Review of: "Is creeping abandon of human cancer defences evolutionarily favoured?"

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Potential competing interests: No potential competing interests to declare.

This paper by Rahm and Pratley, “Is creeping abandon of human cancer defenses evolutionarily favored?” proposes a somewhat unconventional hypothesis. The hypothesis suggests that a phenomenon by which tumor suppressor genes are epigenetically down-regulated in old age gets a selective advantage since it prevents only a dominant male siring females of several generations, which would erode genetic diversity. Simultaneously it may also save calories. Owing to reduced tumor suppressor activity, humans experience a higher incidence of cancer as compared to most wild mammals.

In fields like cancer that are laden with complexity, ambiguities and paradoxes novel hypotheses are welcome but need to be weighed carefully against alternative hypotheses moving to a coherent broader picture. Already the broader picture of cancer is changing rapidly and any new hypothesis has to take into account the trend. Importantly, the somatic evolution of cancer is now shown to be selection limited and not mutation limited (Vibishan and Watve 2020,Casás-Selvesand DeGregori 2011, Rozhok, A. I. and DeGregori 2017) and that takes away Peto’s paradox and a few other classical concepts.

The hypothesis is projected as an explanation for the apparently higher incidence of cancers in the human population compared to most other mammals. This is a slippery ground for any comparative account. Cancer incidence is known to be affected by a large number of environmental, nutritional, developmental and behavioral factors. The authors recognize the role of carcinogens, but beyond that behavior and lifestyle factors have a substantial but underappreciated role. Particularly remarkable are the reproducible experiments showing the tumor suppressing effects of behaviorally enriched environments (Cao et al 2010, Li et al 2015, Takai et al 2019, Watanabe et al 2020, Xiao et al 2021, de Sousa Fernandes et al 2022). Constraints on fetal development (Logan et al 2009, Heck et al 2015), dietary deficiencies (Hung et al 2015), obesity (Avgerinos 2019) also affect cancer incidence. Human lifestyle today has drifted substantially from ancestral one and this mismatch might be responsible for the higher incidence. Cancer incidence in hunter gatherer societies versus animal populations might be a fairer comparison but we have scanty data on it. So humans are inherently more susceptible to cancers is a slippery statement. Many other factors may account for the difference in incidence.

If we ignore that for the time being and assume higher susceptibility in humans, the hypothesis still needs to cross a number of hurdles. One is that of alternative mechanisms to achieve the same evolutionary advantage. If andropause evolves in males similar to menopause in females, the problem of single old male contributing to the gene pool can be eliminated. Why down-regulating tumor suppressors might be a better solution than andropause needs an explanation, albeit speculative at this stage.

The idea of increasing genetic diversity of the group/tribe by preventing a single male from siring females of several generations is a group selection-based idea. What the authors call a tribe based selection is essentially group selection. This comes at a cost to individual fitness. Many evolutionary biologists disregard group selection right away. This extreme is not justified. But group selection based ideas need to be examined with rigorous multilevel selection models. Group advantage may work under a restricted set of conditions but the model should specify the conditions so that whether the set of conditions exist in real life can be examined. The authors say that they intend to develop such a model and they might do so after receiving suggestions from reviewers. This is quite unusual from traditional publication point of view. Let's consider this as a different system enabled by open peer reviews and wait for a rigorous model coming from the authors showing why group advantage works over individual advantage in this case.

Similar to the group selection debate, the hypothesis also relates in some way to the programmed versus non-programmed aging debate. The hypothesis needs to be examined in the light of this debate as well.

We can see another possible paradox in the model. The individual disadvantage by down-regulating tumor suppressor mechanisms in later age might be small if cancer incidence is small. But if this is so, the group advantage would also be small because the dominant male has good chances of surviving. If selection favors reduction in tumor suppression, cancer incidence might increase but that increases individual cost due to which the overall advantage might vanish. This apparent paradox can be addressed only with a carefully constructed model. It is likely that the two contradicting factors may lead to a stable equilibrium. This can be explored only by writing an appropriate model.

One more possible weakness of the hypothesis is that all oncogenes as well as tumor suppressor genes have many normal physiological functions as well, often related to regulation of wound healing (https://www.preprints.org/manuscript/202303.0431/v1). If tumor suppressor genes are under-expressed the other functions would also be impaired. This cost could be much greater than the relatively small probability of developing cancer. And this would be an individual cost. This also needs to be incorporated in the hypothesis appropriately.

The writing is unnecessarily complex in many places and the reader has to read some sentences repeatedly to get the intended meaning. Breaking up complex sentences into smaller ones would help the reader.

Specific issues:

1. Context: line 9 onwards. Two issues appear to be mixed up here. Cancer incidence being related to body mass and total lifespan is one issue and increase in incidence after menopause is another. Including both in the same sentence increases confusion.
2. About human ancestral life and hunter-gatherer lifestyle – too many generalizations have been made without citing any source. In fact, today's anthropology shows wide diversity of human social life across the globe since ancient times (Graeber et al 2021).
3. Mortality due to infectious diseases is a mixed bag. While incidence of externally acquired infections comes down a little bit for reasons you mentioned, incidence of infection by opportunistic pathogens increases by orders of magnitude in old age. See the patterns here (Baig et al 2020). Mortality by infection in general increases with old age.

4. We appreciate the question raised why chimpanzees do not show reduction in cancer defense, but the question is not addressed further, even speculatively.
5. It's good that some ways of testing the hypothesis are suggested. There are certain problems with the suggested experiments.

a. All tumor suppressor genes have multiple normal physiological functions. Selection can act on them w.r.t. the other functions as well. Therefore even if you find altered expression in old age, interpretation won't be straightforward. This applies to your suggestions 1 as well as 2.
b. The idea of modeling is good. We will at least know whether the idea is mathematically sound and whether group selection works in this context. However, if a mathematical model works, it is not evidence that the phenomenon exists in real life. On the other hand, something that is mathematically impossible cannot exist in real life. Model results need to be interpreted this way. The model can make further testable predictions which is the advantage of having a model.

In general, we feel it is quite unlikely that the hypothesis would cross all the hurdles. But the best way is to try to cross the hurdles. Giving up a hypothesis open mindedly if it cannot cross one of them is good science, certainly not to be taken as a defeat.

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