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The questionable premises underlying the search for cancer driver mutations and cancer susceptibility genes

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Commentary on
Tokheim CJ et al., 2016, Evaluating the evaluation of cancer driver genes, *Proceedings of the National Academy of Sciences*, vol. 113, no. 50, pp. 14330-14335 doi: **10.1073/pnas.1616440113.**

Extensive efforts are underway to find cancer driver mutations (Tokheim, 2016) and additional cancer susceptibility genes, particularly for breast cancer (Couch, 2015). The rationale behind these searches are premises that are often not discussed and which may be questionable.

The search for cancer driver mutations

The theory that cancers arise from somatic mutations dates from the early 1900's (Weimberg, 2008). Multistage models for carcinogenesis, proposed in the 1950's, explain the increasing incidence of cancer with age as the consequence of a series of cellular changes (Armitage, 1954). The 1960 finding of a chromosomal abnormality in leukemia (Nowell, 1960) and the 1976 finding of similarity between a gene in chickens and a gene in avian sarcoma virus (Stehelin, 1976) strengthened the theory that mutations cause cancer. More direct evidence of a causal link between mutations and cancer came with transgenic animal experiments in the 1980's demonstrating that induced mutations led to cancer (Adams, 1985). The next step was to try to identify mutations in humans that lead to cancer. With large numbers of mutations associated with tumors, a distinction was made between driver mutations, which confer a selective growth advantage, and passenger mutations which do not (Vogelstein, 2013). In recent years, there have been extensive efforts to use bioinformatics to try to identify driver mutations. However, because there is no generally accepted gold standard for driver mutations, bioinformatics can only prioritize mutations that are most likely to be drivers of cancer (Tokheim, 2016) and not prove the existence of driver mutations. Nevertheless, researchers are continuing to pursue a bioinformatics search for driver mutations (Tokheim, 2016).

It seems that the underlying rationale for this search for driver mutations is the following unstated premise: mutations cause cancer in transgenic experiments, and carcinogens cause cancer by creating driver mutations. However, there is an alternative premise: mutations cause cancer in transgenic experiments by altering an intermediate biological state and carcinogens cause cancer by altering the same intermediate biological state. Possible intermediate biological states include the abnormal interactions between stroma and parenchyma

in a morphogenic field (Baker, 2015; Potter, 2007; Soto & Sonnenschein, 2011) and fibrosis (Brücher, 2014). An advantage of the alternative premise is that it can explain paradoxical observations, such as foreign body carcinogenesis, where there is no obvious role for mutations in carcinogenesis (Baker, 2015). If the alternative premise is correct, the search for driver mutations is an endeavor of questionable scientific benefit.

The search for cancer susceptibility genes

Besides the search for driver mutations there is also an extensive search for cancer susceptibility genes. For example, it is well known that women with *BRCA1* and *BRAC2* mutations are at high risk of breast cancer (Anglian Breast Cancer Study Group, 2012), and there is a continuing search for additional breast cancer susceptibility genes (Couch, 2015; Goussaini, 2012) (In light of the above discussion, the cancer susceptibility genes could directly lead to cancer or indirectly lead to cancer through intermediate biological states). A key premise, based on familial aggregation studies and twin studies, is that there is a substantial inherited susceptibility to breast cancer (Goussaini, 2012; Lichtenstein, 2000). However, results from a novel method for the analysis of twin data have shown that it is unlikely that there are any high penetrance cancer susceptibility genes in addition to *BRCA1* and *BRCA2* (Baker, 2016). As only high penetrance genes would likely make good targets for cancer prevention, the search for low or intermediate penetrance genes may have little public health importance.

Discussion

The search for additional genetic changes causing cancer, either driver mutations or cancer susceptibility genes, is not likely to yield much scientific progress or public health benefits if the underlying premises are incorrect. Because the premises are rarely discussed, researchers typically do not appreciate their significance or question their validity. To avoid reliance on a questionable premise involving driver mutations, researchers need to consider a broader view of cancer involving interactions among tissues rather than focusing only on cellular changes in tumors. To avoid reliance on a questionable premise of a large genetic contribution to breast cancer, researchers need to be more open to the possibility that rare genetic variants could have little impact on the risk of breast cancer.

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