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In Focus

Contributions of the Intrinsic Mutation Process to Cancer Mutation and Risk Burdens

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> "And by this experience his knowledge was reduced to diffidence, so that when asked how sounds were created he used to answer tolerantly that although he knew a few ways, he was sure that many more existed which were not only unknown but unimaginable" From "The Assayer", by Galileo.

Recently, debate has intensified on the role of intrinsic vs extrinsic vs modifiable factors in cancer etiology and prevention, and this has become intertwined with misconceptions of the role of 'bad luck' in cancer onset, which has garnered the attention of the public and lay media. This primarily arose from a line of investigation into the role and contribution of intrinsic factors in the pathogenesis of cancer. Here, we provide evidence that the contribution of unmodifiable intrinsic mutations to cancer mutations and burden is modest if not minimal.

Some confusion in the debate has arisen from a lack of clear definitions. Here we proffer the following definitions. 1. Intrinsic risk factors. We follow the definition of Tomasetti et al. (Tomasetti et al., 2017) that this represents the basal mutation of normal dividing human cells at approximately 5×10^{-10} per nucleotide per cell division (Wu et al., 2016), which is commonly recognized as unmodifiable. Also, similar to Tomasetti et al., we attribute cancers due to intrinsic risk to those arising solely from intrinsic risk factors (i.e. cancers where intrinsic risk factors are sufficient). 2. Extrinsic risk factors including: (2a) External risk factors from environment and lifestyle, and (2b) Internal risk factors arising internally per inheritance, aging, hormones, inflammation, etc. In addition, these risk factors may interact as there are well-documented gene-environment interactions in cancer such as APE1 and XRCC1 with smoking in lung cancer (Ito et al., 2004). Thus the phrase non-intrinsic risk refers to all risk except intrinsic risk, or equivalently, the sum of risks due to extrinsic factors, their interactions and the interactions between intrinsic and extrinsic factors (i.e. cases where intrinsic risk factors may be necessary but not sufficient).

In a thought-provoking study, Tomasetti and Vogelstein correlated the lifetime stem cell division to tissue-specific lifetime risk of cancer (Tomasetti and Vogelstein, 2015). Although initially this correlation was interpreted as the intrinsic risk accounting for 2/3 risk for cancer, subsequent analysis by our group demonstrated that this correlation does not distinguish the role of intrinsic from extrinsic factors that act through enhanced mutations and/or cell division (Ito et al., 2004). This conclusion was supported recently in an analysis by Nowak & Waclaw (Nowak and Waclaw, 2017).

This then calls for better estimation of the intrinsic risk. We had performed a genomic mutational signature analysis (Wu et al., 2016) based on published signatures (Alexandrov et al., 2013) for cancer, where signatures that increase linearly with time would suggest the operation of intrinsic risk. For lung cancer, we find the fraction of gene mutations due to intrinsic risk to be 9.1% for adenocarcinoma (accounting for 40% of all lung cancers), and 0% for both small cell and squamous lung cancer, yielding an overall intrinsic contribution of 3.6%—drastically lower than that by Tomasetti et al. of 33.4% (Tomasetti et al., 2017). This obvious discrepancy may largely be explained by risk factors omitted/unidentified by Tomasetti et al., including second hand smoking, radon and air pollution (Swanton et al., 2016). Additionally, applying a stochastic cancer stem-cell model (Wu et al., 2016), we estimate the probability of acquiring 3 diver mutations to be under 4.6×10^{-5}, far below the observed lifetime risk for non-smokers of 0.0045 for an 80-year lifespan. This suggests that even for non-smokers, the non-intrinsic risk is predominant.

In this context, it is crucial to discuss how Tomasetti et al. deduced their intrinsic risk (Tomasetti et al., 2017). They postulated that mutation risk due to intrinsic factors as that not currently known to be due to the external or hereditary factors. However, this assumes that we know all extrinsic factors. Therefore, adopting this assumption results in a gross overestimation of the intrinsic risk.

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For example, mutation signature analysis (Alexandrov et al., 2013) has identified around ½ of the current signatures as due to unknown factors. With ongoing research, some of these factors are beginning to be assigned to specific carcinogens such as Arsitolochic acid (Hoang et al., 2013). Thus, at the very least one should not assume that we know all extrinsic factors for any given cancer.

Moreover, a new study (Klutstein et al., 2017) has found that DNA methylation correlates equally as strongly as the total stem cell divisions with the lifetime cancer risk, and the effects of methylation appear to override the effects of stem cell division. Notably, this opens the possibility that epigenetic and not mutagenic effects exert a significant role in explaining the variation in tissue-specific cancer incidence, and thus cancer burden. This supports the role of environmental factors as DNA methylation is highly plastic and prone to environmental influences.

Thus, intrinsic risk has a rather limited role in *mutation burden*. A more important question then arises as to the contribution of intrinsic risk to *cancer burden*, which must be less than the contribution to mutation burden since many cancers are not driven solely by specific mutations. For example, HPV drives nearly all of cervical cancer through viral oncogenes independent of mutagenesis altogether.

To further estimate this role of intrinsic risk, we evaluated epidemiologic evidence. Plotting the lifetime risk of each cancer based on the World Cancer Registry for an 80-year lifespan (Table S2 (Tomasetti et al., 2017)) and segregating those into the regions with the very lowest (non-zero) incidence rates (Fig. 1 minimum) versus those with maximum rates, one finds that the main 'Western' type cancers (prostate, breast, lung and colorectal cancers) demonstrate the largest variations in lifetime cancer risk (along with esophageal cancers common in parts of China). For robustness, we further evaluated the top 90th vs the lowest 10th percentiles of the lifetime cancer risk. In this case, the patterns were nearly identical except for esophageal that disappears because it is high in only 3 regions in China (Fig. 1). Since intrinsic risk arises from endogenous mutation, it should not show large geographic (or time-dependent) variations. This suggests the excess cancers in high incidence regions are largely due to non-intrinsic factors.

Based on that, one can compute cancer burden arises from non-intrinsic factors for the 4 most common cancers that together account for half of cancer cases in the US and UK. For the US, the estimated percentages of lifetime risk due to non-intrinsic factors (US_average - minimum)/US_average, are 93% (breast), 97% (colorectal), 99% (lung), 99% (prostate), and for all cancers, 88%. The same percentages hold true for UK.

Fig. 1 also includes the estimated lifetime intrinsic risk based on our stochastic cancer stem-cell model (Wu et al., 2016), assuming most conservatively that all normal cells in an organ are stem cells (model_minimum in Figure). We find the model-based estimate of intrinsic risk closely mimics the registry-based minimum lifetime risk, lending more credibility to that model.

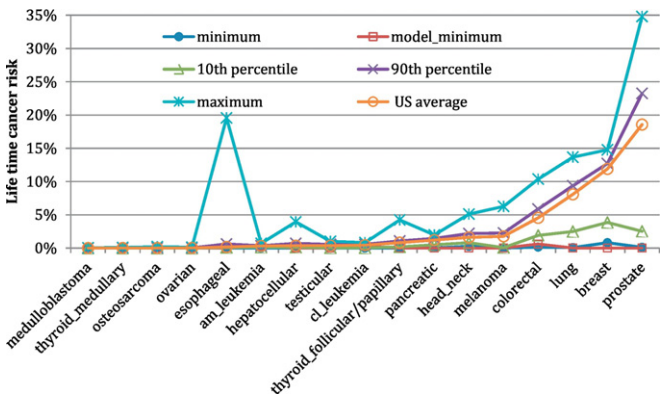

Fig. 1. The (conservative non-zero) minimum, the 10th and 90th percentiles, the US average, and the maximum of the lifetime cancer risk based on World cancer registry, and the stem-cell-model based minimum. The huge disparity between the US average and world minimum indicates that cancer is unlikely the end result of a universal endogenous carcinogenesis mechanism unaffected by exogenous factors.

These considerations then raise the question of what portion of cancer burden is preventable. Notably, Cancer Research UK has concluded that currently 42% of cancers are preventable from known risks. It is obvious that as additional new risk factors are identified, more cancers would become preventable, and therefore the 42% is a conservative estimate representing a subset of cancers with known extrinsic effects.

The conservative nature of the estimates by Cancer Research UK becomes evident in the case of prostate cancer. Epidemiologic data have indeed shown a large effect of geographic variation on risk of prostate cancer: for an 80-year lifespan, the maximum risk was attributed to African Americans in Delaware at 34.81%, while the minimum risk was found within Indians residing at Dindigul, Ambillikai, at merely 0.12% (Fig. 1). This 288 folds difference can hardly be explained by intrinsic risk alone. Moreover, immigrants from low-incidence country (Japan) quickly adapt the high incidence in their host country (US) (Shimizu et al., 1991), suggesting strong environmental roles in prostate cancer etiology. Given these data we find Tomasetti et al.'s estimation of 95.5% prostate cancer mutations due to intrinsic risk alone (Tomasetti et al., 2017), simply inconceivable. The fact that we know very little about risk factors does not negate their existence or their impact.

How does the analysis of intrinsic factors contribute to the issue of bad luck? Cancers that arise from the operation of only intrinsic factors may be largely unpreventable and therefore carry the element of luck. However, luck would still operate even in the cases of known and highly preventable exposure. For regular smokers, the lifetime risk of developing lung cancer is under 10%. In essence, exposure to smoking (and other risk) simply increases the odds tremendously, but does not negate the element of luck. Therefore employing the 'luck' factor, especially a grossly over-estimated 'bad luck', is no justification for lack of prevention.

Lastly we point out that cancer can result from alterations in the protein-coding as well as the non-coding genome regions (Schmitt and Chang, 2016). Although some carcinogenesis models are based on the more tractable protein coding cancer driver genes (Tomasetti et al., 2017), our analysis based on the World cancer registry is independent of any models and reflects the end result of all existing cancer-driving mechanisms.

Contributors

WZ, SW and YAH contributed to the design, the interpretation of results, and the writing of this study. WZ performed the data analysis.

The authors declared no conflicts of interest.

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