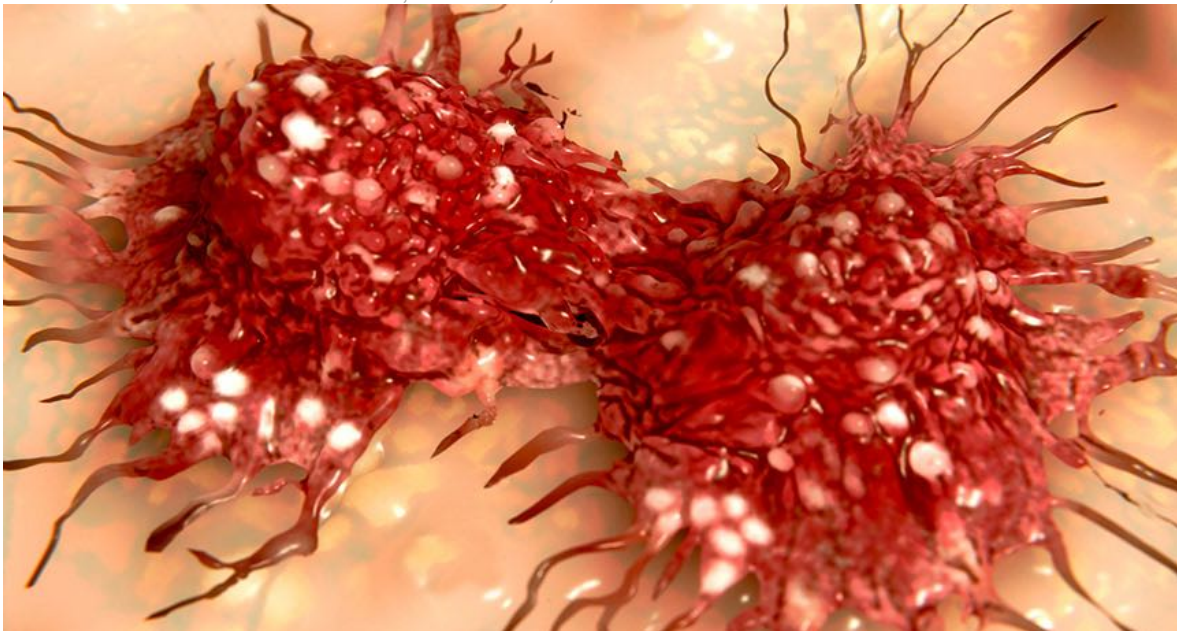


Random mutations play large role in cancer, study finds

Analysis suggests that cell division produces more malignancy-linked errors than environment, inheritance

BY **TINA HESMAN SAEY** 2:00PM, MARCH 23, 2017



GROWING PAINS As cells divide and grow to replenish and repair organs, accidental mutations may crop up in cancer-associated genes. A new study suggests such random mistakes are the source of 66 percent of mutations in cancer cells (illustrated here) across the board.

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Researchers have identified new enemies in the war on cancer: ones that are already inside cells and that no one can avoid.

Random mistakes made as stem cells divide are responsible for about two-thirds of the mutations in cancer cells, researchers from Johns Hopkins University report in the March 24 *Science*. Across all cancer types, environment and lifestyle factors, such as smoking and obesity, contribute 29 percent of

cancer mutations, and 5 percent are inherited.

That finding challenges the common wisdom that cancer is the product of heredity and the environment. “There’s a third cause and this cause of mutations is a major cause,” says cancer geneticist Bert Vogelstein.

Such random mutations build up over time and help explain why cancer strikes older people more often. Knowing that the enemy will strike from within even when people protect themselves against external threats indicates that early cancer detection and treatment deserve greater attention than they have previously gotten, Vogelstein says.

Vogelstein and biomathematician Cristian Tomasetti proposed in 2015 that **random mutations are the reason some organs are more prone to cancer** than others. For instance, stem cells are constantly renewing the intestinal lining of the colon, which develops tumors more often than the brain, where cell division is uncommon. That report was controversial because it was interpreted as saying that most cancers are the result of “bad luck.” The analysis didn’t include breast and prostate cancers. Factoring in those common cancers might change the results, some scientists said. And because the researchers looked at only cancer within the United States, critics charged that the finding might not hold up when considering places around the world where different environmental factors, such as infections, affect cancer development.

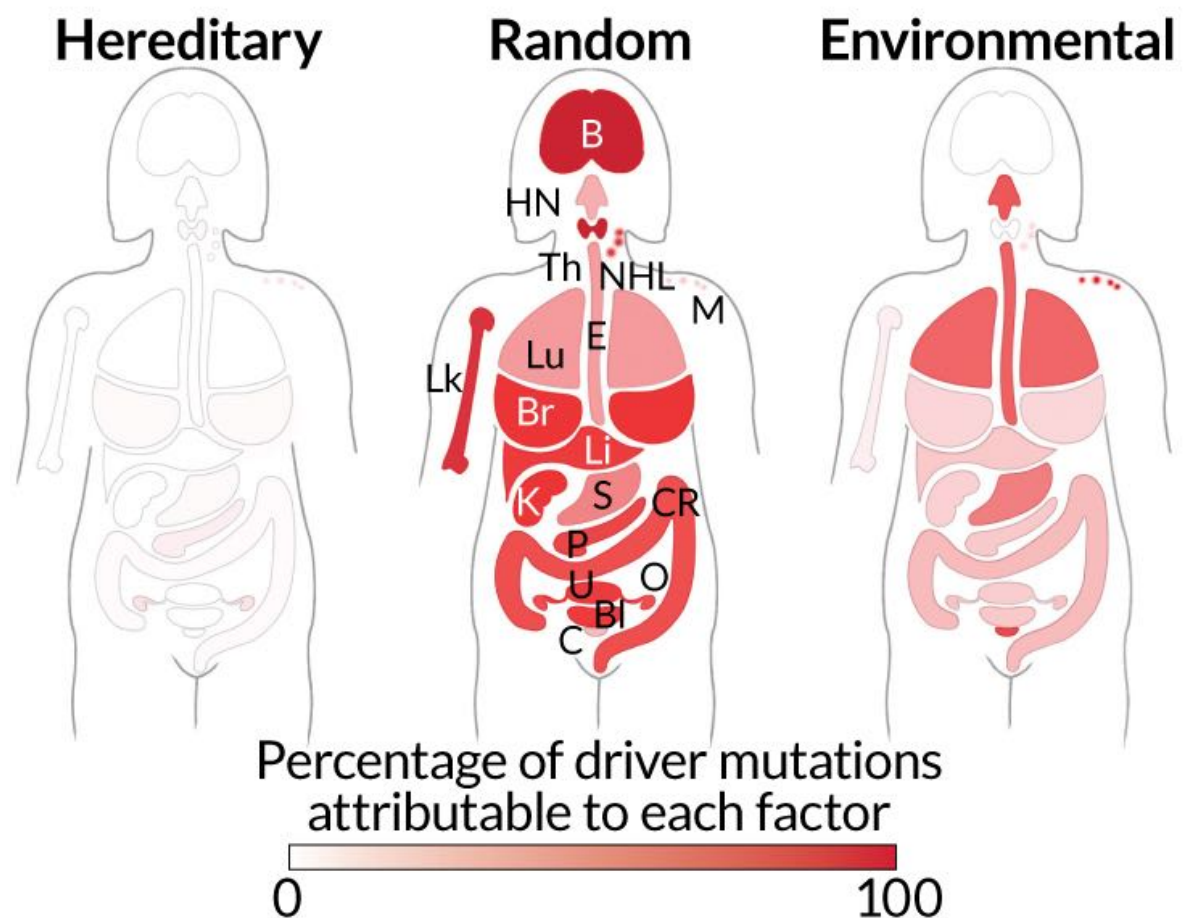
In the new study, Vogelstein, Tomasetti and Hopkins colleague Lu Li examined data from 69 countries about 17 types of cancer, this time including breast and prostate. Again, the researchers found a strong link between cancer and tissues with lots of dividing stem cells. The team also used DNA data and epidemiological studies to calculate the proportions of mutations in cancer cells caused by heredity or environmental and lifestyle factors. Remaining mutations were attributed to random errors — including typos, insertions or deletions of

genes, epigenetic changes (alterations of chemical tags on DNA or proteins that affect gene activity) and gene rearrangements. Such errors unavoidably happen when cells divide.

Story continues below image

Chance cancer

For many organs, more of the mutations that lead to cancer come from random mistakes in DNA made when cells divide (center) than from the environment (right) or inherited factors (left).



Cancers depicted in the diagram: B, brain; Bl, bladder; Br, breast; C, cervical; CR, colorectal; E, esophagus; HN, head and neck; K, kidney; Li, liver; Lk, leukemia; Lu, lung; M, melanoma; NHL, non-Hodgkin lymphoma; O, ovarian; P, pancreas; S, stomach; Th, thyroid; U, uterus.

Usually cancer results after a cell accumulates many mutations. Some people will have accumulated a variety of cancer-associated mutations but won't get cancer until some final insult goads the cell into becoming malignant (*SN: 12/26/15, p. 28*). For some tumors, all the mutations may be the hit-and-miss result of cell division mistakes. There's no way to evade those cancers, Vogelstein says. Other malignancies may spring up as a result of different combinations of heritable, environmental and random mutations. Lung cancer and other tumor types that are strongly associated with environmentally caused mutations could be eluded by avoiding the carcinogen, even when most of the mutations that spur cancer growth arise from random mistakes, Tomasetti says.

"They are venturing into new territory," says Giovanni Parmigiani, a biostatistician at the Harvard T.H. Chan School of Public Health. Tomasetti, Li and Vogelstein are the first to rigorously estimate the contribution of environment, heredity and DNA-copying errors to cancer, he says. "Perhaps the estimates will improve in the future, but theirs seems like a very solid starting point."

Now that the Hopkins researchers have pointed it out, the relationship between dividing cells and cancer seems obvious, says biological physicist Bartłomiej Waclaw of the University of Edinburgh. "I don't think that the existence of this correlation is surprising," he says. "What's surprising is that it's not stronger."

Some tissues develop cancers more or less often than other tissues with a similar number of cell divisions, Waclaw and Martin Nowak of Harvard University pointed out in [a commentary on the Hopkins study](#), published in the same issue of *Science*. That suggests some organs are better at nipping cancer in the bud. Discovering how those tissues avoid cancer could lead to new ways to prevent tumors elsewhere in the body, Waclaw suggests.

Other researchers say the Hopkins team is guilty of faulty reasoning. “They are assuming that just because tissues which have high stem cell turnover also have high cancer rates, that one is causing the other,” says cancer researcher Anne McTiernan of the Fred Hutchinson Cancer Research Center in Seattle. “In this new paper, they’ve added data from other countries but haven’t gotten away from this biased thinking.”

Tomasetti and colleagues based their calculations on data from Cancer Research UK that suggest that 42 percent of cancers are preventable. Preventable cancers are ones for which people could avoid a risk factor, such as unprotected sun exposure or tanning bed use, or take positive steps to lower cancer risks, such as exercising regularly and eating fruits and vegetables. But those estimates may not be accurate, McTiernan says. “In reality, it’s very difficult to measure environmental exposures, so our estimates of preventability are likely very underestimated.”

To attribute so many cancer mutations to chance seems to negate public health messages, Waclaw says, and some people may find the calculation that 66 percent of cancer-associated mutations are unavoidable disturbing because they spend a lot of time trying to prevent cancer. “It’s important to consider the randomness, or bad luck, that comes with cellular division,” he says.

In fact, Tomasetti and Vogelstein stress that their findings are compatible with cancer-prevention recommendations. Avoiding

smoking, tanning beds, obesity and other known carcinogens can prevent the “environmental” mutations that combine with inherited and random mutations to tip cells into cancer. Without those final straws loaded from environmental exposures, tumors may be averted or greatly delayed.

People with cancer may be able to take some comfort from the study, says Elaine Mardis, a cancer genomicist at the Nationwide Children’s Hospital in Columbus, Ohio. “Perhaps the positive message here is that, other than known risk factors, such as smoking, radiation exposure and obesity, there is a component of cancer that is simply a consequence of being human.”

Citations

C. Tomasetti, L. Li and B. Vogelstein. [Stem cell divisions, somatic mutations, cancer etiology, and cancer prevention](#). *Science*. Vol. 355, March 24, 2017, p. 1330. doi: 10.1126/science.aaf9011.

M.A. Nowak and B. Waclaw. [Genes, behavior, and "bad luck."](#) *Science*. Vol. 355, March 24, 2017, p. 1266. doi: 10.1126/science.aam9746.

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Further Reading

R. Ehrenberg. [Cancer mutation patterns differ in smokers, nonsmokers](#). *Science News*. Vol. 190, November 26, 2016, p. 14.

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