

DNA Mutations Point to Possible Kidney Cancer Causes, Including Exposure to Certain Plants

Kidney cancer is more common in some countries than others. New data looking at genetic changes may help explain the global differences.

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By Edward Winstead

A genomic study of kidney cancer has revealed new clues about possible causes of the disease in different parts of the world.

[Kidney cancer](#) is more common in some countries than in others. But this geographic variation cannot be fully explained by known risk factors for the disease, such as tobacco smoking, high blood pressure, and obesity.

To better understand global differences in the incidence of kidney cancer, researchers have [conducted the largest survey of DNA mutations in kidney cancer to date](#). The study was designed to identify mutational signatures—characteristic patterns of DNA mutations—in cancer cells from kidney tumor samples.

In recent years, mutational signatures have been used to help understand the causes of cancers. For instance, researchers have [linked certain signatures in cancer cells to exposure to harmful substances in the environment](#), such as chemicals in tobacco smoke or ultraviolet light.

In the new study, researchers sequenced tumor and normal DNA from nearly 1,000 people with kidney cancer in 11 countries. Using computational tools, they sifted through the results to find mutational signatures in kidney tumors and analyzed the patterns according to where the participants lived.

Some of the signatures they found had been identified in earlier studies. But several had not been reported previously and could help identify unknown risk factors for kidney cancer, according to findings published May 1 in *Nature*.

The survey also revealed mutational signatures linked to *Aristolochia* plants, which are commonly found in Europe and other parts of the world. The findings suggest that exposure to chemicals

from these plants—which can cause cancer—may be far more widespread than previously thought, the researchers wrote.

“This study highlights the potential for new opportunities to use mutational signatures to gain new insights into the causes of cancer,” said study coauthor Sergey Senkin, PhD, of the International Agency for Research on Cancer.

If scientists can identify what’s causing the patterns of genetic mutations, that information might be used to inform strategies for preventing kidney cancer, Dr. Senkin added.

Using mutational signatures to solve mysteries

Genetic changes such as DNA mutations can be inherited from a parent or arise from certain environmental exposures over a person’s lifetime. Genetic changes can also arise from mistakes that occur as cells copy their DNA and divide.

Not all genetic changes, however, lead to cancer. Researchers need to distinguish DNA alterations that drive the disease from changes that do not drive the progression of cancer.

“This work is like finding needles in haystacks,” explained study coauthor Stephen Chanock, MD, who directs NCI’s Division of Cancer Epidemiology and Genetics.

Identifying mutational signatures is also a challenge. Researchers recruit large groups of individuals with cancer and conduct [genomic](#) analyses to compare cancerous tissue with healthy tissue from each person.

“Scientists can use mutational signatures in much the same way as detectives use fingerprints collected at a crime scene,” Dr. Chanock said.

“With these signatures, we can work backwards and understand events that happened in the past,” he continued. “It’s like Sherlock Holmes solving a case, but with genetics.”

Newly identified mutational signatures, new questions

For the new study, the research team collected DNA from the tumors and healthy tissues of 962 people with [clear cell renal cell carcinoma](#), the most common type of kidney cancer.

They focused on kidney cancer in part because the kidneys act as a natural filter in the body. “We thought it would be a good tissue to detect any DNA-damaging compounds that get filtered out of the blood,” Dr. Senkin said.

Tissue samples were collected from people in countries with relatively high rates of kidney cancer, such as Lithuania and the Czech Republic, as well as from countries with relatively low rates, such

as Brazil and Thailand. The DNA in those tissues was subjected to extensive genomic analysis.

One of the newly identified mutational signatures was present in tumor samples from each of the 11 countries represented. The signature correlated strongly with biological markers of reduced (or impaired) kidney function.

This finding suggests that a widespread substance that damages the kidneys may be responsible for the signature, Dr. Senkin said.

Another mutational signature of unknown cause was present in more than 70% of the tumor samples from Japanese participants but in less than 2% in those from all other countries. The finding suggests that there may be an unknown exposure prevalent in Japan, the researchers concluded.

Is exposure to aristolochic acids more common than previously thought?

And as for the mutational signatures linked to exposure to Aristolochia plants, these signatures were present in most tumor samples from Romania, Serbia, and Thailand but were rare elsewhere.

“Aristolochia plants have been a known public health hazard for years now, and the geographic distribution of their toxic effects was thought to have been fairly well studied,” said Fran Supek, PhD, of the University of Copenhagen, who co-wrote [an accompanying editorial](#). “The new research shows that the effects are more widespread than anticipated.”

The plants contain chemicals called aristolochic acids, which [can cause cancer when ingested](#). In some parts of the world, the plants have been used as part of herbal remedies for a variety of health problems.

The new research suggests that previous estimates of exposures to these chemicals may have been much too low.

In parts of Eastern Europe, for instance, the extent of signatures associated with aristolochic acid suggests that tens of millions of people could be exposed to the chemicals, the researchers wrote. They noted that sources of the exposures and the public health consequences are both “uncertain.”

Questions raised by the study

More research is needed to learn whether and how the genetic changes that make up the mutational signatures identified in the study play a role in kidney cancer, the researchers noted.

As a next step, the researchers will undertake further epidemiological studies to investigate

specific exposures. This work will include analyzing information on patients' lifestyles to see whether they may share certain environmental exposures to known cancer-causing substances, or carcinogens.

In addition to identifying the sources of the underlying mutations, future studies could document which populations are affected and how certain exposures might lead to mutations, according to the researchers.

Ultimately, such knowledge could inform efforts to prevent kidney cancer in individual countries.

"This study demonstrates that large-scale, systematic genomics studies can provide valuable insights that are relevant to understanding tumor biology and that have implications for public health," Dr. Supek said.

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<http://beta.docker.cancerhealth.com/blog/dna-mutations-point-possible-kidney-cancer-causes-including-exposure-certain-plants>