

# Most Cancers Are Not Due to 'Bad Luck'

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This year began with the media buzzing over a study that suggested many cancer types can be chalked up to "bad luck." As the year draws to a close, a new study that reanalyzed some of the previous data concludes that bad luck accounts for only a small portion — up to a third — of cancers, and that external factors, such as environmental toxins and behaviors, account for the vast majority (90% to 70%).

As [previously reported](#) by *Medscape Medical News*, researchers from Johns Hopkins University, Baltimore, Maryland, reported that in about two thirds (22 of the 31) of cancer tissue types that they had investigated, the development of cancer could be largely explained by the bad luck of random mutations that arise during DNA replication in normal nonmalignant stem cells.

The [new study](#), published in *Nature*, challenges those findings and instead states that there is much more at stake than just a bout of bad luck.

A team led by Yusuf Hannun, MD, director of the Stony Brook University Cancer Center, in New York, found that intrinsic or internal risk factors contribute only modestly — less than approximately 10% to 30% of lifetime risk — to cancer development.

Their research concluded that instead, cancer risk is heavily influenced by extrinsic or external factors, such as environmental toxins, behaviors, and infections.

"We used four distinct analytic approaches to assess cancer risk," Dr Hannun told *Medscape Medical News*. "Interestingly, each of the approaches used different datasets, and all of them came up with similar conclusions — that 70% to 90% of cancer risk seems to be attributed to extrinsic factors, and this is more in line with what we've seen with epidemiologic studies.

"Efforts should be aimed at identifying the factors and then doing something to prevent them," Dr. Hannun said. "We can't identify every factor or prevent them. We have to accept that, but efforts should be made at identifying and mitigating them."

## Backlash and Media Mangling

The original study on bad luck was [published](#) in *Science* on January 2 and immediately generated quite a bit of discussion, scrutiny, and opinion pieces, as well as many questions regarding the methods and calculations used in the study.

Even the International Agency for Research on Cancer, the World Health Organization's specialized cancer agency, [issued a press release](#) saying that it "strongly disagrees with the conclusion" and warned that the message could harm cancer research and public health.

Part of the problem related to how the media reacted to the study. Headlines appeared with titles such as, "Most Cancers Caused by Bad Luck" and "Cancer Is Down to Bad Luck," misinterpreting the study's findings to mean that two thirds of all cancer cases occur as if by a simple roll of the dice.

In response to the backlash, the study authors issued further comments in a Johns Hopkins University [statement](#) that included a press release that had been "amended for clarity." In addition, *Science* ran a [follow-up piece](#) that further clarified the research.

"The authors made their conclusions without paying attention to the fact that they really needed to qualify them," Dr Hannun told *Medscape Medical News* in an interview. "And if they had done that early on, we wouldn't have had all of this hoopla."

Although many of the news articles reporting the study's findings presented a distorted simplification of those findings, that is only part of the story, he explained. "The real issue is that in the data they showed and analyzed initially, they made a conclusion that the number of divisions in stem cells correlates strongly with the risk for cancer, and that explains a lot of the variation incidence.

"That conclusion is okay," continued Dr Hannun, "but somehow they added snippets here and there, like in the abstract and the end of the paper, that phrased it in a way that was ambiguous. They did use the term 'bad luck' and how that can explain the total incidence of two thirds of cancer, and that was not warranted for this type of analysis."

In addition, there are two aspects of the study as a whole. "We have really no quarrels with their data, and in fact, we used their data for at least one part of our paper," he said. "We have no quarrels with the conclusions they are making right now, that these data can explain some of the variation and incidence. But this cannot be translated into causation. That was an overstretch, and the media picked up on that, and suddenly it was all about causation part."

## Four-Step Approach

Dr Hannun's study was prompted by this earlier work. He and his team used a multipronged approach to try to pinpoint the contribution of environmental factors to cancer risk.

First, they demonstrated that the correlation between stem cell division and cancer risk does not distinguish between the effects of intrinsic and extrinsic factors. Using a data-driven approach, they re-examined the quantitative relationship between the observed lifetime risk for cancer and division of the normal stem cells in those groups that were initially reported in the *Science* article. If intrinsic risk factors did play a major role, then similar stem cell divisions would be associated with similar observed lifetime cancer risk.

However, the authors found that this pattern was rare, and they determined that intrinsic factors played a vital role in only about 10% of cancers. In support of this finding are epidemiologic data, such as those that show that immigrants who move from countries with lower cancer incidence to countries with higher rates generally acquire the higher risk as they become more assimilated into their new country.

Second, the authors analyzed recent studies on mutational signatures in cancer and found that the majority of cancers, including colorectal, lung, bladder, and [thyroid cancer](#), express mutations that are likely caused by extrinsic factors.

Third, analysis of data from the Surveillance, Epidemiology, and End Results Program showed that for many cancers, incidence and mortality have been increasing, suggesting that external factors contribute heavily.

Finally, computational modeling to dissect the contribution of the intrinsic processes in the development of cancer showed that when three or more mutations are required for cancer onset (a currently accepted parameter), intrinsic factors are far from sufficient to account for the observed risk. This indicates the small percentages of intrinsic cancer risks in many cancers.

## A Game of Russian Roulette

The question now is, does bad luck fit into it at all? The role of random mutations as an intrinsic cause has been very well studied and quantified in various human cells, Dr Hannun said in an interview. "In one of our approaches, we asked if it takes three hits in a cell on a specific gene to cause cancer, and what would be the expectation that the intrinsic rate would generate cancer. The answer to that was only 10%."

But this is not to say that intrinsic mutations are not important in cancer pathogenesis. Many, if not all, of the external factors cause cancer by increasing these mutations, by accelerating them, or allowing cells to survive in spite of mutations. "But when you talk about intrinsic risk, it should only refer to that basal level of mutation," Dr Hannun emphasized.

A good analogy is with the risk associated with Russian roulette. "If you have a gun, and you have one bullet, then you have a 1 in 6 risk, and that's the intrinsic risk," he said. "But if you load in more 'bullets,' such as smoking or sun exposure, then you increase that risk."

The more bullets that are put in the gun, the more the risk goes up. "There is still the element of luck, but the odds are increasingly stacked against the person," Dr Hannun explained. "Not everyone who smokes gets lung cancer, not everyone who goes into the sun will get skin cancer, not everyone who gets [hepatitis](#) gets [liver cancer](#), so there is still that element of uncertainty — a word that I like better than luck."

## Experts Support New Data

Commenting on the new article, Paul Pharoah, BM BCh, PhD, professor of cancer Epidemiology, University of Cambridge, United Kingdom, noted that the current study uses a number of data modeling approaches to demonstrate that the majority of cancer risk comes from external factors.

"While each of the methods used has different assumptions, any of which might be challenged, all of them result in the same conclusion, suggesting that in general terms, the conclusion is robust," Dr Pharoah said in a statement. "The results are also broadly in line with other published data."

However, he also pointed out that the "estimates of 10% to 30% of the variation in risk being intrinsic is not cancer specific, and the data for any one cancer are not accurate enough to be able to state with any certainty what the contribution of intrinsic and extrinsic factors are to any one cancer. Nor do the data tell us about specific external risk factors other than those we already know about.

"It is important to realize that these results do not tell us anything about the absolute risks of any given cancer," Dr Pharoah said.

Another expert agreed. "I don't think these authors are really claiming that 70% to 90% of all cancers are caused by external risk factors," said Kevin McConway, PhD, professor of applied statistics, the Open University, Milton Keynes, United Kingdom. "But

they do provide pretty convincing evidence that external factors play a major role in many cancers, including some of the most common.

"Even if someone is exposed to important external risk factors, of course, it isn't certain that they will develop a cancer. Chance is always involved," he said in a statement. "But this study demonstrates again that we have to look well beyond pure chance and luck to understand and protect against cancers."

Dr McConway added that the aim of the authors was to "calculate what percentage of cancers would not arise if we could wave a magic wand and get rid of all possible external risk factors. There would still be cancers, because of the way that cells divide in the body, but there would be fewer of them."

*The authors, Dr Pharoah, and Dr McConway have disclosed no relevant financial relationships.*

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