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A critical examination of the "bad luck" explanation of cancer risk

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Abstract

Tomasetti and Vogelstein (1) argue that lifetime cancer risk for particular tissues is mostly determined by the total number of stem cell (SC) divisions within the tissue, whereby most cancers arise due to "bad luck" – mutations occurring during DNA replication. We argue that the poorly substantiated estimations of SC division parameters and assumptions that oversimplify somatic evolution prevent such a conclusion from being drawn.

Cell divisions are required for the generation and tumorigenic manifestation of oncogenic mutations, an idea appreciated for decades. Likewise, the critical role for aging in cancer development, independent of external factors such as sun exposure or smoking, has long been recognized. Tomasetti and Vogelstein propose that the critical factor linking mutations and cancer is the cumulative number of divisions that tissue-restricted stem cells undergo. Thus, for their argument to hold, one must have reliable measurements of the number of stem cells in the tissue and their division rates, and assume that cancers are unlikely to arise from mutations occurring in non-stem cells. However, the following considerations reveal that these critical parameters and assumptions lack experimental substantiation.

For multiple tissues, Tomasetti and Vogelstein use mouse data to derive human SC division rates, but these rates for human SC have not been verified experimentally and may be off by orders of magnitude. For example, hematopoietic SC (HSC) division rates were estimated from mouse data at once per month, while evidence shows that human HSCs divide once in 7–14 months (2–4). Moreover, the estimates of HSC numbers (1.35×10^8) based on surface marker detection is orders of magnitude higher than those obtained using functional assays or modeling (10^4–10^5) (5, 6). These estimates were used for acute myeloid and chronic lymphocytic leukemia. Mouse derived data were similarly used to estimate the fraction of thyroid SC (medullary thyroid carcinoma) and pancreatic SC (pancreatic endocrine

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carcinoma and ductal adenocarcinoma). Oral mucosa SC estimates (head and neck squamous cell carcinoma) reference HSC and murine intestinal SC studies (their Supplemental references 39 and 65). While tissue development and maintenance in different mammals have many clear similarities, the evolution of body size and other life history traits in animals affects the relative ratios of mass, volume and surface areas of different tissues, as well as their function and maintenance, thus impacting the underlying SC pools (including pool sizes and division frequencies). Tomasetti and Vogelstein actually mention one example, in that mouse small intestinal SCs undergo more divisions than mouse large intestinal SCs, which is the opposite for humans.

The reality is that we do not currently have a good understanding of SC numbers, their division frequencies for most human tissues, and the diversity of cell types or environmental perturbations that can initiate cancer and lead to progression. For example, the authors assume that hepatic SCs represent 0.5–2% of total hepatocytes. The applicability of this number to estimating total cell divisions is questionable as hepatocytes are the major contributors to liver maintenance and are suspected to be involved in cancer initiation (7). In the pancreas, definitive SCs remain a matter of debate, and there is an increasing consensus that pancreatic cancer can be initiated by injury- or inflammation-induced acinar-ductal reprogramming to generate stem-like cells (e.g., see (8)). For the esophagus, Tomasetti and Vogelstein used a SC frequency of 0.4%, citing a paper in which the authors provide evidence disfavoring the existence of esophageal stem cells, and rather supporting a model in which injury reprograms progenitors to enable repair (9) (the 0.4% of “label-retaining cells” were shown to be hematopoietic in this paper). In the colon, tuft cells encoding an oncogenic lesion remain differentiated until exposed to persistent inflammation, which induces de-differentiation and generation of stem-like cells that initiate invasive adenocarcinoma (10).

While Tomasetti and Vogelstein argue that their correlations maintain significance over ~100-fold changes in estimated SC divisions in either direction, this does not guarantee that the differences in cancer risk among tissues explained by SC divisions will not be lower than the estimated 65% claimed by the study. Even with four logs of possible variance in their calculations, other factors such as injury and chronic inflammation likely play significant roles in cancer initiation and progression. Combined, these concerns suggest that the actual impact of tissue cell divisions on cancer risk may differ substantially from that obtained by the authors, with a note also that correlation itself does not generally imply causation.

Importantly, the “bad luck” model (and the somatic mutation theory of carcinogenesis in general) does not consider other differences between tissues that could significantly affect driver mutation acquisition, or the conditions needed for such mutations to impact carcinogenesis. This model does not discriminate between the likelihood of mutations happening anywhere in a tissue and the probability of *multiple* driver mutations happening in one cell (most cancers require multiple mutations). Clonal expansions driven by oncogenic mutations cause a manifold increase in the number of dividing cells that all carry the same oncogenic driver. This proportionally multiplies the likelihood of other drivers arising in this context. Even a small expansion into a 100 cell clone increases this probability by two orders of magnitude. The cumulative number of SC divisions analyzed by Tomasetti

and Vogelstein does not consider the effects of an oncogenic mutation on clonal expansion, which will underlie the chances for the next mutation to occur. On this point, tissue structure clearly comes into play. Gut epithelial SCs are fragmented into small clusters of competing SCs (15–20 cells) hidden in crypts, and their clonal dynamics and the fate of oncogenic mutations in the crypts have been shown to be strongly governed by random drift (11–13), consistent with the classic Wright-Fischer and Moran models of the drift/population size relationship. Thus, in the gut epithelia, the expansion of an oncogenically-initiated clone will be limited by crypt space and buffered by drift, and the total number of cells (the "context") harboring such a mutation will primarily depend on the number of crypts in which it occurs. In HSC pools, on the other hand, which represent large competing populations (14), the probability of sequential driver acquisition can be elevated by orders of magnitude via selection-driven clonal expansion of oncogenically-initiated cells. Such a dramatic effect of tissue-specific SC pool architecture is a factor overlooked in the correlation-derived "bad luck" explanation for tissue-specific cancer risk. Moreover, the correlation that has led to the conclusions of this study also did not take into account that different cancers require different numbers of cancer driver mutations, which should confer corresponding differences in cancer risk per equal numbers of cell divisions. For example, it is not clear from the "bad luck" perspective why cancers, such as CML, thought to be driven by a single oncogenic mutation (15), increase in incidence at similar ages as other cancers that require multiple mutations. This suggests that microenvironmental factors likely impact the genesis of even mutationally "simple" cancers.

The "bad luck" model does not take into account the many situations whereby SC division rates and/or mutation accumulation do not correlate with cancer risk for a particular tissue or organism. For example, contrasting with humans, commonly used mouse strains exhibit a much higher incidence of hematopoietic cancers relative to carcinomas (16). This is at odds with the postulate that SC division numbers and the resulting mutations are the main cause of cancer risk, as tissues such as the heart, liver and small intestine actually accumulate more mutations than the spleen in mice (17). Moreover, the observation that mice with a mutation in DNA polymerase δ (L604G), which leads to a ~5 fold increased mutation rate, do not show an increase in cancer incidence (18), argues against the simple model that the occurrence of mutations limits cancer incidence. The conclusions by the authors are also inconsistent with the delay in the incidence of most cancers (largely after age 50), while roughly half of all SC divisions, mutations and epigenetic changes occur by about age 20 due to much faster SC division rates during body maturation (19, 20). Finally, the model also cannot explain why larger animals, like whales, which should experience many more SC divisions than a mouse, do not have proportionally more cancers. Combined, these examples argue that cell divisions and mutation accumulation frequently do not correlate with cancer occurrence, arguing against a simple relationship between the two.

From the theoretical perspective, the "bad luck" model of cancer risk is based on the somatic mutation theory of cancer, which argues that cancer is limited by the occurrence of oncogenic mutations. However, the key problem is the discrepancy of this prevalent paradigm of cancer with evolutionary theory. It is generally postulated that oncogenic mutations confer a set fitness advantage to cells, thus defining fitness as a cell-intrinsic and stationary property. The occurrence of oncogenic mutations is therefore assumed to trigger

clonal expansion upon incidence. However, genetic changes are only known to have defined phenotypic effects, but fitness is a dynamic property imposed by external environments. A particular somatic genotype may confer a hypoxia or drug resistance phenotype, but its relative fitness advantage only appears under hypoxic or drug application conditions and is proportional to the severity of the condition. This dynamic fitness definition explains why populations adapted to an environment are dominated by stabilizing selection, and positive selection becomes mostly promoted by altered environments. In terms of cancer, it suggests that the aged tissue microenvironment during the post-reproductive period of life, to which selection for tissue fitness is “blind” at the germline level, should alter (increase) the selective value of particular somatic mutations and promote somatic evolution as tissue microenvironments progressively deviate from the youthful state (towards which SCs evolved to be adapted) (21). With the substantial role of clonal expansions in determining the probability of sequential driver acquisition discussed above, tissue changes, such as with aging, or associated with inflammation, obesity, etc., could influence somatic evolution rate and significantly alter the odds of multi-driver cancers. Yet, the somatic mutation theory and the “bad luck” model overlook the forces that determine the balance of drift, stabilizing and positive selection, as well as the evolutionary mechanisms that govern the fitness value of phenotype-altering genetic changes. Thus, from the evolutionary standpoint, we should be able to reduce the risk of cancer by modifying lifestyle to improve tissue fitness, better preserving cancer-suppressing microenvironments that prevent oncogenic driver mutations from manifesting themselves.

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