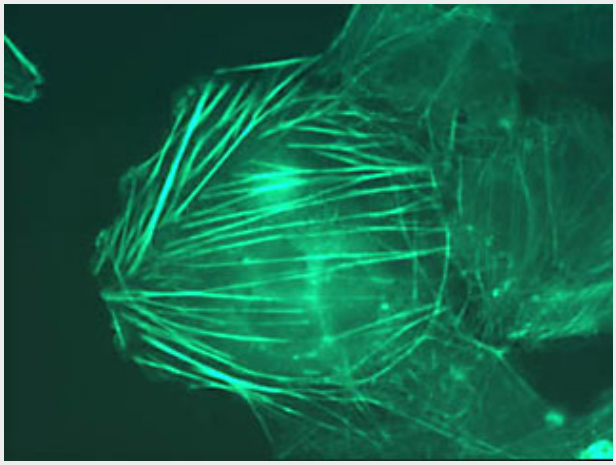
Cancer: Cells behaving badly



An internal scaffold of the protein *actin* (in green) gives shape and structure to bladder cancer cells. Actin is important in the structure and function of many cell types. *Cells courtesy of Marinpharm GmBH.*

It's quite likely your body is harboring precancerous cells. Don't panic: this doesn't mean you have cancer. Many of us have cells here and there with defense mechanisms that don't work as they should, creating the potential for these cells to grow into cancerous tumors.

In the vast majority of cases, though, they haven't.

Why not? Given the surprising frequency of precancerous cells in the body, some cancer researchers have shifted their questioning from "What causes cancer?" to "What keeps these precancerous cells under control?" They hope that by understanding potentially cancerous cells at their earliest stages, they can stop cancer before it starts.

The basics: What is cancer?

Cancer isn't just a single condition; it's actually a complex collection of diseases that can arise in almost any tissue in the body. What characterizes full-blown cancer cells is that they've become decidedly anti-social, carrying on their activities without regard to the other cells and tissues around them. Most normal cells are monitored by a myriad of mechanisms that keep them working in cooperation with other cells. When damage prevents them from doing so, they fix themselves or die. Every cancer starts as a disruption of this normal activity. For example, most cells know it's time to divide when they get signals from nearby cells or other parts of the body. Cancer cells, however, will divide whenever they please, regardless of how much they crowd

their neighbors. They'll also move to places they don't belong, attract blood vessels to themselves, and stop obeying aging signals. In short, cancer cells misbehave, and their mischief gives rise to tumors.

Each cancer has its own unique pattern of bad behavior determined by the tissue in which it was formed, the mutations the cells have adopted, and the chemistry in an individual's body. Because every cancer is unique, a treatment that works wonders for a leukemia patient, for example, might do little or nothing for a woman with breast cancer. Even patients who have the same kind of cancer will have different responses to the same therapy, because the way the cancer arises and plays out depends on unique cellular events and the patient's individual genome.

Profile of a cancer cell

Even though every cancer is different, there's a shared set of behaviors that characterizes all cancer cells:

Uncontrolled growth: Normal cells grow and divide when they get messages from the cells around them that it's time to do so. Cancer cells, on the other hand, are able to jump-start growth by themselves, and therefore can divide and make new copies of themselves independent of what's going on in the cells around them.

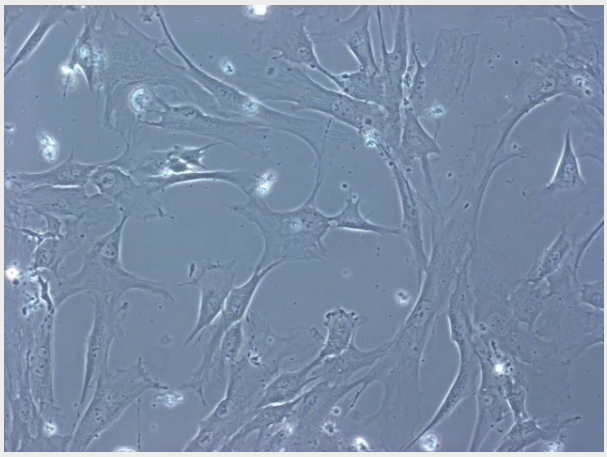
Lack of response to stop signals: A healthy cell will stop dividing when one of two things happens: it receives signals from nearby cells that the "neighborhood" is crowded enough, or its cellular machinery is damaged. Ordinarily, a cell will take time out to repair problems. Cancer cells just keep on going, proliferating under conditions that would stop normal cells, and making new copies of cells with damaged DNA.

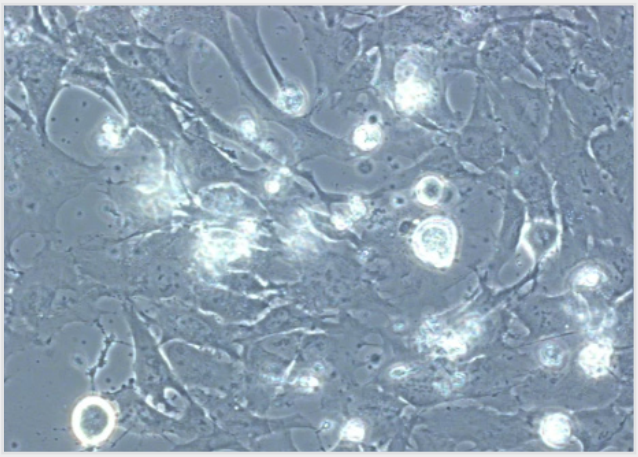
Immortality: Almost all the cells in your body are programmed to stop functioning or commit suicide when cellular machinery is damaged beyond repair, when they're infected by a virus, when there are too many cells, or when cellular functions begin to break down. An aging cell may simply stop dividing, or it may undergo a sequence of events called programmed cell death or apoptosis. Cancer cells ignore these stop signals, and are thus able to expand their numbers.

Ability to divide infinitely: Healthy cells eventually stop dividing but continue to live. Their growth is stopped by the fact that their DNA is programmed to tolerate a certain number of replications, and sends a "stop" signal when it's reached its limit. Cancer cells evolve new ways to evade these signals. As a result, they continue to replicate, producing new cells that have miscopied or mutated DNA strands.

Recruiting a food supply: All cells need to be fed by oxygen and nutrients in the blood. Ordinarily, the body's systems carefully regulate the growth of new feeder blood vessels, a process called angiogenesis. A tumor of cancerous cells typically skirts these systems and independently signals the body to feed it, causing new vessels to grow into the tumor. This vascularization of a tumor marks one of the defining moments when a precancerous tissue crosses the line and becomes a true cancer.

Random migration: In healthy tissues, the cells stay where they are, adhering to each other in structures that characterize the tissue and assist in its function. Mature cancer cells, in contrast, can let go of these molecular handholds, and relocate to other parts of the body. This cell movement, called metastasis, is one of the most defining characteristics of malignance. The resulting eruption of tumors in distant parts of the body is what brings about the majority of deaths from cancer. tumors in distant parts of the body is what brings about the majority of deaths from cancer.





One of the hallmarks of cancer cells is aggressive, disorderly growth. Compare the field of normal cells (on the left) to the messier caner cells (on the right).

Taken together, these rogue qualities are considered the hallmarks of cancer. Precancerous cells may show uncontrolled growth and lack appropriate response to stop signals and so they may divide repeatedly. Each new division is subject to frequent genetic errors. When such cells proliferate, they continue to pass along their disruptive mutations and likely acquire new ones, eventually creating a cancerous tumor. Tumor cells often acquire the first five characteristics before they move out to other parts of the body. This helps explain why catching a cancer early is important: If you detect it before it has acquired all the hallmarks, you can prevent metastasis.

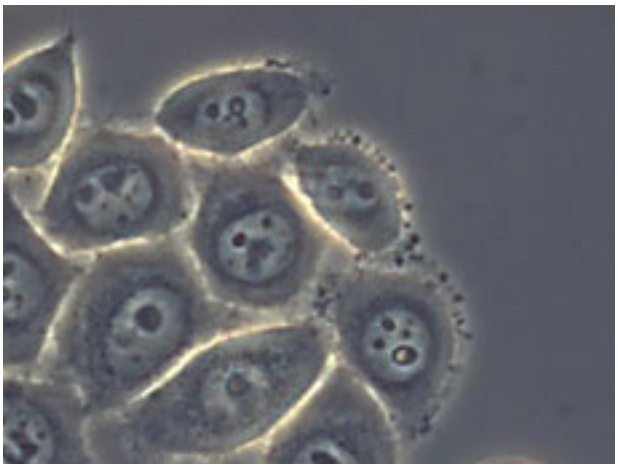
How does cancer happen?

For the most part, every cell in your body has the same DNA in it, contained in 23 pairs of chromosomes, which must be copied with extraordinary accuracy each time the cell

divides. Sometimes, though, there are mistakes, called mutations, in the DNA. Surprisingly, most damage to the DNA happens through "normal" cellular metabolism. In addition to this normal rate of damage, our cells are constantly acquiring mutations in other ways as well, from ultraviolet rays in sunlight or exposure to certain elements in the environment. Other things can go wrong inside the cell: Its machinery can stop working properly, creating problems replicating or dividing up DNA during cell division, or sometimes viral DNA can take up residence in the cell.

Fortunately, we have lots of built-in mechanisms to correct these errors when they happen. Usually a cell with mutations will stop and fix its DNA; if it can't, it will undergo apoptosis. But every now and then, a damaged cell slips through the repair checkpoint and the immune system's surveillance system. The more damage inflicted on the cell, the more likely it is to malfunction and potentially become precancerous.

What happens then? Most mutations will kill a cell rather than give it super powers. But if the cell survives, it will pass its mutations along as it divides. Mutations that affect DNA replication can give rise to new genetic changes as the cell divides. As these random changes accumulate, they can affect the cell's behavior, bestowing upon it the qualities associated with cancer: uncontrolled growth, lack of response to signals, etc. This proliferation of misbehaving—but well adapted—cells is a microcosmic example of genetic variation and natural selection, a kind of malicious cellular evolution.



HeLa cells

HeLa cells: Immortal cancer in culture

HeLa cells are the workhorses of cancer research. They are derived from cervical cells taken from Henrietta Lacks, a young cancer patient, in 1951. Lacks died of cervical cancer eight months later, but her cells live on in laboratories around the world.

HeLa cells were the first human cells continuously grown in culture. They've literally been immortalized: they will continue to grow and divide indefinitely, as long as they're in the right environment.

Many researchers have used HeLa cells in their labs, particularly in the early days of cancer research, because the cells are readily available and easy to culture. Scientists now have malignant cells from many other tissue types to study.

An important characteristic of HeLa cells--and other cultured cancer cells--is that they are very malleable: they can exist in conditions that would kill other cells, and can adapt to almost any environment. Because they are so robust, HeLa cells have been known to occasionally contaminate other cell lines used for research.

Targeting the root

The tiny precancerous lesions that lurk in many of us are a far cry from an dangerous tumor. Most of them will never become cancerous, kept in check by a host of defenses within the body. Even if they do begin to get out of hand, they've got a lot of dividing and mutating to do before they become a tumor: most of them would take 10 to 15 years to reach a stage where they could be detected.

At these early, precancerous stages, the number of cells in a lesion is small, and the body has many ways to intercept them. Your immune system, for example, may see precancerous cells as foreign, and kill them. Alternatively, mutations in a young cancer cell may trigger a defense system, directing the cell to commit suicide. Most potentially cancerous cells are, in fact, destroyed. For the ones that slip through, the time needed for them to develop into troublesome tumors provides a window during which these lesions might be taken out of commission by cancer treatments of the future. The key is to identify and attack them. Such early treatments would be a significant improvement over current therapies designed to knock out battle-hardened, surviving cells from an already-problematic tumor, but they will require a better understanding of the earliest changes that provoke cancer.

Many researchers have recently focused their attention on just these moments in a cancer cell's life. Thea Tlsty, a researcher at the University of California, San Francisco, examines the early events in a cancer cell's life. By characterizing key changes in a precancerous cell, she hopes to find ways to strike cancers down in their earliest, most vulnerable stages. Tlsty (pronounced TIL-stee) likens a cancerous tumor to a weed. "It has a root and a top to it. The current treatments we use now only take off the top, but you're left with the root. The cancer regresses, but it can grow back."

"The new medicine that people are trying to develop would target the root," she continues. Tlsty studies the role of telomeres, the DNA at the ends of chromosomes, and centrosomes, organelles within the cell that are involved in the separation of chromosomes as the cell divides. For example, while a normally dividing cell has two centrosomes, each pulling one set of chromosomes to each new cell, a cancer cell can have three or four, making the DNA separate unevenly or even making one cell divide into three or more. Variations in the number of centrosomes "...is one of the earliest genetic changes in the development of a cancer cell," Tlsty explains. "What we really want is for medicine to be predictive and preventative. If we can understand what those first few little changes are and eliminate those cells, the hope is that we can eliminate cancer before it forms."