Open Peer Review on Qeios

Is creeping abandon of human cancer defences evolutionarily favoured?

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Funding: No specific funding was received for this work.

Potential competing interests: No potential competing interests to declare.

Abstract

Among the animal species on which observations are available, humans have a uniquely high lifetime risk to suffer from cancer - over 38%, compared to less than 10% for all observed other species (except species suffering from environmental pollution). Peto's paradox shows that this cannot simply be explained by mathematical models which view cancer genesis as a stochastic process, with resulting risks polynomial in lifespan and body mass - whales have a longer lifespan and about 30 times the human body mass, however their cancer risk remains constant throughout their life rather than increasing sharply after female reproductive age as observed in humans. Rather, it is well documented in the literature that species-specific tumour suppression mechanisms allow for large lifespan and body mass. Data which was examined on chimpanzees, being closely related to humans, make it likely that there is a major difference between chimpanzee and human cancer risk, and hence the weakness of human cancer defence is likely to have resulted from the specific development of Homo sapiens. As this weakness appears past the reproductive years, a prominent hypothesis blames it to antagonistic pleiotropy. However, Homo sapiens having lived in small tribes during most of its development, natural selection is likely to also have acted at the level of tribes, which lets us derive our hypothesis, *is creeping abandon of human cancer defences evolutionarily favoured?*from two alternative speculative scenarios. One of them is based on that lowering tumour suppression activities might save calories and hence benefit tribes with limited food production, the other one suggests that creeping abandon of cancer defences benefits genetical diversity.

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1. Context

Among the animal species on which observations are available, humans have a uniquely high lifetime risk to suffer from

cancer - over 38%, compared to less than 10% for all observed other species [1][2][3][4] (except species suffering from environmental pollution [5]). 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. However, and though with some uncertainty, the literature lets us suspect [6] that these modern carcinogens do not explain all of the high modern human cancer mortality, so a significant share of it may be due to differences in species-specific cancer defences. Peto's paradox [7] shows that this cannot simply be explained by mathematical models which view cancer genesis as a stochastic process, with resulting risks polynomial in lifespan and body mass - whales have a longer lifespan and about 30 times the human body mass, however their cancer risk remains constant throughout their life rather than increasing sharply after female reproductive age as observed in humans [8]. Rather, it is well documented in the literature that species-specific tumour suppression mechanisms allow for large lifespan and body mass [9][10]. Data which was examined on chimpanzees, the extant species most closely related to humans (and with particularly matching cancer genes [11]), make it likely that there is a major difference between chimpanzee and human cancer risk [6], and hence the weakness of human cancer defence (which is supported by reduced apoptotic function compared to chimpanzee and macaque cells [12] is likely to have resulted from the specific development of *Homo sapiens* (see also a study on oncogene development since the chimpanzee/human last common ancestor [13]). As this weakness appears past the reproductive years, a prominent hypothesis blames it to*antagonistic pleiotropy* [14][10] (with as a consequence the development of menopause to protect descendants[15]). We want to argue in favour of a different hypothesis here, the one stated in the title of this paper.

2. The hypothesis

Therefore, we think that research on the question

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could facilitate cancer prevention. In a study which modelled cancer defence activities as species- and life-history-dependent but constant over age [16], it was already suggested that a model with age-dependent cancer defence activities could provide a better explanation for Peto's paradox; and in view of the above argumentation, we would expect human cancer defences to reduce their activity with progressing age.

A positive answer to our question would then of course open the question why creeping abandon of cancer defences cannot be observed in chimpanzees, which also live in patriarchal groups --- does their pattern have to do with not enough chimps living into old age, or do they have a more favourable diet free of modern day carcinogens, or does the fact that reproductive value increases or remains high into older age drive greater anti-cancer adaptations?

3. Framework of the hypothesis / caveats

Our hypothesis is in no way aimed at trying to overthrow knowledge that has already been gained about cancer. In particular,

- There are cancers which are provoked by exposure to carcinogens (including tobacco, pollutants, and industrial chemicals), and before investigating cancer defences of a population or individual, the potential presence of carcinogens should be investigated first, because they may break also a strong cancer defence.
- Considering modern human populations, the changes in human diet and the shift to sedentary lifestyles have certainly made a strong impact on human susceptibility to cancer. Our hypothesis just has to explain complementary developments.
- Concerning the potential antagonistic pleiotropies mentioned above: Evolution involves trade-offs, where the development of certain traits or adaptations may come at the expense of others. It is possible that the unique characteristics and evolutionary pressures that shaped humans, such as increased brain size and energy demands, may have constrained the allocation of resources towards cancer defences. It will have to be investigated on a case-by-case basis whether our hypothesis or antagonistic pleiotropy can explain a specific cancer defence development.
- Finally, also random genetic mutations can have made an interference.

In view of the arguments made for the tumor suppression theory of aging[17], we should also think about replacing "creeping abandon of cancer defences" by "creeping switch of cancer defences from energy-intensive operations like inducing apoptosis to low-energy operations like inducing cellular senescence", where cellular senescence would yield the desired caloric reduction of the below scenario A, and its cost of aging the body would yield the genetic diversity enhancement of the below scenario B.

4. Scenarios favouring the hypothesis

We now set up two speculative scenarios, from each of which our hypothesis would follow quite naturally, and which are compatible with each other. They each require several assumptions, stated below, which cannot be checked thoroughly, because they require projecting back into an undocumented past.

Scenario A

Homo sapiens have developed a large brain compared to their ancestral species, which requires a constant supply of a large amount of calories. In hunter-gatherer societies of the human past, this may have quickly reached the limits of resources available across the seasons. The telomere caps mechanism may have addressed this problem by making body cells senescent after a certain number of cell divisions, so to slow down the metabolism of aged individuals and get a bigger portion of the available food to reach young members of the population. The senescent cells may then operate with less calories, but show a weaker performance on various tasks, including cancer defence.

Scenario B

Homo sapiens have lived in small hunter-gatherer tribes during most of the species development. In hunter-gatherer

tribes of the 20th century, on which anthropological literature is available, men did hunt individually, and there were no social differences between them [18]. However those modern tribes were marginalized into territories unsuitable for agriculture and pastoralism, and little animals were available for them to hunt, while cave paintings tell us that in contrast, early humans did attack mega-fauna like mammoths, bears, etc., which they had to do in bands. So we suppose that each tribe was growing around a hunting band, and as a consequence, males born into the tribe would become members of the hunting band, and women would have had the opportunity to move to a different tribe once reaching adulthood. This immediately breaks the egalitarian social structure and gives a claim for the boss of the hunting band to become also chieftain of the tribe, and we have some evidence for such tribal structures from the historic fact that patriarchal societies were much more frequent than matriarchal ones. 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. Then higher degrees of inbreeding would quite certainly have been detrimental to a tribe. And males of high social status can attract new reproductive partners again and again until an age that has seen several generations grow [19], which in case of a not-so-large tribe would have considerably narrowed down its genetic pool. Of course, as skeleton findings suggest that highly aged individuals were rather rare among prehistoric humans (among Early and Middle Pleistocene Homo, 42 old adults and 166 young adults have been found [20]), one could just dismiss the influence of such individuals on the genetics of a tribe. But extended lifespans are possible for hunter-gatherers according to observations in modern tribes [21], and lowering tumour suppression activities as part of a state of ageing would actually have reduced the chances of individuals to reach a high age in the first place, so to contribute explanation to the age distribution of prehistoric skeletons (mortality due to infectious diseases should have decreased in adult age when all regionally circulating germs were known to the immune system, and mortality due to predation should have decreased as well for adults experienced with predating animals). Furthermore, as tumour suppression involves killing a lot of suspect cells, lowering tumour suppression activities might save a decisive amount of calories (so to account for sometimes observed lower appetite of aged persons) and hence benefit tribes with unreliable food collection; and individuals suffering from cancer after female reproductive age could still have made contributions to parental/grandparental care, while no more being attractive as a reproductive partner. Now if epigenetic deactivation of tumour suppressor genes as part of the telomere-triggered senescence process is coded on a dominant gene, then individuals within a tribe would not have been able to betray a tribe-wide lowering of tumour suppression activities, because the men of a tribe do in our setting all carry that gene, and it would remain active when combined with the genes of women entering the tribe from outside.

5. Suggested experiments

1. The hypothesis could be tested directly by analysing cell kernels of present-day aged persons, and checking if tumour suppressor genes have been deactivated epigenetically.
2. Among the DNA found in prehistoric human remains, oncogenes and tumour suppressor genes could be tracked. This would potentially give some indications on whether the former increased and the latter decreased over a long timespan. So far, mainly agricultural societies of just a few hundred generations ago have been studied from an

evolutionary perspective for genetic markers of cancer defence [22], but DNA can now be collected and analysed from much older human remains [23].

3. The life cycle events in a prehistoric tribe could be modelled stochastically, along with resources (particularly food) accessible to the tribe and influencing its prosperity, keeping track of the health of individuals throughout the modelled years, and a sample of their genes to track the effects of incest over generations (via detrimental recessive genes); then epigenetic mechanisms which decrease the cancer defences after female reproductive age could be introduced in a variant of this Monte Carlo simulation. This could potentially make it more plausible that creeping abandon of cancer defences increases the evolutionary competitiveness of a tribe. The authors can implement such an *in silico* model themselves, but will wait for eventual comments (maybe from people interested in collaborating on *in silico* experiments on this) before doing so. It is obvious that such a simulation will involve so many parameters that they cannot just be varied in order to find plausible values for them by conclusions from the output they produce, but instead the tribes need to be modelled using anthropological literature about 20th century hunter-gatherer tribes, in order to make informed guesses.

Acknowledgements

We would like to thank the reviewer Jose M. Estrela for helpful suggestions, which were used for a revision of the present paper.

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