.

In southern and eastern China, where coal use is less frequent, a different story emerged. Studies of home life in places such as Shanghai, Hong Kong and Taiwan made the case that cooking oils were to blame for higher lung cancer rates in those areas. Oils, including rapeseed, heated to high temperatures in woks for stir-frying food emit volatile carcinogens that can be inhaled.

In 2006, leaning on the overwhelming evidence presented in studies such as those published by Lan and Hosgood, the World Health Organization's International Agency for Research on Cancer formally addressed the carcinogenicity of coal and cooking oils. Nineteen scientists met in Lyon, France, and agreed that burning coal in households was carcinogenic to humans and that emissions from frying at high temperatures were probably carcinogenic to humans.

Researchers now know that repeated exposure to coal smoke in poorly ventilated areas

can double the likelihood of developing lung cancer. But there is still more to be learned. “What component of coal causes lung cancer? That’s an important area that needs to be studied,” says Lan. She has early evidence that immunoregulatory genes involved in inflammatory pathways may play a part, but says larger studies are needed to establish this link.

A DIFFERENT DISEASE

Some clinical oncologists are making the case that lung cancer in never-smokers is a distinct disease and are starting to recognize its calling card. Never-smokers' lung cancers seem to be missing some of the genetic characteristics found in smokers' tumours. Mutations of the tumour suppressor gene *TP53* are abundant in cancers of all kinds, and frequently appear in the lung cancers of smokers. Yet, never-smokers rarely carry such mutations in their own cancer tissue.

On the flip side, researchers have found that 58% of lung cancers in non-smokers carry a specific mutation in the epidermal growth factor receptor gene, *EGFR*, compared with only 13% of smokers who have the same mutation. That the *EGFR* mutation is seen more frequently in lung tumour samples from east Asians than other populations — and more often in women than men — suggests that an associated mechanism will shed light on what makes east Asian women particularly vulnerable to the disease.

Continuing research is leading to a better understanding of lung cancer. Lan and other teams who have studied Xuanwei have established the carcinogenicity of coal smoke, spurring action to minimize the use of coal cookstoves in unventilated houses. They have also found that environmental factors are only part of the story. The abundant incidence of non-smokers' lung cancer among east Asian women has given researchers a rare opportunity to tease out the genetic variants that have a role in the disease. It is increasingly clear, says Seow, that the disease behaves differently in east Asian women.

For her own part, Seow has dual motivations for studying this group. One is from a public health perspective: understanding the dense web of risk factors will offer opportunities for lung cancer prevention. And her aunt's death all those years ago gave “a face to the disease”, personalizing her efforts of the past two decades. Through her work, she hopes other Angela Tans can be saved. ■

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