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Intrinsic vs. Extrinsic Cancer Risk Factors and Aging

Dmitriy I. Podolskiy¹ and Vadim N. Gladyshev^{1,*}

¹Division of Genetics, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115, USA

Abstract

Two recent stimulating publications have examined the causes of cancer, comparing “bad luck” vs. environment as main risk factors for cancer incidence. However, bringing aging into the picture might question the entire debate.

Certain individuals develop cancer at some point in their lifetime, while others do not, and certain human tissue types give rise to cancers more often than others. Understanding the main risk factors of cancer development as well as their interplay may inform on avenues for cancer research as well as prevention strategies. A recent debate on the nature and contribution of cancer risks has attracted much attention from scientists as well as mass media, centering on the relative importance of extrinsic *versus* intrinsic risk factors. One study has reported that environmental risk factors such as smoking, UV exposure or high-fat diet account for at least 70–90% of lifetime cancer incidence [1]. However, another study argued that only a third of the variation in cancer risk among tissues was attributable to environmental factors or inherited predispositions, suggesting that the majority of cancers simply result from “bad luck,” i.e. random mutations arising during DNA replication in normal stem cells (SC) [2]. So, which risk factors, “bad luck” or extrinsic environmental factors, lead to the majority of cancers? Here, we argue that intrinsic and extrinsic risk factors are not always mutually exclusive and furthermore, that they strongly co-depend on each other. We posit that this debate omits another important risk factor, aging, which at least for some malignancies can dwarf the contributions of both “bad luck” and extrinsic factors.

For most cancer types, oncogenic incidence is known to grow exponentially during adulthood [3]. Age-associated malignant growth, first explained by Armitage and Doll [4], shows a strong correlation with age-dependent mutation load and burden [5]. In fact, cancer incidence and mutation load doubling rates are similar to human mortality rates. As such, age-dependent mutation load, burden and cancer incidence may be viewed as proxies for the accumulation of molecular damage with age and the aging process itself.

*Correspondence should be addressed to V.N.G. (vgladyshev@rics.bwh.harvard.edu).

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It is then natural to ask how much of an age-dependent mutation load can be attributed to a given intrinsic or extrinsic risk factor? The answer to this question can be provided by an analysis of the contributions of different ‘mutational signatures’ to a mutational load (which itself is proportional to the probability of initiating malignant clonal expansion from a cancer cell). Mutational signatures are common specific mutational patterns for different cancers, believed to be imprints of various mutational processes on the human genome, resulting from various external or internal stressors [6]. Since the contributions of different mutational signatures to the total mutation load can change with the age of a patient, so do the relative contributions of different external and internal risk factors to the total risk of cancer incidence.

Among the 30 known mutational signatures, only Signature 1 (due to spontaneous deamination of 5'-methylcytosine) and Signature 5 (of unknown etiology, possibly due to errors in transcription-induced repair) contribute consistently across cancer samples and cancer types to incidence and correlate with the patient's age. Other signatures contribute to incidence based on the cancer type, correlating very weakly (or not at all) with age [7]. However, it is easy to see that for all considered cancer samples the cumulative mutational load due to only Signatures 1 and 5 is lower than the total age-dependent mutation load (Figure 1). The apparent conundrum might be explained if one considers that the total age-dependent mutational load which correlates with cancer incidence, might also comprise contributions from other mutational signatures, and perhaps, other mutational processes.

Moreover, the rate of aging is determined by a large number of internal factors (such as epigenetic instability or immune system dysregulation with age) as well as external stressors (such as exposure to UV light or smoking). Consequently, one should expect different mutational processes to provide interacting, synergistic contributions to the age-dependent mutation load and burden. The dynamics of aging, in turn, affect the age-dependent change in sensitivity of an organism to stressors. In addition, SC division rates (through age-dependent SC niche depletion), as well the probability of inducing mutation(s) during DNA replication (through the loss of transcription-induced repair efficacy) may also change with age. Deleterious mutations causing cancer can arise within this age-dependent background.

To manage the rise in mutations as a function of age, it might be beneficial to target the rate of aging, as an orthogonal strategy to identifying and eliminating extrinsic factors that contribute to cancer risk or accepting the inevitability of “bad luck”. It is well-known that the modulation of average lifespan and the rate of aging in animal models by genetic, dietary and pharmacological interventions also strongly affects cancer incidence [8]. Indeed, it has already been established that some of the same interventions can affect tumorigenesis and proliferation of cancer cells in humans as well [9,10]. Considering examples across species, mice and naked mole rats have similar body weights, but the latter live approximately 10 times longer. In laboratory conditions, mice mostly die from cancer, while cancer in naked mole rats is extremely rare. Furthermore, tumors can be easily induced in mice, whereas naked mole rats are exceptionally resistant to cancer. Thus, being subjected to similar extrinsic factors, and exhibiting similar numbers of SC divisions, different species may have widely different neoplastic occurrences.

Wu *et al.* [1] suggest that controlling for known and currently unknown extrinsic factors may dramatically reduce cancer incidence, whereas the implication of the Tomasetti and Vogelstein study [2] is that little can be done about “bad luck”. However, while it is clear that the elimination of some extrinsic factors such as smoking can indeed reduce incidence of certain cancers, other extrinsic factors leading to mutations (such as nutrients and molecular oxygen) simply cannot be avoided. Instead, approaches that might be successful in slowing aging could decrease the sensitivity to these types of DNA damage as well as affect SC division rates, hence influencing the “bad luck” factor. They thus harbor the potential of reducing the incidence of many cancers and ultimately, might offer a decisive advantage in dealing with this type of malady.

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Figure 1. The Total Age-dependent Mutation Load Exceeds the Contributions of Age-Related Mutational Signatures

A graph depicting the age-dependent mutation load (red) vs. the cancer incidence (green) as a function of patients' age is shown for breast invasive carcinoma in females. Contributions of mutational signatures 1 and 5 to the age-dependent mutation load are shown in dark red and purple, respectively. While these are the only signatures with the associated mutation load consistently growing with age in all cancers (see text), their contribution to total age-dependent mutation load is relatively small. Age-dependent mutation load and cancer incidence were estimated as described in reference 5. The contributions of mutational signatures 1 and 5 to the total mutation load were estimated using the data from reference 7.