

Gene variants foretell the biology of future breast cancers, study finds

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A Stanford Medicine study of thousands of breast cancers has found that the gene sequences we inherit at conception are powerful predictors of the breast cancer type we might develop decades later and how deadly it

might be.

The study challenges the dogma that most cancers arise as the result of random mutations that accumulate during our lifetimes. Instead, it points to the active involvement of gene sequences we inherit from our parents—what's known as your germline genome—in determining whether cells bearing potential cancer-causing mutations are recognized and eliminated by the [immune system](#) or skitter under the radar to become nascent cancers.

"Apart from a few highly penetrant genes that confer significant cancer risk, the role of heredity factors remains poorly understood, and most malignancies are assumed to result from random errors during [cell division](#) or bad luck," said Christina Curtis, Ph.D., the RZ Cao Professor of Medicine and a professor of genetics and of biomedical data science.

"This would imply that [tumor initiation](#) is random, but that is not what we observe. Rather, we find that the path to [tumor development](#) is constrained by hereditary factors and immunity. This new result unearths a new class of biomarkers to forecast tumor progression and an entirely new way of understanding [breast](#) cancer origins."

Curtis is the senior author of the [study](#), which is published in *Science*. Postdoctoral scholar Kathleen Houlahan, Ph.D., is the lead author of the research.

"Back in 2015, we had posited that some tumors are 'born to be bad'—meaning that their malignant and even metastatic potential is determined early in the disease course," Curtis said. "We and others have since corroborated this finding across multiple tumors, but these findings cast a whole new light on just how early this happens."

A new take on cancer's origin

The study, which gives a nuanced and powerful new understanding of the interplay between newly arisen [cancer cells](#) and the immune system, is likely to help researchers and clinicians better predict and combat breast tumors.

Currently, only a few high-profile cancer-associated mutations in genes are regularly used to predict cancers. Those include BRCA1 and BRCA2, which occur in about one of every 500 women and confer an increased risk of breast or ovarian cancer, and rarer mutations in a gene called TP53 that causes a disease called Li Fraumeni syndrome, which predisposes to childhood and adult-onset tumors.

The findings indicate there are tens or hundreds of additional gene variants—identifiable in healthy people—pulling the strings that determine why some people remain cancer-free throughout their lives.

"Our findings not only explain which subtype of breast cancer an individual is likely to develop," Houlahan said, "but they also hint at how aggressive and prone to metastasizing that subtype will be. Beyond that, we anticipate that these inherited variants may influence a person's risk of developing breast cancer."

The genes we inherit from our parents are known as our germline genome. They're mirrors of our parents' genetic makeup, and they can vary among people in small ways that give some of us blue eyes, brown hair or type O blood. Some inherited genes include mutations that confer increased cancer risk from the get-go, such as BRCA1, BRCA2 and TP53. But identifying other germline mutations strongly associated with future cancers has proven difficult.

In contrast, most cancer-associated genes are part of what's known as our somatic genome. As we live our lives, our cells divide and die in the tens of millions. Each time the DNA in a cell is copied, mistakes happen and

mutations can accumulate. DNA in tumors is often compared with the germline genomes in blood or normal tissues in an individual to pinpoint which changes likely led to the cell's cancerous transformation.

Classifying breast cancers

In 2012, Curtis began a deep dive—assisted by machine learning—into the types of somatic mutations that occur in thousands of breast cancers. She was eventually able to categorize the disease into 11 subtypes with varying prognoses and risk of recurrence, finding that four of the 11 groups were significantly more likely to recur even 10 or 20 years after diagnosis—critical information for clinicians making treatment decisions and discussing long-term prognoses with their patients.

Prior studies had shown that people with inherited BRCA1 or BRCA2 mutations tend to develop a subtype of breast cancer known as triple negative breast cancer. This correlation implies some behind-the-scenes shenanigans by the germline genome that affect what subtype of breast cancer someone might develop.

"We wanted to understand how inherited DNA might sculpt how a tumor evolves," Houlahan said. To do so, they took a close look at the immune system.

It's a quirk of biology that even healthy cells routinely decorate their outer membranes with small chunks of the proteins they have bobbing in their cytoplasm—an outward display that reflects their inner style.

The foundations for this display are what's known as HLA proteins, and they are highly variable among individuals. Like fashion police, [immune cells](#) called T cells prowl the body looking for any suspicious or overly flashy bling (called epitopes) that might signal something is amiss inside the cell. A cell infected with a virus will display bits of viral proteins; a

sick or cancerous cell will adorn itself with abnormal proteins. These faux pas trigger the T cells to destroy the offenders.

Houlahan and Curtis decided to focus on oncogenes, normal genes that, when mutated, can free a cell from regulatory pathways meant to keep it on the straight and narrow. Often, these mutations take the form of multiple copies of the normal gene, arranged nose to tail along the DNA—the result of a kind of genomic stutter called amplification. Amplifications in specific oncogenes drive different cancer pathways and were used to differentiate one breast cancer subtype from another in Curtis' original studies.

The importance of bling

The researchers wondered whether highly recognizable epitopes would be more likely to attract T cells' attention than other, more modest displays (think golf-ball-sized, dangly turquoise earrings versus a simple silver stud). If so, a cell that had inherited a flashy version of an oncogene might be less able to pull off its amplification without alerting the immune system than a cell with a more modest version of the same gene. (One pair of overly gaudy turquoise earrings can be excused; five pairs might cause a patrolling fashionista T cell to switch from tutting to terminating.)

The researchers studied nearly 6,000 breast tumors spanning various stages of disease to learn whether the subtype of each tumor correlated with the patients' germline oncogene sequences. They found that people who had inherited an oncogene with a high germline epitope burden (read: lots of bling)—and an HLA type that can display that epitope prominently—were significantly less likely to develop breast cancer subtypes in which that oncogene is amplified.

There was a surprise, though. The researchers found that cancers with a

large germline epitope burden that manage to escape the roving immune cells early in their development tended to be more aggressive and have a poorer prognosis than their more subdued peers.

"At the early, pre-invasive stage, a high germline epitope burden is protective against cancer," Houlahan said. "But once it's been forced to wrestle with the immune system and come up with mechanisms to overcome it, tumors with high germline epitope burden are more aggressive and prone to metastasis. The pattern flips during tumor progression."

"Basically, there is a tug of war between tumor and immune cells," Curtis said. "In the preinvasive setting, the nascent tumor may initially be more susceptible to immune surveillance and destruction. Indeed, many tumors are likely eliminated in this manner and go unnoticed. However, the immune system does not always win.

"Some tumor cells may not be eliminated and those that persist develop ways to evade immune recognition and destruction. Our findings shed light on this opaque process and may inform the optimal timing of therapeutic intervention, as well as how to make an immunologically cold tumor become hot, rendering it more sensitive to therapy."

The researchers envision a future when the germline genome is used to further stratify the 11 breast cancer subtypes identified by Curtis to guide treatment decisions and improve prognoses and monitoring for recurrence.

The study's findings may also give additional clues in the hunt for personalized cancer immunotherapies and may enable clinicians to one day predict a healthy person's risk of cancer from a simple blood sample.

"We started with a bold hypothesis," Curtis said. "The field had not

thought about tumor origins and evolution in this way. We're examining other cancers through this new lens of heredity and acquired factors and tumor-immune co-evolution."

More information: Kathleen E. Houlahan et al, Germline-mediated immunoediting sculpts breast cancer subtypes and metastatic proclivity, *Science* (2024). [DOI: 10.1126/science.adh8697](https://doi.org/10.1126/science.adh8697).
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