Is creeping abandon of human cancer defences evolutionarily favoured?

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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. Chimpanzees, being closely related to humans, have a very low 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, and 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, which in case of a not-so-large tribe would have considerably narrowed down its genetic pool. Furthermore, lowering tumour suppression activities might save calories and hence benefit tribes with limited food production; 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. Is creeping abandon of human cancer defences evolutionarily favoured?

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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 [5, 16, 21, 22] (except species suffering from environmental pollution [12]). Peto's paradox [14] 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 [13]. Rather, it is well documented in the literature that species-specific tumour suppression mechanisms allow for large lifespan and body mass [1, 11]. Chimpanzees, as the extant species most closely related to humans (and with particularly matching cancer genes [15]), have a very low cancer risk [19], and hence the weakness of human cancer defence (which is supported by reduced apoptotic function compared to chimpanzee and macaque cells [2]) 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 [8]). As this weakness appears past the reproductive years, a prominent hypothesis blames it to *antagonistic pleiotropy* [6, 11] (with as a consequence the development of menopause to protect descendants [17]). 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, and 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 [18], 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 [4]), 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 [10], 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 skeleta (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, lowering tumour suppression activities might save calories (so to account for sometimes observed lower appetite of aged persons) and hence benefit tribes with limited food production; 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.

Therefore, we think that research on the question

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could facilitate cancer prevention. In a study which modeled cancer defence activities as species- and life-history-dependent but constant over age [3], 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 progresssing age.

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Suggested experiments.

1. 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 defense [7], but DNA can now be collected and analyzed from much older human remains [9].

2. The life cycle events in a prehistoric tribe could be modeled stochastically, along with resources (particularly food) accessible to the tribe and influencing its prosperity, keeping track of the health of individuals throughout the modeled 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.

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