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COMMENTARY

"Bad luck" hypothesis and cancer prevention: translating the debate to more actions

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Etiologic research constitutes an essential part of both biology and epidemiology. For cancer, our biological understanding about its root cause has been significantly advanced by genetic research in the past few decades. It is now widely accepted that cancer is the result of accumulation of gene mutations that successively increase cell proliferation [1]. On the other hand, population-based epidemiologic studies have focused on extrinsic and hereditary causes of cancer and identified a variety of modifiable risk factors. These data have been translated into effective prevention strategies (e.g., tobacco control) that have largely contributed to the decline in cancer mortality in the recent decades (e.g., 27% decrease between 1991 and 2016 in the United States) [2].

While each of the two major branches of cancer research—molecular biology and epidemiology—has made substantial contributions to cancer etiology, they have developed largely independently and the threads that connect them are often thin [3]. This thin connection is bluntly unfolded by the widespread controversies on a *Science* paper led by Tomasetti and Vogelstein in 2015 [4]. The study found a high correlation ($r=0.81$) between the number of stem cell divisions of a given tissue and the lifetime risk of cancer in that tissue, leading to the conclusion that only a third of the variation in cancer risk among tissues is attributable to environmental factors (E) or hereditary predispositions (H), while most is due to random mutations (R) arising during stem cell divisions, so-called bad luck. This provocative "bad luck" hypothesis led to an intense scientific debate regarding the role of R, E and H factors in cancer etiology, as highlighted in numerous commentaries and modeling studies.

In the current issue of the Journal, Perduca et al. review the debate, identify some misinterpretations of the data, and examine the underlying assumptions of different modeling studies that may have contributed to their divergent conclusions. Several important points are worth noting. First, while the stochastic effects of DNA replication have long been recognized, the work by Tomasetti and Vogelstein represents the first effort to numerically estimate their impacts on the variation in cancer rates *across organs*. However, this estimation itself does not inform about the preventability of a certain cancer *in the population*, which should be and has been estimated on the basis of the comparison of cancer rates across populations with different risk factor profiles [5]. This point has appeared to be the major source of confusion in the media coverage and controversy about the "bad luck" hypothesis, despite the attempt for clarification by Tomasetti et al. in a follow-up study in 2017 [6]. The hypothesis has been wrongly viewed by many as a contradiction to the substantial evidence that environmental factors are the major cause of cancer and that at least half of cancer deaths can be prevented by changing modifiable risk factors [7].

To clarify some of the confusions, we recently contributed a joint commentary, in which we specifically highlighted the distinction between mutation etiology and cancer preventability [3]. Because mutation is necessary but not sufficient for cancer development, cancers can still be preventable as long as one of the mutations driving toward cancer is caused by E. Therefore, the "bad luck" hypothesis does not contradict the preventability of cancer. In fact, research in both molecular biology and epidemiology supports that a greater focus on various forms of prevention, rather than on curing patients with advanced disease, is necessary to substantially reduce deaths from cancer in the future [3].

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Second, a key assumption of the "bad luck" hypothesis is that R is completely independent of E, because R is considered as the baseline mutation rate that has been measured in the absence of any external influences. While this is true theoretically for truly random mutations, in reality it is almost impossible to identify the mutations that occur in a completely stochastic manner from those induced by extrinsic factors. Recently, whole-genome sequencing studies have revealed the diversity of mutational processes in cancer [8] and attempted to link different combinations of mutation types, termed 'signatures', to specific environmental exposures [9, 10]. For example, a study compared the mutation landscape of lung cancer between smokers and nonsmokers, and found that compared to non-smokers, smokers had significantly higher mutational load, different mutation spectrum, and distinctive sets of mutations (e.g., mismatch repair gene mutations) that might confer high susceptibility of cancer cells to more mutations and uncontrolled cell proliferation [11]. These investigations are critical to strengthen the ties between molecular biology and epidemiology, and shed light on the mechanisms through which environmental exposures may influence cancer.

To illustrate the importance of these investigations, Perduca et al. also present an original analysis by leveraging the cancer genome sequencing data in smokers and the epidemiologic data on the association between smoking and risk of seven cancers, for which tobacco smoking is an established risk factor. They found a correlation of $r = 0.93$ between mutation rates in smokers and cancer risk elevation associated with smoking across different organs. In contrast, a nonsignificant inverse association ($r = -0.65$) was found between lifetime stem cell divisions of a given organ and the smoking-related risk elevation of cancer in that organ. These data led to the conclusion that mutations due to environmental exposures might be a better predictor of cancer risk than random mutations.

The analysis by Perduca et al. provides a different perspective to study the heterogeneity of cancer risk across organs. Instead of examining absolute cancer risk, Perduca et al. focused on the relative risk associated with a specific exposure and then examined its correlation with the exposure-related mutation rate. By integrating the genomic and epidemiologic data, the analysis elucidated the potential contribution of exposure-induced mutations to the risk variation across different cancers, which provides a complementary view to the "bad luck" hypothesis.

As a preliminary analysis, however, it has several limitations, including examination of only a small number of smoking-related cancers, lack of consideration of the intensity- and duration-dependent effect for smoking, derivation of the relative risk estimates from a single cohort study (the European Prospective Investigation into Cancer and Nutrition study), and missing mutation data for some cancers. Moreover, while relative risk was used to estimate the effect of smoking on cancer development, absolute mutation rates in smokers were used to represent the mutational effect of smoking. Because some of the mutations in smokers are presumably caused by other factors than smoking (e.g., age, alcohol, and other environmental exposures) and these factors may have variable effects on the studied cancers, there may be confounding in the correlation estimation. Therefore, further systematic studies are needed to better evaluate the relationship between exposure-related mutations and cancer risk.

Finally, while it has been more than 4 years since the beginning of the debate, the next legitimate question is how we can move forward based on the reconciliation and remaining divergence about the "bad luck" hypothesis. Perduca et al. proposed several next-step questions from a modeling perspective, including integrating hereditary and environmental factors into estimation of stem cell divisions, and accounting for other cancer-causing mechanisms besides mutation, such as epigenetics, DNA repair system, and immune surveillance. These are all important directions for future research, which will likely lead to a better understanding about the link between R, H, and E factors in cancer development, and strengthen the connection between epidemiologic and molecular perspectives on cancer etiology. In the meantime, as highlighted in our recent commentary [3], continued effort is needed to identify more modifiable risk factors, particularly early-life factors, and to study the molecular mechanisms underlying the role of environmental factors in cancer. Last but not least, while we have known that most of cancer cases and deaths are preventable, what is lacking is to translate available evidence into action, by designing and implementing cost-effective strategies tailored to region-specific demographics, risk factor profiles, and resource availability. These efforts together will help us better understand cancer etiology and accelerate the full realization of the potential of cancer prevention.

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Compliance with ethical standards

Conflict of interest The author has no conflict of interest to disclose.

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