Cancer and the bad luck of random mutations

At some point in our lives, we've all heard about or talked to someone who was diagnosed with cancer. A friend, a grandfather, an aunt, or even a parent or sibling. Worse yet, maybe you've received the diagnosis yourself. In every case, one of the first questions that comes to mind is 'Why?'

As much as well know about cancer in its many forms, the question of what causes it continues to be one of the biggest medical mysteries we've had for decades. In some cases the reasons are clear. Inheriting a mutated BRCA1 gene or smoking dramatically increases the risk. And then there are the other cases where the reason seems to be less clear. Why do some children develop lukemia even without inheriting any mutations? Does drinking coffee increase or decrease your risk for cancer?

Earlier this year researchers at Johns Hopkins University attempted to answer one of these questions. They investigated why some cancers are more likely to occur than others. Publishing their results in the journal *Science*, they found that two thirds of the difference in risk of certain cancers could be explained by the number of stem cells in those tissues. The underlying idea was that more stem cells meant more dividing cells, which meant more opportunities for random mutations that could potentially cause cancer to accumulate.

But by the time the research went from the pages of the *Science* to the pages of news outlets everywhere, the crux of the story had morphed into 'cancer is mostly bad luck.' Headlines reporting the study went along the lines of "Cancer's Random Assault" and "Most cancer types 'just bad luck'". The study evoked stringent criticism from all sides including researchers, public health experts and even the WHO's International Agency for Research on Cancer as many thought it dismissed important cancer prevention efforts. The press release and media coverage received it's share of the blame as well, for what many considered irresponsible reporting. Johns Hopkins eventually released an explainer, interviewing the authors Cristian Tomasetti and Bert Vogelstein. (For more on how the earlier controversy played out, you can read this piece I wrote for GLP.)

Now the focus is back once again on what contributes to cancer risk as a new study that appears to contradict the findings of the *Science* paper was published yesterday in the journal Nature. According to the authors of the new study, between 70 and 90 percent of cancers risk can be attributed to environmental factors such as exposure to UV radiation or carcinogens rather than just random mutations.

Unsurprisingly, the results have led to reporting that is on the other end of the spectrum from how the *Science* study was reported, claiming "Most cancer cases due to lifestyle choices, not 'bad luck,' study suggests" and "Up to 90 percent of cases 'could be wiped out by avoiding triggers caused by our unhealthy lifestyles'."

The backlash has already begun, with one opinion piece in The Independent titled "My mother's cancer wasn't her fault." The author calls the study an 'offense' to people like her mother who have fought breast cancer and ends with a plea to "tread the line between advocating prevention and attributing blame carefully."

Does the study place blame on individuals as the author of the opinion suggests? What do experts think about the new findings and what can we take away from it?

According to a news report in Nature, Yusuf Hannun, the senior author of the new study and a cancer researcher at New York's Stony Brook University, didn't quite believe the results by Tomasetti and Vogelstein and decided to do an analysis himself, taking a different approach. Hannun and his team used multiple methods, including mathematical modeling, recorded epidemiological data on cancer incidence and information on genetic mutations that were known to be associated with cancer to come to their conclusion.

Andrew Maynard, Director of the Risk Innovation Lab at Arizona State University in a statement to the Genetic Expert News Service (GENeS) said the new study was robust as it used more than one approach to look at the issue of cancer risk,

> [The authors] set out to challenge the "bad luck" hypothesis that suggests some cancers are dominated by uncontrollable random cell mutations, rather than controllable environmental factors. Using four separate approaches, Wu and colleagues demonstrate that many observed cancer rates can be convincingly understood by assuming environmental factors have a substantial role to play.
> Each of the methodologies used by the research team has its assumptions and limitations. Yet together, they build a picture of a complex interplay between internal random biological processes, and external factors, in the formation and development of cancers. Their analysis supports conventional thinking around cancer formation and development, and casts doubt on the idea that some cancers are relatively independent of how you live and what you're exposed to.

However, other experts are not so sure that the numbers of the new study can be taken at face value. Giles Hooker, a statistician with expertise in said,

> [The authors] rely on a very simplified model of cancer mutation and the resulting numbers should at best be regarded as ballpark estimates. The authors attempt to separate intrinsic and external risks by producing a baseline, using tissues with lowest lifetime cancer risk relative to their number of cell divisions. Any tissues with cancer risk above this baseline is suggested to be associated with environmental factors.

And by using only the lowest risk cancers, the study "maximizes the risk attributed to environmental factors," said Hooker. According to him, the model also assumes that mutation rates are the same in different types of cells. Why does this matter? In this case, a tissue with a high propensity for

accumulating random mutations could be categorized by the model as one with a high environmental risk, which may skew the findings.

Tomasetti and Vogelstein, authors of the original Science publication, agreed with Hooker, suggesting in an interview to GENeS that by choosing cancers with the lowest incidence, the authors "pre-guaranteed their conclusion: that intrinsic factors played a less important role in all other cancers." They also pointed out that the model doesn't reflect what we know about some cancers.

> The mathematical flaw of this approach is also clear from the results. The authors concluded that >95% of brain cancers, >99% of prostate cancers, >98% of thyroid cancers, and >94% of testicular cancers are due to extrinsic factors. Epidemiologists have studied these cancers for decades and estimate that virtually none of the risk for any of these cancer types can be ascribed to extrinsic factors.

In an interview with Nature News, Tomasetti also noted that their results were "meant to explain only why some cancers are more prevalent than others" and not why cancers develop in the first place.

So where does that leave us? What all the experts agree on, including Tomasetti and Vogelstein is that cancer isn't just caused by "bad luck" or environment alone.While these models are useful to estimate risk, they only help us get closer to the truth. But reality, as always is much more complex. We do have significant evidence that certain lifestyle choices put us at risk for some cancers. And those cases provide a strong foundation for public health interventions that can improve the health of our society as a whole. In discussing the Nature study published yesterday, Jian-Min Yuan, the Arnold Palmer Endowed Chair in Cancer Prevention at the University of Pittsburgh Cancer Institute said,

> The current epidemiological evidence strongly supports an important role of environmental factors in the development of cancer. For example, people who stop smoking at 55 years would cut their lung cancer risk by half compared with those who continue smoking by 85 years of age. HBV vaccine has resulted in the reduction of hepatocellular carcinoma incidence by 70 percent. These results demonstrate that a large proportion of cancer is caused by environmental factors and are preventable if their underlying environmental causes are identified.

However, one can also easily visualize how these findings and news reports may be taken as further cause for alarm by individuals or advocacy groups with beliefs about how environmental factors are putting them at risk for cancer, even if some of those claims may be unsubstantiated by science.

In these cases, what risk communication expert Andrew Maynard recently wrote in his personal blog is worth keeping in mind.

> In reality both this paper and the earlier "bad luck" one provide partial insights into the causes of cancer that are informative, but not conclusive. Taken in isolation – especially if used to

support strongly held beliefs – [these findings] are open to misinterpretation and misuse. However, as part of a growing body of research on how different factors impact the chances of developing cancer, they add to an important and evolving tapestry of knowledge.

Arvind Suresh is a science media liaison at the Genetic Expert News Service. He is also a science communicator and a former laboratory biologist. Follow him @suresh_arvind.