Author's response to reviews

Title: Natural resistance to cancers: a Darwinian hypothesis to explain Peto's paradox

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Responses to referee 1

We would like to sincerely thank the referee for his helpful comments. Below, we respond to the points raised by the reviewer (their comments are in italics).

The “Debate” manuscript by Roche et al discusses Peto’s Paradox, or the observation that larger or longer-lived animals do not have more cancers. The manuscript introduces this paradox, but is deficient on a research “direction”, mainly urging that more “research” is needed. Though it is hard to argue that this general approach is wrong, the “needed” approaches are vague and described as “mathematical and statistical approaches” and “We need to uncover the selective (biotic and abiotic) landscapes in which species evolved”.

The manuscript could be greatly improved and be of greater value if it could be more specific on what data are needed to help resolve Peto’s Paradox. As currently written, it is difficult for this reviewer to quite understand exactly what is being proposed or “Debated”. For example, this “Debate” could be framed within the context of carcinogenesis in the mouse, which is very well-studied with a research database probably equivalent to human—how has this research helped to resolve Peto’s Paradox and how would it be useful to study other species?

We agree that more clarity is needed as the reviewer suggests, and have changed the Discussion as follows:

- “We need to understand the selective (biotic and abiotic) landscapes in which species evolved and continue to evolve. Indeed, natural selection is the product of how environments favour specific heritable phenotypes. Cancer vulnerability amongst wildlife species is
likely to have been shaped by natural selection, depending on which fitness-reducing risks predominate (somatic diseases including cancer, infectious and parasitic diseases, predation and adverse environmental conditions). For instance, small rodents in natura may succumb to cancer, but only if they do not first die from any one of numerous other causes, such as predators, infectious diseases, or environmental vagaries such as floods, temperature extremes, etc. Natural selection will tend to promote resistance to sources of mortality prior to reproduction, meaning that for blue whales to grow so large and live so long, they need to both develop defences against predators and resistance to somatic diseases like cancer. There is clearly a chicken-and-egg problem here, since changes in body size, longevity and life history strategy will alter the selective influence of different mortality factors, including the probability of cancer emergence.

Studying this complexity (i.e., numerous environmental factors acting and interacting in opposite directions and/or with reciprocal effects (Figure 2)) requires the development of a theoretical approach. Adopting a quantitative framework, such as adaptive dynamics (6), widely applied to understanding the evolution of pathogens and life-history traits, can help understand how different biotic and abiotic selective pressures affect trait evolution and especially those involved in cancer protection.

Since wildlife species are subjected to a large variety of selective pressures and are found in a diverse range of habitats, it should be possible to use comparative genomics (7) to understand how
oncogenes and TSGs covary with certain environmental characteristics. Indeed, comparing genomic regions of interest for cancer research, *e.g.*, proto-oncogenes or Tumor Suppressor Genes widespread in mammals, according to the biotic and abiotic environments where these species are found can give important insights into how these classes of genes have been shaped by natural selection as a function of the environment.

Addressing these considerations is undoubtedly relevant for human populations living in different environmental conditions (*e.g.*, presence or absence of pathogens). Indeed, evidence suggests that many human populations lack alleles with enhanced protection against certain cancers, possibly because their short life-spans have precluded selection for those alleles (4, 5, 8).”
Responses to referee 2

We would like to thank the referee for his/her comments, and we respond to them below.

*In the penultimate paragraph, the authors make the claim that, "given this complexity, ... we need to develop global theoretical approaches." The two examples that follow illustrate the complexities involved, but shed little light on what is meant by "global theoretical approaches." Clarification of this intriguing claim--what is meant by "global" in this context, and what shape would such a theoretical approach take?--would be helpful.*

This is a reasonable criticism from the referee and is virutally identical to the issue raised by the other referee. We have revised our manuscript as follows:

- “We need to understand the selective (biotic and abiotic) landscapes in which species evolved and continue to evolve. Indeed, natural selection is the product of how environments favour specific heritable phenotypes. Cancer vulnerability amongst wildlife species is likely to have been shaped by natural selection, depending on which fitness-reducing risks predominate (somatic diseases including cancer, infectious and parasitic diseases, predation and adverse environmental conditions). For instance, small rodents *in natura* may succumb to cancer, but only if they do not first die from any one of numerous other causes, such as predators, infectious diseases, or environmental vagaries such as floods, temperature extremes, etc. Natural selection will tend to promote resistance to sources of mortality prior to reproduction, meaning that for blue whales to grow so large and live so
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Since wildlife species are subjected to a large variety of selective pressures and are found in a diverse range of habitats, it should be possible to use comparative genomics (7) to understand how oncogenes and TSGs covary with certain environmental characteristics. Indeed, comparing genomic regions of interest for cancer research, e.g., proto-oncogenes or Tumor Suppressor Genes widespread in mammals, according to the biotic and abiotic environments where these species are found can give important insights into how these classes of genes have been shaped by natural selection as a function of the environment.
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The bibliography issues highlighted by the referee have been also fixed.