More Evidence That Most Cancer Mutations Are Simply The Result Of Bad Luck

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For decades we've been told if we don't smoke, don't drink, use sunscreen and eat right, we can hope to have a fighting chance against cancer. And while this is certainly true, and genes, lifestyle and the environment do play significant roles in cancer, new research shows that we can follow all of the advice to the letter and still get cancer, leading scientists to rethink how to approach the disease that kills nearly 600,000 Americans each year.

So what do we do about it? Scientists say we find it earlier.

The study—published this month in *Science* by a team from the Broad Institute at MIT and Harvard and led by Gad Getz and postdoctoral fellow Keren Yizhak, along with colleagues from Massachusetts General Hospital—shows, among other things, that one of the reasons why many people get cancer is quite simply bad luck. And ironically, that bad luck is the result of the normal process of cell division that keeps our bodies growing and healthy.

"Every time one of our cells divides, its 6 billion letters of DNA are copied, with a new copy going to each daughter cell," wrote National Institutes of Health director and geneticist, Dr. Francis Collins two years ago when Oncology Associate Professor Cristian Tomasetti, PhD, Lu Li, and Bert Vogelstein of Johns Hopkins University School of Medicine through mathematical analyses and DNA sequencing data estimated the number of DNA "typos" in 32 cancers that could be attributed to heredity, environment or random DNA copying errors. "Typos inevitably occur during this duplication process, and the cell's DNA proofreading mechanisms usually catch and correct these typos. However, every once in a while, a typo slips through—and if that misspelling happens to occur in certain key areas of the genome, it can drive a cell onto a pathway of uncontrolled growth that leads to cancer. In fact, according to a team of NIH-funded researchers, nearly two-thirds of DNA typos in human cancers arise in this random way."

At that time, Collins hoped the findings would reassure people being treated for many forms of cancer that they likely could not have prevented their illness. "They also serve as an important reminder that, in addition to working on better strategies for prevention, cancer researchers must continue to pursue innovative technologies for early detection and treatment."

Scientists have known for a long time that when cells divide, mistakes happen, Tomasetti said. When a mother cell divides to make two daughter cells, the DNA of the mother cell must be copied. And it's during this division that mutations and mistakes happen. Now there is no doubt that environmental factors—such a smoking or exposure to UV light—can cause mutations in DNA or mistakes. "But it's also known that if you could take away all of the exposures, mistakes would still be made when the DNA is copied, about 3-6 mutations per cell division," he said. "Every time a cell dies, another has to divide in two. And every time the cell divides, mistakes are made."

Tomasetti likened the process to using a typewriter. If one is overly tired while typing, that person will invariably make more mistakes. If the typewriter is missing a key, there will be unavoidable mistakes in the typesetting. But even if the person is perfectly rested and the typewriter is adequately functioning, there will still be mistakes because the user is human. It's the same way with our cells, he said. "Of course there are more mistakes made [in DNA during cell division] with harmful exposures, but even without those harmful exposures there will still be mutations because nothing in nature is perfectly replicated, or we would not have evolution."

However, until Tomasetti's mathematical modeling and statistical analysis of cancer tissues in 2013, the mutations found in the great majority of cancers were thought to be a consequence of the process of carcinogenesis and inherited susceptibility—in other words, from outside influences and an individual's genetics. That study provided indirect evidence that a substantial amount of mutations found in cancers would have been present in those cells even in the absence of cancer. "We found that actually a majority of mutations were estimated to have been there anyway," he said.

But that wasn't the final proof, he said. Though it was the first time the concept was expressed, Tomasetti and his colleagues were making their inferences from cancer tissues, not normal, healthy cells. Other studies of healthy tissues in the esophagus, skin and blood, including those of Giulio Genovese, Ph.D. and others, followed and provided direct evidence. The results were comparable. Researchers found large numbers of mutations and of microscopic mutational clones in normal cells.

Then in 2017, Tomasetti, Lu Li, and Vogelstein took their analysis further and declared: "there is evidence that the majority of mutations in cancer are not due to environmental exposures such as smoking, alcohol, etc., but that they are the result of the normal processes of our DNA being duplicated." This

suggests that in several cases people could get cancer even if they never smoked or drank or did any of the things medical science has told them not to do.

To be clear, Tomasetti is not saying that following those risk prevention guidelines is not important. It is very important. But what he is saying is that his findings "have the potential to explain an important fraction of the approximately 60% of cancer cases for which today we do not have any evidence of harmful exposures or heredity, and that in many cases people should let go of the guilt often associated with cancer, and that a significantly larger amount of money should be spent on finding all cancers earlier."

This discovery was preceded by the revelation in their 2015 study that healthy tissues that have more cells and divide more often have a greater chance of developing cancer than tissues with fewer cells that divide more slowly. An example is the colon, as its lining is replaced almost twice a week, versus the bones or the muscles, which have very slow cell division rates. A finding supported by the new study led by Getz.

Researchers in the new study discovered that almost all of the nearly 500 people whose tissues they analyzed, had some seemingly healthy tissue that contained pockets of cells bearing particular genetic mutations. “Some even harbored mutations in genes linked to cancer,” Collins said. “The findings suggest that nearly all of us are walking around with genetic mutations within various parts of our bodies that, under certain circumstances, may have the potential to give rise to cancer or other health conditions.”

Collins said efforts such as NIH’s The Cancer Genome Atlas (TCGA) have extensively characterized the many molecular and genomic alterations underlying various types of cancer. “But it has remained difficult to pinpoint the precise sequence of events that lead to cancer, and there are hints that so-called normal tissues, including blood and skin, might contain a surprising number of mutations —perhaps starting down a path that would eventually lead to trouble.”

Tomasetti said of the Broad Institute study: “We can finally say that one measure at play in cancer is just our normal tissue function which is to renew and which also brings mutations. It remains critical to avoid harmful exposures like smoking, but probably a good number of people get cancer just because our tissues are working normally.”

So it turns out normal tissues are not so normal after all. “And how harmful the mutations they contain are depends on where these mutations hit the genome,” Tomasetti said.

“This is a more complete and comprehensive analysis,” Tomasetti said of the Broad Institute’s latest research. “Instead of looking at only a single tissue, they have now looked at essentially all tissues and used a different technique to look at a much larger set of expressed genes.” All told, MIT, Harvard and Massachusetts General Hospital researchers analyzed 29 tissues, including heart, stomach, pancreas and fat, and matched DNA from 488 individuals in the database from the NIH’s Genotype-Tissue Expression (GTEx) project.
That project is a comprehensive public resource that shows how genes are expressed and controlled differently in various tissues throughout the body.
“Those analyses showed that the vast majority of people—a whopping 95 percent—had one or more tissues with pockets of cells carrying new genetic mutations,” Collins said.

While many of those genetic mutations are most likely harmless, some have known links to cancer, Collins said. “The data show that genetic mutations arise most often in the skin, esophagus, and lung tissues,” he said. This suggests that exposure to environmental elements—such as air pollution in the lung, carcinogenic dietary substances in the esophagus, or the ultraviolet radiation in sunlight that hits the skin—may play important roles in causing genetic mutations in different parts of the body.”

Collins went on to say that the findings prove that the DNA even in our normal cells, isn’t perfectly identical and that mutations constantly arise, both harmful and benign.

“It’s not yet clear to what extent such pockets of altered cells may put people at greater risk for developing cancer down the road,” he said. “But the presence of these genetic mutations does have potentially important implications for early cancer detection. For instance, it may be difficult to distinguish mutations that are truly red flags for cancer from those that are harmless and part of a new idea of what’s ‘normal.’”

Tomasetti said the implications of all of this research are tremendous. “The most important implication—besides the point [for many cancer patients] that it may not have been anything they did that gave them cancer—is that if we want to reduce cancer mortality, we must not only focus on cancer therapy and primary prevention, but also on early detection,” he said. “This aging process,

that accumulates mutations in our organs, is not going to go away. As a population, we are aging, and so that is only going to increase over time. Even in an ideal world where everyone stopped smoking and no one was exposed to UV light or other harmful exposures, we would still accumulate mutations, as we age. It's important then to spend more money on research efforts for the earlier detection of cancer. If we can find cancer earlier, then typically that cancer will be dealt with through surgery, radiation and other measures. Cancer kills us because we find it in later stages, when it metastasizes."

Collins said it's worth noting that so far, the researchers have only detected these mutations in large populations of cells. "As the technology advances, it will be interesting to explore such questions at the higher resolution of single cells."

Tomasetti said studying the evolution of normal mutations in healthy human tissues over time will allow scientists to discover at what point the normal becomes abnormal and even dangerous. "Understanding how often our cells have mutations raises questions of what is normal versus what is not," he said. "We could create measures to assess what is normal and what is not by following the mutational load in our tissues over time. It might help doctors put patients in different groups based on their risk."

Tomasetti said he doesn't believe we will ever eliminate cancer. "As long as we age, we'll have cancer," Tomasetti said. "But if we can significantly reduce the stage at which cancer is detected, we can dramatically reduce the proportion of people who die from cancer."

Scientists will continue to study cell mutation through the Pre-Cancer Atlas—a project designed by the NIH to comprehensively explore and characterize pre-malignant human tumors.

https://www.forbes.com/sites/robinseatonjefferson/2019/06/24/more-evidence-that-most-cancer-mutations-are-simply-the-result-of-bad-luck/#656e98657025