Y Chromosome Loss Plays Complex Role in Cancers

Loss of the Y chromosome in both tumor and immune cells may hamper immune protections and lead to poorer outcomes for men with cancer.

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The Y chromosome is generally known for its role in determining biological sex. Most males have both an X and a Y chromosome in all their cells at birth. Most females have two X chromosomes in each cell and no Y.

Scientists have long known that as men get older, some of their cells tend to lose the Y chromosome. Loss of this chromosome in circulating blood cells has been linked to several health problems. These include an increased risk of cancer, heart disease, and Alzheimer's disease. However, the factors that lead to these health risks have been unclear.

An NIH-supported research team set out to better understand how loss of the Y chromosome might lead to poorer cancer outcomes. The team was led by Dr. Dan Theodorescu of the University of Arizona and Simon Knott of Cedars-Sinai Medical Center. An earlier study led by Theodorescu found that loss of the Y chromosome could lead to more aggressive bladder cancers.

The scientists analyzed data from different types of human and mouse tumors in The Cancer Genome Atlas, an NIH-supported program that gathers and shares huge datasets related to cancer cell genomics. Their results appeared in Nature on June 4, 2025.

The team first identified nine genes that could serve as a "signature" of gene activity that identifies cells lacking the Y chromosome. They then searched for this signature among data that represents 29 types of human tumors from more than 4,000 men. Their analysis showed that, across the many tumor types, patients who lacked Y chromosomes had worse outcomes. This included poorer overall survival than men who still had Y chromosomes in their tumor cells.

Additional studies of both human and mouse tumors showed that the greatest loss of Y chromosomes occurred in cancerous epithelial cells. Epithelial cells line many internal organs. Epithelial tumors also tended to lack Y chromosomes even in nearby non-cancerous cells.

Notably, Y chromosomes were missing from many immune cells in tumors, which reduced their ability to fight cancer growth. The greatest decline in immune cell function was seen in CD4 and

CD8 T cells. Outcomes for people who lacked Y chromosomes in epithelial cells and T cells were worse than for those who still had Y chromosomes.

“Our work showed that if cancer cells lost the Y chromosome, it was very likely immune cells would also have lost the Y chromosome. Losing the Y chromosome in both these cell types at once correlated with hyperaggressive cancer cells and malfunctioning immune cells that are meant to attack the cancer cells,” Knott says. “This creates an aggressive tumor with very poor outcomes.”

“These findings represent a big step forward in our understanding of why men with loss of Y in their blood cells have a higher mortality from cancer,” Theodorescu adds. “It turns out that loss of Y in either cancer cells or immune cells makes the immune system less effective.”

The findings suggest that T cell cancer therapies might be less effective in patients who lack Y chromosomes. More study is needed to understand how tumors drive the loss of the Y chromosome in other cells. Why loss of this chromosome leads to more aggressive tumors also isn’t known.

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