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

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Different reviewers have different approaches of critiquing and providing feedback. I agree with certain general points raised by other reviewers on this manuscript. My attitude is to provide thorough comments that would help the authors increase clarity and suppress vagueness in their claims and statements. Below, I will provide my specific comments on different parts of the manuscript with the utmost respect, and I hope the authors will take them on with full consideration:

> *Obviously many cases of human cancer are due to carcinogens which we eat, breathe and receive in other ways through our modern lifestyle, which were not available to prehistoric humans, nor are they to observed animals.*

1. The unavailability of modern sources of carcinogens does not preclude the possibility of carcinogens coming from sources unknown to us during prehistoric times.
2. Is observed here used as a synonym to studied or examined?

> *…so a significant share of it may be due to differences in species-specific cancer defenses.*

How did you reach the conclusion that it would be a significant share if this is still a conjecture?

> *…however their cancer risk remains constant throughout their life rather than increasing sharply after female reproductive age as observed in humans.*

How is this risk measured? Is the risk measurement methodology the same between whales and humans? Are measurement errors on the same scale? Are the number of predictors the same?

> *…in the literature that species-specific tumour suppression mechanisms allow for large lifespan and body mass.*

I don't know if large is a correct qualifier for lifespan. Greater or longer is more adequate

> *…which is supported by reduced apoptotic function compared to chimpanzee and macaque cells…*

Does this reduced function directly relate to a weakness? Is it not possible that the apoptotic function could be reduced but another cancer suppressing function increases through some trade-off or compensation compared to closely related species? Is it not a leap to go right from this observation to calling it a weakness

> *…from the specific development of homo sapiens…*

Genus names start with a capital letter

> *…with as a consequence the development of menopause to protect descendants…*

This is vague. What kind of protection is referred to here? Menopause is directly related to end of fertility due to a fixed amount of reproductive germ cells. Is there a vague indication of an evolutionary advantage of menopause in this line?

> *were no social differences betweem them*

Slight typo here

> *However those modern tribes were marginalized into territories unsuitable for agriculture and pastoralism, and little animals were available for them to hunt…*

This claim should be substantiated. How were they marginalized? This statement makes it seem that if it was the case that whatever marginalization the authors are alluding to did not occur, then these HG societies would have moved towards agriculture and pastoralism. Why would this be true? Even the second part of this statement is very weak. Where is the ethnographic evidence of this?

> *…while cave paintings tell us that in contrast, early humans did attack mega-fauna like mammoths…*

Though this is true, the cave paintings do not give an indication on the frequency of these hunts? It is quite possible that the cave paintings are commemorating very rare events where multiple hunting bands banded together momentarily to share the spoils of a big hunt.

> *So we suppose that each tribe was growing around a hunting gang…*

First, the word band is preferred to gang due to negative connotations of the latter terms. Second, this view is very ahistorical. Hunter-gatherer groups (though some anthropologists disagree with the ubiquity of such a strategy), the name contains gathering, which many agree that is actually the more important aspect of the lifestyle of these human groups. The historical argument here is weak and lacking of evidentiary support given current thoughts in anthropology and

archeology. This is a line from one the citations you provide here: “Because cultures change through time, we cannot simply project ethnographic data from the present to the past”

> *…and women would have had the opportunity to move to a different tribe once reaching adulthood.*

How is this known to be the ubiquitous case? There is evidence of the contrary though, that men are the ones that change tribes through marriage. It seems like the authors have selected specific and possibly outdated HG cultural strategies that fits the narrative setup of their hypothesis.

> *and we have some evidence for such tribal structures from the historic fact that patriarchal societies were much more frequent than matriarchal ones*

1. citations
2. This is confusing to me. The authors are willing to use ethnographic data on modern small-scale societies to project onto earlier HG groups, but are not willing to accept that given the presence of matrilineal societies in modernity that it could've existed in the past, and maybe was common.

> *Then natural selection is likely to have acted at the level of tribes, because the paternal genes of the tribe all come from the same kin, and the survival of the kin's genes is linked to the survival of the tribe.*

I am having trouble understanding what the authors are claiming here. If natural selection is acting at the level of the tribes, then that means you are looking at the differential success between tribes, not within tribes. I don’t understand how within a tribe the paternal genes all come from the same kin? Whatever degrees of inbreeding or outbreeding is going on, the type of genetic uniformity the authors are contending doesn't justify group or kin selection. Though those two selection models are directly related to the relatedness within and across tribes, there still isn’t strong empirical evidence supporting these models to explain major adaptive patterns.

> *Then higher degrees of inbreeding would quite certainly have been detrimental to a tribe.*

There are types of marriages involving related individuals with high consanguinity that would lead to high inbreeding in their offspring but does not lead to fitness decreases. There are cases where outcrossing can lead to larger fitness losses due to genetic incompatibilities. Indeed, an increase in inbreeding immediately increases genetic diversity by allowing for an increase in the frequency of homozygotes of recessive alleles and then allowing more purging through selection. If the authors are referring to inbreeding load, then this is a different concept.

> *…which in case of a not-so-large tribe would have considerably narrowed down its genetic pool.*

This result requires important assumptions that the authors do not make clear. Migration for example. The authors are treating the tribe as living in isolation across generations which ethnographic data shows is not true

> *But extended lifespans are possible for hunter-gatherers according to observations in modern tribes…*

This is again an unsubstantiated projection of modern data onto past data. While this might be the only way to gleam into the past, the authors do not mention this caveat and pitfalls of such projections

> *…while no more being attractive as a reproductive partner.*

I don't understand the choice of language here. This sounds like sexual selection is being proposed which adds another layer of complexity around what the authors are proposing would be the evolutionary mechanism in action.

> *…would not have been able to betray a tribe-wide lowering of tumour suppression activities,…*

I do not understand the use of language here. Are the authors claiming that this epigenetic modification increases to fixation in males in the tribe by having the benefit of lowering calorie usage or through a weaker selection at higher age? The authors completely disregard the evolutionary dynamics of the supposed modified gene in females. Unless the gene is sex-linked, I don't understand the justification in the leaps done here in the dynamics of such a gene.

> *…because the men of a tribe do in our setting all carry that gene,…*

Again this claim is based on the claim that all men are descended from one ancestor that carried that epigenetically modified dominant gene. First, where is the proof that such an epigenetic modification is transmitted with fidelity where it would have the same phenotypic effect in the next generation and in new environments.

> *…and it would remain active when combined with the genes of women entering the tribe from outside.*

Why? Gene flow is an important evolutionary process and it is likely that for the same gene, new alleles will do better or as good as native alleles.

> *…why creeping abandon of cancer defences cannot be observed in chimpanzees, which also live in patriarchal groups…*

Why not mention that there is also another closely related species, Bonobos, that live in matrilineal societies and can also serve as a good comparison with both humans and chimpanzees

> *but DNA can now be collected and analyzed from much older human remains.*

But what are the chances that the reconstructed DNA will have information on those specific genes?

> *…to track the effects of incest over generations (via detrimental recessive genes);*

There is a difference between incest and inbreeding. The authors should look into those differences before conflating the two.

> *…cancer defences increases the evolutionary competitiveness of a tribe.*

To reiterate, if the authors want to look at the evolutionary competitiveness of a tribe, you have to simulate multiple tribes and pit them together in some competitive resource-limited scenario. That would follow from your previous comment on group-level selection, or even kin selection.

> *It is obvious that such a simulation will involve so many parameters…*

Before worrying about the magnitude of parameterization, there is the issue of reaching the simplest model that can take the relevant inputs for the intended process under study and then give the desired outputs.

> *…they cannot just be varied in order to find plausible values for them by conclusions from the output they produce…*

I don't understand the issue here. It is absolutely okay to use the output of the model based on certain parametrizations to readjust the values to at least reach a suitable output, for example, having tribes reach some equilibrium state.

> *…using anthropological literature about 20th century hunter-gatherer tribes, in order to make informed guesses.*

I would suggest to the authors that since, essentially, they are interested in genetic dynamics, that they look into population genetics models which can readily allow for such simulations.