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The effect of placentation type, litter size, lactation and gestation length on cancer risk in mammals

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Reproduction is a central activity for all living organisms but is also associated with a diversity of costs that are detrimental for survival. Until recently, the cost of cancer as a selective force has been poorly considered. Considering 191 mammal species, we found cancer mortality was more likely to be detected in species having large, rather than low, litter sizes and long lactation lengths regardless of the placentation types. However, increasing litter size and gestation length are not *per se* associated with an enhanced cancer mortality risk. Contrary to basic theoretical expectations, the species with the highest cancer mortality were not those with the most invasive (i.e. haemochorial) placentation, but those with a moderately invasive (i.e. endotheliochorial) one. Overall, these results suggest that (i) high reproductive efforts favour oncogenic processes' dynamics, presumably because of trade-offs between allocation in reproduction effort and anti-cancer defences, (ii) cancer defence mechanisms in animals are most often adjusted to align reproductive lifespan, and (iii) malignant cells co-opt existing molecular and physiological pathways for placentation, but species with the most invasive placentation have also selected for potent barriers against lethal cancers. This work suggests that the logic of Peto's paradox seems to be applicable to other traits that promote tumorigenesis.

1. Introduction

Cancer is a group of diseases, widespread across the tree of life, in which cells break cellular collaboration and proliferate abnormally [1,2]. It is increasingly suggested that oncogenic processes have been influencing the evolutionary ecology of their hosts since the dawn of multi-cellularity, approximately 1 billion years ago [3,4]. Tumoral cells, especially malignant ones, can be detrimental to the host by directly or indirectly imposing fitness costs on them, reducing for instance their survival and/or their reproductive potential [4–7]. These effects have in return promoted the evolution of defence mechanisms in hosts [8], as well as compensatory adaptations [9]. For example, tumour-bearing females in *Drosophila melanogaster* reproduce earlier compared with healthy ones to buffer the fitness costs of tumours [10]. In the Tasmanian devils (*Sarcophilus harrisii*) affected by a

lethal transmissible cancer (the devil facial tumour disease), which killed more than 80% of individuals in certain areas since 1996, females are now reproducing earlier in their life, before they are infected and killed by the transmissible cancer cells [11]. In parallel, reproduction, notably the pregnancy process in humans and other mammals, exacerbates the progression of existing tumors in females as the energy gets primarily allocated in reproduction at the expense of anti-cancer defences, which promotes the evolution of additional defences such as possibly menopause [12]. Like several other biological processes detrimental to health, malignant dynamics can also be embedded in the antagonistic pleiotropy theory [13]. For example, in the fish *Xiphophorus cortezi*, males carrying the *Xmrk* melanoma-promoting oncogene grow larger body sizes and have higher mating success compared with non-carriers, but at the cost of developing lethal melanoma at an increased frequency later in their life, following reproduction [14,15]. Another example are SPANX genes present in primates that are under strong positive selection and are involved both in spermatogenesis and in melanoma progression by promoting cancer cell growth [16]. Understanding the evolutionary trade-off between reproduction and oncogenic processes is complex and remains only partially understood, despite its importance in diverse research areas such as population dynamics, conservation biology, epidemiology and public health [17,18].

Reproduction is a costly process, especially for females that allocate substantial amounts of energy and nutrients to support the growth of their offspring [19]. For example, in mammals, as the litter size increases so does the costs of gestation and lactation [19,20]. Those high physiological costs could exacerbate the progression of existing tumours but not necessarily to a point at which they would result in an increase mortality risk. Indeed, species are expected to have evolved over evolutionary times anti-cancer defences to at least partially counter those negative effects on their health [5,12]. Placentation is also a key feature of mammalian reproduction. Like metastasis, placentation can be seen as an invasive process that involves the transplantation of cells into new environments [21]. Both invasive placentation and metastasis share common cellular and molecular mechanisms, e.g. angiogenesis, including the degradation of the extra-cellular matrix and expression of specialized adhesion molecules check, or avoidance of the immune system [21–24]. Consequently, the existence of mechanistic and evolutionary links between the placentation and cancer metastasis has been suggested [21,22]. For instance, it has been proposed that tumours reactivate similar genes and molecular pathways involved in invasive placentation types to increase their own invasiveness [21,22]. However, we must distinguish between different types of placentation. Based on the number of tissues separating maternal from fetal blood, placentas are classified as epitheliochorial, endotheliochorial or haemochorial [25]. Epitheliochorial placentation is considered non-invasive with no penetration of the maternal tissue by fetal cells (e.g. in pangolins, whales and hoofed mammals). Endotheliochorial placentation is considered partially invasive with a uterine epithelium that is eroded, and the trophoblast located next to intact maternal blood vessels (e.g. sloths, elephants). Finally, haemochorial placentation is considered highly invasive, with the trophoblast in direct contact with the maternal blood (e.g. in primates, rodents) [26]. Haemochorial placentation is also considered the ancestral type for placental

mammals from which the two others evolved [27]. In female placental mammals, the possession of invasive trophoblasts and/or reproductive tissues that are more easily invaded by them is likely to promote fertility, as it favours the implantation of the embryo and its ability to extract resources from the maternal body [28]. However, those attributes can make a more fertile female more vulnerable to metastatic cancers. Therefore, it has been proposed that species with a highly invasive placentation and long gestation periods or maternal care are under increased risk of lethal cancer. This link between placentation and cancer risk has been investigated in a few empirical studies, but their results remain equivocal. Boddy *et al.* [29] used data on 37 mammalian species from the San Diego Zoo and found no difference in cancer prevalence between species with different placentation types but detected a positive relationship between litter size and the risk of cancer-related mortality. Conversely, D'Souza & Wagner [21] used data from 12 United States and Canadian colleges of veterinary medicine on cows, horses, cats and dogs and showed that species with less invasive placentation have lower rates of metastatic cancer compared with those with invasive ones. While valuable, those studies were performed on data with a relatively limited number of species. Furthermore, these studies did not consider that species with highly invasive placentas should have selected for powerful anti-cancer defences in return, as has been proposed in the Peto paradox with the evolution of large sizes [30]. In this study, we therefore used newly published data on 191 mammal species encompassing species with very diverse life histories and placenta types from zoos around the world [30]. The high quality of this unique dataset allows to decipher the complex links between cancer mortality risk, placentation type, litter size and lactation length.

2. Methods

(a) Data collection

To quantify cancer mortality risk, we extracted the data on mammal species provided as supplementary material by Vincze *et al.* [30]. The authors of this study used data from Species360 and the Zoological Information Management System (ZIMS), an international non-profit organization that maintains a real-time and centralized database of animals under human care (regrouping information from over 1200 zoos worldwide). They relied on the high probability of body retrieval of deceased zoo animals and post-mortem pathological records, which allows to detect and document cancer-related mortality (although with lower probability in case of liquid tumours, early stage cancers or small, but lethal tumours; see the original publication for details). Cancer is only registered in this database for deceased animals and only if the inspecting veterinary pathologist considered it to be a factor that contributed to the individual's death. Only species in which post-mortem pathological records were available for at least 20 adult individuals, irrespective of the cause of death, were included in their analyses. Vincze *et al.* also excluded all species that were subject to domestication as well as their wild ancestors, as domestication is widely regarded as a major contributing factor to inbreeding depression and higher risk of developing cancer [31]. In addition, cancer mortality risks provided by Vincze *et al.* were calculated by pooling both male and female data.

Vincze *et al.* calculated two measures of cancer risk, namely the cancer mortality risk (CMR) and incidence of cancer mortality (ICM). They estimated the cancer mortality risk as the

ratio between the number of cancer-related deaths and the total number of individuals whose post-mortem pathological records were entered in the database. Incidence of cancer mortality, which is a metric of cancer risk eliminating potential biases due to disregarding left-truncation (that is, cancer before individuals enter the study) and right-censoring (individuals alive, thus with unknown fate at data extraction), was computed using a Kaplan–Meier estimator (see [30] for full details on the calculation of this metric). Finally, Vincze *et al.* considered species to have cancer if at least one individual with post-mortem pathological record was diagnosed with cancer, a classification we used in our study too.

As classically done, we classified the placentation type of each mammalian species ($n = 191$) into three categories based on their invasiveness (see Introduction and [32–34]): epitheliochorial placentation ($n = 84$), endotheliochorial placentation ($n = 64$) and haemochorial placentation ($n = 43$).

We obtained data on average litter size (number of offspring, $n = 187$), gestation length (in days, $n = 187$) and lactation length (in days, $n = 137$) from the PanTHERIA [35], Animal Diversity Web (<https://animaldiversity.org/>), and Animal Ageing and Longevity databases (<https://genomics.senescence.info/>) [36].

Vincze *et al.* showed that a diet of primarily vertebrate by mammals increased their cancer mortality risk and thus should be considered as a potential confounding variable. Here we consider that diet is part of the cancer risk landscape of animals in which multiple risk factors increase the probability of developing cancer during their lifetime (see [37]). We therefore re-used Vincze *et al.*'s classification, in which each mammal species is binary classified as primary eating vertebrate or not, as initially proposed by Kissling *et al.* [38] ($n = 190$). Missing information on diet for one species, the Californian sea lion (*Zalophus californianus*), classified as primarily eating vertebrates and in which cancer was detected [39]), was manually added to the dataset.

(b) Phylogenetic analyses

We used phylogenetic generalized least-squares (PGLS) regressions to quantify the effect of the placentation type, litter size, gestation length, lactation length and diet on the cancer mortality of mammal species following a two-step protocol (first using binary PGLS then continuous PGLS). We first investigated the potential effect of those risk factors on the probability of detecting cancer in mammal species and then quantified their effect on the cancer mortality risk in a species. Here we used binary PGLS models in order to investigate whether cancer was more likely to be detected in species with a more invasive placentation, longer gestation length, longer lactation length or larger litter size. Because of the high cost of reproduction, we hypothesize those variables will be positively associated with cancer risk. Vincze *et al.* [30] showed that the probability of detecting cancer in a species depended of the number of animals with a pathological record (i.e. the sample size) and observed a non-significant trend in the body size or lifetime expectancy. Peto's paradox predicts that cancer risk does not scale with body size because species evolved anti-cancer defences to reduce the risk of developing malignancies when the number of cells is large. Because of senescence, lifetime expectancy is predicted to be positively associated with cancer risk, especially in zoos in which it is extended [30,40]. We ensured those two last variables had no effect on the probability of detecting cancer by including them in our analyses and model selection procedures.

To quantify the effect of the various risk factors on the probability of detecting cancer, we applied a purposeful selection of covariates to build parsimonious risk factors models. This approach retains confounders at a larger rate than other selection procedures when the response variable is binary (see [41]). We therefore started by fitting univariate binary PGLS models,

using each potential risk factor in separate models on species in which cancer was detected ($n = 144$ species). Then risk factors with significant effect sizes in univariate models were combined into a multivariate binary PGLS to quantify their simultaneous effect on the cancer mortality risk of mammals. When needed we also tested for potential two-way interactions between placentation types and other life-history traits.

To investigate the effect of risk factors on the CMR and ICM of mammals, we applied the model selection protocol from Zuur *et al.* [42]. We started by fitting a univariate PGLS model using either CMR or ICM as response variable for each potential risk factor (using a restricted maximum-likelihood estimator, REML). The risk factors with a significant trend were then combined into a series of multivariate PGLS models (using a maximum-likelihood estimator, ML), and the performance of those models were compared using the Akaike's information criterion (AIC), Δ AIC and AIC weights [43]. Once the best model was identified (lowest AIC, highest AIC weight), we refitted it using a REML estimator to interpret effect sizes.

To account for the lack of independence between species, we re-used the phylogenetic tree from Vincze *et al.* [30] in all the models we fitted in this study. This tree was created by obtaining a rooted consensus from a sample of 1000, equally plausible phylogenetic trees published by Upham *et al.* [44]. Since the precision of the cancer mortality estimates is affected by the sample size used to compute them, we included the log of the number of animals with a necropsy record available as an explanatory variable in the binary PGLS, and also used that number to weight each species in univariate and multivariable continuous PGLS. In addition, we logit transformed cancer mortality values prior to fitting models, to ensure model residual normality and homogeneity of variance (on the link-function) [45]. When required we computed the models' marginal effects to visualize how a variable affected the cancer mortality of mammals [46].

All analyses were performed using R [47] (v. 4.0.2). Phylogenetic analyses were computed using the 'nlme' and 'ape' packages [48,49].

3. Results

(a) Probability of detecting cancer in mammal species

Cancer was detected in 144 out of 191 species. As previously observed, the number of animal necropsies (mean: 62.0 ± 54.7 s.d. individuals, range: 20–413, $n = 191$ species) was the primary driver of the probability of detecting cancer in mammal species (binary PGLS $p < 0.001$, figure 1). We found no significant differences in the probability of detecting cancer between the three different placentation types ($n = 191$ species, binary PGLS, $p > 0.05$, figure 1a). Based on model selection approach, gestation length (mean: 160.5 ± 88.6 s.d. days, range: 16.7–455.3, $n = 187$ species), body mass (mean: 74.3 ± 159.6 s.d. kg, range: 0.02–1499.5, $n = 191$ species), life expectancy (mean: 3664.4 ± 1814.2 s.d. days, range: 402.2–11 385.0, $n = 191$ species), and the consumption of vertebrates ($n = 191$ species) had no effect on the probability of detecting at least one cancer-related death (binary PGLS, $p > 0.05$, see electronic supplementary material for detailed results for the model selection approach). However, cancer mortality was more likely to be detected in species with large litter sizes ($\beta = 1.12 \pm 0.44$ s.e., mean litter size: 1.9 ± 1.4 s.d., range: 0.9–11.3, $n = 187$, figure 1b) and species with a longer lactation length ($\beta = 0.0071 \pm 0.0022$ s.e., mean lactation length: 183.8 ± 213.1 s.d., range: 5.0–1670.5, $n = 136$, figure 1c). Cancer mortality was detected in nearly all mammal species with a litter size of at least six offspring or a lactation length superior to 1000 days (a

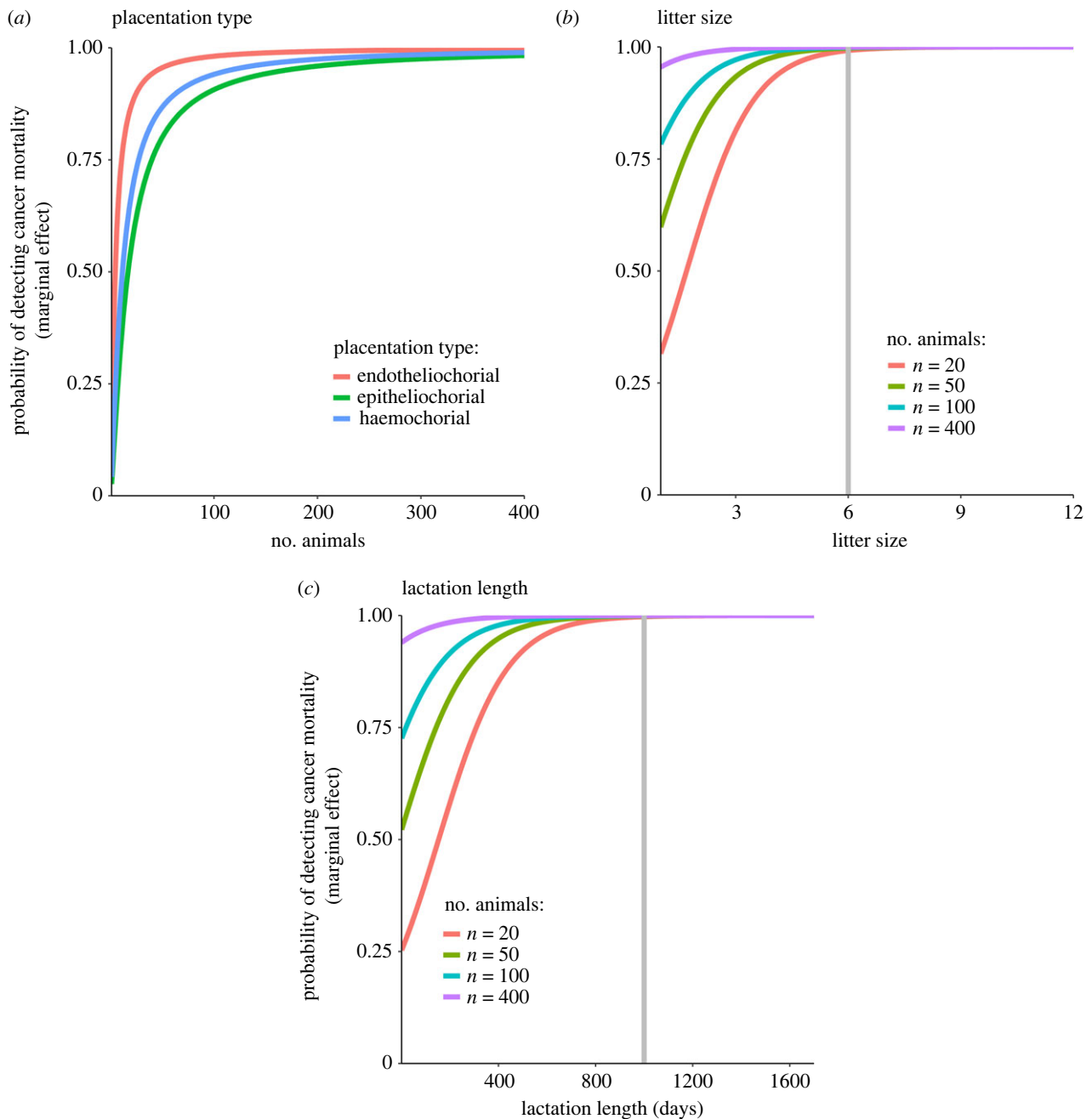


Figure 1. (a) Effect of the placentation type and the number of necropsied animals on the probability of detecting cancer mortality in mammal species. The differences between placentation types are not statistically significant. (b) Effect of the litter size or (c) the lactation length and the number of animals with available post-mortem pathological record on the probability of detecting cancer in mammal species. For a given number of necropsied animals, the probability of detecting cancer significantly increases with litter size and weaning age. The vertical grey line indicates a litter size of six in (b) and a lactation length of 1000 days in (c).

length that decreased as the number of animals necropsied for a given species increased, figure 1). We found no significant interaction terms between placentation type and litter size or lactation length in the models we tested (binary PGLS, $p > 0.05$, see electronic supplementary material S1).

(b) Cancer mortality risk in mammal species

Based on the model selection approach, gestation length, body mass, life expectancy, litter size and lactation length had no significant effect on cancer mortality risk of mammals (based on univariate continuous PGLS model, $p > 0.05$, electronic supplementary material S2). The placentation type was the only variable retained in the model and we found that species with an endothelial placentation had a significantly higher CMR compared with species with epitheliochorial (twice as large) and haemochorial placentation, (half larger) which are

not significantly different from each other (figure 2). One species had an unusually large cancer mortality risk (the kowari, *Dasyuroides byrnie*, cancer mortality = 57%) and was therefore excluded from the models. Removing that species from the dataset had little effect on the results and the effect of placentation remained significant (see electronic supplementary material S2). Similarly, based on the model selection, we found a significant interaction between diet and placentation type, with endotheliochorial and haemochorial species eating vertebrates being more at risk of dying of cancer compared with epitheliochorial species (continuous PGLS, $p < 0.05$, see electronic supplementary material S2).

(c) Incidence mortality risk in mammal species

We found that mammals with an endothelial placentation had the highest ICM, on average 1.9 times larger compared with

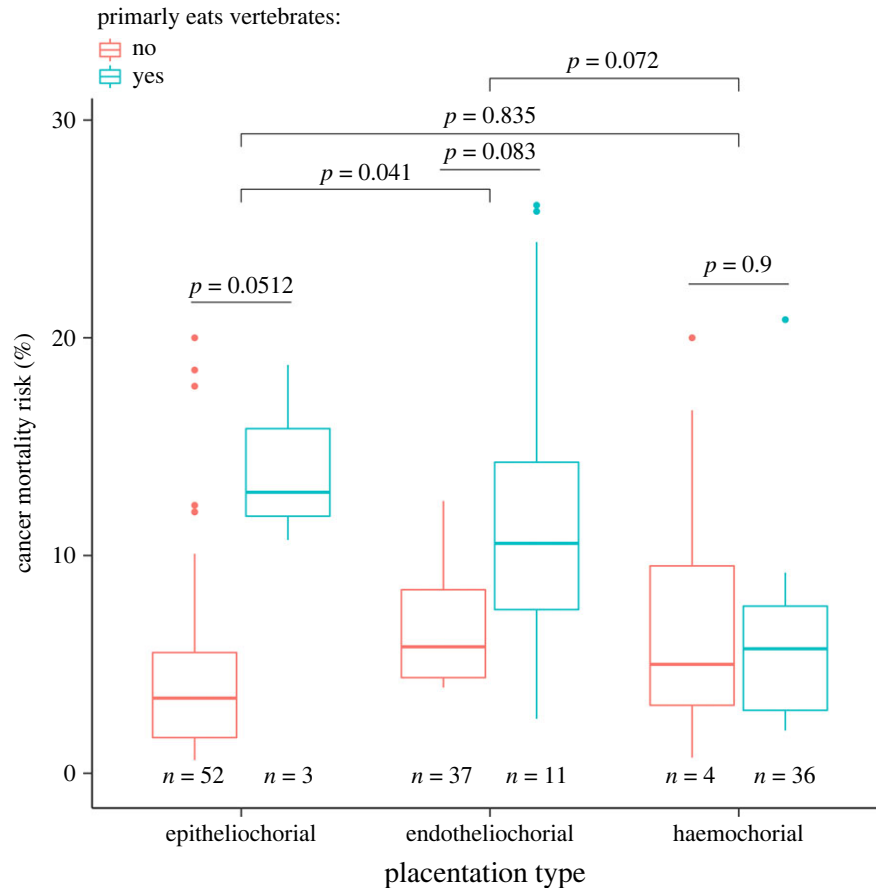


Figure 2. Cancer mortality risk of mammals in function of their placentation type and their diet. p -values were obtained by comparing the average cancer mortality risk for the relevant groups using PGLS models for each subset of the data. Placentation types are sorted from least to most invasive. The kowari, *Dasyuroides byrnie*, an outlier, was excluded from this plot.

species with an epitheliochorial and 2.0 times larger compared with species with haemochorial placentation. For all three placentation types, longer gestation lengths were associated with a decrease in ICM indicative of a lower of dying of cancer ($\beta = -0.004 \pm 0.001$ s.e., mean gestation length: 154.8 ± 92.4 s.d., range: 16.7–455.5, $n = 129$, figure 3). Like the CMR, including or excluding the kowari from the analyses had little effect on the results. We found no strong evidence that the other risk factors we tested affected the ICM of mammal species (see electronic supplementary material S3).

4. Discussion

Mammals with large litter sizes and long lactation lengths had a higher probability to have at least one cancer-related death registered irrespective of the type of their placentation. These results suggest that species whose allocation per reproductive episode is high, may, all else being equal, have a lower ability to prevent and/or eliminate oncogenic processes leading to the formation of tumours [12]. Reproduction is one of the most energetically demanding life-history stages, with the lactation length being typically more costly than gestation itself [50]. Therefore, breeding individuals are expected to experience trade-offs, where energy is diverted away from self-maintenance (cell repair, immune function) towards reproduction, favouring the development of tumours [5,12]. However, the effect on the fitness may be small, as the cancer mortality risk of species did not scale with litter size and lactation length. It is likely that those oncogenic processes do not systematically impact the survival, or other fitness-related

parameters in their hosts (see for instance [51]). Our results thus support the hypothesis that cancer defence mechanisms in animals are most often adjusted to align reproductive life-span with the mortality pattern of ageing individuals (see also [12,52]). Our results are consistent with Boddy *et al.*'s [29], which detected a positive association between litter size and cancer prevalence. They, however, found no evidence for an association between placental depth and malignancy prevalence as we observed in our study. The present analysis covers 191 species ($n = 11\,840$ animals with pathological records), 144 in which cancer was observed ($n = 9769$ animals with pathological records) compared with 37 species and a total of 800 individuals in Boddy *et al.*'s study. Compared with the latter, our study relies on a wider taxonomic range and larger number of individuals for each species, thus offering a more reliable estimation of the role of reproduction in oncogenesis. Moreover, the trend observed by Boddy *et al.* could have been biased by the inclusion of some species in their study with a relatively high cancer prevalence, but unreliably small sample size (e.g. the prairie dog *Cynomys ludovicianus*, the Tasmanian devil *Sarcophilus harrisii* or the Virginia opossum *Didelphis virginiana*). Our results confirm the general trends observed in the two studies.

The incidence of cancer mortality was the highest in mammals with an endothelial placentation compared with the two other placentation types (a pattern also observed at least partially in the cancer mortality risk data with endothelial placentation having higher cancer mortality risk compared with the two other types). Thus, contrary to what might have been predicted, the risk of developing metastatic cancer is not highest in species with the most invasive placentas.

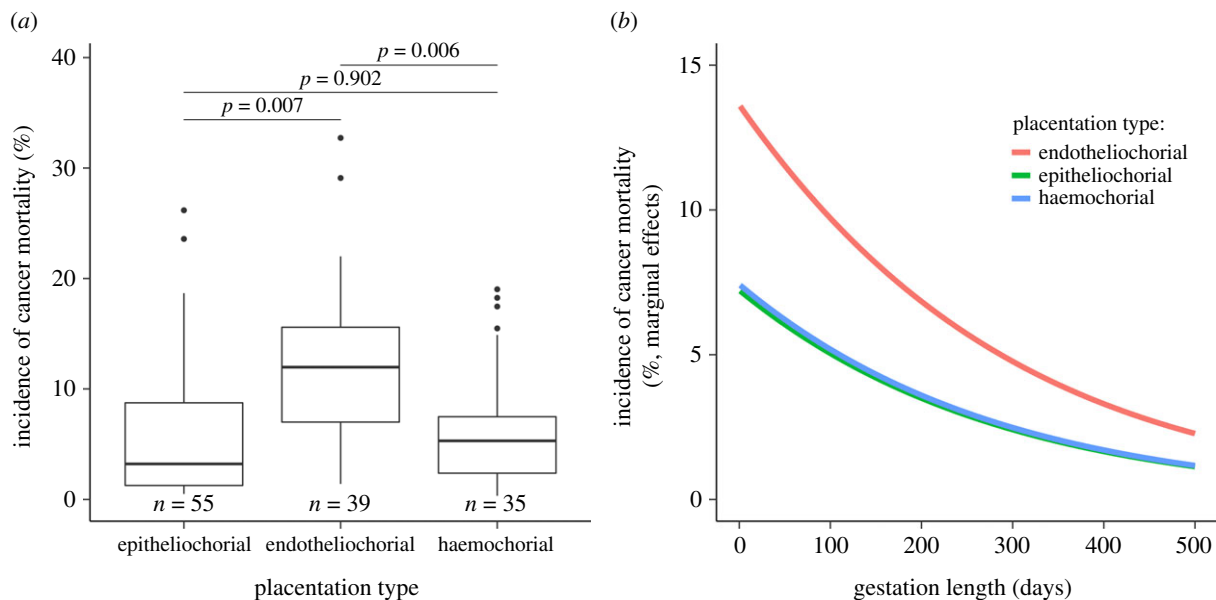


Figure 3. Incidence of cancer mortality of mammals in function of their (a) placentation type and their (b) gestation length. p -values were obtained by comparing the average incidence of cancer mortality for the relevant groups using PGLS models while accounting for the effect of gestation length. Placentation types are sorted from least to most invasive. The kowari, *Dasyuroides byrnei*, an outlier, was excluded from this plot.

The risk of dying from cancer was also decreased with longer gestation length for all three placentation types, suggesting a protective role of long gestation length. We argue here that a likely explanation for these apparently paradoxical results is the same as that of Peto's paradox for size [30], namely that the species most at risk of cancer death, here because of a high cellular invasive potential, are also those that have developed the strongest anti-cancer defences to counteract this vulnerability. Thus, our results are on average consistent with the hypothesis that malignant cells activate the same molecular and physiological pathways used during placenta formation to become more invasive (see for instance [21,23,24,26]), but that only species that have developed strong anti-cancer defences have been able to maintain over evolutionary times haemochorial placentas.

Endotheliochorial placentation evolved from the more invasive haemochorial placentation at least twice in the evolutionary history of mammals [27]. It has been suggested that the evolution of less invasive placentation is an adaptation that reduces the risk of female offspring conflict during gestation [53]. In the light of our results, we argue here that the risk of developing early lethal cancers may also have acted as a selective force favouring a transition to endotheliochoroid placentation, when selection for potent anti-cancer defences was not possible.

Collecting lifelong cancer data on wildlife species remains a difficult task and a key challenge. This is especially important as wildlife species is increasingly exposed to a range cancer risk factors directly linked to human activities [37,54]. The dataset used in this study, while relatively large compared with previous studies (e.g. [29]) has some limitations. For instance, female and male data are pooled. Similarly, the CMR and ICM values are calculated based by aggregating data collected on different tumour types and we cannot completely exclude the presence of biases which cannot be tested using Vincze *et al.*'s data [30]. Differential vulnerability between cancer types has been well documented in humans [55,56] but global data are lacking for most mammalian species. A possible consequence of including males in our study is an underestimation of the cancer risk

associated with different placentation types across mammals. Said differently, including only female data would be likely to lead to a larger effect size than we have quantified. As the size of the datasets collected on zoo animals steadily increases, we encourage scientists to revisit our study to account of those potential biases. In addition, the data we used in this study are limited to species kept in captivity and for which there are enough available data in the Species 360 database. Certain very large species with a long lifespan such as whales or elephants were not included in our analysis. Thus, cautiousness should be applied when translating the findings to wildlife species [57].

In conclusion, our study highlights the value of collecting data on a relatively large number of species to test key eco-evolutionary hypotheses related to cancer. This type of approaches will improve our understanding of how trade-off shaped anti-cancer defences and potentially to design strategies to mitigate the negative effects of cancer on species, ecosystems and human populations. Finally, this work also confirms that the logic behind the Peto's paradox can probably be applied to other traits that increase the risk of cancer mortality.

Data accessibility. Data used for this paper are provided as electronic supplementary material [58].

Authors' contributions. A.M.D.: conceptualization, data curation, formal analysis, investigation, methodology, software, validation, visualization, writing—original draft, writing—review and editing; O.V.: data curation, validation, writing—original draft, writing—review and editing; J.-F.L.: methodology, validation, writing—original draft, writing—review and editing; C.A.-P.: validation, writing—review and editing; P.P.: validation, writing—review and editing; M.G.: writing—review and editing; B.U.: funding acquisition, project administration, resources, writing—review and editing; F.T.: conceptualization, funding acquisition, project administration, resources, supervision, validation, writing—original draft, writing—review and editing.

All authors gave final approval for publication and agreed to be held accountable for the work performed therein.

Conflict of interest declaration. We declare we have no competing interests.

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