Medical Xpress

New mathematical model may help better define roles of environmental and intrinsic factors in cancer initiation

April 20 2016

A mathematical model that takes into account the number of mutations required to initiate a specific type of cancer to estimate mutational activity, rather than cancer initiation, as the elementary event (as reported in two studies last year, one of which generated the "bad luck" hypothesis) may help better define the contributions of environmental factors and cellular factors in cancer initiation, according to data presented here at the AACR Annual Meeting 2016, April 16-20.

"Understanding the impact of environmental and cellular factors in causing cancer is important because it will help define the amount of emphasis needed on cancer prevention versus early detection," said Sven Bilke, PhD, staff scientist in the Genetics Branch of the National Cancer Institute (NCI). "This knowledge would also give some insight into the feeling of guilt people may have when they are diagnosed with cancer."

Bilke and colleagues developed a new mathematical model to reanalyze the data that were used by Cristian Tomasetti and Bert Vogelstein in their study published in *Science* last year, which found a correlation between the number of cell divisions in different tissues and the risk of getting cancer in that tissue. The study concluded that about two-thirds of variations in cancer risk can be explained by the number of stem cell divisions.

Another paper published last year in *Nature* by Song Wu and colleagues

questioned that interpretation by pointing out that the mathematical model the authors had chosen was intrinsically insensitive toward changes in the environment that can influence cancer risk, and therefore, cannot distinguish between environment and accident.

"However, both Tomassetti and Wu analyzed 'cancer initiation' as the elementary process," Bilke explained. Both studies found that the cancer incidence rates closely track the number of cell cycles. But they disagreed on how to choose the baseline that defines the intrinsic cellular, or "bad luck" component of the risk, he said. Consequently, they disagreed on what constitutes the excess, environmentally driven cancer risk.

"In our analysis, we studied 'cancer-driver mutations' as opposed to 'cancer initiation,'" Bilke continued. "It is well established that cancer is the consequence of driver mutations, and the immediate impact of environmental as well as accidental factors is mutation, not cancer initiation." Excess mutations caused by the environment (or lack thereof) should thus be seen in the mutation rate, with the cancer initiation rate recapitulating that excess in a complex way, he added.

"Our work estimates this mutation rate from the same data the other two studies used by taking into account that different cancer types require a different number of driver mutations to occur. For example, it takes about six mutations on average to initiate colorectal cancer, while only two mutations are sufficient to initiate retinoblastoma," Bilke said.

Tomasetti and Vogelstein estimated that less than about 40 percent of cancer incidence is caused by environmental factors, with the exception of lung and skin cancer, and genomic predispositions, continued Bilke. Reinterpretation by Wu and colleagues led to a much higher estimate (more than 90 percent) of environmental contributions in many cancers.

"In our study, we find that the mutation rate, not cancer incidence, follows a much narrower distribution, largely taking away the possibility for competing interpretations. We find that more than 80 percent of the mutation rate is accidental, with the exception of colorectal, skin, and lung cancer, where a significant excess was detectable," he added.

"Using our mathematical approach, we found that with the exception of environmental factors such as smoking, ultraviolet (UV) radiation, and diet, which are associated with some cancers, in most cases, cancer-driving mutations are largely random chance occurrences," Bilke said. "Even in the absence of excessive carcinogens in the environment, mutations still occur and are difficult to prevent. Therefore, it is paramount to follow cancer screening recommendations."

"The results of our study do not at all question the carcinogenic role of smoking, diet, and UV radiation in lung, colon, and skin cancer, respectively. Instead it confirms their role by identifying an increased rate of mutation in these cancers compared with baseline, as in the case of lung cancer among smokers," Bilke noted. "Carcinogens remain dangerous and should be avoided."

As a limitation, Bilke noted that the study estimated the number of required driver mutations using epidemiologic data based on somewhat stringent assumptions. Some frequent cancers not following these assumptions, like hormone-dependent cancers, were therefore not included in this study.

More information: C. Tomasetti et al. Variation in cancer risk among tissues can be explained by the number of stem cell divisions, *Science* (2015). DOI: 10.1126/science.1260825

Song Wu et al. Substantial contribution of extrinsic risk factors to cancer development, *Nature* (2015). DOI: 10.1038/nature16166