A 20-year study may upend long-held theory about chromosomes and cancer

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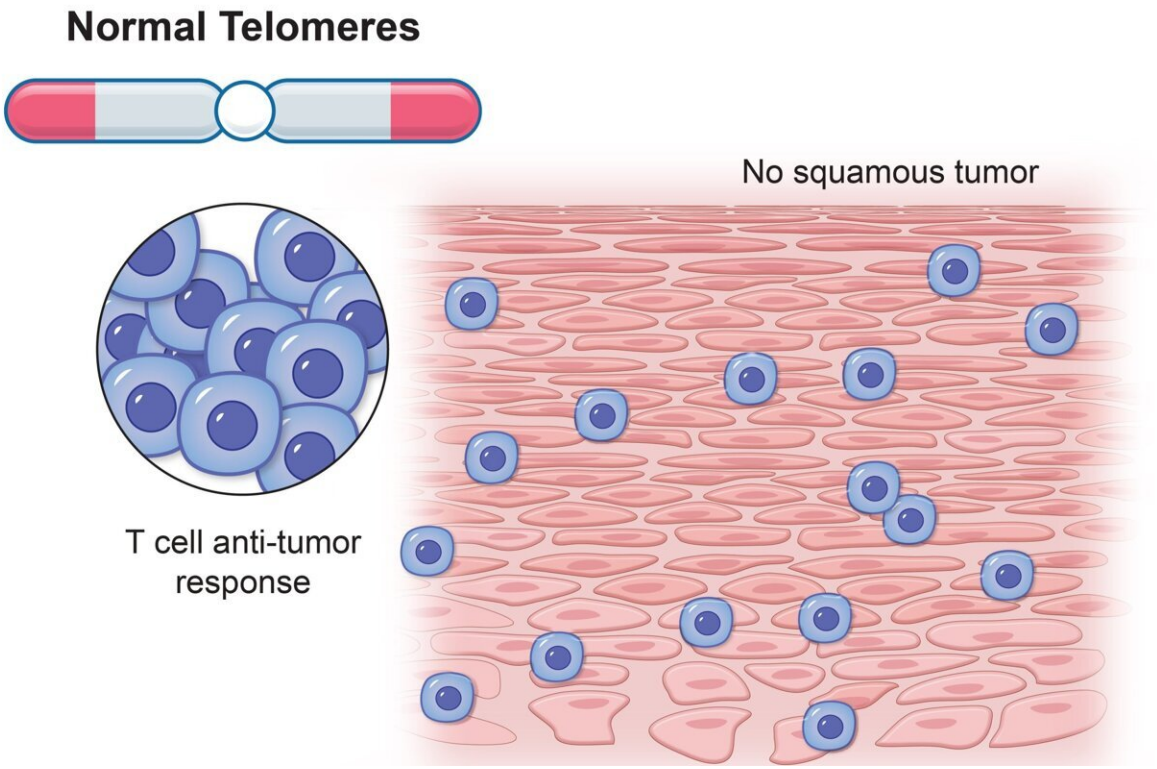

Illustration of the link between short telomeres and squamous cancer. Credit: Jennifer Fairman

Johns Hopkins Medicine scientists say their 20-year study of more than 200 people with premature aging syndromes caused by abnormally short

telomeres, or shortened repetitive DNA sequences at the ends of chromosomes, may upend long-held scientific dogma and settle conflicting studies about how and whether short telomeres contribute to cancer risk.

The research, which has the potential to guide treatments and cancer screening among people with short telomere syndromes, appears in the April 10 issue of *Cancer Cell*.

For decades, some studies in animal models and cells have linked the existence of extremely short telomeres with instability of chromosomes, the X-shaped structures that house genes. Such instability is a common feature of cancer cells.

The new study suggests that chromosomal instability may not be the reason that people with short telomere syndromes are prone to a small but increased risk of certain types of solid cancers. Rather, the researchers say cancer predisposition in these patients may be linked to immune system cells that age and die or vanish prematurely.

"This study reinforces how incredibly important the immune system is in surveilling our cells for cancer as we age," says Mary Armanios, M.D., professor of oncology and director of the telomere center at the Johns Hopkins Kimmel Cancer Center, and professor of genetic medicine, molecular biology and genetics, and pathology at the Johns Hopkins University School of Medicine.

Telomeres naturally shorten with age. People whose telomeres are highly truncated—at or below the 10th percentile of human telomere lengths—have some traits of premature aging. Their hair turns gray at a young age, for example, and they develop pulmonary fibrosis, or scarring of the lungs, earlier than most people do.

While short telomere syndromes are relatively rare, it's estimated that some 50% of people with the most common type of pulmonary fibrosis have short telomeres.

For the new study, Armanios and pediatric oncologist Kristen Schratz, M.D., kept track of some 226 people with short telomere syndromes seen and diagnosed at The Johns Hopkins Hospital and other hospitals across the U.S. between 2003 and 2022. More than half of the participants were male, and their median age was 50 by the end of the study.

Over the two decades, 35 people (15%) in the group developed cancer, nearly all identified in adulthood. Twenty-one had blood cancers, either myelodysplastic syndrome or acute myeloid leukemia, both of which have long been associated with short telomere syndromes.

Of the 35, 14 developed 16 solid tumors, and 14 of them were squamous cancers, including those of the mouth, anus and skin that may also develop in people whose immune systems are suppressed. Half of these cancers were diagnosed early and were removed by surgery.

"The number of cancers was lower than what would be expected if short telomeres fueled genome instability, and these are not the types of cancers you'd expect in people with syndromes that mimic premature aging," says Armanios.

In addition, most of the patients who developed solid tumors (13 of 14) were males, and the molecular reasons why males with short telomeres tend to develop these tumors is worth further study, says Armanios.

During the 20-year span, population statistics suggest the 226 people in the study should have experienced about 19 cases of the most common lethal cancers mostly associated with aging, including lung, colon,

pancreatic, kidney, bladder and uterine cancers.

The researchers sequenced the whole genome of eight of the squamous cancers to look for chromosomal instability, and found no parts of chromosomes had become fused or swapped with other chromosomes, which are major hallmarks of chromosomal instability. "In fact, these cancers seem to have less chromosomal instability than comparable squamous cancers that arise in people without short telomere syndromes," says Armanios.

Looking more closely at the immune systems of the 14 patients with squamous cancers, 12 had levels of T-cells that were several standard deviations below the median range for people.

In a related set of experiments with a group of mice genetically engineered to have short telomeres, the researchers found low quantities of cancer-fighting immune cells, similar to levels in people with short telomeres. Mice with short telomeres were not able to fight off implanted cancers long term nor could they recruit T-cells effectively to the tumor site.

"Our data suggest people with short telomeres may have a lower incidence of most cancers with some cancers arising in a small subset," says Armanios, who adds that short telomeres may not destabilize people's genomes, but in rare cases, affect the capacity of T-cells to expand and maintain their memory to fight cancer in the long-term.

Armanios says the findings will help physicians target cancer screening to high-risk individuals with short telomeres and avoid exposing them to excess immunosuppressive drugs known to increase their risk for infection.

In addition to Armanios and Schratz, other researchers contributing to

the study are Diane Flasch, Wentao Yang and Jinghui Zhang from St. Jude Children's Research Hospital; Robert Vonderheide from the University of Pennsylvania; and Christine Atik, Zoe Cosner, Amanda Blackford, Dustin Gable, Paz Vellanki, Zhimin Xiang, Valeriya Gaysinskaya and Lisa Rooper from Johns Hopkins.

More information: Mary Armanios, T cell immune deficiency rather than chromosome instability predisposes patients with short telomere syndromes to squamous cancers, *Cancer Cell* (2023). DOI: 10.1016/j.ccell.2023.03.005. www.cell.com/cancer-cell/fullt … 1535-6108(23)00078-8

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