Cells Accumulate Cancer-Causing Mutations With Age

Oncogenic mutations are common, and vary in different tissue types, before people develop cancer.

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Cells with cancer-causing mutations become increasingly common as people age, according to findings published in Aging and Cancer.

To understand how cancer develops, researchers have been keen to examine genetic changes in human cells at different ages. Advanced sequencing technology has helped show that large numbers of human cells carry oncogenic, or cancer-causing, mutations—even in people who have not yet developed cancer. According to the National Cancer Institute, about 40% of people will develop cancer over the course of their lifetime—which means a majority of people won't.

"To understand the genesis of cancer, we need to look at normal tissue," Edward Evans, PhD, of the University of Colorado Anschutz Medical Campus, said in a press release. "By the time it's developed into cancer, all the mutations are there, and we don't always know which ones are contributing to the actual genesis of cancer."

Evans and James DeGregori, PhD, carried out a meta-analysis of genetic sequencing data in normal tissues to identify mutations that are usually found in cancer cells. They also quantified cells with oncogenic mutations that were seen in people without cancer. They focused on so-called somatic mutations—those that develop over time—rather than inherited cancer-causing alterations, such as BRCA gene mutations.

The researchers looked at cells with cancer-causing mutations that fell into one of three categories: genetic mutations known to be drivers of cancer, mutations included in the Cancer Gene Census (CGC) and CGC genes considered to be pathogenic.

With age, the proportion of cells with all three categories of cancer-related genes rises greatly. In people who are elderly, more than 50% of cells possess oncogenic mutations across various tissue types. The researchers noted that older people without cancer have around 100 billion cells with at least one cancer-causing mutation.

"We have about 3 trillion nucleated cells in our bodies, so to put it in perspective, 100 billion cells

with oncogenic mutations isn't a majority of our total number of cells," Evans said. "But that's a surprisingly high number considering that it only takes one cell to cause cancer. If there are billions of cells with these mutations but no indication of cancer, what does that mean? What does it mean to have these oncogenic mutations in the body?"

Different tissues in the body had varying levels of mutations. For instance, half of the cells in the skin, colon, esophagus and the endometrium that lines the uterus have plenty of mutations in the oldest individuals. "Before we began this research, I had no idea that almost 90% of colon cells become occupied with cancer-causing mutations," DeGregori said. "That the number was so high was quite surprising, but a relatively low percentage of us will get colon cancer." Conversely, fewer liver and blood cells carry such mutations. These differences between tissues need further study.

The presence of such mutations in older cells suggests a high level of selection for their encoded traits, likely with some benefit in fitness. "Their high prevalence throughout cancer-free individuals necessitates a reconsideration of the oncogenicity of these mutations, which could shape methods of detection, prevention and treatment of cancer as well as of the potential impact of these mutations on tissue function and our health," wrote the researchers.

Since most mutations are seemingly harmless and do not lead to cancer, these data might help improve screening tests for cancer-causing mutations. "Every cell in our bodies has dozens and dozens of mutations, if not hundreds or thousands, so we have an opportunity to begin asking whether these patterns of mutations that we see can dictate whether someone is at high risk of cancer," said DeGregori.

Click here to read the study in Aging and Cancer.
