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

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This manuscript presents the thought-provoking hypothesis that human life-time risk of cancer may be unexpectedly high because some defense mechanism (e.g. a tumour suppressor) has been lost during evolution. The authors base their argument on the much lower cancer risks in other long-lived species, including chimpanzees, and an evolutionary effect of dominant older males in small prehistoric tribes. Finally, they propose potential ways of testing their hypothesis. The manuscript refers to Pet's paradox, i.e. that mammalian species have approximately similar cancer risks independent of their body size (and thus numbers of cells and cell divisions). However it goes beyond that in trying to explain why humans seem to have higher risks than similar species, e.g. chimpanzees.

Overall the authors present their case in a clear manner. However, the manuscript would benefit from a discussion of the limitations in terms of uncertain or controversial aspects. Firstly, the evidence for the claim that the lifetime cancer risk in humans is higher than comparable species should be critically examined. Modern humans are under much more intense medical surveillance than even pets and other domesticated animals or animals kept in captivity. Thus detection and diagnosis of tumours is likely to be much more efficient in humans than in animals, perhaps with the exception of laboratory animals in cancer studies. Similarly, studies on wild animals such as whales examine only animals that were alive up until being found and do not include animals that have died and perished. Because of tumour growth dynamics, the time an animal is alive with a tumour may constitute only a short part of its lifespan. In addition, animal age is difficult to assess and it is known that cancer risk increases very strongly with time (to the power of six according to Peto (Phil Trans R Soc B 370:20150198, 2015; ref. #7). Is the age distribution known in the large studies on wild animals such as whales? Chimpanzees are not only somewhat smaller than humans but also have a markedly shorter lifespan, even in captivity. This needs to be taken into consideration when comparing species. Secondly, species with low risk of developing cancer may have developed additional defense mechanisms such as slow proliferation or additional copies of *TP53* pseudogenes (see review by Seluanov et al. Nat. Rev Cancer 18:433-41, 2018). When comparing cancer incidences of these animals with humans, the alternative hypothesis of enhanced defenses in other long-lived species should be discussed. Thirdly, the proposed mechanism how dominant males in small tribes may affect the evolution of cancer defense is rather speculative as the authors point out themselves. Why would this mechanism be specific to human evolution but not in species that live in harems with a dominant male? When testing the authors' hypothesis, it seems that other species will need to be included as controls for the results on humans.

In summary, the authors present an interesting hypothesis that seems worth testing. Even if the hypothesis is not

confirmed it would be helpful to exclude this possibility and much could be learned about human cancer risk in the process. In addition to the proposed experiments with DNA sequencing, cell culture might be a way of comparing the response of different species to replicative senescence and agents causing mutation or epigenetic modification. In this way, cellular defense mechanisms could be studied and compared across species, including in wild animals.

Minor comment: on p. 4, section 5.1: “cell kernels” should probably be “cell nuclei”?