

Is creeping abandonment of human cancer defences evolutionarily favoured?

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Abstract

Among observed animal species, humans exhibit a remarkably elevated lifetime cancer risk (over 38%), in stark contrast to less than 10% seen in other observed species (excluding those affected by environmental pollution). Peto's paradox suggests that these observations defy explanation through mathematical models treating cancer genesis as a stochastic process, with risks resulting from lifespan and body mass. For instance, whales, despite longer lifespans and roughly 30 times the size of humans, maintain consistent cancer risk throughout life, differing from the pronounced increase after female reproductive age observed in humans. It is well-documented in the literature that species-specific tumor suppression mechanisms allow for large lifespan and body mass. Examination of data from chimpanzees, a closely related species, suggests—without definitive evidence—a major difference between chimpanzee and human cancer risk. This leads to the conjecture that vulnerability of cancer defence mechanisms in humans might have emerged due to the unique evolutionary trajectory of the genus *Homo*. Given that this vulnerability emerges after reproductive years, a prevailing hypothesis attributes it to antagonistic pleiotropy. However, considering *Homo*'s historical existence in small tribes throughout much of evolution, we suggest that natural selection may have also operated at the tribal level. Consequently, our hypothesis, "Is creeping abandonment of human cancer defences evolutionarily favored?" arises from two alternative speculative scenarios. One proposition rests on the notion that diminishing tumor suppression activities could confer a calorie-saving advantage, particularly beneficial for tribes with limited food resources. The other proposition suggests that creeping abandonment of cancer defences might promote genetic diversity.

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1. Context

Among animal species for which observations are available, humans possess a unique and substantial lifetime cancer risk -- over 38%, compared to less than 10% for all other observed species [1][2][3][4], excluding species affected by environmental pollution [5]. Many cases of human cancer stem from carcinogens linked to modern lifestyles, neither present in prehistoric times, nor are the studied contemporary animals exposed to them. However, some literature (although inconclusive) indicates that these modern carcinogens might not solely explain elevated human cancer mortality, suggesting that species-specific cancer defences also play a role [6]. Peto's paradox [7] challenges explanations rooted in mathematical models that consider cancer genesis as a stochastic process, with resultant risks influenced by lifespan and body mass. Whales, despite having longer lifespans and being roughly 30 times the human body mass, maintain a constant cancer risk throughout life, in contrast to humans where the risk sharply increases post-female reproductive age [8]. Species-specific tumor suppression mechanisms are well-documented in the literature, enabling larger lifespans and body masses [9][10]. Data from chimpanzees, humans' closest extant relatives, suggest—with no definitive evidence—a substantial disparity in cancer risk [6]. The vulnerability of human cancer defences, supported by reduced apoptotic function compared to chimpanzee and macaque cells [11], likely arose from the unique development of the genus *Homo* (also explored through oncogene development since the chimpanzee/human last common ancestor [12]). Given that this vulnerability emerges after reproductive years, a prevailing hypothesis attributes it to *antagonistic pleiotropy* [13][10], possibly leading to the development of menopause to safeguard descendants [14]. This paper advocates a distinct hypothesis, as articulated in its title.

2. The Hypothesis

Hence, we suggest that investigating the hypothesis:

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could yield novel insights that may benefit cancer prevention research and understanding of cancer etiology in *Homo sapiens* and other (closely related) species. In support of this hypothesis, a study that structured cancer defence activities based on species and life-history specifics, while remaining constant over age [15], has already suggested that a model accounting for age-dependent cancer defence activities could offer a more robust explanation for Peto's paradox. Given the reasoning presented earlier, we anticipate a diminishing activity of human cancer defences as age advances. Data that supports our hypothesis would prompt further questions concerning the absence of a similar pattern of declining cancer defences in chimpanzees, which also live in patriarchal groups. Is their pattern associated with a scarcity of aged chimpanzees, or could their dietary preferences, potentially devoid of modern carcinogens, be influential? Alternatively, could the persistence or increase in reproductive value into older ages stimulate heightened anti-cancer adaptations?

3. Framework of the Hypothesis / Caveats

Our hypothesis does not intend to challenge established knowledge regarding cancer in humans and related species. Notably,

- We recognize there is a well-established literature on cancers resulting from environmental or individual exposure to

carcinogens (e.g., tobacco, pollutants, industrial chemicals), and in addition to exploring cancer defences of a population or individual, prevention efforts should be aimed at understanding and minimizing exposure to these preventable causes of disease, as they may even cause cancer in the presence of robust cancer defences.

- Consideration must be given to the influence of modern human behaviors—such as dietary shifts and sedentary lifestyles—which have significantly altered human susceptibility to cancer. Our hypothesis seeks to address complementary evolutionary aspects.
- Regarding the proposed antagonistic pleiotropies: Evolutionary processes entail trade-offs, where the emergence of specific traits or adaptations may come at the expense of others. It's plausible that distinctive features and evolutionary pressures shaping humans, like heightened brain size and energy demands, could have constrained resource allocation towards cancer defences. Determining whether our hypothesis or antagonistic pleiotropy explains specific cancer defence developments requires investigation on a case-by-case basis.
- Random genetic mutations may have caused interference.

In light of arguments for the tumor suppression theory of aging^[16], we could consider rephrasing "creeping abandonment of cancer defences" to "A gradual transition of cancer defences from energy-intensive processes like the induction of apoptosis to low-energy processes like cellular senescence", where cellular senescence might provide the desired caloric reduction as seen in scenario A below, while its aging-related costs could contribute to genetic diversity enhancement as in scenario B below.

4. Scenarios favouring the hypothesis

We present two scenarios, each lending support to our hypothesis while remaining mutually consistent. Both scenarios involve several assumptions, and project into an undocumented past that prevents thorough verification.

Scenario A

Homo sapiens developed a large brain compared to their ancestral species, requiring a constant supply of a large amount of calories. Within the context of ancestral human hunter-gatherer societies, this demand might have rapidly reached the constraints posed by seasonal resource availability. In response to the challenges imposed by such hardship, it is possible that telomeres underwent reduction in length, triggering cellular senescence. After a number of divisions, this hardship-induced accelerated senescence slows down older individuals' metabolism, with an added advantage that caloric resources can be redirected to the younger population. But this cellular senescence also comes with a trade-off in performance of cellular function, including cancer defence.

Scenario B

Throughout most of the evolutionary history of the genus *Homo* (from *Homo habilis* to *Homo sapiens*), small-scale hunter-gatherer tribes were the dominant social structure. In 20th-century hunter-gatherer tribes, the available anthropological

literature indicates that males engaged in individual fishing, hunting and gathering; it features observations of social homogeneity [17]. However, it is important to emphasize that these modern tribes were not subject to substantial predation pressure from large carnivores.

Conversely, the transition of *Homo ergaster* from arboreal habitats to the open savanna necessitated coordinated defence strategies against a diverse array of now-extinct carnivores [18][19][20][21]. Current models have proposed chimpanzee-like, large fission-fusion societies characterized by numerous bonded males organized into bands, alongside immigrating females [22]. We hypothesize that this departure from an egalitarian social structure may have created a hierarchy, with the leader of coordinated defence efforts against carnivores attaining elevated social status. Consequently, natural selection is presumed to have operated at the level of these bands, given that the paternal genetic lineage within a band derived from shared kin, thereby linking the survival of kin genes to the band's collective survival.

Then higher degrees of inbreeding would quite certainly have been detrimental to a band. And males of high social status can attract new reproductive partners again and again until an age that has seen several generations grow [23], 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 [24]), 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 [25], 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/grand-parental 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

- The hypothesis could be tested directly by analysing cell nuclei of present-day aged persons, and checking if tumour suppressor genes have been deactivated epigenetically.
- 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 time-span. 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 [26], but DNA can now be collected and analysed from much older human remains [27].

- 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 abandonment 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.

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