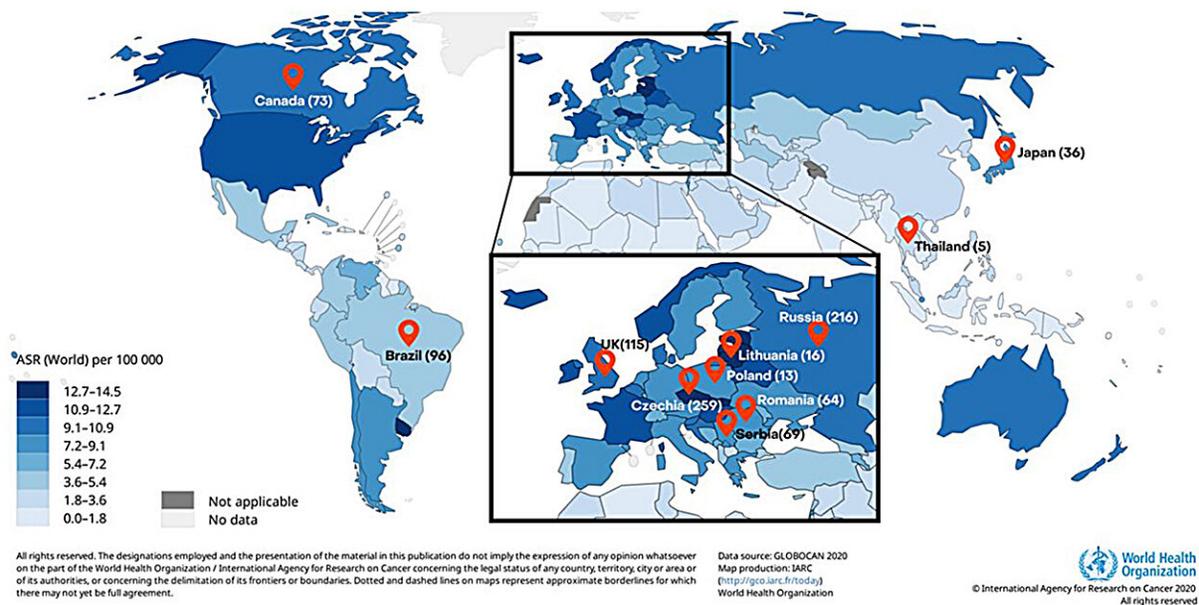


Unknown risk factor linked to high rates of kidney cancer, DNA study finds

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Eleven participating countries and estimated age-standardized incidence rates of clear cell renal cell carcinomas. Incidence of clear cell renal cell carcinomas (ccRCC), men and women combined, age-standardized incidence rates (ASR) per 100,000, data from GLOBOCAN 2020. Markers indicate countries included in this study (number of participating ccRCC patients per country). Credit: *Nature* (2024). DOI: 10.1038/s41586-024-07368-2

Researchers analyzing the DNA of people with kidney cancer worldwide have found evidence of an unknown trigger that could explain the

longstanding mystery of why some countries have a higher incidence of the disease.

In a paper [published](#) in *Nature*, scientists from the Mutographs Cancer Grand Challenges team, based at the Wellcome Sanger Institute, the International Agency for Research on Cancer, and a large group of international collaborators, describe how they analyzed tumor and [blood samples](#) from 962 people with kidney cancer from across the world and discovered the [genetic mutations](#) or 'fingerprints' of an unknown mutagen present in a high number of them.

This trigger may be something in the environment, such as a chemical, although the researchers were not able to identify it as part of this research.

The cancers contained more of the mutations in countries with a higher incidence of kidney cancer. The researchers suggest the mutation—labeled SBS40b by the team—could be caused by a mystery environmental factor.

"This finding is remarkable. It is like being unaware that smoking exists as a habit, yet finding the mutational signature caused by tobacco smoke in [cancer genomes](#) from around the world. From here, we will extend and refine our understanding of the international geographical differences in signature SBS40b," says Professor Sir Mike Stratton, Mutographs team leader, Wellcome Sanger Institute.

"We will study the habits, lifestyles and environments of patients who have generously donated their samples, to track down what exposure causes this signature and explore whether it can be avoided in future."

There are around 13,800 new cases of kidney cancer diagnosed each year in the UK, and the disease is responsible for about 4,800 deaths

annually.

This study spanned 11 countries, including over 100 samples from the UK. Other participating countries included the Czech Republic and Russia, which have some of the highest kidney cancer incidence rates globally.

Kidney cancer has high incidence rates in Central and Northern Europe, particularly in the Czech Republic and Lithuania, and case numbers have risen in high income countries—including the UK—in recent decades. While obesity, hypertension, and tobacco smoking are known risk factors for kidney cancer, they do not account for the geographical variation of the disease.

Most cancers contain thousands of mutations that have occurred over the course of an individual's lifetime. These mutations can be caused by mistakes made by cells during processes such as [cell division](#), or by exposure to carcinogens such as ultraviolet light or [tobacco smoke](#). Each of these processes causes its own distinct pattern of mutations, known as a "mutational signature."

By analyzing these signatures, we can understand more about what caused the cancer in the first place.

In the paper, the Cancer Grand Challenges team describe how they investigated the mutations by examining 962 cases of clear cell renal cell carcinomas, the most common type of kidney cancer, from 11 countries. As well as the cancer genome sequences, data on sex, age at diagnosis, and important risk factors such as high BMI, hypertension and tobacco smoking were analyzed.

They extracted the mutational signatures from the genome of each patient's cancer and compared them to those found in the Catalog of

Somatic Mutations in Cancer (COSMIC) database, the world's largest database of cancer mutations.

One mutational signature that was not in the database was SBS40b. It was present in cancers from all 11 countries, and the average mutational burden—the number of mutations in each cancer—in each country correlated with kidney cancer incidence in that country.

This means that the more SBS40b mutations found in the kidney cancer samples from a country, the more people are diagnosed with kidney cancer in that country. The highest mutational burdens were in the Czech Republic and Lithuania.

The Mutographs program seeks to make radical progress against cancer's toughest challenges. One of those challenges is developing ways to examine the fingerprints left on our DNA to identify unknown causes of cancer and help prevent more people from developing the disease.

"These incredible findings are a culmination of almost seven years of painstaking research by the Mutographs team, using tumor samples taken across four continents to develop a rich genetic dataset, and one of the largest of its kind," says Dr. David Scott, director of Cancer Grand Challenges.

"Understanding more about how kidney cancer develops and what causes it through research like this is critical to developing preventative interventions and improving public health measures. Cancer Grand Challenges unites the world's brightest minds against cancer's toughest challenges."

Further findings point to large scale exposures to mutagens in southern Europe and East Asia

The Mutographs team also report that they've found evidence in patient samples of widespread exposure to aristolochic acid, a known carcinogen produced by some flowering plants in parts of south-eastern Europe, in particular, Romania and Serbia.

The carcinogenic effect of aristolochic acid was first unearthed in the early 2000s, but researchers have found that the extent of exposure is much greater than previously thought, likely affecting millions and possibly tens of millions of people. One known route of exposure to aristolochic acid is through the consumption of unregulated herbal products.

Use of *Aristolochia* species in herbal medicines is prohibited in the UK. The researchers caution that they still do not know the full extent of the exposure, nor when it took place or whether it is still happening now. It is also unclear if mutations linked to exposure are enough to cause cancer.

The team also uncovered a particular mutational signature caused by exposure to an unknown mutagen in Japan. This was present in about 70 percent of [kidney cancer](#) cases, as well as some liver cancers. The nature and source of the mutagen is unknown, although it is also likely to be affecting tens of millions of people in the East-Asia region.

"These findings are pointing to the presence of strong mutagen exposures affecting many millions of people, that have not been detectable using previous epidemiology studies. This new type of study, linking genetics and epidemiology across multiple populations, will hopefully lead to uncovering new and important causes in cancer that have so far remained hidden," says Dr. Paul Brennan, lead author from the International Agency for Research on Cancer.

More information: Sergey Senkin et al, Geographic variation of mutagenic exposures in kidney cancer genomes, *Nature* (2024). [DOI: 10.1038/s41586-024-07368-2](https://doi.org/10.1038/s41586-024-07368-2)

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