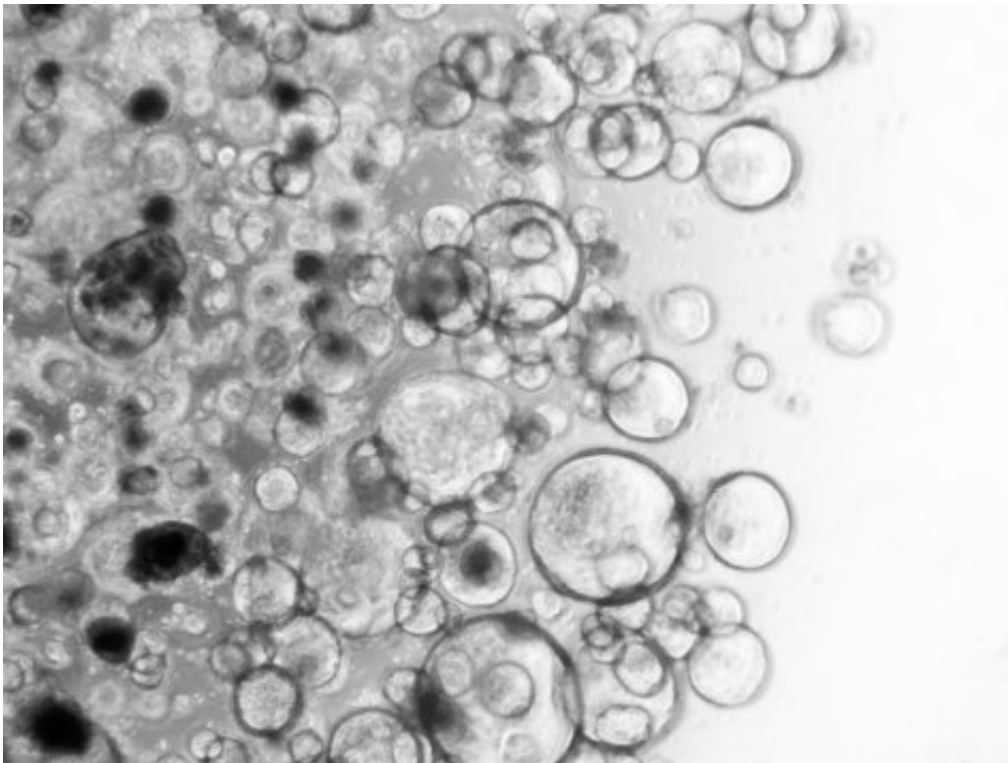


# Cancer's origin story features predictable plot line, researchers find

July 8 2023, by Krista Conger

---



Scientists grew human gastric organoids from stomach cells in a laboratory for two years, tracing patterns of genetic changes associated with pre-cancer. Credit: Wing Wong

Cancer cells-to-be accumulate a series of specific genetic changes in a predictable and sequential way years before they are identifiable as pre-malignancies, researchers at Stanford Medicine have found. Many of these changes affect pathways that control cell division, structure and

internal messaging—leaving the cells poised to go bad long before any visible signs or symptoms occur.

The study is the first to exhaustively observe the natural evolution of the earliest stages of human cancers, starting with [cells](#) that have a single cancer-priming mutation and culminating with a panel of descendants harboring a galaxy of genetic abnormalities.

Identifying the first steps associated with future cancer development could not only facilitate earlier-than-ever diagnosis—when a deadly outcome is but a twinkle in a rogue cell's eye—but may also highlight novel interventions that could stop the disease in its tracks, the researchers say.

"Ideally, we would find ways to intercept this progression before the cells become truly cancerous," said Christina Curtis, Ph.D., professor of medicine, of genetics and of biomedical data science. "Can we identify a minimal constellation of genetic alterations that imply the cell will progress? And, if so, can we intervene? The striking reproducibility in the genetic changes we observed from multiple donors suggests it's possible."

Curtis is the senior author of the research, which was published on May 31 in *Nature*. The lead authors of the study are former postdoctoral scholar Kasper Karlsson, Ph.D., and visiting graduate student Moritz Przybilla.

## **Cells of nefarious beginnings**

The research builds on previous [work](#) in Curtis's laboratory indicating that some [colon cancer cells](#) are seemingly born to be bad—they acquire the ability to metastasize long before the disease is detectable.

"Our studies of established tumors showed us that early genomic alterations seem to dictate what happens later, and that many of these changes seem to happen before tumor formation," Curtis said. "We wanted to know what happens at the very earliest stages. How does a cancer cell evolve, and is this evolutionary path repeatable? If we start with a given set of conditions, will we get the same result in every case?"

The researchers studied tiny, three-dimensional clumps of human stomach cells called gastric organoids. The cells were obtained from patients undergoing gastric bypass surgery to treat obesity. At the beginning of the study, the researchers nudged the cells toward cancers by disabling the production of a key cancer-associated protein called p53 that regulates when and how often a cell divides. Mutations in p53 are known to be an early event in many human cancers, and they trigger the accumulation of additional genetic changes including mutations and copy number alterations—in which repetitive regions of the genome are lost or gained during [cell division](#).

Then they waited.

Every two weeks, for two years, Karlsson cataloged the [genetic changes](#) occurring in the dividing cells. When Karlsson and Przybilla analyzed the data they found that, although changes occurred randomly, those that conferred greater fitness gave their host cells an evolutionary advantage over other cells in the organoid. As the cells continued to divide and the cycle of mutation and competition repeated over many iterations, the researchers saw some common themes.

## **Predictable pathways**

"There are reproducible patterns," Curtis said. "Certain regions of the genome are consistently lost very early after the initial inactivation of p53. This was repeatedly seen in cells from independent experiments

with the same donor and across donors. This indicates that these changes are cell-intrinsic, that they are hardwired into tumor evolution. At the same time, these cells and organoids appear mostly normal under the microscope. They have not yet progressed to a cancer."

The researchers found that these early changes usually occur in biological pathways that control when and how often a cell divides, that interfere with a cell's intricate internal signaling network coordinating the thousands of steps necessary to keep it running smoothly, or that control cell structure and polarity—its ability to know what is "up" and "down" and to situate itself with respect to neighboring cells to form a functioning tissue.

The researchers saw similar patterns occur again and again in cells from different donors. Like water flowing downhill into dry creek beds, the cells traced tried-and-true paths, gaining momentum with each new genetic change. Several of these changes mirror mutations previously observed in stomach [cancer](#) and in Barrett's esophagus, a pre-cancerous condition arising from cells that line the colon and stomach.

"These changes occur in a stereotyped manner that suggest constraints in the system," Curtis said. "There's a degree of predictability at the genomic level and even more so at the transcriptomic level—in the biological pathways that are affected—that gives insights into how these cancers arise."

Curtis and her colleagues plan to repeat the study in different cell types and initiating events other than p53 mutation.

"We're trying to understand exactly what malignant transformation is," Curtis said. "What does it mean to catch these cells in the act, about to topple over the edge? We'd like to repeat this study with other tissue types and initiating mutations so we can understand the early genetic

events that occur in different organs. And we'd like to study the interplay between the host and the environment. Do inflammatory factors play a role in promoting progression? We know that it matters that the cells in these organoids are communicating with each other, and that is important to understanding progression and treatment response."

Researchers from Karolinska Institutet, the University College London and the Chan Zuckerberg Biohub also contributed to the study.

**More information:** Kasper Karlsson et al, Deterministic evolution and stringent selection during preneoplasia, *Nature* (2023). [DOI: 10.1038/s41586-023-06102-8](https://doi.org/10.1038/s41586-023-06102-8)

Provided by Stanford University Medical Center

Citation: Cancer's origin story features predictable plot line, researchers find (2023, July 8) retrieved 1 February 2024 from <https://medicalxpress.com/news/2023-07-cancer-story-features-plot-line.html>

This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.