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CANCER RISK

Debating the odds

Understanding tumour initiation is important as it has implications for prevention, early detection and accurate modelling of cancer. An analysis by Tomasetti and Vogelstein prompted considerable debate about the origins of the genetic mutations that drive tumour initiation. Further fuel to this debate has recently been provided by an analysis from Wu *et al.*

There are many curiosities in cancer incidence rates that cannot be explained by exposure to exogenous carcinogens or inherited susceptibility. For example, cancer of the small intestine is very rare, yet cancers of other regions of the gastrointestinal tract are common. Tomasetti and Vogelstein proposed that DNA replication errors in stem cells, which occur independently of environmental and inherited factors, could be an important intrinsic source of tumour-initiating events. This postulate was based on the argument that stem cells are the only cells in which mutations can cause tumour initiation. The authors identified 31 tissues in which the number of stem cell divisions was satisfactorily quantified. The total number of stem cell divisions over a lifetime was strongly correlated with the lifetime risk of developing cancer in those 31 tissues. Their data suggested that 65% (with a 95% confidence interval of 39–81%) of the variation in cancer risk could be explained by the total number of stem cell divisions in a tissue.

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The extra risk score (ERS) was formulated as the lifetime cancer risk plus the total number of stem cell divisions and this was used to classify tumours from the included tissues relative to other tissues. The nine tumour types with the highest ERS were known to be associated with exogenous carcinogens and inherited risk factors. But intrinsic stem cell replication errors were still found to be an important risk factor in these tumours. However, the relative risk of the 22 tumour types with lower ERS was considered to be more strongly affected by intrinsic replication-induced alterations in stem cells than by exogenous factors. These tumours included many paediatric cancers, rarities such as small intestine cancer, but also others that are associated with exogenous risk factors.

Tomasetti and Vogelstein concluded that endogenous factors have a much greater influence on cancer risk than previously considered and that random mutagenesis from these endogenous factors cannot be prevented and are thus ‘bad luck’. Debate has centred around the importance of intrinsic versus exogenous risk factors and the implications for the efficacy of cancer prevention strategies.

In response, Wu *et al.* sought to estimate the extent to which exogenous factors influence cancer risk. They carried out a regression analysis of cancer risk for 30 cancer types, including those with known exogenous risk factors (as determined by epidemiology) and common cancers such as breast and prostate cancer. The analysis considered stem cell divisions or total cell divisions because these authors reasoned that all cells could be cancer cells of origin. The results were the same whether total cells or stem cells were considered, indicating that the correlation with stem cells is not specific. Intrinsic risk was estimated as the lowest lifetime cancer risk estimates for each corresponding tissue (including the data of Tomasetti and Vogelstein) and when overall risk was higher than intrinsic risk, the difference was proposed to represent the influence of exogenous factors. They concluded that exogenous factors account for 70–90% of the risk of developing most cancer types.

Wu *et al.* also analysed mutation signatures that have been detected in cancer samples. Two of the ~30 mutation signatures exhibited increased incidence with age, indicating that they are most likely derived from intrinsic factors. However, the remainder of the signatures occurred at different rates and did not correlate with age, and Wu *et al.* assumed these were probably derived from exogenous sources. Most cancers had a high level of mutation signatures from exogenous factors, whereas some cancers (such as small intestine cancer) had mostly intrinsic mutation signatures. However, it is important to note that it is unclear whether these mutations have a causal effect in tumour initiation and thus in cancer risk estimates .

Finally, the authors estimated the theoretical lifetime cancer risk from intrinsic mutations in stem cells and all cells. In their model, they varied the number of driver gene mutations needed for tumour initiation. When they modelled three or more initiating mutations they found that intrinsic lifetime risks were substantially lower than the observed intrinsic risks, indicating that exogenous factors account for the remainder of the risk.

As is usually the case with cancer, one size does not fit all. So, for some cancers (such as lung and colorectal cancer) exogenous sources play an important role, whereas for others, such as small intestine cancer, intrinsic factors must be the predominant source of tumour initiation. Importantly, both analyses demonstrate that intrinsic and exogenous factors influence tumour initiation (to different extents, depending on the tissue) and further work is required to examine these intrinsic factors and whether they can be prevented.

Gemma K. Alderton

ORIGINAL ARTICLES Tomasetti, C. & Vogelstein, B. Variation in cancer risk among tissues can be explained by the number of stem cell divisions. *Science* **347**, 78–81 (2015) | Wu, S. *et al.* Substantial contribution of extrinsic risk factors to cancer development. *Nature* **529**, 43–47 (2016)