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

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The authors suggest that the exceptionally high lifetime cancer risk in humans has been evolutionary favoured as a means to limit the contribution of a single dominant male to the gene pool of a tribe, so limiting inbreeding in early, small hunter-gatherer troupes. This is evidently an idea worth thinking about as indicated by the number of reviews the paper already attracted. Previous reviewers have extensively commented on the limitations in the assumptions related to group structure and dynamics of early humans. They also indicated limitations in the assumption that higher cancer incidence could decrease calory spend at tribe level. I would like to focus on three points that so far have not been extensively covered:

1. At present, the authors see the main risk of old dominant males contributing to the gene pool of the group in enhanced inbreeding. What about increased mutation rate in sperm from old fathers that is transmitted to their children (Kong et al. Nature 2012)? To me, this might make a stronger argument in favour of natural selection, which would be less dependent on assumptions about group dynamics. It could also explain why there is still an age-dependent decrease of anti-tumour defences in modern humans (see point 2 below). However, this would open the question whether the sperm genome is better maintained with age in chimps or whales than in humans.
2. There is no doubt that much of the high lifetime cancer susceptibility of modern humans is due to an age-dependent decrease of anti-tumour defences. Mechanisms include mutations and epimutations of tumour suppressors, but also cell senescence, immunosenescence, chronic inflammation, etc. If, as the authors suggest, this is a consequence of evolutionary selection working via epigenetic mechanisms in our distant past, why does it still remain in modern populations in which the type of inbreeding focussed at by the authors would have a very low prevalence since thousands of years? Epigenetics-mediated evolutionary selection outcomes are highly flexible and can shift dramatically over very few generations (F Drenos et al Biogerontology 2006).
3. The essential underlying assumption for the author's suggestion is that cancer actually was a significant cause of mortality and morbidity in early hunter-gatherer groups. This assumption has not been clearly stated in the paper so far, and I actually doubt that it is true. The authors try to exclude infections and accidents by arguing that older hunters would be experienced with respect to both accident risk and infectious agents. This might be true for adults in their prime, but this age group would also still be pretty resistant against cancer, even today. I am not aware of evidence showing that early human groups were not be much more similar to chimps, e.g. with rather low cancer incidence for up to, say, 30 to 40 years of age and low impact of cancer on the population as a whole.

Taken together, I feel that the hypothesis that evolutionary selection could drive specifically an (age-dependent) lowering

of anti-cancer defences via its impact on gene pool variation in early human groups invokes too many, too weakly supported assumptions to be plausible. It could however be interesting to try to widen the argument: Instead of looking at cancer protection mechanisms in isolation, one could think about whether there could have been (and still be) selective pressure to induce ageing altogether (including weaker cancer defences, higher risk of inflammation, lower physical fitness etc) as a mechanism to reduce mutational load. This would all depend on how good the evidence is for the statement that “ageing does not occur in the wild”. Maybe it did occur in dominant members of early tribes (could as well have been females in matriarchal groups), as suggested by the authors? A very careful search for any evidence supporting such a statement would be necessary.