

Lung cancer's long hibernation may be its weak spot

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Cancer can sit dormant in a person's lungs for decades, waiting to diversify and spread. The discovery sounds scary but could actually be key to reducing the disease's devastating toll, raising the possibility of early detection, screening and maybe even preventative treatment.

Lung cancer is the [leading cause of cancer deaths globally](#), and one of the [least researched](#). Since most people with lung cancer are only diagnosed after the disease has started spreading, [less than a third](#) survive for more than a year after diagnosis.

But new work on how the cancer evolves could change that picture. The research suggests that the genetic seeds of cancer can sit dormant in a person's lungs for decades, providing hope that the disease could be detected early. However, it also shows that when the cancer does develop, it has a spectacular amount of [genetic diversity](#) – essentially evolving into several diseases at once.

"If we can nip the disease in the bud and treat it before it has started travelling down different evolutionary routes we could make a real difference in helping more people survive the disease," says [Nic Jones](#), chief scientist at Cancer Research UK in London, where the work was done.

Sketching the tree

[Charles Swanton](#) and colleagues from Cancer Research UK examined the tumours of seven people with the most common form of the disease, [non-small-cell lung cancer](#). It affects both smokers and non-smokers. They sequenced the complete genomes of multiple regions in each tumour and reconstructed the evolutionary tree. They looked at which mutations are present in all cells and all regions of those cells, and which are present in just some. By comparing these, they were able to reconstruct which mutations were at the trunk of the tumour's evolutionary tree, and which evolved later, forming the branches or

leaves.

Of particular interest were two participants who were ex-smokers. Cigarette smoke causes telltale mutations in a tumour. Since the researchers knew when these two people had quit, they were able to match parts of the evolutionary tree – those when smoking-related mutations were emerging – to rough time periods in their lives. This revealed that many of the key mutations that allow the cancer to spread had developed more than 20 years before, when the people still smoked.

It's impossible to know what was actually going on in their bodies at this time – whether these mutations immediately led to the development of a ball of cancerous cells, or whether physical manifestations of cancer came only later. Either way, the findings imply that many of the genetic characteristics associated with cancer are present well before they cause any symptoms – possibly many years.

Two-faced tumours

Next, the team examined the leaves and branches of the tumour's evolutionary tree. By looking at multiple regions of each tumour, they found that some important cancer-associated mutations were present in all cells from one region, but completely undetectable in another. This makes deciding on a course of treatment difficult. For example, in one person, they found that taking a biopsy from one region of the tumour would suggest treatment with one type of chemotherapy but a biopsy from another would suggest a completely different type of drug. Treating a patient with either one alone would have allowed the other region to spread.

This diversity drives home the importance of the cancer's dormant period, says Swanton. "The vast majority of lung cancers that I see are diagnosed late, once they have developed these multiple genetic differences that make them difficult to treat," he says. "So anything you can do to diagnose them early is going to make a big difference to the outcome."

One option is screening those at high risk of lung cancer because they are current or past smokers of a certain age. [Annual lung cancer](#)

screening using CT scans to identify tumours has already been trialled in 55,000 people in the US with good results, and there are ongoing studies in Europe.

But Swanton thinks his team's work opens the door to much earlier detection via a blood test that picks up on someone's genetic predisposition. Such a test could search for smoking and other lung-associated mutations in the DNA that cells release into the blood. "There are some companies that have circulating free DNA [as this is known] down to one molecule resolution, so we're not a million miles away from a blood test."

"Clearly this would have to be proven to be clinically useful and cost-effective, but given that in the US the majority of the costs of cancer care are spent in the last two weeks of life, such early stage screening would seem to make sense", says Swanton.

It would at least offer better demarcation of those at the highest risk who could then be sent for regular CT screening, potentially reducing the number of people that receive unnecessary treatment as a result, says David Thomas from the Garvan Institute in Sydney, Australia. "The benefit of screening comes by limiting it to the population that is at the highest risk. If you can demonstrate a group that are at the highest risk of lung cancer, then your CT screening would be more effective," he says.

Immune breakdown

But what is it that triggers the cancer to develop to the point where symptoms are detectable, after lying dormant for so long? "Good question," says Swanton. At this point, it's all speculation, he says. But the cancer biologists *New Scientist* spoke to all raised the same two possibilities.

It could just be one last random mutation on top of a pile of others that finally provides the cells with all the genetic wherewithal they need to become malignant, says Thomas.

Or "it could be a general breakdown of the body's immune surveillance ability as you age", Swanton says. We know the immune system is able to clean up some mutations when it is operating normally, and one of the

tricks cancer evolves to become a killer is evading the immune system. So an ageing immune system may allow the cancer the freedom to get going.

These are certainly the first possibilities you'd want to rule out before looking for other explanations, says [Andrew Futreal](#) from the Cancer Prevention and Research Institute at the University of Texas in Austin. "And it could be a combination of the two."

If Swanton's ageing immune system theory is right, it raises the tantalising possibility of using immunotherapy to reduce the risk of developing lung cancer. The idea would be to boost the immune system before symptoms of the cancer appear and before the tumour's genetic diversity has set in in earnest. "You could give heavy smokers or ex-smokers maybe six months of an immunomodulatory compound that would release T-cells," he says, to see if that reduces the development of new lung cancers, compared to a control group.

Thomas independently had the same idea. "In principle, there may be an opportunity for chemo-prevention," he says. "If the root events were treatable then one might contemplate potentially intervening in high-risk individuals." It would be a risky strategy – tinkering with the immune systems of people yet to be diagnosed with cancer – but given lung cancer's prognosis, it may prove worth it.

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