New study finds that most cancer mutations are due to random DNA copying 'mistakes'

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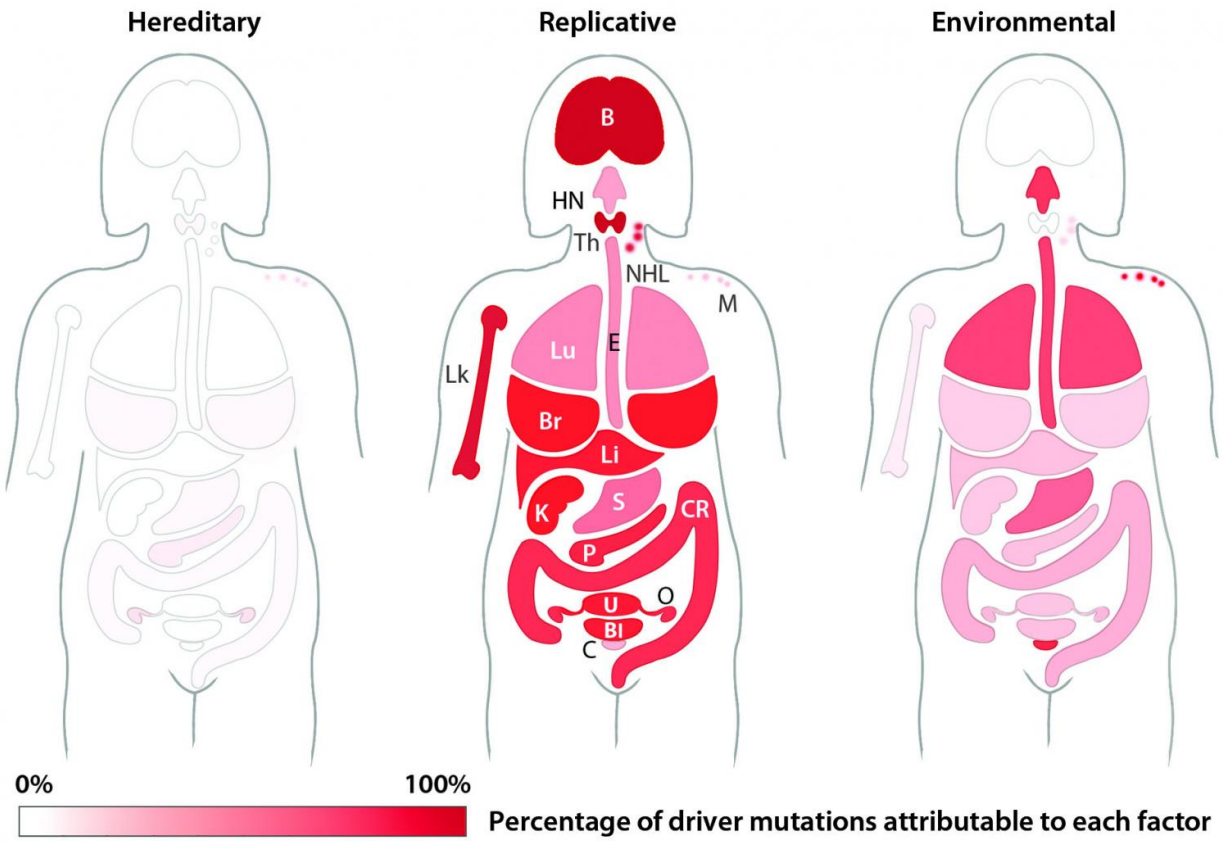

This image depicts the mutations attributable to environmental factors (right), DNA replication (center) and heredity (left) in the UK female population. Credit: C. Tomasetti et al,. Science (2017)

Johns Hopkins Kimmel Cancer Center scientists report data from a new

study providing evidence that random, unpredictable DNA copying "mistakes" account for nearly two-thirds of the mutations that cause cancer. Their research is grounded on a novel mathematical model based on DNA sequencing and epidemiologic data from around the world.

"It is well-known that we must avoid environmental factors such as smoking to decrease our risk of getting cancer. But it is not as well-known that each time a normal cell divides and copies its DNA to produce two new cells, it makes multiple mistakes," says Cristian Tomasetti, Ph.D., assistant professor of biostatistics at the Johns Hopkins Kimmel Cancer Center and the Johns Hopkins Bloomberg School of Public Health. "These copying mistakes are a potent source of cancer mutations that historically have been scientifically undervalued, and this new work provides the first estimate of the fraction of mutations caused by these mistakes."

"We need to continue to encourage people to avoid environmental agents and lifestyles that increase their risk of developing cancer mutations. However, many people will still develop cancers due to these random DNA copying errors, and better methods to detect all cancers earlier, while they are still curable, are urgently needed," says Bert Vogelstein, M.D., co-director of the Ludwig Center at the Johns Hopkins Kimmel Cancer Center.

Tomasetti and Vogelstein conducted the new study described in a report published March 24 in the journal *Science*.

The researchers say their conclusions are in accord with epidemiologic studies showing that approximately 40 percent of cancers can be prevented by avoiding unhealthy environments and lifestyles. But among the factors driving the new study, say the researchers, is that cancer often strikes people who follow all the rules of healthy living—nonsmoker, healthy diet, healthy weight, little or no exposure to

known carcinogens—and have no family history of the disease, prompting the pained question "Why me?"

Tomasetti and Vogelstein believe the answer to this question rests in random DNA copying errors. Current and future efforts to reduce known environmental risk factors, they say, will have major impacts on cancer incidence in the U.S. and abroad. But they say the new study confirms that too little scientific attention is given to early detection strategies that would address the large number of cancers caused by random DNA copying errors.

"These cancers will occur no matter how perfect the environment," says Vogelstein.

In a previous study authored by Tomasetti and Vogelstein in the Jan. 2, 2015, issue of *Science*, the pair reported that DNA copying errors could explain why certain cancers in the U.S., such as those of the colon, occur more commonly than other cancers, such as brain cancer.

In the new study, the researchers addressed a different question: What fraction of mutations in cancer are due to these DNA copying errors?

To answer this question, the scientists took a close look at the mutations that drive abnormal cell growth among 32 cancer types (Supplemental Materials, Table S6). They developed a new mathematical model using DNA sequencing data from The Cancer Genome Atlas and epidemiologic data from the Cancer Research UK database.

According to the researchers, it generally takes two or more critical gene mutations for cancer to occur. In a person, these mutations can be due to random DNA copying errors, the environment or inherited genes. Knowing this, Tomasetti and Vogelstein used their mathematical model to show, for example, that when critical mutations in pancreatic cancers

are added together, 77 percent of them are due to random DNA copying errors, 18 percent to environmental factors, such as smoking, and the remaining 5 percent to heredity.

In other cancer types, such as those of the prostate, brain or bone, more than 95 percent of the mutations are due to random copying errors.

Lung cancer, they note, presents a different picture: 65 percent of all the mutations are due to environmental factors, mostly smoking, and 35 percent are due to DNA copying errors. Inherited factors are not known to play a role in lung cancers.

Looking across all 32 cancer types studied, the researchers estimate that 66 percent of cancer mutations result from copying errors, 29 percent can be attributed to lifestyle or environmental factors, and the remaining 5 percent are inherited.

The scientists say their approach is akin to attempts to sort out why "typos" occur when typing a 20-volume book: being tired while typing, which represents environmental exposures; a stuck or missing key in the keyboard, which represent inherited factors; and other typographical errors that randomly occur, which represent DNA copying errors."You can reduce your chance of typographical errors by making sure you're not drowsy while typing and that your keyboard isn't missing some keys," says Vogelstein. "But typos will still occur because no one can type perfectly. Similarly, mutations will occur, no matter what your environment is, but you can take steps to minimize those mutations by limiting your exposure to hazardous substances and unhealthy lifestyles."

Tomasetti and Vogelstein's 2015 study created vigorous debate from scientists who argued that their previously published analysis did not include breast or prostate cancers, and it reflected only cancer incidence in the United States.

However, Tomasetti and Vogelstein now report a similar pattern worldwide, supporting their conclusions. They reasoned that the more cells divide, the higher the potential for so-called copying mistakes in the DNA of cells in an organ. They compared total numbers of stem cell divisions with cancer incidence data collected by the International Agency for Research on Cancer on 423 registries of cancer patients from 68 countries other than the U.S., representing 4.8 billion people, or more than half of the world's population. This time, the researchers were also able to include data from breast and prostate cancers. They found a strong correlation between cancer incidence and normal cell divisions among 17 cancer types, regardless of the countries' environment or stage of economic development.

Tomasetti says these random DNA copying errors will only get more important as societies face aging populations, prolonging the opportunity for our cells to make more and more DNA copying errors. And because these errors contribute to a large fraction of cancer, Vogelstein says that people with cancer who have avoided known risk factors should be comforted by their findings. "It's not your fault," says Vogelstein. "Nothing you did or didn't do was responsible for your illness."

In addition to Tomasetti and Vogelstein, Lu Li, a doctoral student in Tomasetti's laboratory in the Department of Biostatistics at the Johns Hopkins Bloomberg School of Public Health, also contributed to the research. Funding for the research was provided by the John Templeton Foundation, the Lustgarten Foundation for Pancreatic Cancer Research, the Virginia and D.K. Ludwig Fund for Cancer Research, the Sol Goldman Center for Pancreatic Cancer Research, and the National Institutes of Health's National Cancer Institute (CA006973, CA43460, and CA62924).

Vogelstein is a member of the scientific advisory boards of Morphotek, Exelixis GP, and Syxmex Inostics, and is a founder of PapGene and

Personal Genome Diagnostics. Morphotek, Syxmex Inostics, PapGene, and Personal Genome Diagnostics, as well as other companies, have licensed technologies from The Johns Hopkins University on which Vogelstein is an inventor. These licenses and relationships are associated with equity or royalty payments to Vogelstein. The terms of these arrangements are being managed by The Johns Hopkins University in accordance with its conflict of interest policies.

Questions and Answers with Tomasetti and Vogelstein

What is the take-home message of this research?

Random, unpredictable DNA "mistakes" account for nearly two-thirds of the mutations in cancers. These mutations occur as a result of DNA copying errors made when normal cells divide.

What causes such random DNA copying errors?

Human cells are constantly regenerating. The body makes new cells billions of times throughout a person's lifetime. Each time a cell divides to make a new cell, its DNA is copied and, on average, makes three random mistakes. Most of these mistakes are harmless, but a small fraction of them occur in a gene that will kick-start a cell's uncontrollable replication, leading to cancer. In other words, most of the mutations that occur when our cells divide cause no damage. Occasionally, a mutation occurs in a cancer gene, leading to the disease.

How does the environment and heredity play a role in cancer?

Certain lifestyles or environmental exposures—smoking and

obesity—also cause mutations in DNA. This is why it is so important to avoid such lifestyles and environments. In addition, some people have altered genes that "run" in families, such as BRCA-1 and BRCA-2, that are linked to very high risk of breast and other cancers.

So does this mean there's nothing we can do to prevent cancer deaths?

Not at all. Clearly, some types of the disease, such as lung cancer, are heavily influenced by environmental factors. So maintaining a healthy weight and avoiding exposure to known carcinogens, such as smoking, are critical for preventing deaths from these cancer types. It's estimated that approximately 40 percent of cancers can be prevented if people avoided these risk factors, and our results are in accord with those estimates.

Early detection and intervention can prevent many cancer deaths. Detecting cancers earlier, while they are still curable, can save lives regardless of what caused the mutation. We believe that more research to find better ways to detect cancers earlier is urgently needed.

I follow all the rules of healthy living and don't have any family history of cancer, so why did I get cancer?

Many people will develop cancer no matter how perfect their behaviors are because of random copying errors. These people should not feel guilty about getting cancer—there is nothing they could have done to avoid it.

My child has cancer. Was there anything I could have done to prevent it?

The mutations in virtually all childhood cancers are due to random copying errors, and there's nothing you could have done to prevent it.

What kind of data helped the researchers determine the fraction of mutations caused by random DNA copying errors, environment and heredity?

There were multiple sources of information. In pancreatic cancer, for example, we analyzed genomic sequencing data compiled by The Cancer Genome Atlas. We found that smokers with pancreatic cancer have 16 percent more mutations in their tumors than non-smokers with cancer. We also took into account epidemiologic data on diet and other environmental influences. Finally, we considered the role of inherited factors that have been discovered through studies of families with a predisposition to this disease.

Then, we developed a new mathematical model to determine the fraction of cancer mutations that occur as a result of random DNA copy errors compared with environmental or inherited factors. We found that 66 percent of the total mutations are caused by random DNA copy errors, 29 percent are caused by environmental or lifestyle factors, and the remaining 5 percent are hereditary.

How does this new study compare to their previous research you published in January 2015?

In 2015, we compared cancer incidence in the U.S. to the total number of cell divisions in the organs in which the cancers occurred. This allowed us to explain why certain cancers, such as those of the colon, occur more commonly than other cancers, such as those in the brain. That study suggested that copying errors might play a more important role in cancer than previously believed. However, we did not determine

what fraction of the mutations in cancers were due to these copying errors.

In the new study, the researchers we were able to determine the fraction of mutations due to random copying errors in 32 cancer types. Instead of data on cell divisions, we used a new mathematical model to analyze DNA sequencing and epidemiologic data.

We also addressed whether the correlations we found in 2015 between cancer incidence and cell divisions were universal rather than confined to the U.S. For this purpose, we compared stem cell division rates with cancer incidence data in 68 countries other than the U.S, representing 4.8 billion people, more than half of the world's population. We also included data on breast and prostate cancer, which were not included in the 2015 study. We found the same striking relationship between cell division and cancer incidence in various organs, regardless of the country and its environment.

More information: "Stem cell divisions, somatic mutations, cancer etiology, and cancer prevention," *Science*, science.sciencemag.org/cgi/doi… 1126/science.aaf9011

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