Reviewer's report

Title: Can Peto's paradox be used as the null hypothesis to identify the role of evolution in natural resistance to cancer? A critical review.

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Reviewer: Cees Cornelisse

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Review manuscript BMC cancer ' Can Peto's paradox be used as the null hypothesis to identify the role of evolution in natural resistance to cancer? A critical review
Ducasse et al.,

This paper critically reviews the different hypotheses explaining the absence of a correlation between cancer prevalence and body size known as Peto's paradox. It involves a review of the relevant literature (up to April 2015, 104 references).

The paper contains three Figures.

1. Background

Clear introduction, Fig 1 summarizes adequately summarizes the cancer risks at different scales

The three assumptions underlying Peto's hypothesis are clearly described as is the rationale for a critical analysis of their legitimacy.

Line 120-122: ‘… and argue that apart from body size, additional ecological, environmental and behavioral factors, together with the number of stem cells at the tissue/organismal levels should be considered….

This is a rather global description of the different factors that are considered in Part 2. ‘ Underlying hypotheses' which also include the tumor microenvironment and epigenetic factors.

2. Underlying hypotheses …..

Line 141-142 ‘ Certain type of differentiated cells cannot initiate propagation of malignant phenotypes because they cannot divide, e.g. myocytes, adipocytes, skin cells ?? only those in the stratum basale divide.

Line 156-157 ‘ Including cell size as a parameter for the prediction of cancer risk shows that the correlation between body/organ size is weaker (34)..

This needs more elaboration! Ref 34 provides a new perspective on the Peto’s paradox not only including the role of cell size but, even more importantly, the difference in basal metabolic rate between small and large animals. This certainly needs to be addressed! Although in line 177 it is mentioned that the level of oxidative stress is very different across different tissues, the relationship with
metabolic rate needs to be addressed here as well.

Line 182-189: ….DNA instability in specific cell types such as T and B lymphocytes ….The enzymes involved in initiating the hypermutation events could potentially also increase the genomic instability of these cells and favor errors leading to lymphoid transformation (42).

Potentially, yes, but lymphomas and leukemias are only a minority among the malignant neoplasms!

2.3.1. Variation in mutation numbers required to trigger tumor formation and progress
The relevance of this section for the main topic of the paper is not clear.

2.3.2 Epigenetic
I presume that the authors mean ‘epigenetic alterations/changes/factors/mechanisms? This section needs more elaboration and more recent references should be included e.g. Feinberg, J. Intern. Med, 2014;276, 5-11

2.3.2. Tumor microenvironment
Again, this section needs more elaboration. Although the authors briefly refer to the paper of Bissell et al., (ref 1), there is much more in that paper that is relevant for the present manuscript e.g. the role of the tumor stroma, relationship with inflammation and tissue/wound repair etc. ‘tumours are wounds that don’t heal’.

3.1 Sampling bias
Line 256-257: ‘While the role of artificial selection for certain traits has been recognized (69), ity seems to also apply to the emergence of cancer phenotypes’… What’s the evidence for that? The cited paper (ref 69 only studies the effect of locomotor activities on the circadian period

3.2 Environmental factors triggering the development of cancer phenotypes
Line 293-297 …..’ it is expected that selection will favor cancer resistance in small, but long-lived animals… This expectation is now supported by several recent studies on the naked mole rate e.g.
Faulkes et al., ‘Molecular evolution of the hyaluronan synthase 2 gene in mammals: implications for subterranean niche and cancer resistance, Biol. Lett. 11, 2015, 0185,
Keane et al., ‘The naked mole rat genome resource: facilitating analysis of cancer and longevity-related adaptations.

3. Discussion
Figure 3 shows virtual data, and as such does not significantly contribute to the content of this paper.

Quality of written English: Acceptable
**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

no