Loss of Y Chromosome in Men Makes Bladder Cancer More Aggressive

As males grow older, some of their cells may naturally lose the Y chromosome. This may affect bladder cancer protection and treatment.

August 10, 2023 By National Cancer Institute

By Nadia Jaber

It was once thought that after guiding the development of male sex organs in a fetus, the Y chromosome didn't do much else. But over the past few years, results from multiple studies have challenged that belief. The most recent evidence comes from a new study that suggests that the Y chromosome may actually protect men from aggressive bladder cancer.

Most biological females have two X chromosomes in every cell, whereas most biological males have one X and one Y chromosome. But as males grow older, some of their cells may naturally lose the Y chromosome. More than half of males in their early 90s have lost the Y chromosome in some of their blood cells.

Females have two X chromosomes in their cells, while males have one X and one Y. As males age, some of their cells may lose the Y chromosome.Courtesy of NCI/National Human Genome Research Institute

The new study, carried out in both mice and humans, found that loss of the Y chromosome in bladder cancer cells helped tumors evade the immune system and grow unchecked. On the upside, loss of the Y chromosome also appeared to make bladder cancer more susceptible to immunotherapy drugs called immune checkpoint inhibitors, the researchers reported June 21 in Nature.

“It’s stunning that losing the Y chromosome would have such a biological implication” for the immune system, said the study’s lead investigator, Dan Theodorescu, MD, PhD, director of Cedars-Sinai’s Samuel Oschin Comprehensive Cancer Institute. “It wouldn’t have been expected at all, based on prior science,” Dr. Theodorescu added.

Many studies have shown that losing the Y chromosome puts men at higher risk of getting cancer and of dying from cancer, but it hasn’t been understood why that is, said Konstantin Salnikow, of NCI’s Division of Cancer Biology, who was not involved in the study.

Findings from the new study, which was partially funded by NCI, start to answer that question, Dr. Salnikow said. And they may begin to unravel the long-standing mystery of why men have higher rates of many cancers than women, he added.

Tumors with Loss of Y Evade the Immune System

The Y chromosome is one of the smallest of the bunch, and it carries only a few genes. Most of those genes are involved in sex development or sperm production, giving rise to the idea that the Y chromosome is a one-trick pony.

But "it actually does a lot more than we thought," Dr. Theodorescu said. Loss of Y has been linked with higher rates of Alzheimer's disease and heart disease, and has been found in several types of cancer. For instance, up to 40% of older men with bladder cancer lack the Y chromosome in their tumors.

Because men are three to five times more likely to develop bladder cancer than women, the researchers wondered whether there may be a connection between Y chromosome loss and bladder cancer. To explore that possibility, the researchers looked at data from a large group of men with bladder cancer.

Men with little to no expression of Y chromosome genes in their tumors (Y-negative tumors) didn't live as long as men with high expression of Y chromosome genes in their tumors (Y-positive tumors), they found.

To learn why, the researchers turned to mouse bladder cancer cells with (Y-positive) and without (Y-negative) a Y chromosome. Both groups of cells grew at the same rate in lab dishes and when implanted into male mice without immune systems, they found.

But when the researchers implanted the cells into male mice with normal immune systems, the Y-negative cells grew twice as fast. That was the first hint that Y-negative cells were better at evading the immune system, Dr. Theodorescu explained.

Another clue emerged when the team saw that Y-negative tumors in both mice and men had higher levels of PD-L1, a protein that shuts down T cells—immune cells that are primarily responsible for seeking out and destroying cancer cells. Indeed, T cells in Y-negative tumors appeared to be less active than those in Y-positive tumors.

Not only that, but T cells in Y-negative tumors showed signs of exhaustion, a phenomenon that occurs when T cells run out of steam trying to rid the body of cancer or a chronic infection.

These findings illustrate that "cells with loss of Y chromosome somehow influence the immune response and … the immune system is really affected," Dr. Salnikow said.

Immunotherapy for Y-negative Bladder Cancer?

Immune checkpoint inhibitors are a type of immunotherapy that help get exhausted T cells back into attack mode. If loss of the Y chromosome leads to T cell exhaustion, the team wondered, would an immune checkpoint inhibitor help rally the T cells against Y-negative tumors?

Treating mice with an immune checkpoint inhibitor slowed the growth of Y-negative tumors far more than Y-positive tumors. And in the Y-negative tumors, T cells showed fewer signs of exhaustion.

Data from a 2016 clinical trial of the immune checkpoint inhibitor atezolizumab (Tecentriq) for bladder cancer also revealed that men with Y-negative tumors lived longer than men with Y-positive tumors.

“We are at the beginning of understanding this process, but loss of the Y chromosome could … be a biomarker for telling us that these [tumors] will be more sensitive to checkpoint inhibitors,” Dr. Salnikow noted.

Dr. Theodorescu and his colleagues are now developing a test that looks for loss of the Y chromosome in tumors.

Controlling Gene Expression Across the Genome

The research team did additional experiments to find out more about the role of the Y chromosome in bladder cancer. They zeroed in on two genes on the Y chromosome whose absence seemed to be responsible for faster growth of Y-negative tumors.

The genes, called UTY and KDM5D, affect how DNA is packaged into chromosomes. That packaging, in turn, affects the activity of genes on those chromosomes.

“[It] appears that chromosome Y contains important factors that are involved in the regulation of gene expression,” Dr. Salnikow said. That regulation could extend beyond the Y chromosome to the entire genome, he added.

“The big question for us is, how do you connect those genes back to the immune system?” Dr. Theodorescu said. “There are a lot of pieces in between UTY and KDM5D—and potentially other genes on the Y chromosome—and inducing [T cell] exhaustion. We’re going to try to find those pieces now.”

A separate study, also published June 21 in Nature and partially funded by NCI, found that KDM5D may have the opposite role in colorectal cancer. In mice, the loss of KDM5D made colorectal tumors less able to evade T cells and less likely to spread.

Sex Differences in Cancer

Compared with women, men have higher rates of nearly 30 different types of cancer, including bladder, colon, and brain cancer, Dr. Salnikow said.

Researchers have historically attributed this discrepancy to different sex hormones and different lifestyles, he explained, noting that males are more likely to drink, smoke and be exposed to

cancer-causing chemicals at work.

But newer studies have shown that lifestyle and hormonal factors alone can't account for the stark differences between men and women in incidence and death rates of many cancers. Now there is growing evidence that biological differences between males and females in everything from epigenetics to metabolism and immunity could potentially contribute to differences in cancer outcomes.

That evidence, along with findings from the new study, make it clear that "we really need to be mindful of sex-specific issues when we do experimental biology, and sex and gender when we do human biology [research]," Dr. Theodorescu emphasized.

"Obviously, males and females aren't the same. And we need to be mindful of both the biological and gender differences when we do experiments," he added.

NCI's Division of Cancer Biology is planning to host a workshop on the biological basis of sex differences in cancer, Dr. Salnikow noted. He hopes that bringing experts together will help identify existing gaps in research and facilitate collaborations to address the remaining mysteries.

"I think there's going to be quite a bit of activity in this whole field now," Dr. Theodorescu said. "This is very exciting as I think it will lead to impactful clinical advances for our patients."

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