CANCER

Coevolution of cooperative lifestyles and reduced cancer prevalence in mammals

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Why cancer is so prevalent among mammals, despite the fact that some species evolved resistance mechanisms, remains an open question. We hypothesized that cancer prevalence and mortality risk might have been fine-tuned by evolution. Using public databases, we show that species with cooperative habits have lower cancer prevalence and mortality risk. By developing a mathematical model, we provide a mechanistic explanation: An oncogenic variant that elicits higher cancer mortality in older and less-reproductive individuals is detrimental to cooperative mammalian societies but can lead to a counterintuitive overcompensation in population size and fitness within competitive contexts. The phenomenon of a population increasing in response to a decrease in its per capita survival rate is called the hydra effect, a process never explored in the field of cancer before. Therefore, cancer can be considered as a selected mechanism of biological obsolescence in competitive species.

INTRODUCTION

Cancer, a set of pathologies associated with exacerbated cell division and invasion, is often understood as a by-product of constraints and trade-offs related to other processes undergoing selection (*1*, *2*). Alternatively, cancer has been also conceived as a negative selection force, acting on young individuals (*3*). Since cancer is associated with the accumulation of genetic and phenotypic changes throughout the life of a multicellular organism, the probability of developing cancer increases as an individual gets older. In this regard, oncogenic gene variants have been traditionally associated with either negative or neutral fitness value. In the first case, in line with the best-accepted theory for the evolutionary origin of aging, these variants are proposed to be related to other phenotypic traits on which positive selection operates, a mechanism called antagonistic pleiotropy (*4*–*6*). This mechanism maintains positively selected traits but at the same time generates "side effects," such as cancer or aging, that eventually harm organisms. On the other hand, many oncogenic variants are conceived as neutral, since cancer usually appears after reproduction, in late stages of species life cycles, and therefore does not substantially influence the ability to leave offspring (*6*, *7*). However, some mammals—such as mole rats, whales, elephants, bats, and squirrels—present molecular mechanisms that confer strong resistance to developing tumors (*8*), confirming that multicellularity can evolve without high levels of cancer incidence as an inevitable by-product. Despite this, cancer is widely distributed throughout the tree of life (*8*–*10*). The existence of several mammalian species with high prevalence of malignant tumors—such us several carnivores, rodents, and marsupials—has been reported (*10*). This raises the possibility that an increased prevalence of cancer and a higher cancer mortality risk (CMR) late in life may have been preserved in the evolution of some species not as a side effect (i.e., through antagonistic pleiotropy or genetic drift) but as a mechanism positively selected for its ability to increase the mortality, especially of aged individuals, taking into account that the frequency of a gene variant that reduces survival could be increased if it ensures differential reproductive success. The term phenoptosis (programmed organism death), in analogy with the concept of apoptosis (programmed cell death), has been suggested to define a built-in self-destruction program to interrupt the life of an organism (*11*, *12*). This type of phenomena might involve not only individual selection but also supraindividual selection (*13*). In this sense, the conceptual framework of "inclusive fitness" and "fitness interdependence" takes into account the possible effects of a trait on the survival or reproduction of other individuals (*14*). Under certain conditions, ecological systems can experience counterintuitive increases in population size or stability by selection of supraindividual traits. Positive effects of within-population mortality differences at the population and community level have been reported in many different species (*15*, *16*). The phenomenon of a population increasing in response to a decrease in its per capita survival rate has been named the hydra effect (or the hydra paradox) (*17*), in relation to the mythological monster that had the virtue of regenerating new heads for every one that was lost. Model simulations and analysis have shown that to accurately model these density overcompensation dynamics, structure should be introduced, for example, considering differences between individuals in age, stage, size, or other life history traits (*16*, *18*). A decrease in the size of a population has also been shown to stabilize population fluctuations during environmental perturbations, improving the resilience of a given population to extreme or stressful conditions (*19*). Similarly, it has been shown that a reduction in life expectancy favors the development of adaptations to cope with changing environmental conditions (*20*).

Here, we worked under the hypothesis that cancer prevalence and mortality risk across the tree of life might have been fine-tuned by evolution. A high prevalence of cancer late in life could have a neutral, negative, or even positive adaptive value in relation to life history and

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lifestyle traits associated with the ecological and evolutionary context of each species. In our work, we analyzed correlations of cancer prevalence and mortality risk with different phenotypic traits in mammalian species (Fig. 1A), moving from morphological and physiological traits (where individual selection would mainly operate) to life history and lifestyle traits (in which fitness interdependence should be taken into account). We combined this analysis with mathematical modeling to show that an oncogenic gene variant that elicits higher cancer mortality late in life can increase population size and genotype fitness in a context of intraspecific competition due to the hydra effect, while in a cooperative context (in which older individuals help in caring, breeding and/or feeding tasks), population size and fitness will decrease as cancer mortality in older individuals increases.

RESULTS

Cancer and morphophysiological traits

Larger body masses or increased metabolic rates could lead to a higher prevalence or CMR, due to the accumulation of mutations caused by increased number of cell divisions or by cellular damage triggered by reactive oxygen species, respectively. However, consistent with previous results (*10*), our phylogeny-corrected generalized linear mixed model (phylGLMM) revealed neither significant correlation between CMR and log body mass [$n = 190$, false discovery rate (FDR) $P = 0.999$; Fig. 1B and table S1A] nor between CMR and log metabolic rate ($n = 52$, FDR $P = 0.999$; Fig. 1C and table S1B) in the first dataset.

A second dataset, which assessed the prevalence of neoplasia rather than CMR, again showed, as previously reported (*21*), no significant correlation with log adult mass or log metabolic rate, according to our phylGLMM (Fig. 1, D and E, and table S2, A and B).

Similarly, a third dataset that included archetypal mammalian species with especially high or low malignancy prevalence also failed to show a consistently different proportion of these species between high and low body mass or between high and low metabolic rate groups (fig. S1). If higher cancer prevalence and mortality risk were only a side effect of the evolution of morphophysiological traits such as increased body mass or increased metabolic rate, a significant correlation between cancer and at least one of these variables should be expected. However, the analysis of different databases showed that this is not the case and that other explanations must therefore be pursued.

Cancer and life history traits

We next asked whether cancer prevalence and mortality risk might be associated with the evolution of supraindividual traits affecting the survival or reproduction of other individuals through competitive or cooperative interactions, under the theoretical framework of fitness interdependence. In contrast to what was observed for morphophysiological variables, we found a significant correlation between CMR and different life history traits. Larger litter sizes are associated with higher fertility rates (fig. S2) and with greater intraspecific competition among the pups. These juveniles receive less care from their mothers who tend to spend shorter periods of time with their young (*22*, *23*). Consistent with recent findings of Vincze *et al.* (*10*), our phylGLMM revealed a positive and significant correlation between log litter size and CMR ($n = 190$, FDR $P < 0.001$; Fig. 2A and table S1A). Similarly, higher CMR can be found in polytocous species, i.e., those with litter size bigger than 1.5 ($n = 190$, FDR $P < 0.001$; Fig. 2B and table S3A). Furthermore, in polytocous species, CMR increased with greater log body mass; meanwhile, in monotocous species, the opposite relationship is observed, leading to a significant interaction between both variables ($n = 190$, FDR $P = 0.049$; Fig. 2C and table S3B). Mammal orders with a higher proportion of polytocous species (such as Carnivora and Rodentia) also displayed significantly larger CMR (litter index, FDR $P < 0.001$; Fig. 2D and table S4).

The second dataset showed a closely similar trend to the dataset based on CMR. As reported by Boddy *et al.* (*21*), our phylGLMM revealed a positive and significant correlation between log litter size and neoplasia, while monotocous species tend to have less cancer than polytocous species (fig. S3 and table S2E).

In line with the results presented above, in the third dataset (rank20, 20 species with the highest and 20 species with the lowest malignancy prevalence), the ratio between species with high and low prevalence of malignancies was eight times higher in polytocous species than in monotocous species (Fig. 2E). These differences increased even further when we narrowed the rank (rank15 and rank10; Fig. 2E). Consistent with recent findings of Dujon *et al.* (*24*), we found in two different datasets that mammalian species with larger gestation time, and consequently greater maternal investment and increased caring, have significantly less CMR ($n = 190$, FDR $P = 0.002$; Fig. 2F and table S1A) and neoplasia (fig. S3 and table S2D).

Last, unlike Vincze *et al.* (*10*), we found that mammal life expectancy, another life history trait related to competitive or cooperative habits (*25*), is significantly and positively correlated with CMR ($n = 190$, FDR $P < 0.001$; fig. S4 and table S1A). On the contrary, a nonsignificant negative association was observed in the second database based on neoplasia prevalence, which includes more longer-lived species than the first dataset (fig. S4 and table S2C). No clear differences were found in the third database of archetypal mammals with high or low malignancy prevalence (fig. S4), implying that there are no consistent differences between cancer incidence and life expectancy in our three different analyses.

Cancer and lifestyle traits

The analysis of a possible association between ecological and behavioral characteristics (lifestyle traits) with cancer prevalence and mortality risk remains largely unexplored. We found that gregarious species of mammals, which is those living in groups, showed significantly less CMR ($n = 144$, FDR $P = 0.012$; Fig. 3A and table S5A). In addition, we found that in solitary species, CMR increases with greater body mass, while in gregarious species, the opposite relationship is observed ($n = 144$, FDR $P = 0.004$; Fig. 3B and table S5B). Consistently, we found that mammal orders with a higher proportion of solitary species—such as Carnivora—tends to have significantly more CMR than orders with more gregarious species—such as Primates and Artiodactyla—(group living index, FDR $P < 0.001$; Fig. 3C and table S4). Similarly, species that aggregate during breeding (plural breeders) have significantly less CMR than singular breeding species ($n = 146$, FDR $P = 0.002$; Fig. 3D and table S6A). In addition, we found that in singular breeding mammals, CMR increases with greater body mass, while in plural breeding species, CMR decreases with greater body mass ($n = 144$, FDR $P = 0.024$; Fig. 3E and table S6B). Consistently, mammal orders with a higher proportion of singular breeding species tend to have significantly more CMR than orders with a higher proportion of plural breeding species (breeding system index, FDR $P < 0.001$; Fig. 3F and table S4).

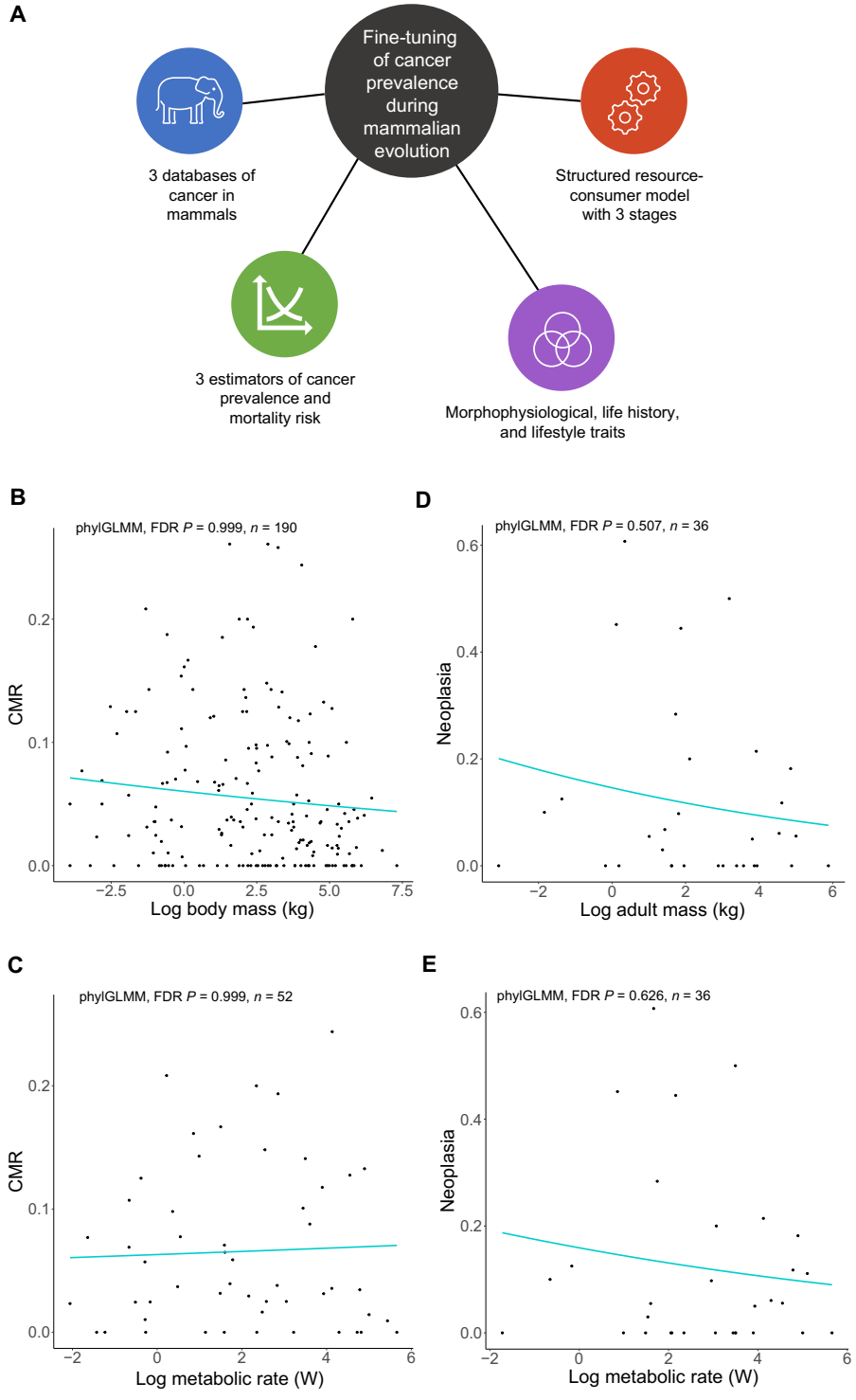

Fig. 1. No significant correlation between cancer risk and morphophysiological traits across mammals. (**A**) Overview of the analysis strategy followed in this work. (**B**) CMR plotted against log body mass (expressed in kilograms) using the first dataset. Black circles represent CMR values for each species, and the line is the regression slope obtained from phylGLMM analysis. (**C**) CMR plotted against log metabolic rate (expressed in watts). (**D**) Neoplasia plotted against log adult mass (expressed in kilograms) using the second dataset. Black circles represent neoplasia values (%) for each species, and the line is the regression slope obtained from phylGLMM ($n = 36$, estimator = −0.122, SE = 0.139, FDR $P = 0.507$). (**E**) Neoplasia plotted against log metabolic rate (expressed in watts) using the same dataset and phylGLMM ($n = 36$, estimator = −0.085, SE = 0.169, FDR $P = 0.626$).

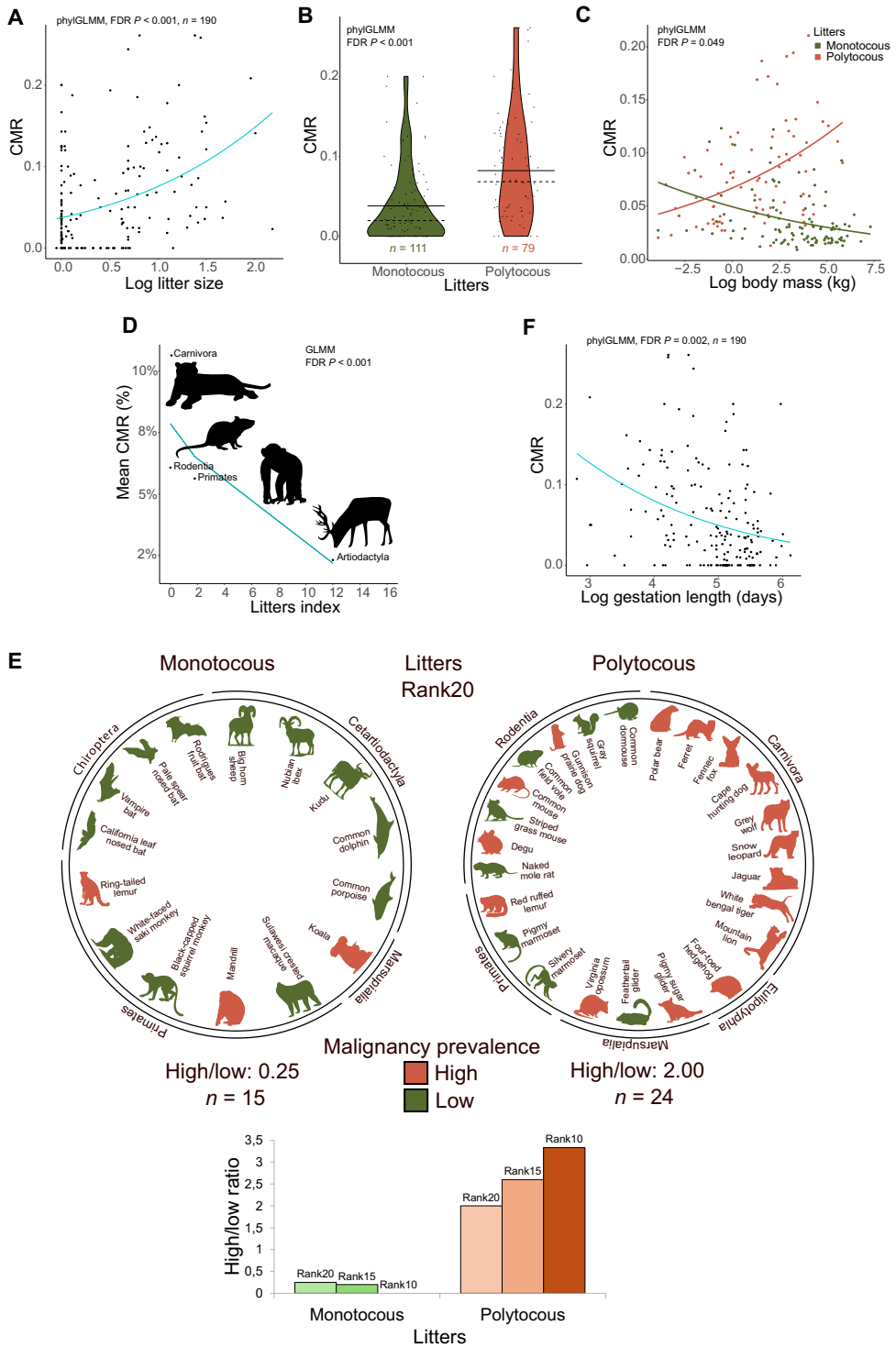

Fig. 2. Association between cancer risk and life history traits across mammals. (**A**) CMR plotted against log litter size (first dataset). Black circles represent CMR values for each species, and the line is the regression slope obtained from phylGLMM. (**B**) Violin plots of CMR in polytocous (red) and monotocous species (green). Horizontal lines represent the mean (full line) and the median (dashed line) values (first dataset). (**C**) CMR plotted against log body mass (first dataset) in monotocous species (green) and polytocous species (red). (**D**) Mean CMR plotted against the ratio between polytocous and monotocous species within each order (litter index, first dataset). (**E**) Distribution of archetypal species with very high or low malignancy prevalence (rank20, third dataset) in monotocous and polytocous mammals. The orders within the infraclass Marsupialia were unified under this category. A comparison between different ranks is shown (*10*, *20*, *15*). (**F**) CMR plotted against log gestation length (expressed in days, first dataset).

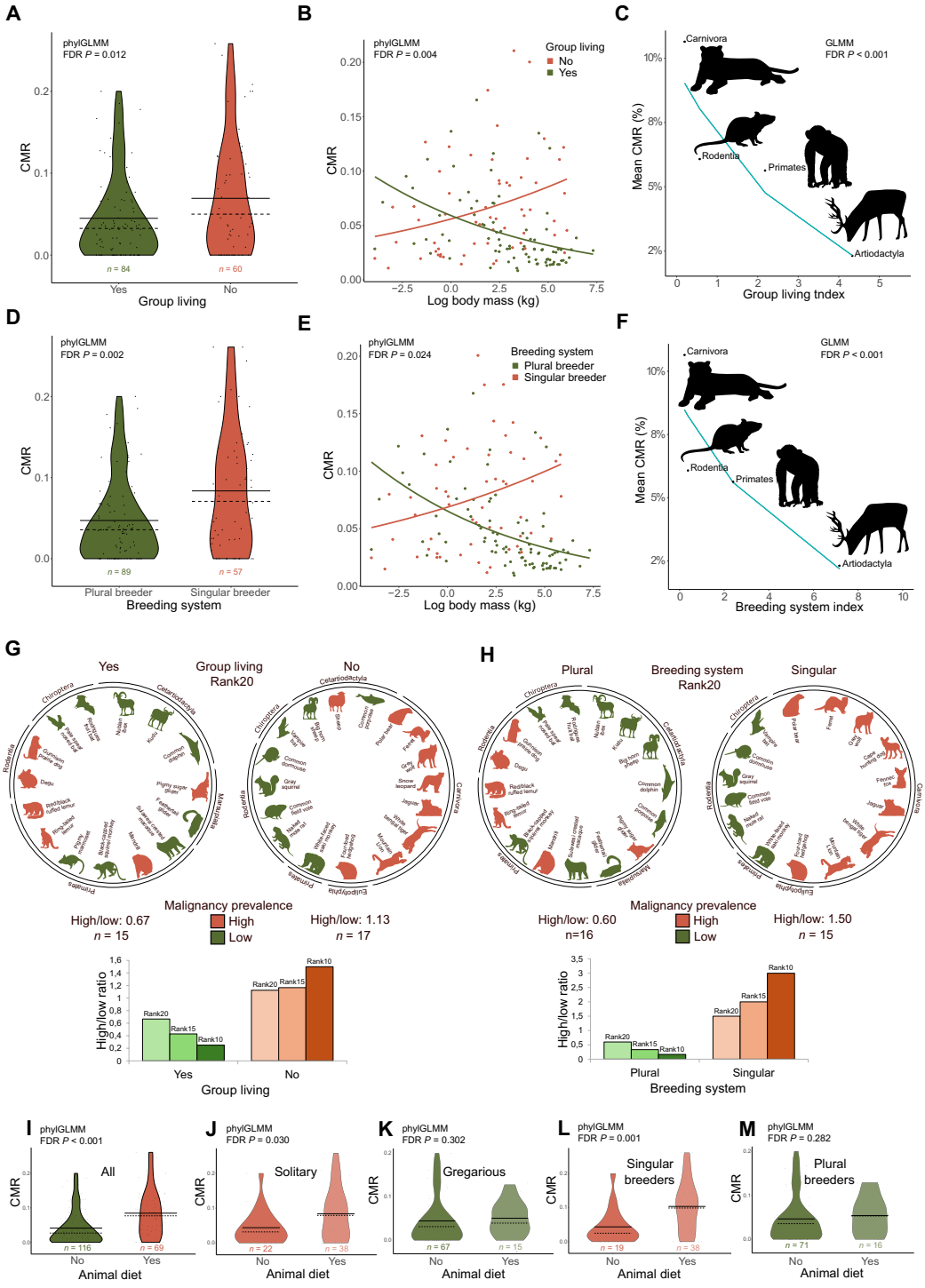

Fig. 3. Association between cancer risk and lifestyle traits across mammals. (**A**) Violin plot of CMR in mammal species with (green) or without (red) group living (first dataset). Black circles represent CMR values for each species, and horizontal lines represent the mean (full line) and the median (dashed line). (**B**) CMR plotted against log body mass in mammal species with (green) or without (red) group living (first dataset). Black circles represent CMR values for each species, and the line is the regression slope obtained from phylGLMM. (**C**) Mean CMR plotted against the ratio between group living and solitary species within each order (group living index, first dataset). (**D**) Violin plot of CMR in plural (green) or singular (red) breeding mammal species (first dataset). (**E**) CMR plotted against log body mass in plural (green) or singular (red) breeding species (first dataset). (**F**) Mean CMR plotted against the ratio between plural and singular breeding species within each order (breeding system index, first dataset). (**G** and **H**) Distribution of archetypal species with very high or low malignancy prevalence (rank20, third dataset) depending on gregariousness (G) and breeding system (H). The orders within the infraclass Marsupialia were unified under this category. A comparison between different ranks is shown (*10*, *20*, *15*). (**I** to **M**) Violin plots of CMR in carnivorous versus noncarnivorous mammal species (first dataset) depending on gregariousness (J and K) and breeding system (L and M). Carnivores were defined as those whose primary or secondary food are animals (animal diet). Noncarnivores are those who rarely or never eat animals.

The second dataset based on the prevalence of neoplasia showed a closely similar trend to the dataset based on CMR when comparing group living versus solitary species and plural versus singular breeders (figs. S5 and S6). Similarly, in the third dataset, the ratio between species with high and low prevalence of malignancies was higher in solitary and singular breeding mammals than in group living and plural breeding species (rank20; Fig. 3, G and H). These differences increased even further when we narrowed the rank (rank15 and rank10; Fig. 3, G and H). The presence of paternal caring, which is parental investment provided by a male to his own offspring, is not associated with lower CMR or less neoplasia (FDR $P = 0.4$; fig. S7 and table S7).

Since carnivorous mammals have been shown to display higher cancer-related mortality than noncarnivorous species (*10*), we decided to evaluate whether social lifestyles may affect on this association ($n = 185$, FDR $P < 0.001$; Fig. 3I and table S8). Notably, while solitary carnivorous mammals have significantly higher CMR than solitary noncarnivorous mammals ($n = 60$, FDR $P = 0.03$; Fig. 3, J and K, and table S8), carnivorous species living in groups do not ($n = 82$, FDR $P = 0.302$, table S8). We observed similar results comparing singular ($n = 57$, FDR $P = 0.001$; table S8) and plural breeders ($n = 87$, FDR $P = 0.282$; Fig. 3, L and M, and table S8), which further confirms that the social variables analyzed in our work are bona fide factors for cancer prevalence that can even neutralize significant effects of animal diet on CMR.

Modeling cancer, population size, and fitness

To mathematically test our working hypothesis that a high prevalence of cancer late in life could have a neutral, negative, or even positive adaptive value, depending on life history and lifestyle traits, we developed a resource-consumer model (Fig. 4A and Eqs. 1A to 1D) in which the consumer population depends on its resources (R) for subsistence and is structured on a three stages life cycle: prereproductive juveniles (J), reproductive adults (A), and senior postreproductive adults (S). This structure highlights reported age-related differences in fertility (g_A), foraging (f), and mortality (μ) in mammals (*26*, *27*). Resource density depends on the density of each consumer population stage and on its capacity to consume resources, which enables an indirect intraspecific competition for resources. Resource consumption is converted into physiological processes of reproduction and sexual maturation (functions g_A and g_J, respectively) with an efficiency given by the β_A and γ_A parameters, respectively (Eqs. 4A to 4D).

To simulate species with higher CMR, which affects mostly aged individuals, we set the per-capita mortality rate of senior adults (μ_S) as the control variable. In this framework, a system in which the carrying capacity for the consumer population (total population density per unit area, at dynamical equilibrium, N^*) increases, in response to higher values of senior mortality, is defined as exhibiting hydra effect, in contrast to the intuitively expected decrease (Fig. 4, B and C) (*15*, *17*). We first analytically determined necessary and sufficient conditions for a given set of population parameters to produce the hydra effect, using a simplified version of the system with no direct cooperation or competition among individuals. We found that higher CMR can lead to an increase in the population density (hydra effect) when the population exhibits high adult reproductive efficiency and therefore higher fertility rates (Fig. 4C). This is consistent with the observation of a positive correlation between log litter size and CMR (Fig. 2), taking into account that litter size positively correlates with fertility rate (the average total number of litters produced by an individual over its lifetime; fig. S2). On the contrary, high juvenile mortality and maturation efficiency rates diminished or abrogated the hydra effect (fig. S8, A and B). Noteworthy, higher cancer mortalities only triggered the hydra effect when this increase in mortality occurs in seniors but not in juveniles or adults (fig. S8C).

Not only adult fertility was relevant for a population to show hydra effect. Also, the presence of cooperative or caring interactions that reduce juvenile mortality (modeled by $\alpha > 0$) abolished the hydra effect: the steady state population decreased with higher CMR (intuitive effect; Fig. 4D). We found similar results using variations of the cooperation mechanism in the model, i.e., senior adults helping juveniles to forage for resources, raising juveniles to become adults, or increasing the reproductive capacity of adults (fig. S9 and data S1 to S3). On the contrary, when we simulated interstage intraspecific competition that diminished juvenile survival, adult reproductive efficiency, or juvenile maturation ($\omega > 0$), we observed a stronger hydra effect on the population (Fig. 4E and fig. S10, A and B). In a more realistic situation, higher CMR triggers a more marked increase in the population size (hydra effect) when resources are limited and intraspecific competition is stronger (fig. S10C).

In addition, since only a few mammalian species exhibit complete cessation of reproductive activity in older stages (menopause), we modeled a population in which senior adults, S, are less reproductive (rather than postreproductive) relative to younger adults ($\beta_A > \beta_S > 0$). A population of these characteristics may exhibit hydra effect, even without interstage intraspecific competition (fig. S11 and data S4). Furthermore, we expanded the model to consider an additional phenomenon related to reproductive senescence, frequently reported in the literature as the Lansing effect, in which older individuals have shorter survival progeny than young adults. If senior-born juveniles are simulated to have lower survival rates to adulthood ($\mu_{JS} > \mu_{JA}$), then, again, we find a hydra effect (in this case facilitated by the Lansing effect) for increasing CMR (fig. S12 and data S4).

Our mathematical modeling confirms the hydra effect for homogeneous populations in a context of intraspecific competition and higher cancer mortality in older individuals. However, it could happen that in heterogeneous populations, individuals with lower CMR become more frequent, while those with higher CMR tend to extinction, making the hydra effect disappear and thus destroying the causal explanation of a possible adaptive value of higher levels of cancer mortality in populations with higher competition. Therefore, we performed mathematical modeling of mixed populations in which the relative frequency at which the oncogenic variant appears is 0.5, e.g., through a migration process in which two genetically different subpopulations of equal size merge (data S5). In populations with high intraspecific competition, although individuals with lower CMR grow in greater proportion than individuals with higher CMR, the population stabilizes reaching a larger total population size at equilibrium (hydra effect) than a homogeneous population with low CMR (fig. S13A and data S5; $\alpha = 0$, $\omega = 0$, $\beta_{S1} = \beta_{S2} = 0$). This effect persists even if the allele that induces higher senior mortality by cancer appears at a very low initial frequency (0.05 of the adult-born juveniles) in the mixed population (e.g., through a point mutation; fig. S13B and data S5; $\alpha = 0$, $\omega = 0$, $\beta_{S1} = \beta_{S2} = 0$).

In these scenarios, we found that modeling the appearance and evolution over time of an oncogenic variant can lead not only to an increase in direct or absolute fitness (the proportional change in the abundance of that genotype attributable to selection) but also to an

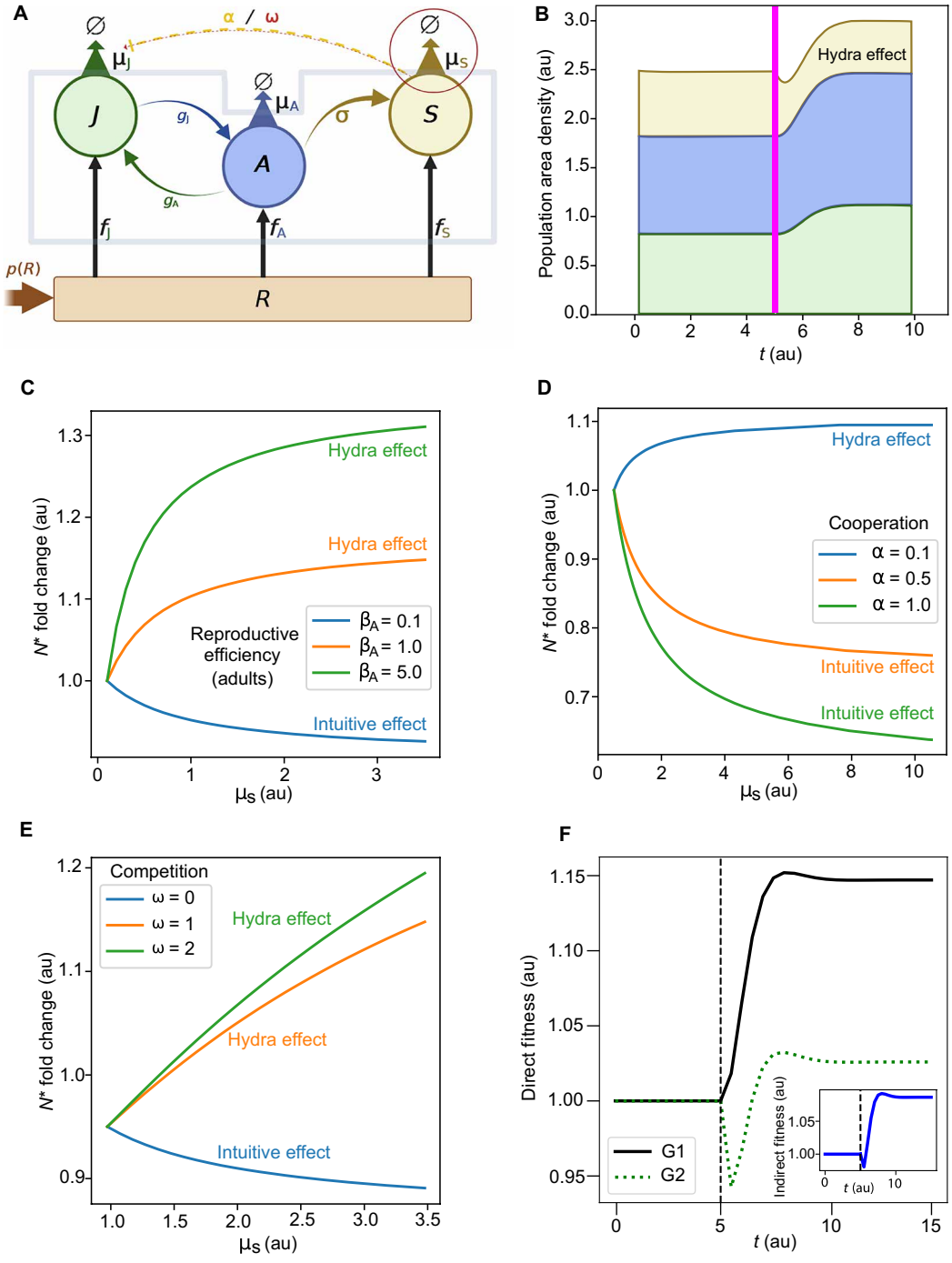

Fig. 4. The effect of increased cancer mortality in a structured resource-consumer model. (**A**) Resource-consumer model with three stages: juveniles (*J*), reproductive adults (*A*), and postreproductive seniors (*S*). The transitions between stages are color coded according to the stage whose density increases as a result of this transition. The function g_J stands for juvenile maturation rate, while g_A stands for adult fertility rate. Senior mortality (μ_S) is the parameter (circled in red) on which different CMR values were tested. The parameter α represents the ability of senior individuals to reduce juvenile mortality (interpreted as care or protection by senior individuals toward juveniles). On the contrary, the parameter ω reflects increasing intraspecific social competition (resulting in a higher mortality of juveniles triggered by senior individuals). (**B**) At $t = 5$, an increase in CMR (higher μ_S) triggers a reduction in the subpopulation of senior individuals (light brown) but a paradoxical increase (hydra effect) in total population at equilibrium (N^*), due to an increase in the subpopulations of adults (light blue) and juveniles (light green). au, arbitrary units. (**C**) Higher reproductive efficiencies in adults [β_A, where $g_A(x) = \beta_A x$] allow and potentiate the hydra effect. (**D**) The hydra effect is overturned with increasing caring interactions by older individuals (α). (**E**) The hydra effect is potentiated by increasing intraspecific competition triggered by the presence of senior individuals (ω). (**F**) An oncogenic variant (G2) arising at $t = 5$ with a relative frequency of 0.5 and increasing cancer mortality at the end of life (higher μ_S) can enhance direct fitness and indirect fitness. Indirect fitness includes that of G1 and G2. All variables were relativized to fitness values before $t = 5$. In the case shown, the gene variant (G2) neither completely displaces the other gene variant (G1) nor becomes extinct.

increase in indirect or inclusive fitness (which also includes the fitness of genetically related individuals). In these cases, the oncogenic variant (G2) neither completely displaces the nononcogenic version (G1) nor becomes extinct (Fig. 4F and figs. S13, C to F, and S14A). Last, we modeled how cooperation and competition affect fitness dynamics when we introduce reproductive capacity in seniors ($\beta_S > 0$). In cooperative and caring contexts ($\alpha > 0$), an oncogenic gene variant that increases the mortality of less-reproductive seniors decreases both direct and indirect fitness (Fig. 5A). The opposite is found in competitive contexts ($\omega > 0$; Fig. 5B). These results are stronger if cooperative and competitive interactions occur only among individuals of the same genotype (asymmetric interactions; Fig. 5, C and D). In cooperative contexts, an oncogenic variant that appears with an initial relative frequency of 0.5 (e.g., through a migration process in which two genetically different subpopulations of equal size merge) may disappear over time (Fig. 5E). Conversely, in competitive contexts, such an oncogenic variant can stabilize and even exceed the relative frequency of a nononcogenic variant over time (Fig. 5F). Similar results are obtained by simulating the appearance of such an oncogenic variant with a low initial relative frequency (e.g., through a point mutation; fig. S14, B and C).

DISCUSSION

The high prevalence of cancer throughout the tree of life (*28*) raises an inevitable question: Why are some species so prone to developing malignant tumors, while others are endowed with molecular defenses against them? Cancer prevalence has been previously shown to correlate with litter size across mammalian (*21*, *29*) and bird species (*30*). A trade-off between investment in reproduction, somatic maintenance, and growth has been postulated as a possible explanation (*31*). However, there are still no mechanistic explanations or conclusive arguments as to why, how, and when these functions should be negatively correlated. Recently, it has been shown that the order Carnivora displays the highest CMR among mammals, possibly due to a high-fat, low-fiber diet and to the biomagnified exposure to carcinogens in relation with Carnivora's place at the top of the food chain (*10*, *32*). Although diet may explain part of the differences in cancer prevalence and mortality risk between species, this hypothesis does not explain two fundamental questions. First, why have some species that should be more prone to cancer (for example, elephants and whales, which have many cell duplications due to bulky bodies) developed molecular mechanisms to resist cancer, while others (such as Carnivora) have not? Second, why do different carnivorous species belonging to orders of mammals other than Carnivora, i.e., many carnivorous cetaceans and several primates, have low cancer-related mortality rates? Many carnivorous cetaceans and primates live in gregarious and cooperative groups, with small litter sizes, while on the contrary, many species from Carnivora are solitary hunters with large litter sizes.

Here, we have analyzed supraindividual level traits to show that species with higher intraspecific competition (solitary and singular breeding animals with large litter size and short-term gestation) display higher cancer prevalence and mortality risk than gregarious species with cooperative and caring habits, even if they are carnivorous (Fig. 3, J to M), consistent with the coevolution recently found between social organization and longevity in mammals (*33*). In particular, many mammalian species with the highest level of social organization (division of reproductive labor, overlapping generations, central role of older individuals in care, breeding, or feeding), such as mole rats, some primates, and several cetaceans, are among the species with the lowest cancer prevalence and mortality risk. Some of these are referred to as eusocial species, while in other cases, they have been termed cooperatively breeding vertebrates (*34*, *35*). In this sense, phylogenetic reconstructions suggested that there have been 14 transitions to cooperative breeding from other breeding systems (*36*). Many of these transitions seem to have coevolved with mechanisms of cancer resistance, as in the case of mole rats and voles (Rodentia), as well as marmosets and tamarins (Primates) (*29*, *37*). A similar case can be glimpsed for at least some species of seals, belonging to the order Carnivora. Consistently, we found many species of mammals that share the characteristic of having very low levels of cancer along with life in groups, collective reproduction, and small litters. Examples are as varied as the common dolphin, the Rodrigues fruit bat, the Nubian ibex, and the black-capped squirrel monkey, among others. Even in the case of some exceptions to the rule, such as the naked mole rat, listed in the database used in this study as a singular breeder and as an animal without group living, but with very low cancer prevalence, we strongly argue that it should be reclassified as a cooperative breeding and gregarious species (*36*). The common porpoise, which alternates between solitary and gregarious life, represents a similar case, classified in our database as a nongroup living animal, but whose category may need revision (see the "Morphophysiological, life history, and lifestyle traits" section).

Our findings showing that CMR and neoplasia prevalence decrease with gestation length, similar to those recently reported (*24*, *29*), can be reinterpreted in terms of greater maternal investment and increased caring per litter. Similarly, it has recently been observed that species living in resource-limited environments, where competition for resources is greater, have a higher prevalence of cancer late in life (*38*). On the contrary, paternal caring does not correlate with cancer prevalence and mortality risk, while the correlation of cancer rates and longevity seems to depend on the database chosen. Biases in the proportion of long-lived species in each database could also represent differences in life history and lifestyle of the species analyzed between the different databases. In particular, the only database in which a positive and significant association between cancer prevalence and mortality risk and longevity is observed is precisely the one with the lowest proportion of long-lived species (fig. S4A). Discrepancies with previous reports (*10*) regarding statistical significance are due to differences in statistical modeling and analysis (see the "Statistical analysis" section).

In this work, we also demonstrated by developing a mathematical model that within-population mortality differences affect population dynamics. Higher cancer mortality rates in older less- or postreproductive individuals can increase population size in a context of intraspecific competition, a process known as the hydra effect, which has never been explored in the field of cancer biology until now. This phenomenon can be explained under the theoretical framework of inclusive fitness, taking into account not only the reproductive success of an individual but also its effects on the survival and reproductive success of its kin (*14*). Our results in mammalian species [which normally exhibit reproductive senescence (*26*)] show that homogeneous populations with higher CMR late in life display larger population size than those with low cancer rates in a competitive context. Moreover, we show that the existence of oncogenic gene variants in heterogeneous populations, even when introduced at low frequencies, can enhance absolute and inclusive fitness in these competitive contexts,

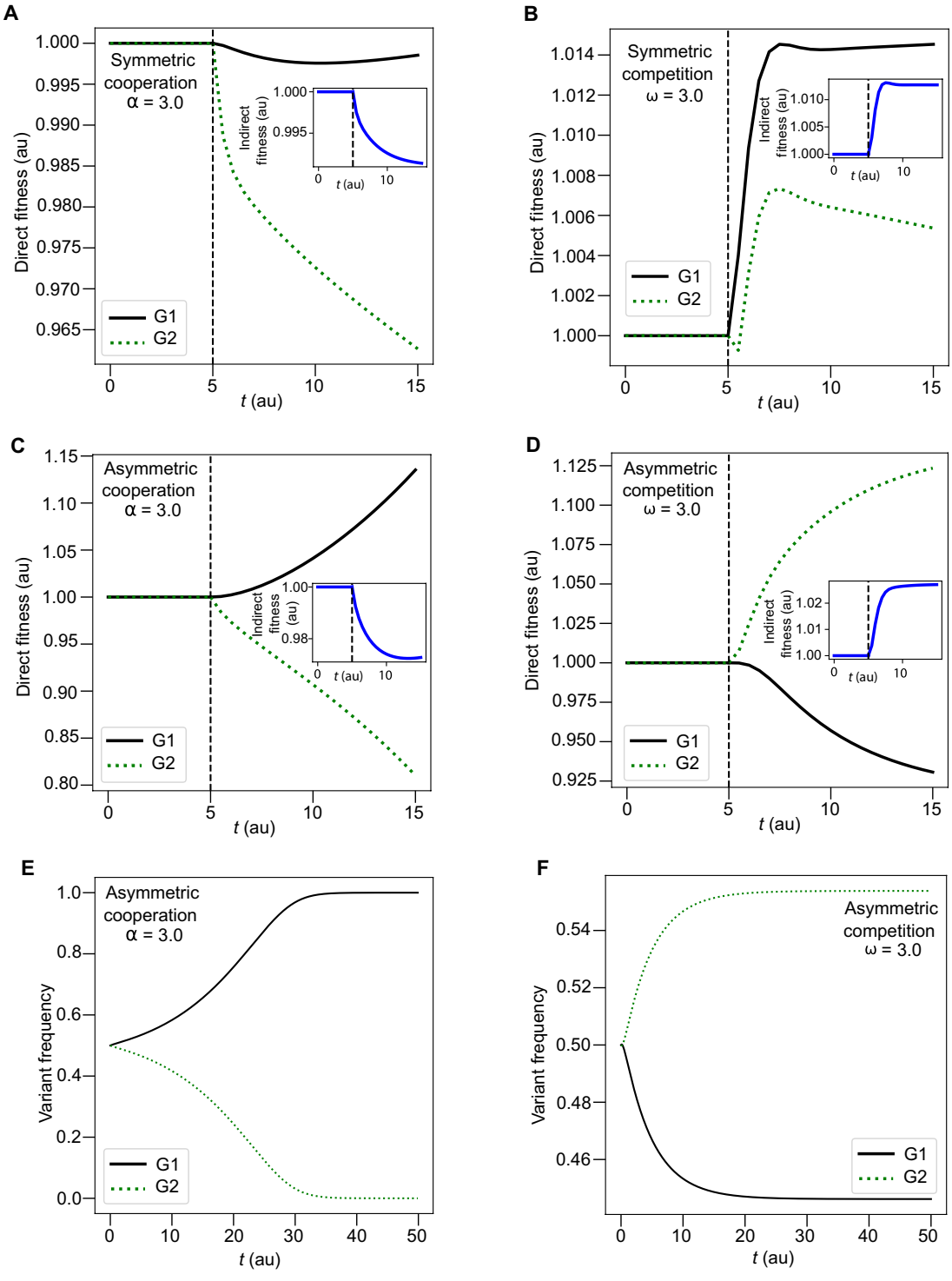

Fig. 5. Cooperation and competition differentially affect fitness dynamics of oncogenic variants in contexts of symmetric or asymmetric interactions. A model was used in which seniors have (low) reproductive capacity: $\beta_A > \beta_S > 0$. Social interactions from older individuals reduce (cooperation, $\alpha > 0$) or increase (competition, $\omega > 0$) juvenile mortality only among individuals of the same genotype (asymmetric) or irrespective of juvenile genotype (symmetric). All variables were relativized to fitness values before $t = 5$. Indirect fitness includes that of G1 and G2. (**A**) An oncogenic variant (G2) arising at $t = 5$ and increasing cancer mortality at the end of life (higher μ_S) negatively affects on direct and on indirect fitness in a context of symmetric cooperation. (**B**) The opposite is observed in a context of symmetric competition. (**C**) A context of asymmetric cooperation makes the impact of oncogenic variants on fitness even more negative, especially on G2 fitness. (**D**) On the contrary, a context of asymmetric competition makes the impact of oncogenic variants on fitness particularly positive, increasing the relative fitness of G2 over that of G1. (**E** and **F**) Frequencies of each variant over time for the same conditions evaluated in [(C) and (D)].

enabling a plausible hypothesis as to why oncogenic variants occur at low or even at high frequencies in different mammalian populations. These results, which support an adaptive value of cancer under certain boundary conditions, are consistent with recent reports suggesting evolutionary selection of aging (*20*, *39*). Our working hypothesis does not imply any a priori assumption of a selective antagonism between reproductive capacity, growth, self-maintenance, and/or cancer resistance. On the contrary, this antagonism appears in our simulations driven by the existence of a hydra effect that, although it has been described in the field of ecology, has not yet been applied to the field of cancer biology.

The counterintuitive phenomenon where an increase in a population's per-capita mortality rate can lead to an increase in its population size was first identified in 1954 by Ricker (*40*). This outcome was later termed the hydra effect by Abrams and Matsuda (*41*), defined as an increase in the mean population size in response to greater mortality. Later theoretical work identified the temporal separation between the action of density-independent mortality and the density-dependent processes that counteract it as one of the mechanisms responsible for the hydra effect (*17*). In a continuous time model, this temporal separation requires some age or stage structure. On the other hand, according to de Roos (*16*), the hydra effect occurs in unstructured consumer-resource models and is driven by an increase in resource productivity that happens when the resource density rises because of increased consumer mortality. In contrast to this specific definition of the hydra effect in unstructured models, de Roos introduces the concept of density overcompensation defined as an increase in the equilibrium density of a specific stage within a consumer population in response to increased mortality. This phenomenon, observed in stage-structured models such as the juvenile-adult consumer-resource model examined by de Roos, results from a different mechanism. As consumer mortality increases, a relatively larger proportion of the ingested resources is directed toward population growth (through maturation and reproduction) rather than maintenance requirements. de Roos emphasizes that this density overcompensation in structured models differs mechanistically from the hydra effect he describes for unstructured models. While de Roos distinguishes between "hydra effect" (as a specific mechanism in unstructured models) and "density overcompensation" (in structured models), there is some overlap in the literature suggesting a broader usage of the term hydra effect when referring to positive population responses to mortality in specific life stages. In our work, we used this broader notion of the hydra effect indistinctly with other terms such as overcompensation or counterintuitive effect.

In particular, our article introduces a consumer-resource model based on a three-stage life cycle for the consumer population, distinguishing between prereproductive juveniles, reproductive adults, and less- or postreproductive seniors. This structure captures age-related variation in key vital rates—such as fertility, foraging, maturation, and mortality—all of which depend on resource availability. What makes this model particularly original is that, beyond its explicit three-stage framework—an element often lacking in unstructured ecological models—it specifically incorporates distinct forms of intraspecific interactions. Specifically, it includes parameters for both cooperation (α) and competition (ω), which quantify the intensity of these intraspecific interactions and their influence on population dynamics, with special attention to interactions mediated by senior individuals. This comprehensive framework enables us to explore how senior-driven intraspecific dynamics, in conjunction with age structure, shape overall population dynamics and influence the potential emergence of the hydra effect.

Taking into account that cancer is associated with the accumulation of genetic and phenotypic changes throughout the life of a multicellular organism, it would be expected that species with larger bodies should display higher levels of cancer, since they accumulate errors from a greater number of cell divisions. However, several independent investigations have shown that cancer prevalence and mortality risk do not seem to correlate with body mass or lifespan among species, an observation referred to as Peto's paradox (*10*, *42*). These studies propose that for a species to acquire a larger size or longer life expectancy, additional cancer resistance mechanisms must have evolved to reduce the cumulative lifetime probability of developing tumors. For instance, it has been shown that molecular changes that increase lifespan antagonize cancer growth (*43*). Different cancer resistance–associated genes have been recently identified through cross-species genomic analysis (*44*). However, it has been shown that Peto's paradox is not always observed (*29*, *45*). Our results are particularly relevant since they address the specific scenarios when a correlation between cancer risk and body mass should be expected. We found that in mammalian species with cooperative and caring habits, there is no positive correlation between higher cancer risk and larger body size. On the contrary, in species that display competitive behaviors, there is a positive correlation between the two variables. This can be explained by the simple fact that the same molecular mechanisms that create resistance to cancer in cooperative species coevolve with the possibility of developing larger bodies. This is of relevance in the species in which older animals play an important role for the survival of young individuals. In contrast, competitive species lack these mechanisms and show both higher cancer rates and a correlation between increased body length and elevated cancer prevalence and mortality risk, allowing for the hydra effect to arise.

Tumors have been already shown to elicit direct positive effects in populations of some species. For instance, it has been shown that tumoral phenotypes can affect biotic interactions within ecosystems, particularly for the cnidarian *Hydra oligactis*. The tumorous phenotype in this organism increases both predation abilities and more effective commensal ciliate colonization (*46*). On the other hand, it has also been shown that molecular mechanisms that elicit cancer diminish genetic predisposition to disease in the population (*47*). As we show here, under certain boundary conditions, cancer can be considered as a phenoptotic program, in particular, as a positively selected mechanism of planned obsolescence taking into account that increasing the mortality of a subpopulation (older and less-reproductive individuals) might also increase population size (hydra effect) (*16*, *18*). Phenoptosis has been defined as the death of an individual caused by its own actions or by actions of close relatives, which is influenced by genes that are favored by natural selection (*13*). Phenoptotic processes are not a collection of rare phenomena. Examples of these processes are the apoptotic death of older yeasts that provide nutrients to younger individuals; the sudden death after reproduction (semelparity) in different species of plants, fish, and mammals; and the death of adult individuals serving as food for their own offspring (*13*). While more than 3% of all mammalian genes have been already implicated via mutation in cancer (*48*), every gene can and possibly will be associated with cancer (*49*). This implies that one of the simplest and most flexible ways in which genomic variation followed by natural selection can modify mortality and life expectancy

between species is through variation in cancer prevalence and mortality risk rates. In this sense, while stabilizing selection models have been shown to best fit the distribution of the prevalence of neoplasms across vertebrate species, the evolution of malignancy prevalence has been best explained by sudden changes, followed by stasis in phenotype (*29*). The prevalence of cancer late in life could then be considered as an exaptation, a trait that could have originated in an abnormal regression in multicellular organisms to an ancestral single-cell stage (*50*, *51*) and was subsequently kept under control, eliminated, or coopted for a different function during evolution. The interface between genetics, environment, and epigenetics hints that cancer-related mortality might vary not only cross-species during evolution but also within the life of a given organism, depending on epigenetic regulation of proto-oncogenes and tumor suppressors by environmental signals (*52*).

One limitation of this work is that the databases used include different numbers of species and necropsies analyzed. While the first (*10*) and the third (*29*) datasets used rely on more than 20 necropsies per species (191 and 102 species, respectively), the second database (37 species) has an average of 23 necropsies per species but includes 8 species with less than 10 necropsies each (*21*). While caution should be exercised in interpreting data based on small sample sizes, the results and conclusions reported in this work are similar regardless of the database and cancer variable used. A second limitation is that our mathematical model does not simulate cancer per se but, instead, simulates increased mortality rates of post- or less-reproductive adults. It has long been established that cancer has a much greater impact on older individuals and older age is one of the most important risk factors for cancer (*8*, *10*). Although not all the increase in mortality in old age can be expected to be caused by oncological pathologies, cancer is one of the most common and effective ways in which mortality and life expectancy can be modified through genetic variation and selection. It stands to reason that the prevalence of other diseases that affect older ages, such as cardiovascular or neurodegenerative diseases, can also be shaped by evolution in a similar way. Future work will determine whether it is feasible to analyze the impact of other diseases from the perspective used in this article in relation to cancer.

Our results address the cancer phenomenon from a multidimensional perspective and are compatible with a coevolution of cancer prevalence and both life history and lifestyle traits across the tree of life. In summary, in this work, (i) we show a correlation between sociality (group living and plural breeding) and lower cancer prevalence and mortality risk. We also show (ii) that when mammalian species are competitive, higher body mass correlates with higher cancer prevalence and mortality risk, whereas for cooperative animals, no correlation is found, presenting a plausible explanation for the discrepancies reported in the literature regarding Peto's paradox. (iii) We confirm and extend to different databases the finding that gestation length and litter size correlate with cancer prevalence and mortality risk, proposing that longer gestation lengths and small litter sizes should be conceived or reinterpreted in terms of increased care and support, which, as well as group living and plural breeding, are associated with lower cancer prevalence and mortality risk. (iv) By creating a model of resource consumption structured on a three-stage life cycle, which also incorporates intraspecific interactions such as competition and cooperation, we show that increasing mortality rates of less- or postreproductive senior individuals (to model higher CMR of senior adults) can elicit a negative impact in cooperative animals. On the contrary, a positive impact is observed in species that exhibit higher levels of intraspecific competition. (v) The phenomenon of a population increasing in response to a decrease in its per capita survival rate has been described in the field of Ecology and named the hydra effect (or the hydra paradox), but it has never been explored in the field of cancer biology until now. In our work, we link the concept of the hydra effect with the phenomena of reproductive senescence and cancer to mathematically demonstrate why competitive species are more prone to benefitting from higher cancer mortality rates, while on the contrary, social, cooperative, and caring species may benefit from lower cancer mortality rates. (vi) We also explored the hypothesis that oncogenic variants, even appearing at low frequencies, can be maintained in mammal populations by enhancing both direct and indirect fitness, which is higher fitness of genetically related individuals (inclusive fitness). Our model predicts that in species with highly structured intraspecific competition, the relative frequency of oncogenic variants that boost mortality of senior individuals can increase over time. (vii) We propose that, under certain boundary conditions, cancer can also be considered as a selected mechanism of biological obsolescence and, therefore, cancer mortality late in life could be then considered as an exaptation, a trait that has been co-opted for a different function over the evolution course of multicellular organisms. (viii) We propose that one of the simplest and most flexible ways in which genomic variation followed by natural selection can modify mortality and life expectancy among species is through variation in cancer prevalence and mortality risk rates. Therefore, cancer can then be conceived as a robust phenoptotic program associated with producing increased mortality in less- or postreproductive aged multicellular individuals. (ix) Together, we propose that cancer evolution and progression, as complex phenomena, must be studied as multilevel selection processes (*53*), exploring how increasing cancer mortality rates affect population structure as a function of ecological and behavioral aspects of each species, allowing molecular mechanisms of cancer resistance to evolve in cooperative and caring animal societies, even if they follow an animal diet.

Life history theory offers a powerful framework to analyze variation in cancer prevalence and mortality risk across the tree of life (*21*). Moreover, this theory provides an evolutionary framework for phenotypic plasticity with important clinical consequences (*52*). While the evolution of multicellular organisms involved a variety of cooperative foundations at the cellular level, cancer implied on the other hand cheating, breaking each of these cooperative foundations (*9*). Here, we propose that a similar association can be found at a higher level of organization: Species with a lower cancer prevalence and mortality risk are those with a higher presence of cooperative and caring habits, while the opposite is found in those species with higher intraspecific competition. In this context, at least part of the advantages for species with lower cancer prevalence and mortality risk can be explained by the concept of inclusive fitness and fitness interdependence, where cooperation emerges from mutual dependence for survival and reproduction (*14*).

MATERIALS AND METHODS

CMR, neoplasia, and malignancy prevalence in mammalian species

First dataset

CMR was calculated for each species as the proportion of cancer-related deaths out of the total number of records, based on postmortem

pathological records ($n = 11{,}840$) (*10*). This information was sourced from Species360 and The Zoological Information Management System. The dataset initially included 191 species, but *Dasyuroides byrnei* was removed because of its extremely high CMR, which was considered an outlier. This CMR data were gathered from mammals in zoos worldwide, providing high-resolution cause-of-death data (table S9). CMR was estimated from neoplastic samples that substantially contributed to the animal death, as confirmed by necropsies. The CMR estimated for each and every species included in this dataset is based on more than 20 necropsies per species (mean = 62).

Second dataset

Prevalence of neoplasia was estimated as the prevalence of any neoplasm in mammalian species from San Diego's zoos (*21*). The dataset initially included 37 species, but *Loxodonta africana* was removed because of incongruences with other publications reporting lower cancer rates. The prevalence of neoplasia estimated for the species included in this dataset is based on an average of 23 necropsies per species. *Vulpes zerda*, *Puma concolor*, *Canis mesomelas*, *Lama glama*, *Lycaon pictus*, *Tarsius syrichta*, *Macropus rufus*, and *Equus asinus* are the only species with less than 10 necropsies analyzed (table S10).

Third dataset

We used a recently curated and standardized dataset of malignancy prevalence across mammalian species (*29*) that is based on more than 20 necropsies per species. This resource includes additional species not considered in the other datasets. In this analysis, a list of archetypal species with very high or very low malignancy prevalence was constructed: All species were ranked according to their malignancy prevalence, and three subsets were defined using different cutoffs: rank10, rank15, and rank20, each including the 10, 15, or 20 species with the highest and lowest malignancy prevalence, respectively. These ranked groups consisting of 20, 30 and 40 species, respectively, were then used for downstream comparative analyses. The total dataset comprised 102 mammalian species (table S11).

Morphophysiological, life history, and lifestyle traits

Data on body mass (in kilograms) and life expectancy (in days) used for the first dataset have been extracted from Vincze *et al.* (*10*) ($n = 190$ species). Data on adult mass (in kilograms) and maximum lifespan (in days) used for the second ($n = 32$ and $n = 36$ species, respectively) and third databases ($n = 94$ species, in both cases) were obtained from the COMBINE database (*54*). Data on metabolic rate ($n = 52$ for the first dataset, $n = 31$ for the second dataset, and $n = 52$ for the third dataset) were obtained from the AnAge database (*55*) and expressed in watts. For the third database, a categorization was made for variables adult mass, metabolic rate, and maximum lifespan to divide the species into two categories, with a threshold such as to have two groups with a comparable number of species.

We defined life history traits (litter size, litters, gestation length, life expectancy, and maximum lifespan) as those that depend on the history of the individual but are not clearly behavioral such as lifestyle traits (group living and breeding system). We chose litter size, gestation time, and life expectancy as three classic life history traits (*16*, *45*, *56*). In particular, life expectancy is a well-determined variable in many species, which helps to have a larger sample size.

Data on litter size (mean number of descendants per female; $n = 190$ species for the first dataset, $n = 32$ for the second dataset, and $n = 94$ for the third dataset) and gestation length (days; $n = 190$ for the first dataset and $n = 32$ for the second dataset) were obtained from the COMBINE database (*54*). The variable "litters" was used to classify species as either monotocous or polytocous, using a litter size of 1.5 as threshold (*57*). Transforming litter size into a dichotomous variable allowed us to statistically test its interaction with body mass, similarly to what we did with dichotomous variables such as group living. Total litters was calculated as the number of litters per year multiplied by litter size and the difference between the maximum longevity and female sexual maturity for each species. All the data for the calculations were obtained from the COMBINE database (*54*). Group living ($n = 144$ species for the first dataset, $n = 24$ for the second dataset, and $n = 77$ for the third dataset) was determined by integrating data from two sources: Pérez-Barberia *et al.* (*58*) and Lukas and Clutton-Brock (*59*). The variable is dichotomous, indicating whether a species engages in group living based on regular associations among individuals. A species was classified as group living if it showed sociality or was listed as group living by either source. Conversely, it was classified as not having group living if it exhibited no sociality or was listed as solitary or socially monogamous by either source. When data from both sources were available, a species was included only if both sources agreed; otherwise, it was either excluded, or a choice was made on the basis of available literature. Data on breeding system (singular breeders or plural breeders; $n = 147$ species for the first dataset, $n = 28$ for the second dataset, and $n = 79$ for the third dataset) were gathered from Lukas and Clutton-Brock (*57*). The category of singular or plural breeders was assigned whether the females occupy a separate or common territory or range during the breeding season, respectively. Data on the dichotomous variable paternal care ($n = 157$ species for first dataset and $n = 29$ for second dataset) were also obtained from Lukas and Clutton-Brock (*59*).

Data on animal diet (consumption of animals, including vertebrates and invertebrates) were sourced from Vincze *et al.* (*10*), who compiled the information from a global mammalian diet database (*60*). This dataset categorizes dietary components into four hierarchical levels: never consumed, occasionally consumed, secondary food item, and primary food item. For our analysis, we focused solely on whether animal matter was present in the diet, without differentiating between specific types. Since the intermediate categories (occasional and secondary consumption) included relatively few species, Vincze *et al.* (*10*) consolidated the dietary classifications into two broader levels: rarely/never consumed and regularly consumed (i.e., as a primary or secondary food source). Diet information was included only for the first dataset due to the strength of the analysis and the sample size available. The data and detailed references for each variable in the databases can be found in tables S9 to S12.

Statistical analysis

Correlations of CMR and neoplasia with the different traits were performed using phylGLMMs using phyr (*61*) in R Statistical and Programming Environment, version 4.2.3 (*62*). Previous investigations with the species included in these datasets showed that there is a phylogenetic signal for CMR and neoplasia among mammal species (*10*, *21*). To control for phylogenetic relatedness among species, we performed phylGLMMs using the original robust phylogeny by Vincze *et al.* (*10*). phylGLMMs used a binomial error distribution and a logit link function (*63*), adding a random variable at the level of observations (*64*) to avoid overdispersion problems. This random variable, called "species," was constructed with the identity of each species analyzed. Not all analyses using CMR data were performed with the full set of species, since the information for some of the

traits analyzed was not available for all species. All models performed were evaluated for overdispersion and zero inflation using DHARMa package (*65*). All model tests showed $P > 0.05$, which indicates that no fit problems were detected, and therefore, unlike previous investigations, we chose to perform the analyses using species with both zero and nonzero CMR (*10*).

Models used (the codes are available on GitHub, see the "Data and materials availability" section):

1) An additive phylGLMM was performed with CMR as response variable and log transformed continuous variables of covariate traits body mass, litter size, life expectancy, and gestation length. Log-transformed variables were used as fixed effects, as well as species as a random variable at the observation level (table S1, model a, $n = 190$). The physiological trait metabolic rate was also log transformed and analyzed in a separate model to avoid collinearity problems with log body mass (table S1, model b, $n = 52$).

2) A simple model for dichotomous variable litters was performed (table S3, model a, $n = 190$) to test for CMR differences in monotocous or polytocous species. This dichotomous variable was tested in a model with continuous variables log life expectancy and log body mass to evaluate interaction (table S3, model b, $n = 190$).

3) For lifestyle dichotomous variables group living, breeding system, and paternal care, we performed separate analyses to avoid collinearity problems, in all cases with CMR as the response variable, as well as species as a random variable at the level of observations (tables S5 to S7, model a). For group living and breeding system variables, we also performed models with the continuous variables (log body mass, log litter size, and log life expectancy) and tested the interaction with log body mass (tables S5, model b, $n = 144$; and S6, model b, $n = 146$).

4) Animal diet as a dichotomous variable was analyzed using CMR as the response variable, as well as species as a random variable at the level of observations. The association between animal diet and CMR was also assessed in relation to the other life history and lifestyle traits using four different models that include species of animal diet and group living (gregarious/solitary) and breeding system (singular/plural) (table S8).

5) To perform an order level analysis, mean CMR for all the species belonging to each order with at least 15 species (i.e., Artiodactyla, Carnivora, Primates, and Rodentia) was calculated. We also built indexes for each trait of interest: (i) litter index, ratio between monotocous and polytocous species within each order; (ii) group living index, ratio between the species with and without group living within each order; and (iii) breeding system index, ratio between plural and singular breeding species within each order (table S12). The analysis was performed with GLMs using a binomial error distribution and a logit link function (*63*), using the glmmTMB package (*66*) (table S4). The total set of *P* values derived from analysis using CMR data was corrected for multiple testing using FDR correction (*67*).

6) Neoplasia data on 36 species from the second dataset were analyzed using the same phylGLMM simple models with one variable per model as before but with a different phylogeny of the 36 mammal species constructed from the updated mammalian supertree (*68*). The same data for the different morphophysiological, life history, and lifestyle traits as before were used, with the exception of log body mass and log maximum lifespan where the analyses were performed with adult mass (in kilograms) and maximum lifespan (in days) from Boddy *et al.* (*21*) (table S2). The total set of *P* values derived from analysis using this dataset was corrected for multiple testing using FDR correction (*67*). Statistical analyses for dichotomous variables were not performed on this dataset because the power of the model is not strong enough to test small samples.

The analyses of the archetypal species with the highest or lowest levels of malignancy prevalence from the third database were performed qualitatively. For each dichotomous variable, a group was judged to be more enriched in species with a high prevalence of malignancies if we observed differences greater than 50% in each and every one of the three ranks (cutoffs of 10, 15, and 20) and only if these differences became larger as we narrowed the rank (which is expected to occur whether there is a direct relationship between both variables).

Mathematical modeling and simulation

We developed a system of ordinary differential equations (ODEs; codes available on GitHub, see the "Data and materials availability" section) representing a consumer population of any mammal species depending on its resources for subsistence (Eqs. 1A to 1D) (*18*)

$$\frac{dR}{dt} = p(R) - f_J(R)J - f_A(R)A - f_S(R)S \tag{1A}$$

$$\frac{dJ}{dt} = g_A\left[f_A(R)\right]A - g_J\left[f_J(R)\right]J - \mu_J\frac{1+(\omega S)/\left(1+\rho R^2\right)}{(1+\alpha S)}J \tag{1B}$$

$$\frac{dA}{dt} = g_J\left[f_J(R)\right]J - \sigma A - \mu_A A \tag{1C}$$

$$\frac{dS}{dt} = \sigma A - \mu_S S \tag{1D}$$

The population is stage structured on the basis of age: prereproductive juveniles (J), reproductive adults (A), and senior postreproductive adults (S) (*69*). This emphasizes the reproductive capacity of individuals depending on age. Resources (R) are kept unstructured, and their dynamics are governed by a production function p and by consumer foraging f. The function p does not increase with the resource density R and is therefore independent of it. This allows the system to reach a steady state of nonnegative values (*69*). Furthermore, consumer foraging is organized in stage-specific functions, f_J, f_A, and f_S (all of which depend on R) associated with the age of the consumer group. The resulting resource intake is translated into physiological processes with an efficiency given by nonnegative and nondecreasing functions g_A (fertility rate) and g_J (rate of juvenile sexual maturation to become reproductive adults). The senescence process, given by $\sigma > 0$, represents a fixed quantity by which adults age into senior individuals. Likewise, all per-capita mortality rates (μ_J, μ_A, and μ_S) are positive constants. Changes in cancer mortality were modeled through the value of the μ_S parameter. Dependence on resources (R) for vital processes (e.g., transition rates between life stages) conveys nonsocial intraspecific competition between life stages. Effects of nonsocial competition are focused on changes in stage density distribution, as the lack of resources limits population growth by preventing juveniles from reaching adult stage and the latter from having further offspring. These life history processes govern transition rates between life stages. In this model, α represents the strength of social intraspecific cooperation. Positive values of α are interpreted as supportive or caring interactions of older individuals toward juveniles. Increasing α values result in a decrease of juvenile mortality, while $\alpha = 0$ does not take into account these phenomena (α cannot adopt negative values). Similarly, $\omega > 0$ stands for the strength of social

intraspecific competition between seniors and other individuals. Increasing ω values result in higher juvenile mortality (Eq. 1B). In our model, when α adopts positive values, we set ω to zero, and vice versa. Intraspecific competition may also be associated with resource density, in which case $\rho > 0$. Abundance of resources (high values of ρ) diminishes the effect of direct competition. The social parameters α and ω control the nontransitional processes of competitive and cooperative interaction between life stages of the consumer population, respectively. Alternative cooperative or competitive interactions have been also modeled in which the parameter α/ω is the ability of senior individuals (*S*) to influence juvenile (*J*) access to resources, juvenile's development into adults (*A*), or adult's reproductive output (data S1 to S3, respectively).

By mathematical analysis of the ODE system, we were able to find necessary and sufficient conditions for the model to display a hydra effect when $\alpha, \omega = 0$, that is to ensure an increase in the carrying capacity of the population ($N^* = J^* + A^* + S^*$, the population density at dynamical equilibrium) as a result of increasing the value of the parameter μ_S (interpreted as higher CMR). Our inquiry led us to the following inequality, which must hold to ensure hydra effect, for a population with $\alpha, \omega = 0$:

$$\begin{aligned}&\left[f_S(R*)-f_J(R*)\right]g_A\left[f_A(R*)\right]\\&+\left[f_S(R*)-f_A(R*)\right]\left\{g_J\left[f_J(R*)\right]+\mu_J\right\}>0\end{aligned} \tag{2}$$

where all functions therein are evaluated at the resource equilibrium value (R^*) for the system of ODE (Eqs. 1A to 1D). A look at this inequality tells us that if all stages share the same consumption rate (i.e., $f_J = f_A = f_S$), then varying senior mortality has exactly no effect on total consumer equilibrium density value. Furthermore, if the senior stage has the largest consuming rate value at equilibrium, then, for this model, the specific increase in mortality among seniors will lead to the hydra effect, since both terms in the left-hand side (LHS) are positive. Conversely, if the senior consumption rate is the smallest one, then the intuitive effect of a decreasing population equilibrium with increasing mortality of part of their individuals ensues. Considering the per-capita consumption rate of senior adults lower than that of reproductive adults but higher than that of juveniles ($f_A > f_S > f_J$) due to age-related size differences, then the hydra effect is conditioned upon the life history trait parameter values (at equilibrium; Eq. 3). In this case, we can obtain the equivalent condition for hydra effect

$$\frac{\mu_J + g_J}{g_A} < \frac{(f_S - f_J)}{(f_A - f_S)} \tag{3}$$

where we omit the functions arguments for better clarity of exposition.

Expressed in this way, we can see that a larger fertility rate value at the system equilibrium $g_A[f_A\ (R^*)]$ is positively associated with the existence of a hydra effect (all else being equal), since the right-hand side can become greater than the LHS in Eq. 3.

For the purposes of simulations, we used a linearized version of the model to numerically obtain time courses by integration with Python (using Scipy, Numpy, Pandas, and Matplotlib) (*70*–*74*). For this end, we chose a semichemostat model for the resources dynamics, where the resource production function remains constant, $p(R) = \pi$. We also considered linear consuming relations, weighted by different constants associated with a characteristic size and age of the consuming stage, that is, $f_J(R) = \kappa_J R$, $f_A(R) = \kappa_A R$, and $f_S(R) = \kappa_S R$. The resulting resource intake is converted into physiological processes of reproduction and maturation linearly with an efficiency given by the β_A [i.e., $g_A(x) = \beta_A x$] and γ_A [i.e., $g_J(x) = \gamma_A x$] parameters, respectively (γ_A refers to the maturation of juveniles originating from adults to differentiate them from those originating from seniors, γ_S). The remaining life history parameters remain unchanged as constant values (Eqs. 4A to 4D)

$$\frac{dR}{dt} = \pi - \kappa_J RJ - \kappa_A RA - \kappa_S RS \tag{4A}$$

$$\frac{dJ}{dt} = \beta_A \kappa_A RA - \gamma_A \kappa_J RJ - \mu_J \frac{1 + (\omega S) / \left(1 + \rho R^2\right)}{(1 + \alpha S)} J \tag{4B}$$

$$\frac{dA}{dt} = \gamma_A \kappa_J RJ - \sigma A - \mu_A A \tag{4C}$$

$$\frac{dS}{dt} = \sigma A - \mu_S S \tag{4D}$$

Extended versions of these models that allow other processes to occur, such as reproduction of senior adults, distinct survival rates for the senior born juveniles, and, last, the spread of a higher CMR genetic variant on the population were also implemented (data S4 and S5). For the model with mixed populations, we started with a population in equilibrium before the introduction of the oncogenic variant (both subpopulations had the same senior mortality rates $\mu_{S1} = \mu_{S2}$). We performed two types of tests in this initial state. (i) We introduced the oncogenic variant by increasing μ_{S2} in half of the population in equilibrium (a process of migration or subpopulation mixing), and we evolved the system to its equilibrium frequencies. (ii) We introduced the variant as a mutation (low initial frequency), transferring 5% of the juveniles from subpopulation 1 to subpopulation 2 (higher μ_{S2}) and monitored relative frequency time evolution as well.

The direct fitness of a genotype G*x* was calculated as $N_{Gx}(t) / N_{Gx}(0)$, where $N_{Gx}(t)$ is the density over time of subpopulation with the genotype G*x* and $N(0)$ is its density at time $t = 0$. The indirect fitness of the metapopulation was calculated as $[N_{G1}(t) + N_{G2}(t)] / [N_{G1}(0) + N_{G2}(0)]$. The relative frequency of each gene variant over time was calculated as $N_{Gx}(t) / [N_{G1}(t) + N_{G2}(t)]$.

Supplementary Materials

The PDF file includes:

Figs. S1 to S14
Tables S1 to S8
Legends for tables S9 to S12
Data S1 to S5

Other Supplementary Material for this manuscript includes the following:

Tables S9 to S12

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