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The relationship between diet, plasma glucose, and cancer prevalence across vertebrates

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Birds have higher plasma glucose concentrations but lower cancer prevalence than other vertebrates. However, this inverse relationship between glucose and cancer may not hold within vertebrate groups. Given that diet affects blood sugar levels, and carnivores have higher cancer risk than herbivores, we also examined whether diet correlates with plasma glucose concentrations. We collected diet, mean plasma glucose concentration, and neoplasia data for up to 273 vertebrate species from existing databases. Across vertebrates, mean plasma glucose concentration negatively correlated with cancer prevalence, but that was mostly driven by differences in mean plasma glucose concentration and cancer prevalence between birds, mammals, and reptiles. Mean plasma glucose concentration was not correlated with diet across vertebrates nor with cancer prevalence within birds, mammals, or reptiles. Primary carnivores had higher neoplasia prevalence than herbivores when controlling for domestication. A hypothetical explanation for our results may be the evolutionary loss or down-regulation of genes related to insulin-mediated glucose import in bird cells. This may have led to higher mean plasma glucose concentration, lower intracellular glucose concentrations in the form of glycogen, and production of fewer reactive oxygen species and inflammatory cytokines, potentially contributing to lower neoplasia prevalence in extant birds compared to mammals and reptiles.

Explaining patterns of cancer susceptibility among multicellular organisms is a major challenge in comparative oncology. There is extensive evidence that diet affects cancer risk in humans[1–3]. Recently, researchers have begun investigating the role of diet in species' susceptibility to cancer. Vinzce et al.[4] have demonstrated that mammals that eat vertebrate meat or mammalian meat have more cancer-related deaths. Also, within mammals[5,6] and across vertebrates[7], higher trophic levels have higher cancer and neoplasia prevalence. Birds have

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higher plasma glucose concentration than other vertebrates[8–10] (150–300% higher than mammals of similar body size[8]) and less cancer than mammals and reptiles[6,11]. What is the relationship between diet, plasma glucose levels, and cancer across vertebrates, and could it help explain why birds get less cancer than mammals and reptiles?

Glucose is a unifying factor among a number of risk factors for cancer prevalence across species, including larger litter/clutch size[12,13] and carnivorous diet[4,7]. There is conflicting evidence, however, about an association between diet and blood glucose levels in the literature. In humans[14], common voles (*Microtus arvalis*), tundra voles (*Alexandromys oeconomus*)[15,16], and vampire bats (*Desmodus rotundus*)[17], dietary components, such as micronutrients and macronutrients, or food deprivation, can change blood glucose levels. Birds, such as Noisy miners (*Manorina melanocephala*), that eat nectar and fleshy fruits have higher plasma glucose levels than birds, such as Welcome swallows (*Hirundo neoxena)*, that eat insects[18,19]. Across 160 passerine bird species, the species that eat mostly fruit and nectar have higher blood glucose concentrations than other passerine species[20]. Fish, such as sea bass (*Dicentrarchus labrax*), brown trout (*Salmo trutta fario*), and dogfish (*Squalus acanthias*) have lower blood glucose levels after fasting for a few days[21]. Yet mammals like cats (*Felis catus*) and rats (*Rattus norvegicus domestica*)[22], the great fruit-eating bat (*Artibeus lituratus*), and the Jamaican fruit bat (*Artibeus jamaicensis*)[23], maintain their blood glucose levels during fasting. Other studies in birds show that regardless of diet and the frequency of eating, blood glucose concentrations remain fairly constant[24], with no detectable differences in blood glucose concentrations between herbivorous, omnivorous, or insectivorous songbirds[25]. Also, many other fish species have stable blood glucose concentrations when starving[21].

Within individual humans and model organisms, increased levels of glucose in the blood are associated with increased oxidative stress, DNA damage, glycated proteins, and inflammation, all of which could increase cancer risk and development[26–32]. Studies in birds have found a positive correlation between blood glucose levels and species clutch size[20,25], and a positive correlation between clutch size and cancer prevalence[12]. Over evolutionary time we would expect that species with relatively higher blood glucose concentrations would have evolved adaptations preventing these pro-carcinogenic properties[8,33–35], leading to a decoupling of cancer prevalence from glucose concentrations. Thus, we might predict no correlation between plasma glucose concentration and cancer prevalence across vertebrates. However, there may be various unknown confounding variables affecting the association between plasma glucose concentration and cancer prevalence over millions of years of evolution. If we form our hypothesis based on the broadly available data of current vertebrates, we would expect a negative correlation between plasma glucose concentration and neoplasia prevalence across vertebrates. This is because data on extant species show that birds are the taxon with the highest plasma glucose concentration relative to other vertebrate taxa[8–10] and have less cancer mortality than mammals and reptiles[6,11]. Mechanistic support for this hypothesis comes from the fact that extant birds, versus mammals, lack in most of their tissues the GLUT4 protein[8,36] that imports glucose into cells, they have higher energy expenditures and have adapted to thrive on fatty acids rather than glucose[37–39]. Also, extant birds produce fewer reactive oxygen species via mitochondrial respiration in comparison to mammals and reptiles[40], there are higher levels of the antioxidant uric acid in birds than mammals[41,42], and the antioxidant NRF2 is constitutively expressed in most birds[35]. Thus, based on data across extant vertebrate species we might expect a negative correlation between plasma glucose levels and cancer prevalence.

In this study we test for three associations across vertebrate species. Firstly, we test for a relationship between diet and mean plasma glucose concentration. Although one of the largest studies to date on diet and plasma glucose levels across 160 bird species has shown that eating nectar and fruits, versus insects, is associated with higher plasma glucose levels[20], no other study has tested correlations between diet and plasma glucose concentrations across vertebrates. Secondly, we test for a relationship between neoplasia prevalence and mean plasma glucose concentration. Thirdly, we test for a relationship between neoplasia prevalence and different ways of categorizing diet: (a) trophic level (herbivore, invertivore, primary carnivore, and secondary carnivore), (b) percentage of food type in the diet (fruit, invertebrates, plant, seeds, vertebrate ectotherms, vertebrate endotherms, animal-based, plant-based), and (c) overall diet type (herbivore, omnivore, carnivore), with or without controlling for mean plasma glucose concentration and domestication. Even though the associations between trophic level and neoplasia prevalence have been previously studied across vertebrates[7], we reevaluate previous results in a subset of species for which we had plasma glucose data and examine the unknown association between diet and neoplasia when controlling for mean plasma glucose concentration and domestication across vertebrates. We test these associations using literature resources on diet, Species360 data on glucose concentrations in the plasma, and neoplasia prevalence data from up to 273 species. Here, we show that there is: (1) no correlation between diet and mean plasma glucose concentration across vertebrates; (2) a negative correlation between cancer prevalence and mean plasma glucose concentration across vertebrates but not within birds, mammals, or reptiles; (3) higher neoplasia prevalence in primary carnivores than herbivores when controlling the analysis for species domestication.

Results

Mean plasma glucose concentration varied considerably across the examined vertebrate species[43]. The burmese python (*Python bivittatus*) had the lowest mean plasma glucose concentration (1.22 mmol/L), whereas the bird blue-bellied roller (*Coracias cyanogaster*) had the highest mean plasma glucose concentration (21.08 mmol/L). When comparing different classes, the mean of the mean plasma glucose concentrations was lowest in Amphibia and highest in Aves (Fig. 1A[43]). Specifically, the mean of the mean plasma glucose concentrations in Amphibia (4 species) was 2.02 ± 0.42 (mean ± standard deviation) mmol/L, 4.68 ± 4.02 mmol/L in Reptilia (40 species), 6.69 ± 1.57 mmol/L in Mammalia (131 species), and 14.94 ± 2.98 mmol/L in Aves (97 species).

Relationships between diet and plasma glucose

We tested for correlations of diet with plasma glucose concentrations across vertebrates. In the regressions between diet and mean plasma glucose concentrations across vertebrates (11 tests), no *P*-value passed the FDR corrections. We found no association between diet and mean plasma glucose concentration in all our analyses across vertebrate species (Fig. 2; Supplementary Data 1). Trophic levels do not explain the diversity in the concentration of glucose in the plasma across 242 species (Fig. 2A). The percentage of food type in the diet is not associated with mean plasma glucose concentration after multiple testing corrections (Fig. 2B). Similarly, the percentage of animal-based versus plant-based foods ($n = 38$ and $n = 47$ species, respectively), or diet type ($n = 67$ species), is not associated with differences in mean plasma glucose concentration (Fig. 2C, D).

Relationships between plasma glucose and cancer

We tested for correlations of plasma glucose concentrations with cancer and neoplasia prevalence across vertebrates, using phylogenetic regressions to control for non-independence of their phenotypes due to relatedness between species (Supplementary Data 2–5). While it initially appears that species with higher plasma glucose concentrations get less cancer and less neoplasia (Supplementary Fig. 1, and in some multivariable analyses: Supplementary Data 2), this appears to be entirely driven by differences between birds, mammals, and

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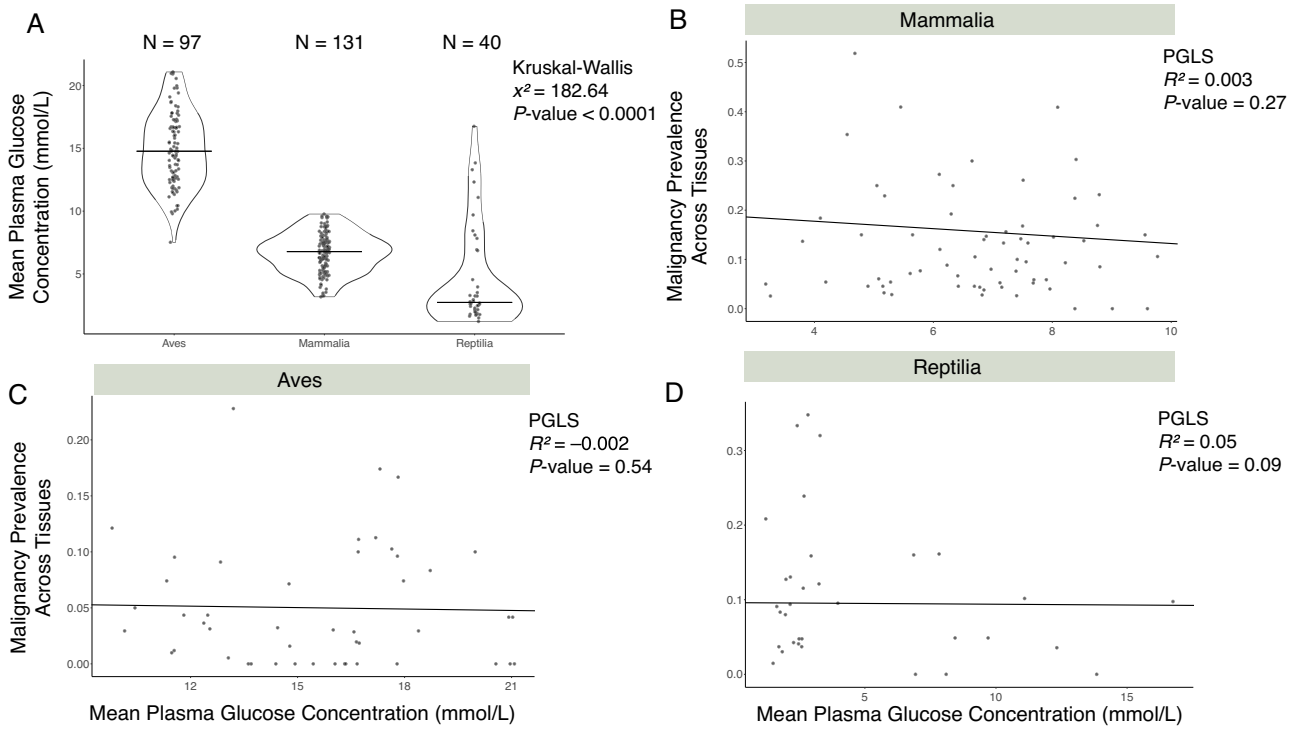

Fig. 1 | Variation in mean plasma glucose concentration in different vertebrate groups, and its relationship with overall cancer prevalence. A Mean plasma glucose concentrations are relatively higher in Aves than Mammalia and Reptilia (Kruskal–Wallis test; *P*-value < 0.0001; degrees of freedom = 2). There is no correlation between mean plasma glucose concentration and malignancy prevalence across tissues for **B** 66 mammalian species, **C** 47 bird species, and **D** 33 reptile species. The statistical tests were two-sided. *P*-values have not been adjusted for FDR corrections. The *P*-values of pgls analyses that passed the FDR correction are noted with an asterisk in Supplementary Data 3–5. The outlier species (Rosner's test) with the highest malignancy prevalence are: *Didelphis virginiana* in panel (**B**) *Gallus gallus* in panel (**C**) and *Lampropeltis triangulum*, *Lampropeltis getula*, and *Pituophis catenifer* in panel (**D**) from top to bottom. PGLS phylogenetic generalized least squares. For information on how to generate this figure, please see Source Data file.

ectotherms (Supplementary Data 2). There are statistically significant differences in plasma glucose concentrations between birds, mammals and ectotherms (Fig. 1A), but within birds (Supplementary Data 4), mammals (Supplementary Data 3), and reptiles (Supplementary Data 5) there is no correlation between plasma glucose concentrations and malignancy prevalence (Fig. 1B–D; Supplementary Fig. 2B, D, 3B, D, 4B, D) or neoplasia prevalence (Supplementary Fig. 2A, C, E, 3A, C, E, 4A, C, E). When we used plasma glucose concentration as the independent variable and controlled for other factors that have been associated with cancer or neoplasia prevalence (e.g., body mass[44], maximum lifespan[44], gestation[44,45], and trophic level[7]) as well as domestication, cancer and neoplasia prevalence remained independent of plasma glucose concentrations within birds, mammals, and reptiles (Supplementary Data 3–5). It is important to control for body mass in particular, because there is a negative relationship between body mass and blood glucose concentrations[8,20,25,46,47]. These same results held when we analyzed gastrointestinal cancer or neoplasm prevalences, or vice versa, non-gastrointestinal cancer or neoplasm prevalences (Supplementary Data 2–5).

We used cancer and neoplasia prevalence across tissues, gastrointestinal malignancy and neoplasia prevalence, and non-gastrointestinal malignancy and neoplasia prevalence as dependent variables. We also used mean plasma glucose concentration as the main independent variable, and controlled for body mass, gestation/incubation length, maximum lifespan, trophic level, birds versus mammals versus ectotherms, and/or domestication. In this setup, we performed univariate and multivariate comparisons using only the subset of vertebrate species in our dataset that had data for all the independent variables (Supplementary Data 2). With plasma glucose concentration as one of the independent variables in all the analyses in the rest of this paragraph, we found that the variation in cancer prevalence across tissues is best explained by the multivariate model controlled for gestation/incubation length, body mass, trophic level, domestication, and birds versus mammals versus ectotherms (lowest AIC and ΔAIC > 2; Supplementary Data 6). High prevalence of cancer is mostly driven by primary carnivores and domestication (*P*-values < 0.05), and not by mean plasma glucose concentrations, body mass, gestation/incubation length, or birds versus mammals versus ectotherms (*P*-values > 0.05; Supplementary Data 6). The variation in neoplasia prevalence across tissues is best explained by the multivariate model controlling for gestation/incubation length, maximum lifespan, trophic level, domestication, and birds versus mammals versus ectotherms (Supplementary Data 6). The second best model fit explaining the variation in neoplasia prevalence across tissues was the model of mean plasma glucose concentration controlling for body mass, gestation/incubation length, maximum lifespan, trophic level, birds versus mammals versus ectotherms, and domestication, and did not change the fit of the model (ΔAIC = 0.13), with the next closest best model fit being the multivariate model controlled for body mass, trophic level, birds versus mammals versus ectotherms, and domestication (ΔAIC = 1.98). High prevalence of neoplasms is mostly driven by long lifespans, primary carnivores, domestication, and mammals (*P*-values < 0.05), and not by mean plasma glucose concentrations, gestation/incubation length, or ectotherms (*P*-values > 0.05; Supplementary Data 6). The variation in gastrointestinal malignancy prevalence is best explained by the multivariate model of mean plasma glucose concentration controlled for birds versus mammals versus ectotherms, with the next closest best model

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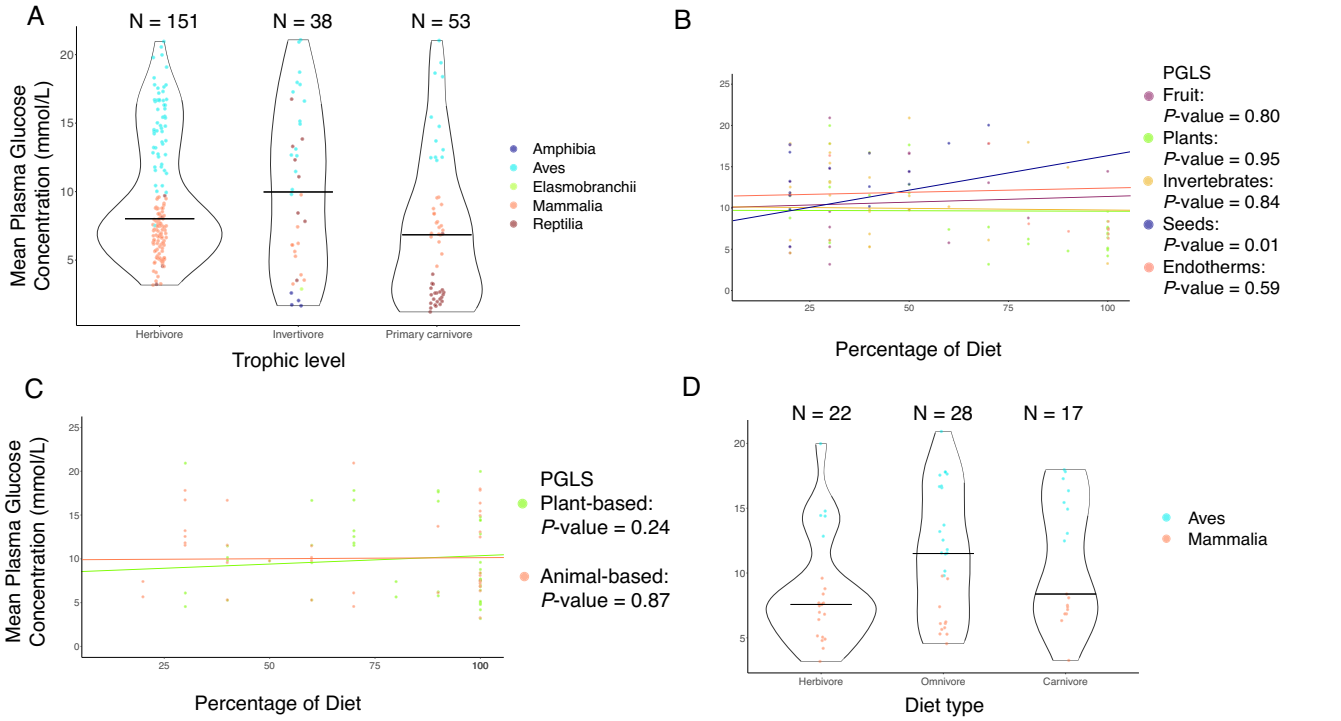

Fig. 2 | The relationship between mean plasma glucose concentration and diet across vertebrates. A Trophic level is not correlated with mean plasma glucose concentrations across 242 species (PGLS: *P*-value ≥ 0.05; Supplementary Data 1). **B** There was no correlation between the percentage of fruit, plants, invertebrates, seeds, or endothermic vertebrates (Endotherms), and mean plasma glucose concentrations for 20, 34, 27, 17, or 10 species, respectively, after correcting for multiple testing. **C** The percentage of plant-based foods or animal-based foods in a species' diet was not correlated with mean plasma glucose concentrations for 47 or 38 species, respectively (PGLS: *P*-value > 0.05). **D** Diet type is not correlated with mean plasma glucose levels for 67 species (PGLS: *P*-value > 0.05; Supplementary Data 1). The horizontal black line in each diet category shows the mean plasma glucose concentration in that trophic (plot **A**) or diet category (plot **D**). In **D**, herbivores refer to animals that have a 100% plant diet, omnivores refer to animals that have >0% plant and meat diet, and carnivores refer to animals that have a 100% meat (invertebrate or vertebrate) diet. The statistical tests were two-sided. *P*-values have not been adjusted for FDR corrections. The *P*-values of pgls analyses that passed the FDR correction are noted with an asterisk in Supplementary Data 1. Each dot shows the mean plasma glucose concentration and diet category of one species. N shows the number of species per diet category (plots **A** & **D**). We added minimal jitter in the plots in order to better visualize individual data points. PGLS phylogenetic generalized least squares. For information on how to generate this figure, please see Source Data file.

fit being the multivariate model controlled for maximum lifespan and birds versus mammals versus ectotherms (ΔAIC = 0.67). The variation in gastrointestinal neoplasia prevalence is best explained by the null model, with the next closest model fit being the multivariate model of mean plasma glucose concentration controlled for maximum lifespan (ΔAIC = 0.38). The variation in non-gastrointestinal malignancy prevalence is best explained by the multivariate model of mean plasma glucose concentration controlled for gestation/incubation length, maximum lifespan, trophic level, domestication, and birds versus mammals versus ectotherms, with the next closest best model fit being the multivariate model controlled for domestication (ΔAIC = 0.33). The variation in non-gastrointestinal neoplasia prevalence is best explained by the multivariate model of plasma glucose concentration controlled for body mass, maximum lifespan, trophic level, birds versus mammals versus ectotherms, and domestication, with the next closest best model fit being the multivariate model controlled for body mass, gestation/incubation length, trophic level, domestication, birds versus mammals versus ectotherms (ΔAIC = 0.94).

Relationships between cancer and diet

We tested for correlations of cancer or neoplasia prevalence across tissues, gastrointestinal malignancy and neoplasia prevalence, and non-gastrointestinal malignancy and neoplasia prevalence, with diet across vertebrates (48 tests, *P*-value < 0.00104 to pass FDR). Among trophic levels, primary carnivores have higher neoplasia prevalence across tissues than herbivores but only when controlling for domestication (Supplementary Data 7), not in univariate analyses or when controlling for the variance in species' plasma glucose concentrations or when controlling for both plasma glucose concentration and domestication (Supplementary Data 7). Unlike the results for neoplasia prevalence across all tissues, there is no correlation between trophic levels and cancer prevalence across tissues, gastrointestinal malignancy prevalence, gastrointestinal neoplasia prevalence, non-gastrointestinal neoplasia prevalence, or non-gastrointestinal cancer prevalence after applying corrections for multiple testing (Figs. 3A, 4A; Supplementary Data 7).

When comparing univariate and multivariate phylogenetic models with neoplasia prevalence across tissues as the dependent variable, and trophic level, mean plasma glucose concentration, and domestication as independent variables (Supplementary Data 7), we found that neoplasia prevalence is best explained by a combination of trophic level and domestication, though adding mean plasma glucose concentration had little effect on the fit of the model (ΔAIC = 1.40).

The percentage of fruit, plants, invertebrates, seeds, or endothermic vertebrates in a species' diet is not correlated with cancer prevalence or neoplasia prevalence across tissues (Fig. 3B; Supplementary Fig. 5A), gastrointestinal malignancy prevalence or gastrointestinal neoplasia prevalence (Fig. 4B; Supplementary Fig. 5B), non-gastrointestinal malignancy prevalence or non-gastrointestinal neoplasia prevalence (Supplementary Fig. 5C, D) after correcting the analyses for multiple testing (Supplementary Data 7).

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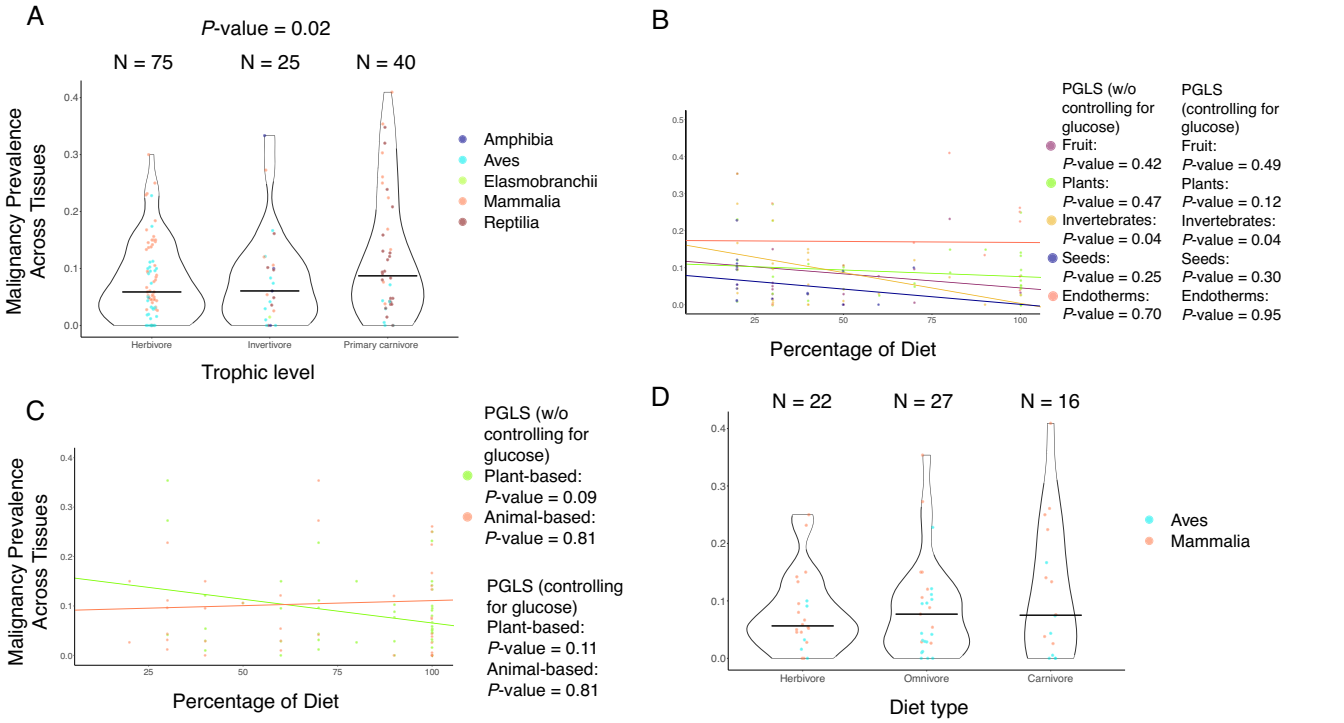

Fig. 3 | Relationships between overall cancer prevalence and diet across vertebrates. A Trophic level is not correlated with malignancy prevalence across tissues for 140 species, even when controlling for variations in glucose concentrations in their plasma, domestication, or both plasma glucose concentrations and domestication, and correcting for multiple testing (PGLS: Supplementary Data 7; *P*-values < 0.05 of between-trophic level comparisons are shown). **B** There is no correlation between the percentage of fruit, plants, invertebrates, seeds, or endothermic vertebrates (Endotherms) in a species' diet and malignancy prevalence across tissues for 20, 34, 27, 17, or 10 species, respectively, after corrections for multiple testing. **C** The percentage of plant-based food in a species' diet is not correlated with malignancy prevalence across tissues for 47 species (PGLS: *P*-value > 0.05). Also, there is no correlation in the percentage of animal-based food in a species' diet and malignancy prevalence across their tissues for 38 species (PGLS: *P*-value > 0.05). **D** Diet type is not correlated with malignancy prevalence across 65 species (PGLS: *P*-value ≥ 0.05). The horizontal black line in each trophic level (plot **A**) or diet category (plot **D**) shows the median malignancy prevalence across tissues in that category. In **D**, herbivores refer to animals that have a 100% plant diet, omnivores refer to animals that have >0% plant and meat diet, and carnivores refer to animals that have a 100% meat (invertebrate or vertebrate) diet. Each dot shows the malignancy prevalence across tissues and diet category of a species. N shows the number of species per diet category (plots **A** & **D**). We added minimal jitter in the plots in order to better visualize individual data points. The statistical tests were two-sided. *P*-values have not been adjusted for FDR corrections. The *P*-values of pgls analyses that passed the FDR correction are noted with an asterisk in Supplementary Data 7. PGLS: phylogenetic generalized least squares. w/o without. For information on how to generate this figure, please see Source Data file.

The percentage of plant-based or animal-based food in a species' diet is not correlated with cancer prevalence across tissues or neoplasia prevalence across tissues (Fig. 3C; Supplementary Fig. 6A; Supplementary Data 7), gastrointestinal malignancy prevalence or gastrointestinal neoplasia prevalence (Fig. 4C; Supplementary Fig. 6B; Supplementary Data 7), or non-gastrointestinal cancer prevalence and non-gastrointestinal neoplasia prevalence, when correcting for multiple testing (Supplementary Fig. 6C, D; Supplementary Data 7).

There is no association between diet type and cancer prevalence (Fig. 3D), neoplasia prevalence across tissues (Supplementary Fig. 7A), gastrointestinal cancer prevalence (Fig. 4D), gastrointestinal neoplasia prevalence (Supplementary Fig. 7B), non-gastrointestinal cancer prevalence (Supplementary Fig. 7C), or non-gastrointestinal neoplasia prevalence (Supplementary Fig. 7D), with or without controlling for the variance in plasma glucose concentrations and after applying corrections for multiple testing (Supplementary Data 7).

Discussion

Similar to previous studies testing glucose concentrations in the plasma and whole blood across vertebrates[8,9], we found that birds have the highest mean concentration of plasma glucose, followed by mammals, reptiles, and amphibia. In our cross-vertebrates (including species of mammals, birds, and reptiles) diet, plasma glucose, and cancer association studies we found the following. There was no correlation between diet and mean glucose concentration in the analyses across species after multiple testing corrections. Mean plasma glucose concentration was not correlated with cancer prevalence across vertebrates when we controlled for differences between birds, mammals and ectotherms. In separate analyses within birds, within mammals, and within reptiles, mean plasma glucose concentration was not correlated with cancer prevalence. However, primary carnivores had higher neoplasia prevalence across tissues than herbivores, specifically when controlling the analysis for domestication. We next explore a potential evolutionary explanation for our results, starting with why and how do birds have the highest mean plasma glucose levels and lowest neoplasia/cancer prevalence across vertebrates.

Approximately 252 million years ago, during the Permian-Triassic boundary, there was a sharp decrease in oxygen concentration in the atmosphere[48,49], from 30% to 11–15%[48,50]. This was followed by a gradual increase in the concentration of atmospheric oxygen in the late Jurassic, Cretaceous, and Tertiary[48,50]. According to Takumi Satoh, these environmental conditions led to a divergence in the metabolic pathways of birds relative to mammals and reptiles[35]. We hypothesize that adaptations around high energy expenditure and fatty acid metabolism rather than thriving on glucose in birds versus mammals and reptiles[37–39], perhaps in concert with the selective pressure of cancer, has led to cancer protective mechanisms in birds potentially including

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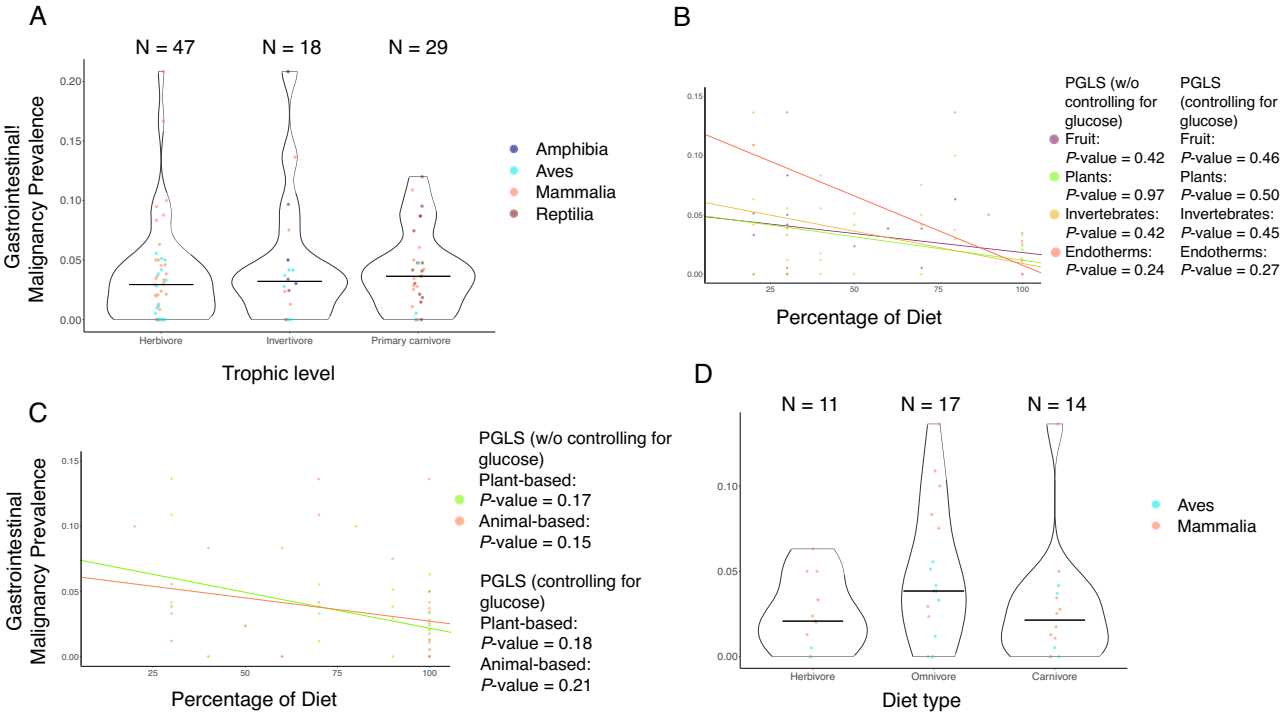

Fig. 4 | Relationship between gastrointestinal cancer prevalence and diet across vertebrates. A Trophic level is not correlated with gastrointestinal malignancy prevalence across 94 species, with or without controlling for domestication, plasma glucose concentrations, both domestication and plasma glucose concentrations, and after correcting for multiple testing (Supplementary Data 7; *P*-values < 0.05 of between-trophic level comparisons are shown). **B** There is no correlation between the percentage of fruit, plants, invertebrates, or endothermic vertebrates (Endotherms) in a species' diet and gastrointestinal malignancy prevalence for 15, 19, 18, or 10 species, respectively, after corrections for multiple testing (Supplementary Data 7). **C** There is no correlation in the percentage of plant-based or animal-based food in a species' diet and gastrointestinal malignancy prevalence for 27 and 27 species, respectively, after corrections for multiple testing (Supplementary Data 7). **D** Diet type is not correlated with gastrointestinal malignancy prevalence across 42 species (PGLS: *P*-value ≥ 0.05) after corrections for multiple testing (Supplementary Data 7). The horizontal black line in each trophic level (plot **A**) and diet category (plot **D**) shows the median gastrointestinal malignancy prevalence in that category. In **D**, herbivores refer to animals that have a 100% plant diet, omnivores refer to animals that have >0% plant and meat diet, and carnivores refer to animals that have a 100% meat (invertebrate or vertebrate) diet. Each dot shows the gastrointestinal malignancy prevalence and diet category of a species. N shows the number of species per category (plots **A** & **D**). We added minimal jitter in the plots in order to better visualize individual data points. The statistical tests were two-sided. *P*-values have not been adjusted for FDR corrections. The *P*-values of pgls analyses that passed the FDR correction are noted with an asterisk in Supplementary Data 7. PGLS: phylogenetic generalized least squares. w/o without. For information on how to generate this figure, please see Source Data file.

reduced glucose transport due to the absence of the GLUT4 immunoreactive glucose transporter protein in most bird tissues[8,36], lower intracellular storage of glucose as glycogen[8], reduced reactive oxygen species production[40] and higher levels of the antioxidant uric acid[41,42]. The antioxidant NRF2 is constitutively expressed in most birds as an evolutionary consequence of the loss of a binding domain in its repressor KEAP1 early in the Tertiary period[35]. The exceptions are fowl, which have maintained a functional KEAP1, and intriguingly, are amongst the birds with the highest cancer and neoplasia prevalence[12,43] (Fig. 1C; Supplementary Fig. 3A–E). The fat tissue and skeletal muscle cells of chickens are less sensitive to insulin than rats[51–53], possibly also explaining the higher plasma glucose concentrations found in chickens versus rats[54,55]. The above may explain the negative correlation between plasma glucose concentration and neoplasia prevalence when birds, mammals, and reptiles are mixed together. The absence of a correlation between plasma glucose concentration and cancer or neoplasia prevalence within each of those groups suggests there may be no direct connection between plasma glucose concentration and neoplasia development.

In multivariate models with the independent variables plasma glucose concentration, gestation/incubation length, maximum lifespan, trophic levels, domestication, and birds versus mammals versus ectotherms, high neoplasia and malignancy prevalence were mostly driven by primary carnivores and domestication (Supplementary Data 6). This result indicates that even though domestication is likely linked to many other factors, its association with neoplasia and malignancy prevalence remains statistically significant after accounting for all the above life history factors and differences in taxonomic groups. Domestication generally causes genetic bottlenecks[56,57] and has strong effects on the genomes of the domesticated organisms[58], potentially also causing increased cancer susceptibility[59], and potentially explaining the observed relatively higher cancer and neoplasia prevalence in domesticated species. Domestication can increase the risk of cancer in animals via the effects of inbreeding depression and the inability of selection to remove deleterious, including potentially carcinogenic, alleles[59]. Domestication may have also led to the decreased levels of circulating glucose in bovids[60] and possibly other domesticated species, relative to their ancestors or close relatives in the wild.

The majority of primary (43/57 species = 75.44%) and secondary carnivores (8/9 species = 88.89%) in our dataset are mammals and reptiles[43]. Mammals and reptiles have previously been shown to have lower median blood glucose levels than birds[9]. It is possible that the lower cancer prevalence in birds relative to mammals and reptiles is mostly driven by the rarity of primary and secondary carnivores among the examined bird species[7] (Supplementary Data 7). Toxins bioaccumulate at higher concentrations in higher trophic levels[61–63]. Also, a study in 95 birds has shown that eating invertebrates or a higher

seed-to-fruit ratio was positively correlated with higher Trolox-equivalent antioxidant capacity and higher concentration of the potential antioxidant uric acid[64]. Overall, (1) the relative abundance of reptiles and mammals in higher trophic levels; (2) the biomagnification of toxins in higher trophic levels; and the (3) oxidative stress and DNA damage associated with eating red meat, may explain the higher neoplasia prevalence[7] (Supplementary Data 7) and cancer prevalence[7] in primary carnivores.

There are a number of limitations and possible future directions for this study. There may be some mismatches between the diet, mean plasma glucose concentration, and cancer prevalence of species in our dataset versus the actual values of diet, mean plasma glucose concentration, and cancer prevalence in a species because each of these three components were most likely collected from different individuals of the same species. Also, even though the data in ZIMS are from healthy individuals, we do not know the exact health status of every individual at the time of data collection. For example, the mean plasma glucose concentrations in our study were collected from animals (data from ZIMS), some of which may have been anesthetized for blood withdrawal, may have been fasted or recently fed, and/or may have been stressed during the method of capture (e.g., being darted, netted, or grabbed). Information about whether the animals were anesthetized, fasted, their exact health status, and method of capture is not provided in ZIMS. Anesthesia or capture can mildly to moderately elevate the blood glucose levels of felines[65], dogs[66], cattle[67], goats[68], mice[69], rats[70], chickens[71], pigeons[72], passerine birds[20], eagles[73], American kestrels[74], and possibly other species, but not of red-tailed hawks[75]. Therefore, it is important for future studies to examine health status, diet, and plasma glucose levels of the exact same individuals, either in zoological institutions or from the wild.

Another limitation is that some data from the 273 species in our dataset are missing. Specifically, we only know the gastrointestinal neoplasia prevalence of 108 species, the non-gastrointestinal neoplasia prevalence of 146 species, the body mass of 252 species, the gestation (incubation in oviparous vertebrates) length of 147 species, maximum lifespan of 239 species, and the diet type or diet percentage of 70 species[43]. Larger datasets are becoming available. For example, scientists can apply for access to Species360's cancer mortality dataset of over 8 million animals (https://species360.org/).

Another potential limitation is that some types of cancer may be harder to detect than others, and if species have a bias in the types of cancer they get, this could skew the data. Our veterinary collaborators have not identified any systematic biases but this may be a source of noise.

There are multiple risk factors for cancer development across species. Researchers have studied for example adult mass[4,44], lifespan[4,12,44], richness of parasite species in the hosts[76], litter/clutch size[12,13,45], diet[4,7], placental invasiveness[13,45], lactation[45], gestation/incubation length[12,44,45], germline mutation rate[77], and chimerism[78] as potential risk factors of the variation in vertebrate species' cancer/neoplasia prevalence or cancer risk. In almost every case, researchers say they would predict a correlation, but sometimes researchers find a correlation, sometimes they do not. A lack of correlation between cancer prevalence and any given factor may be the result of natural selection leading to the evolution of anti-cancer mechanisms that deal with an increased risk. Alternatively, anti-cancer mechanisms may be evolving at a slower pace than the increasing exposure to cancer-inducing factors. The differences in all these studies may also be due to the different types of cancer data used, the different subset of species used in each study, and often different statistical analyses performed.

Future studies should examine the why and how questions related to the links between diet, plasma glucose levels, and cancer prevalence across vertebrates. When trying to understand a biological phenomenon, both the why and how questions are important[79]. We have explained a hypothetical selective force, such as low atmospheric oxygen levels during the Permian-Triassic boundary[35], that may have shaped the divergence in glucose import and cancer prevalence in birds versus mammals and reptiles, but we have a long way to go to completely understand how plasma glucose levels and cancer prevalence evolved. How exactly are trophic levels associated with neoplasia prevalence? Many molecular studies describe the links between diet, plasma glucose concentrations, and cancer prevalence, as mentioned above. These molecular studies, however, have not been confirmed in most species in our dataset. Comparative genomics[80,81] and transcriptional analyses can provide some answers on the diet-, glucose-, and cancer-related gene pathways that are present/absent or differentially regulated in different taxa.

In conclusion, our results suggest that the differences in mean glucose concentration in birds relative to other vertebrates are unrelated to the lower cancer prevalence in birds. This is consistent with Satoh's description on the divergence of birds versus mammals and reptiles during the Permian-Triassic boundary[35]. Future studies should test the hypothesized mechanisms of cancer suppression in birds, and perhaps explore how they might be translated to human cancer prevention. The rise of comparative phylogenomics[80,81] can also bring insights into how particular glucose-transport-related genes and pathways are associated with cancer-related genes and pathways across the animal kingdom. These approaches will bring us closer to explaining the diversity of cancer prevalence across species and developing interventions that might help us live like a bird.

Methods

Inclusion & ethics statement

The authors of this study have met criteria for authorship as required by Nature Portfolio journals. This study was based on publicly available data and complies with all relevant ethical regulations. This study did not require institutional review board approval.

Trophic level, percentage of diet, and diet type data

We identified trophic levels (herbivore, invertivore, primary carnivore, or secondary carnivore) for $n = 271$ species based on their primary diet (Supplementary Data 8, 9). This trophic level classification has also been used in previous literature (e.g., ref. 7). Specifically, the primary diet refers to the primary diet of adult animals in the wild. Herbivores primarily eat plants and/or fungi. Invertivores primarily eat invertebrates. Primary carnivores primarily eat vertebrates, that are not primary carnivores. Secondary carnivores primarily eat primary carnivores. In the trophic level analyses, we only included trophic levels that had at least 10 species, to improve the power of the analyses. We collected diet percentages (endothermic vertebrates, ectothermic vertebrates, fish, fruit, invertebrates, nectar, plant, scavenger, seed, and unknown vertebrates) from Jin Song et al. (2020) for $n = 67$ species[82]. In the analyses of these diet percentages, we only included diets with a percentage of ≥10%. We removed diets (fish, nectar, scavenger, unknown vertebrates) with a sample size smaller than 10 species to improve the power of the analyses. Upon removal of these diets, the percentages were not recalculated to add to 100% in order to keep the percentages consistent with published data. Next, in the analyses of the percentage of animal-based versus plant-based foods, we summed the diet percentage to determine the percentage of animal-based (invertebrates, endothermic vertebrates, ectothermic vertebrates, unknown vertebrates, scavenger, and fish) and plant-based foods (fruit, nectar, seed, and plant) in each diet for each species. Lastly, we assigned diet types (carnivore: 100% animal-based diet, herbivore: 100% plant-based foods, and omnivore: contains both animal- and plant-based foods) based on the diet percentage. In all the above analyses, we excluded species for which the percentage of that food type in their diet was 0% because: (1) we were interested in the effects of eating a particular food type on neoplasia prevalence and

plasma glucose concentrations; and (2) one can already identify the 0% data from our figures and analyses of the other diet types - for example, if a species consumes 100% fruit, it does not consume any of the other food types, in other words the consumption of endothermic vertebrates, ectothermic vertebrates, fish, invertebrates, nectar, plants, scavenging items, seeds, and unknown vertebrates is 0%. We then matched trophic level, diet percentages, and diet types to neoplasia data for analysis.

Plasma glucose concentration, cancer, and life-history data

We obtained records of mean plasma glucose concentrations (measured in mmol/L) from at least 20 different healthy individuals per species as recorded in the ZIMS database (https://www.species360.org/). It is not recorded in the ZIMS database whether the animals were anesthetized, however, common veterinary practice suggests that some animals were anesthetized and some were not. This is a potential source of noise in the data that we acknowledge. Data on mean plasma glucose concentration were the most often reported measure on glucose in ZIMS. We used the mean concentration of glucose rather than median concentration of glucose because there were no detectable outliers in the mean concentration of glucose data across vertebrates, within mammals, and within birds according to Grubbs' test[83,84], and the mean concentration of glucose data within mammals and birds followed a normal distribution (according to Shapiro's test[85]).

Data for neoplasia (malignant and benign tumors) and malignancy prevalence[7,12,44], including gastrointestinal neoplasia and malignancy prevalence as well as non-gastrointestinal neoplasia and malignancy prevalence[7], were collected from previous studies. Specifically, the gastrointestinal tissues included are the oral cavity, esophagus, stomach, gallbladder, bile duct, liver, pancreas, duodenum, small intestine, and colon. Each species' neoplasia and malignancy prevalence is based on data from necropsies of at least 20 individuals in that species. These data are from several zoological and veterinary institutions. The choice of a 20-necropsy threshold is a compromise between accuracy of the prevalence estimates and the number of species in the analysis. A higher threshold would reduce the number of species in the analysis and so reduce our statistical power. A lower threshold would add noise to the dependent variables (malignancy or neoplasia prevalence).

Body mass (grams) and gestation (incubation in oviparous vertebrates) length (months) have been previously shown to correlate with neoplasia prevalence and malignancy prevalence, respectively, across vertebrates[44]. However, larger birds[8,20,25] and mammals[46,47] tend to have lower blood glucose concentration. Compton et al.[44] also showed that maximum lifespan (months) positively correlates with neoplasia prevalence across vertebrates, though not after corrections for multiple testing. Therefore, to control for the effect of body mass, gestation (incubation in oviparous vertebrates) length, and maximum lifespan on neoplasia prevalence and malignancy prevalence across vertebrates, we collected body mass, gestation length or incubation length, and maximum lifespan data for each species from published resources[44,86,87].

Domestication data

The lower genetic diversity found in 13 carnivorous species than 4 omnivorous and 4 herbivorous mammalian species[88] led us to also control for the possible effects of domestication on neoplasia prevalence and malignancy prevalence across species. We obtained species domestication data from the literature[4,12]. We placed domesticated and semi-domesticated species in the same category, and used domestication as a categorical variable (yes/no).

Statistical analyses

We conducted all analyses in R version 4.0.5[89]. We used the R packages CAPER[90], phytools[91], geiger[92], and tidyverse[93], and then performed phylogenetic generalized least squares (PGLS) regressions in all analyses to control for the phylogenetic non-independence among species using TimeTree (Timetree.org). In analyses where one of the dependent variables was malignancy prevalence or neoplasia prevalence, we weighted the analyses by 1/(square root of the number of necropsies per species) (from Revell[91]). When the dependent variable was malignancy or neoplasia prevalence, we arcsine-square-root-transformed those prevalence data since they are proportions. However, for visualization purposes we display the non-arcsine-square-root-transformed data in the figures. We did not use binomial models for modeling the neoplasia prevalence and malignancy prevalence data. We tested all analyses for the presence of detectable heteroscedasticity (Fligner-Killeen test), and if present, we square-rooted the dependent variable. If with this transformation the analysis still did not pass the Fligner-Killeen test, we raised the dependent variable to the power of 1/4. This transformation of the dependent variable to the fourth root led to the analysis passing the Fligner-Killeen test. We obtained R^2 values by running the rr2 package (R2(mod = main_model, mod.r = reduced_model, phy = pruned.tree); where main_model refers to the univariate or multivariate model that we are analyzing, and reduced_model refers to the model where the independent variable is 1; output R2.resid values)[94] on each PGLS analysis. We compared mean plasma glucose concentrations between mammals, birds, and reptiles using the Kruskal–Wallis test. We classified diet type (carnivore, herbivore, and omnivore) and trophic level (herbivore, invertivore, primary carnivore, and secondary carnivore), and domestication (domesticated or semi-domesticated, non-domesticated) as categorical variables. Next, we classified percentage of diet (endothermic vertebrates, ectothermic vertebrates, fruit, invertebrates, plants, seeds, animal-based, and plant-based foods), malignancy prevalence, neoplasia prevalence, body mass, gestation/incubation length, maximum lifespan, and glucose concentration as numerical variables. We conducted univariate and multivariate analyses, with malignancy/neoplasia prevalence across tissues, gastrointestinal malignancy/neoplasia prevalence, or non-gastrointestinal malignancy/neoplasia prevalence as dependent variables, and mean glucose concentration, trophic level, diet type, diet percentage, gestation (incubation in oviparous vertebrates) length, domestication, body mass, and maximum lifespan, as independent variables. We also tested whether the *P*-values passed the False Discovery Rate (FDR) correction using the Benjamini-Hochberg procedure in each of these 8 groups of analyses [1. regressions between diet and mean plasma glucose concentrations across vertebrates (11 tests); 2. regressions between neoplasia and mean plasma glucose concentrations across vertebrates (42 tests); 3. regressions between neoplasia and trophic level across vertebrates (48 tests); 4. regressions between neoplasia and diet type (herbivore versus omnivore versus carnivore) (48 tests); 5. regressions between neoplasia and percentage of diet (152 tests); 6. regressions between neoplasia and mean plasma glucose concentrations within mammals (36 tests); 7. regressions between neoplasia and mean plasma glucose concentrations within birds (30 tests); 8. regressions between neoplasia and mean plasma glucose concentrations within reptiles (30 tests)]. In the subset of species that had all the following variables – body mass, gestation or incubation length, domestication, maximum lifespan, and trophic level – we also compared the AICs of the univariate and all possible multivariate models that included mean plasma glucose as one of the independent variables (e.g., Supplementary Data 2: of the models where malignancy prevalence was the dependent variable and mean plasma glucose concentration was an independent variable), as well as the AIC of the null model without an explanatory variable, and determined the best model fit (lowest AIC and $\Delta AIC > 2$) across those univariate and multivariate models. In the case of regressions between cancer and neoplasia prevalence versus diet that remained statistically significant after FDR multiple testing corrections

(Supplementary Data 7), we compared AICs for all possible models that included trophic level (e.g., model 1: neoplasia prevalence ~ factor(trophic level), versus, model 2: neoplasia prevalence ~ factor(trophic level) + factor(domestication), versus, model 3: neoplasia prevalence ~ factor(trophic level) + plasma glucose concentration, versus, model 4: neoplasia prevalence ~ factor(trophic level) + plasma glucose concentration + factor(domestication)) and the AIC of the null model (e.g., model 0: neoplasia prevalence ~ 1) without an explanatory variable, and determined the best model fit (lowest AIC and ΔAIC > 2).

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

The data used in this study are available in Zenodo[43] (https://zenodo.org/records/14834543). This Zenodo dataset consists of data from various sources. Specifically, the primary diet data are from sources noted in Supplementary Data 8-9. The diet percentages are from Jin Song et al.[82]. The mean plasma glucose concentration data are from the ZIMS database (https://www.species360.org/). The neoplasia prevalence data are from the literature[7,12,44]. Body mass, gestation length or incubation length, and maximum lifespan data are from the literature[44,86,87], and species domestication data are also from the literature[4,12]. Information and instructions for generating figures can be found in the Source Data file. Source data are provided with this paper.

Code availability

We provide the code, Demo code file, phylogenetic tree, and README file, that we used for the statistical analyses, in Zenodo[43] (https://zenodo.org/records/14834543).

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Author contributions

A.J.B. and S.E.K. designed the study, analyzed the cancer data, the diet type data, and wrote the first draft. A.J.B. obtained additional body mass data via AnAge. S.E.K. conceived the idea to compare glucose concentration data with cancer prevalence data, created the figures in R, collected and analyzed the ZIMS glucose data, and performed the statistical analyses. S.E.K. reanalyzed all data after helpful suggestions from three anonymous reviewers. Z.T.C. provided help with the phylogenetic analyses. S.M.R., Z.T.C., E.G.D., T.M.H., and A.M.B. helped in the collection of malignancy prevalence and neoplasia prevalence, body mass, gestation length, incubation length, and necropsy data for each species. K.L.S. and C.C.M. provided guidance during the project. All authors commented on the final versions of the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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