The evolution and ecology of benign tumors

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Abstract

Tumors are usually classified into two main categories – benign or malignant, with much more attention being devoted to the second category given that they are usually associated with more severe health issues (i.e., metastatic cancers). Here, we argue that the mechanistic distinction between benign and malignant tumors has narrowed our understanding of neoplastic processes. This review provides the first comprehensive discussion of benign tumors in the context of their evolution and ecology as well as interactions with their hosts. We compare the genetic and epigenetic profiles, cellular activities, and the involvement of viruses in benign and malignant tumors. We also address the impact of intra-tumoral cell composition and its relationship with the tumoral microenvironment. Lastly, we explore the differences in the distribution of benign and malignant neoplasia across the tree of life and provide examples on how benign tumors can also affect individual fitness and consequently the evolutionary trajectories of populations and species. Overall, our goal is to bring attention to the non-cancerous manifestations of tumors, at different scales, and to stimulate research on the evolutionary ecology of host–tumor interactions on a broader scale. Ultimately, we suggest that a better appreciation of the differences and similarities between benign and malignant tumors is fundamental to our understanding of malignancy both at mechanistic and evolutionary levels.

Introduction

Multicellular organisms are generally composed of normal cooperating cells, but can also harbor host cells that proliferate abnormally and form masses called tumors or neoplasms[1]. Tumors are usually classified into two main categories*:* benign or malignant. Both types of tumors result from aberrant cell divisions and are composed of abnormal cells. The cells in benign neoplasms are usually phenotypically similar to normal differentiated cells; nevertheless, they have mutations that affect their growth, function and interactions with the resident tissue and the whole organism. However, benign tumor cells lack the ability to invade surrounding tissues and to spread to other organs (metastasize). Unlike cells in benign tumors, malignant cells do invade surrounding tissues and may also spread to other parts of the body, thereby causing metastatic cancers[2–4]. Because of their ability to spread, it is often assumed that malignant tumors are more life threatening than their benign counterparts. While this is generally true, there are noticeable exceptions. For instance, benign tumors can be detrimental if they press on vital structures or organs, disrupt hormonal balance, and/or become malignant over time (e.g., benign bone tumors[5], pituitary adenoma[6], colon adenoma[7]). However, in this review, we use the terminology "benign tumor" for any types of tumors that do not have invasive characteristics (see definitions of different tumor types in table 1), independently of their effect(s) on the health of their carrier. Conversely, certain malignant tumors, like *in situ* carcinomas, may never metastasize and therefore will not be associated with health disorders most of the time. In humans, it is estimated that 51% of cancers detected during CT scans will not cause death[8].

As a scientific field, oncology has until recently developed in relative isolation from evolutionary and ecological sciences. Despite pioneering papers during the mid-seventies[9–11], it has only been during the last decade that evolutionary biology and ecology started to profoundly transform our understanding of malignant tumor biology, cancer initiation,

progression and dissemination[4,10,12]. Similarly, the importance of malignant processes for animal evolutionary ecology and ecosystem functioning has only been acknowledged during the last few years [4,13,14]. However, benign tumors are yet to be explored in this interdisciplinary framework. This is likely because of the biased focus on harmful malignant/metastatic forms. In addition, by arbitrarily assuming that benign tumors – as the term "benign" might suggest, have little or no effect on their host's fitness, evolutionary biologists have inherently accepted that such tumors could be neglected when studying animal ecology. Our aim here is to provide a new perspective on the evolutionary ecology of host – benign tumor interactions at different organizational scales as well as to stimulate future research in this area.

---------- Insert Box 1 ----------

Tumors as evolutionary and ecological processes

In the last decade, evolutionary and ecological principles have been extensively applied to understanding cancer – both in terms of its evolutionary history as well as its progression and treatment[14,15]. Specifically, cancer is generally traced back to the dawn of multicellularity in animals, about one billion years ago[16] (but see "Benign tumors in the tree of life" below; and Box 1). The transition to metazoan life required adaptations to optimize the fitness of multicellular individuals, therefore favoring the emergence of mechanisms preventing and/or suppressing abnormal cells that compromise the functionality of multicellular organisms, including cells that proliferate uncontrollably[17]. Cancer is often seen as a striking illustration of the conflict between levels of selection (the multicellular individual and its individual cells), coupled with the inability of the host mechanisms to prevent and/or eliminate abnormal cells, especially during post-reproductive life stages[18].

Cancer progression itself is also an evolutionary and ecological process. Cancer cells evolve by somatic selection during their host's lifespan, and are shaped by interactions with their original tissue and tumor microenvironment as well as the host's defenses. The conventional carcinogenesis/tumorigenesis model proposes a multi-step transition from a normal to a malignant cellular phenotype, resulting from the random accumulation of mutations and/or epimutations[19,20]. Cancer growth and spread is then possible when some alterations in micro-environmental conditions lead to an ecological context that is favorable for the successful proliferation and spread of such mutated/abnormal cells[21–23]. Nevertheless, apart from a few examples of transmissible malignant cells that evolved into parasitic entities[24], the vast majority of cancer cells are an evolutionary dead-end.

Interestingly, although mechanistically and clinically benign and malignant tumors are considered distinct manifestations of abnormal cell proliferation, it is not known whether the initiation and progression of benign tumors is driven by similar evolutionary and ecological factors that underlie the development of malignant tumors. And/or whether there are specific differences in such factors that might be responsible for the distinct evolutionary trajectories and outcomes associated with the two types of tumors. Below, we compare the origin and properties of benign and malignant cells and their interactions within tumors as well as with the host organism. We argue that at the mechanistic level the two types of tumors can be rather similar, but their trajectories are likely influenced by the context in which they develop.

---------- Insert definitions Box ----------

Benign vs malignant tumor cells

Genetic, epigenetic and transcriptomic profiles

Can all benign tumors be considered as neoplasms that lack some specific mutations that can drive them to malignancy? Studies on malignant tumors indicate that the accumulation of mutations over time is often a crucial factor in cancer dynamics that influences tumor

progression and metastasis[25]. In parallel, the adenoma-to-carcinoma sequence also supports the hypothesis that the accumulation of mutations largely determines the trajectory of benign tumors, with one possible direction being the progression toward malignancy. The accumulation of mutations through time is well described in each step, from benign adenoma polyps to metastatic disease[26]. Nevertheless, evidence suggests that most benign tumors remain stable over time, with only a minority of cancers actually developing from benign tumors[2].

Although the hallmarks of benign tumors have been studied less than those of their malignant counterparts, there are clear indications of genomic overlap between the two types of tumors[27]. For instance, it is known that some of the so-called cancer-driver mutations, like those yielding to tumor-suppressor gene inactivation, also exist in benign tumors or even normal tissues[2,28,29]. Nevertheless, that is not always the case as exemplified by the Barrett's esophagus, a precancerous metaplasia in the distal esophagus preceding malignant evolution to esophageal adenocarcinoma, where 25% of cases show no cancer-related genomic changes, suggesting that these benign tumors initiate without driver mutations[30]. In the context of colorectal tumors, the progression of benign adenoma to malignant adenocarcinoma is associated with changes in genome expression and protein maturation, but within a structured continuum of modifications[26]. In addition, even stable benign tumors (tumors that never turn into malignant cancers) can sometimes express oncogenes. For example, meningiomas (benign brain tumors) express the vascular endothelial growth factor (VEGF), which is typically associated with increased risk of metastases in other neoplasms[31,32].

The overlap between benign and malignant genetic factors suggests that some of the genetic hallmarks associated with cancer are also present in benign tumors. However, further work is necessary to determine the extent of this overlap. Until now, studies dedicated to

defining hallmarks have been focused on the most aggressive tumors or those benign tumors that have a high risk of progressing to malignancy. Thus, a more systematic analysis of the hallmarks of benign tumors compared to normal and malignant tissues is required. This lack of information is probably the reason that no common characteristics shared by benign tumors have been identified while many have been described for malignant tumors (e.g., see[27]).

During malignant tumor evolution, epigenetic changes also occur; the extent to which they drive or are a consequence of malignant transformation is still unclear, but epimutations and their diversity are undoubtedly important in the tumoral inheritance system[33]. Benign tumors also have their own epigenetic signatures. For instance, it is possible to distinguish the presence of healthy, benign, and malignant neoplasia in ovarian and breast tissues just by using the methylation profile of free-circulating plasma DNA[34,35]. Hepatocellular tumors also display a different methylation pattern depending on their malignancy level[36]. Methylome microarray-based analyses can also facilitate the distinction between malignant and benign nerve-sheath tumors[37]. Likewise, histone modifications enable the distinction between benign and malignant giant cell tumors of bone[38] or pituitary adenomas[39]. Nevertheless, as for the case of mutational characteristics, some authors have already noticed an overlap between the epigenetic signatures of benign and malignant tumors (e.g., gene and histone hypermethylation in colon[40] and thyroid[41] tumors).

The epigenetic conformation of the DNA is known to, for instance, silence a number of the transposable elements in genomes[42]. The hypomethylation of such elements has been associated with sporadic cancers, and it occurs gradually throughout the normal to adenoma to carcinoma sequence in gastric and colorectal tissues[43]. Alternative splicing is increasingly observed in cancer-related genes, and it can help to discriminate malignant from nonmalignant breast and colorectal tumors[44–46]. Finally, monoallelic expression and nuclear organization are other mechanisms implicated in epigenetic rearrangements in cancer

cells[47,48]. To our knowledge, these mechanisms have never been documented in a benign neoplasm context.

At the transcriptomic level, the same profile has been described in corticotrophinomas (a kind of pituitary tumor) for both benign tumors and in situ carcinomas. Specific and divergent molecular signatures between these two types of tumors mostly occur when malignant cells start to adopt a metastatic behavior [49]. Similarly, a regulatory transcriptional network that exists in esophageal adenocarcinoma is already activated in Barrett' esophagus, providing further evidence that Barrett's is a precursor state to esophageal adenocarcinoma[50]. However, a profound transcriptional similarity has been previously observed between Barrett's esophagus and esophageal submucosal glands, revealing high transcriptional relationships between normal cell populations and cells in a premalignant condition[51]. Thus, there are probably differences in the degree of conservation of the transcriptomic profile in benign lesions depending on the tissue considered.

To conclude, benign neoplasms can accumulate oncogenic mutations, epi-mutations and transcriptional changes over time, but their benign nature cannot solely be explained by an insufficient accumulation of these events. Indeed, even when they possess for instance a set of mutations that should in theory drive them to malignancy[52], their evolutionary trajectory (as is the case for malignant cells) also strongly depends on interactions with the surrounding normal stroma – referred to as the tumor microenvironment (TME)[23,53,54]. Conversely, oncogenic modifications are also widely observed in normal tissues[55], indicating that the presence of such alterations is far from being sufficient to initiate tumorigenesis, even in a benign form, and that microenvironmental disruption is also crucial.

Cellular state, activities and metabolic profiles

Cells with stem-like properties are usually assumed to be largely responsible for cancer initiation as well as to contribute to cancer progression and maintenance. Are stem-

cells also involved in the initiation and progression of benign tumors? Tumor-initiating cells have been identified in a wide spectrum of benign tumors, suggesting that such cells play a crucial role, not only in malignancies, but also in generation and development of benign tumors[56,57]. For instance, stem-like cells with tumor-initiating activity in serial transplantation animal experiments were indeed isolated from pituitary adenomas, which are benign brain tumors[58]. Whether stem cells from benign tumors are different from or similar to normal tissue specific stem cells or to cancer stem cells remains to be determined.

It is well established that the metabolism of cancer cells is different from that of healthy cells[59]. For instance, glycolysis is over activated in cancer cells, which need energy and building blocks to fuel their increased proliferation[60]. Compared to healthy cells, benign tumor cells also have increased glycolysis (e.g., benign breast disease, colorectal adenoma, giant cell bone tumor, adrenal lesions, or even skin tumors[61–65]). However, many benign neoplasms (i.e., breast, prostate, skin, and adrenal tumors) exhibit a glycolytic metabolism that is intermediate between that of normal and malignant cells [61–65]. The enzymes implicated in these metabolic changes are the same as those in malignant tumors[61,62,64]. However, at this time, we cannot exclude that other enzymes are involved specifically in benign tumors.

This increased glycolytic activity is known as the Warburg effect[68]. An essential result of this metabolic change is the conversion of the pyruvate released by glycolysis into lactate by cancer cells. However, the lactate activity in benign tumor cells seems similar to that of normal tissue. Some studies support these conclusions in the majority of benign brain tumors and prostate neoplasms[69,70]. To our knowledge, the pituitary adenoma is the only benign tumor where an increase in lactate dehydrogenase has been reported, although this activity correlates with local invasive and proliferative abilities of the neoplasm[71].

Nevertheless, these tumors express malignant traits, despite being classified as benign by practitioners.

In the absence of oxygen, in parallel to a switch to glycolytic metabolism, cancer cells adapt their metabolism to hypoxic conditions through different pathways. Interestingly, hypoxia-inducible factor 1 (HIF-1), which drives a part of the cell response to hypoxia, is only detected in malignant tumors, and not in benign tumors or healthy tissues[66]. Even in severe hypoxic conditions, cells of benign uterine leiomyomas do not express HIF factors to activate their hypoxic response[67]. In summary, glucose metabolism in benign tumor cells is increased compared to normal cells but to a lower extent than in malignant cells, and nonmalignant neoplastic cells are mostly unable to adapt their metabolism to the hypoxic conditions of the tumor microenvironment.

Another hallmark of cancer that influences tumor growth is the absence of senescence. Senescent cells are observed in different benign or premalignant lesions but usually not in malignant ones[72–76]. Studies comparing telomerase activity (TA; related to the ability of cells to continue to divide) in malignant and benign neoplasms found a correlation between the maintenance of cell divisions and an increase in malignancy level[77–80]. Surprisingly, TA is also detected in benign breast fibroadenoma[81] and meningioma[82]. In breast fibroadenoma, TA is maintained even if the tumor remains benign and is not life-threatening while TA activity is correlated with poor clinical outcome in meningiomas.

Avoidance of senescence is documented in the transition from benign nevus to melanoma (skin cancer). In nevus, the primary senescent path is shared with healthy cells, but an additional senescence mechanism exists and is unique to benign stages[83]. These redundant pathways are of what is called oncogenic-induced senescence[84]. The melanocytes that have acquired oncogenic mutations stop growing after a clonal expansion, not because of normal tissue replicative senescence but because of these additional oncogenic

senescence mechanisms. The first mechanism involves p16-Rb pathways, which mediate the initiation of the first phase of the cell death program, independently of telomere shortening. Remarkably, other redundant mechanisms exists like the insulin-like growth factor-binding protein 7 (that inhibits mitogenic signals), PI3K pathway (that controls the endoplasmic reticulum unfolded protein response) or even FBXO31 (which destroys the Cyclin D involved in transcriptional silencing)[83]. Thus, the maintenance of nevus oncogenic senescence is a key step to reduce the risk of cancer development in individuals that harbor multiple benign nevus. This perfectly illustrates how senescent pathways are crucial in distinguishing between the development of benign and malignant cells. Despite benign tumors being understudied, the acquisition of cell immortality appears to be a barrier that seems rarely crossed by benign tumor cells.

Mitochondrial metabolism also plays a crucial role in determining the outcome of a tumor's trajectory. For example, oncocytomas are made of cells with non-functional mitochondria that form benign neoplasia, but the same cells with functional mitochondria lead to invasive cancers[85]. In osteosarcoma, benign tumor cells have a stable amount of mitochondria compared to cancerous ones, which harbor more mitochondria[86]. Comparatively, the amount of mitochondrial DNA that circulates in plasma samples can be a biomarker allowing the differentiation of benign from malignant tumors of the breast and ovary[87,88]. De Araujo et al. [89] observed an increase in mitochondrial genomic instability in adenocarcinoma compared to adenoma, while adenoma did not show any significant difference in mitochondrial stability compared to normal tissues. Finally, even if some evidence has indicated that nonmalignant tumors like osteosarcomas can retain normal mitochondrial metabolism compared to malignant forms, the oncocytomas example reflect the opposite pattern. Thus, currently, the role of mitochondria in benign neoplasms appears to be tumor specific and understudied.

Autophagy (i.e., the ability to capture and recycle intracellular components to maintain cell growth and homeostasis) can be required for the progression from benign to malignant tumors in some cancers (e.g., liver, colon). In these cases, benign tumors conserve an equal level of autophagy compared to healthy tissues, and the rate of autophagy correlates with the malignant development[90,91]. In mutated mice developing lung cancer, the increase in autophagy level corresponds to a lower occurrence of benign lung oncocytomas[92], underscoring the importance of autophagy in the occurrence of these benign tumors. Nevertheless, in a mouse model of lung cancer, autophagy suppression promoted adenoma and hyperplasia progression while it blocked the progression to adenocarcinoma[93]. This latter example shows the antagonistic function of autophagy in benign compared to malignant tumors. Understanding the mechanisms by which autophagy can promote benign tumor progression can provide new therapeutic insights, especially because targeting autophagy is a complex and controversial therapeutic approach in cancer therapies[94].

Overall, the cellular state and metabolism of benign tumors is different from that of malignant tumors. Although benign cells also display a higher energetic metabolism than normal cells, to our knowledge there has been no report of the Warburg effect or immortalization in benign neoplasia. However, some cellular activities, like autophagy, can act to repress benign tumors but not malignant ones. The role of mitochondria remains unclear in a benign cell context, and there is still much to understand about the cellular activities of benign cells.

Infectious causation

Extrinsic factors, especially pathogen infections, can sometimes determine whether oncogenic development will follow a benign or malignant trajectory. Different papillomaviruses (PV) can induce benign skin lesions or dangerous mucosa cancers[95]. Human PV (HPV) is the most studied, but these viruses have been also reported in 54 different species, predominantly

in amniotes[96]. The study of viral phylogeny revealed that the proteins expressed early in the infection (E5, E6, and E7) evolved concomitantly with pathogenic lesion types[97,98]. It also revealed that oncogenic PVs evolve more rapidly in early expressed protein regions than those PVs that cause benign lesions[99]. Proteins E1 and E2 correlate with viral specialization in mammalian or avian species and mucosal PV evolves more rapidly than cutaneous PV[98]. The L1 and L2 proteins that are expressed later can show different phylogenetic relationships; these are more conserved but have no pathological role in the distinction between benign and malignant infections[100]. To summarize, PV can generate benign or malignant neoplasms, depending on the virus strain and on their corresponding expression of proteins disrupting the cell cycle.

Retroviruses are another family of tumorigenic viruses; they are implicated in malignant (e.g., HTLV causes leukemias[101,102]: ALVs in chickens, FeLV in cats) and nonmalignant tumors (e.g., walleye dermal sarcoma, hemangioma caused by subgroup J avian leukosis in chickens)[103]. These viruses cause tumors because of mutations induced by their insertion into host genomes. However, they also contain oncogenic genes in their genomes that are able to block or induce gene expression so that cellular function is modified. This complex induction system makes it more difficult to formulate general rules explaining why retroviral-induced tumors are benign or become malignant. Only a minority of retroviruses are known to lead to benign tumors (i.e., dermal sarcoma in fishes, avian hemangioma); most cause cancer (predominantly lymphoma, leukemia, and sarcoma). With the exception of retroviruses in fishes, among the thirteen proliferative diseases that have been associated with retroviruses, most are qualified as benign or hyperplastic because they regress seasonally and rarely metastasize. These systems are particularly interesting cases of host control of the tumor[104].

Herpesviruses make up the last category of identified oncogenic viruses. They are widespread: 60 to 90% of humans will be affected during their lifetimes[105]. Even if the link between Hepatitis B Virus (HBV) and colonic adenoma is still debated in humans[106,107], there is no evidence that herpesvirus is implicated in non-malignant tumors. On the contrary, in sea turtles, a well-documented case of herpesvirus is associated with benign tumors in fibropapillomatosis (FP). This virus causes epithelial lesions, has a worldwide distribution, and its prevalence varies from 20 to 60%. The lesions often limit or obstruct vision, feeding, or locomotive abilities[108]. In addition, FP is more prevalent in polluted areas[109,110]. Taken together, this evidence supports the idea that benign lesions might result from a new interaction between an old virus, its host, and recent environmental factors. Moreover, even if mutations or viruses are responsible for the first "oncogenic hits"[2,111], tumor progression as a benign entity also results from strong interactions with the environment. Finally, there is probably a bias in our knowledge of non-malignant tumors with a viral origin. For instance, it is easier to detect the presence of HPV strains in benign lesions that are external, than the presence of Epstein Barr virus in hepatocellular adenoma, because the latter case requires a liver biopsy [112]. Therefore, we probably have a better knowledge of viruses causing benign cutaneous lesions, because they can be studied with noninvasive methods, than of those causing internal tumors for which invasive methods are needed.

The ecology of benign and malignant tumors

The acquisition of enhanced/abnormal cell proliferation is the common starting point for both malignant and benign tumors. However, because there are many differences between the activities and metabolism of benign and malignant cells, the two types of tumors have different internal ecologies, environments, and dynamics that may exert different selective pressures on tumor cells' trajectories (see for instance[113]).

Cell turnover and intra-tumor heterogeneity (ITH)

In healthy tissues, DNA damage and/or deleterious mutations usually activate apoptosis, and this limits the risk of accumulation of mutations that can result in abnormal cell proliferation. In general, tumors develop when this process is altered and when the tissue microenvironment provides conditions that favor abnormal cells with an unbalanced ability for mitosis and apoptosis (see the section on cellular activities above). Benign and malignant neoplasms, however, differ in their cell population dynamics. For example, benign colorectal adenomas have increased mitotic and apoptotic levels compared to healthy tissue, while carcinomas present with reduced cell death compared to benign polyps[114]. As a result, benign adenomas have a higher cell turnover than healthy and malignant (carcinomas) tissues. This differential turnover has substantial consequences concerning the accumulation of genetic alterations.

High ITH is an important feature of tumor biology and is an important topic in evolutionary oncology[115,116]. In adenocarcinomas, for instance, most of the genetic and epigenetic ITH appears at the adenoma stage, which is early in tumorigenesis[32,][117,118]. The heterogeneity of tumors that never develop into malignancy has been examined less thoroughly, but the few existing studies indicate that benign tumors have the same dynamic. On the one hand, the vast majority of uterine leiomyomas, also known as fibroids, remain benign and display a high heterogeneity, with multi-loci mutations and chromosomal rearrangements[119]. On the other hand, in Barrett's esophagus, which allows studying the dynamics of somatic evolution in humans *in vivo*[120], the measurements of the genetic diversity among single cells (in more than 300 Barrett's patients over three years), showed that the more diverse the cell population is, the more likely it will progress to cancer[121]. Moreover, this genetic diversity did not significantly change during the three years,

suggesting that the initial level of genetic diversity among Barrett's cells is essentially fixed over time and predicts reliably which patients are at high risk of developing cancer[121]. More generally, it is well-established that the degree of genetic and epigenetic variability in growing tumor cell populations can predict progression to malignancy[12,15,122,123]. Nevertheless, how does a benign neoplasm like fibroids accumulate heterogeneity without never becoming malignant? This problem requires a more detailed description of the genetic dynamics of benign tumors and offers exciting research prospects.

Cell-cell interactions

Tumor cells have another significant challenge to deal with: overcrowding. Supernumerary cells lack the resources and space to proliferate [124]. While malignant neoplasms can at least partially alleviate this problem by spreading to other parts of the body, benign neoplasms that do not metastasize must cope differently with this constraint. It has been proposed that tumor cells compete with and kill neighboring host tissue to clear space in which they can expand. Research on the role of cell competition in the early steps of tumorigenesis provided some information about the underlying molecular mechanisms. By using an experimental model where mutations in the *adenomatous polyposis coli* (APC) genes induce hyperplasia and benign tumors (adenomas) in the midgut of adult *Drosophila*, Suijkerbuijk *et al* showed that these APC(-/-) adenoma cells compete with and kill surrounding cells[125]. Moreover, the authors showed that preventing cell competition by expressing apoptosis inhibitors restores host tissue growth and contains adenoma expansion. Thus, cell competition is essential for benign tumor growth.

These new constraints disrupt cells previously included in usual tissue networks. In addition to metabolic changes, new interactions appear between cells within the tumor. In cancer, a symbiosis occurs between hypoxic anaerobic tumor cells that release lactate used by aerobic tumor cells[126]. More drastically, some mesenchymal stem cells can even directly

transfer their mitochondria to cancer cells[127]. These are few examples showing the requirement for micro-ecological changes associated with cancer. Consequently, intra-tumor cell interactions in benign tumors must also be important.

Several attempts to establish models describing cellular interactions leading to non-malignant tumors have been reported (Box 2). However, there is a lack of experimental information to corroborate these assumptions in benign neoplasms. Interactions between tumor cells represent an exciting research perspective by underlying metabolic pathways of adaptation to the over-proliferation without increase of the invasiveness.

---------- Insert Box 2 ----------

The role of the tumor microenvironment

Tumor growth requires strong support from the tumor microenvironment (TME)[54], and this strong dependency means that the TME in turn exerts a selective influence on tumor development trajectories[128]. In malignant tumors, it is increasingly acknowledged that cancer development is orchestrated by dynamic and reciprocal interactions between tumor and TME cells (i.e., cancer-associated fibroblasts, bone marrow-derived cells, leukocytes, blood, and lymphatic vascular endothelial cells)[129–131]. As pointed out by Amini et al. [132], studies comparing the microenvironment of benign tumors to that of malignant tumors are lacking. Even in the transition from benign to malignant, the role of tumor-associated stromal cells is only partly understood; the specific assemblage in the benign neoplasm is still unknown.

For instance, it is established that cancer-associated fibroblasts are present in prostate and colon carcinoma but not in adenoma and normal mucosa[133,134]. Similarly, fibroblast growth factor-2 is over-expressed in sporadic cases of invasive pituitary adenoma[135], supporting the idea that tumor-associated fibroblasts are associated with invasiveness. However, benign brain tumors also show an increased presence of various collagen-producing

cells compared to healthy tissue. These cells are fibroblasts, but pericytes, myofibroblasts, and myoepithelial-like cells are also present[136]. Thus, it can be hypothesized that alteration of the extracellular matrix by collagen production is probably not specific to malignant tumors. Still, it occurs in different ways that are variably prone to malignant invasion depending on the cell types involved.

Amini et al. [132] recently explored the global microenvironmental reprogramming in canine benign breast tumors, including healthy, benign, and malignant tumor tissue. This study provided evidence for distinct signatures in these three tissue communities. The authors identified sets of microenvironment genes expressed only in benign breast tumors that were characterized by a lower number of fibroblasts and a higher level of endothelial cells compared to carcinoma. The benign tumor microenvironment is a specific cell community that is more complex than one that is just a simple step away from cancer. More research is needed to understand the extent to which TME parameters can drive a tumor towards benign stabilization or a malignant trajectory.

Whatever the roles of the mutations and the microenvironment, most benign tumors are stable over time, with only a minority of cancers known to derive from benign tumors[2]. However, despite their different developmental trajectory within the organism, benign tumors can still have an impact on the fitness of their host, and this can in return influence their evolution over generations.

The evolutionary and fitness impact of benign tumors

Benign tumors in the tree of life

While it is well established that tumors are widespread across multicellular lineages[3], cancer studies face many biases in non-human species. First, there is the ambiguity of tumor categorization (i.e., cancerous, pre-malignant, benign) for non-vertebrate species. For example, assessing the invasiveness of cells in an animal without distinctly localized organs or with very little differentiated tissues is often a matter of debate (i.e., hydras[137]). This problem led Aktipis et al. in 2015[3] to use the term "cancer-like" to describe neoplasms in some phyla (i.e., fungi, plants, corals), which may imply that these manifestations are malignant (see Box 1 and Figure 1). In addition, tumor sampling in natural populations is biased toward metazoan species, leading to an underestimation and a lack of knowledge concerning possible tumors occurring in other phyla. Besides these taxonomic disparities, benign neoplasms are less often reported than cancer cases in veterinary reports (1,398 versus 6,022; Web of Science 19/02/2021). Finally, organisms harboring symptomatic tumors should be more prone to the development of health problems, like infections, that increase mortality risks, even by extrinsic causes such as higher predation risks[138], increasing their detectability because of symptoms but in the same way reducing their frequency in the natural population.

Despite these detection difficulties, benign tumors seem to be present throughout the animal kingdom. In 2017, Madsen et al.[139] published a list of cancer prevalence in wild and captive animals, in which we can note a substantial number of benign neoplasia. Tumors were reported to be benign in 29% of the cases examined in Aves, 16.6% in Reptilia, and 40% in Mammalia (Figure 1). Concerning mammals, a more recent study evaluated that the percentage of benign tumors in two zoos reached 80.05% in average (CI 71.48- 96.11%) among all tumor cases, which underline the importance of benign tumors in mammals[140]. In a recent veterinary review, neoplasms are reported as less common in fishes than in mammals, mostly cutaneous, induced by viruses, localized, and being benign[141].

Amphibians have the reputation to be more resistant to cancer because of different regenerative and metamorphic abilities[142], but one review reported 38 cases of benign tumors in more than 100 neoplasia in different amphibians[143] (Figure 1). In the well-known *Xenopus laevis* alone, the most commonly encountered neoplasms are benign (i.e., hepatomas, teratomas, and ovarian tumors)[144]. Numerous cases of tumors in insects have been reported, but without systematic identification of the neoplastic origin of the hyperplasia[145]. *Drosophila* is known to host number of tumors in their gut and testis, and interestingly they can harbor benign hereditary forms of tumors known as melanotic tumors[146]. Other invertebrates are affected by benign tumors, for instance, the edible Pacific oyster *Crassostrea gigas*[147]. Interestingly, Newton and Lebwart[148] reported that most of the neoplasms found in invertebrates are benign.

Tumors have also been reported in plants, and although the application of the malignant/nonmalignant distinction is less clear, they best fit the benign category[149,150]. For instance, Doonan and Sablowski argue that the immobility of plant cells prevents the development of malignant cancers. [149,150]. Also, Ewald and Swain Ewald [152] argue that malignancy requires the deregulation of programs for invasiveness, and thus cancers cannot develop in species lacking such programs. Nevertheless, plants remain largely susceptible to tumors of various origins: viral (i.e., Geminivirus-induced hyperplasia[153]), fungal (i.e., *Ustilago maydis*[154]), bacterial (i.e., *Agrobacterium tumefaciens*[155]), or genetic (i.e., Tobacco pith callus[156]). Benign plant neoplasia can even rely on shared genomic mutations with neoplasia in the animal kingdom, especially those concerning cell proliferation like the retinoblastoma pathway[157].

Remarkably, compared to vertebrates, less importance is attached to the distinction between malignant and benign forms in research concerning neoplasms in plants and

invertebrates. This situation can be seen as a difficulty when looking for global neoplastic patterns, but it is also an opportunity to inspire new perspectives on the understanding of tumors, with more connection to other disciplines and less distinction between benign and malignant terminology. Further studies are required to understand the equilibrium between the risks of benign and malignant neoplasia in different taxa to reveal potential evolutionary trade-offs currently overlooked by our narrow focus on malignant manifestations.

---------- Insert box 3 ----------

The impact of benign tumors on fitness

Because malignant tumors have the potential to severely impact their host's health, it is intuitive that they can impact their fitness, especially when the detrimental consequences occur before or during the reproductive period (but also and/or after, in species delivering grand-parental care). Despite important differences between infectious diseases and cancers, there are interesting similarities in their effect on fitness[158]. Parasitic infections are not only able to reduce the reproductive lifespan of their host through premature death or a shorter reproductive life[159], they also have the potential to decrease fecundity through a reduction in the number of descendants[160]; reduce fitness through lowering the quality of the offspring[161]; and/or restrict the number of sexual partners because of sexual selection against individuals suffering from infection[162]. Cancer, like infectious pathologies[163,164], has also been shown to sometimes affect reproductive strategies, with sick hosts reallocating their resources to maximize their immediate reproductive efforts before an early death [165–167]. At the moment little attention has been paid to the impact of subclinical cancers, as well as to benign tumors on fitness.

However, symptomatic benign tumors can also have detrimental effects on host fitness. For instance, benign bone tumors or pituitary adenomas can be a cause of premature

514 death because they disrupt the organism's normal functioning[5,6]. Benign reproductive tract
515 tumors affect reproductive-aged females and can reduce their reproductive potential[168–
516 171]. In humans, the effects of reproductive tract tumors are far from negligible; for instance,
517 60% of women will develop benign fibroids during their lifetime, and these are associated
518 with 10% of infertility cases and lead to twice the risk of pregnancy failure[172,173].
519 Prolactin-secreting pituitary tumors are also implicated in 15 to 20% of the cases of infertile
520 women and an unknown proportion of male infertility[173,174]. Furthermore, benign tumors
521 can interfere with fetus development, especially the ones that disturb hormonal balances such
522 as pituitary adenomas[47,175]. These examples illustrate how benign tumors can negatively
523 impact reproduction through infertility.

524 In contrast to parasites, some symbiotic organisms can have a positive impact on
525 another individual's fitness, an interaction called mutualism[176]. For instance, organisms
526 harboring this category of symbionts may have extended reproductive lifespans or increased
527 fecundity[177,178], better-quality offspring[92], or even increased sexual
528 attractiveness[179,180]. Mutualism has been largely excluded from the evolutionary study of
529 cancer because of the cost of malignancy when cells invade an organism's tissues. While it is
530 admitted that nonmalignant tumors do not harm the organism in most cases, less attention has
531 been devoted to exploring the hypothesis that they could sometimes be beneficial to their
532 host. In plants, for example, some lineages of pea (*Pisum sativum* L) have developed
533 resistance to the pea weevil (*Bruchus pisorum* L.) by developing neoplasia under egg-laying
534 sites, which block the larva's entry into the pod [181]. *Physalis* sp. and *Solanum dulcamara*
535 can even kill eggs deposited by parasitic Lepidoptera (*Heliothis subflexa* and *Spodoptera*
536 *exigua* respectively) by inducing specific neoplasm formations that induce egg detachment
537 and/or poisoning through toxic chemicals[182,183]. Even if increased plant fecundity in the
538 tumor-resistant population needs to be measured to confirm the fitness advantage of these

539 tumors, the previous examples show that in some cases the development of benign neoplasms
540 can be seen as adaptations, thereby increasing host resistance to a parasite. In the fish genus
541 *Xiphophorus*, the spotted caudal fin is a phenotype that is associated with benign and
542 malignant melanocyte proliferation, and the invasiveness of tumor cells is governed by
543 identified genetic factors[184,185]. At the phenotypic level, male *Xiphophorus cortezi*
544 bearing the spotted caudal phenotype in some populations have increased sexual
545 attractiveness, which can explain the maintenance of benign and malignant tumors in these
546 populations[186]. This case exemplifies how a neoplasm can be adaptive through sexual
547 selection. A final example that could be mentioned concerns the evolution of placenta in
548 eutherian since it is the result of a symbiosis of marsupial ancestor with a proliferative
549 retrovirus, which became the endogenous retrovirus that is responsible for placental
550 development [187,188]). Nevertheless, studies reporting tumor benefits of any kind are rare in
551 zoology while they are quite common in the plant sciences. This illustrates another likely
552 bias: since tumors are generally considered to be diseases, it is uncommon to look for
553 potential benefits of neoplastic formations.

554 Whatever the positive or negative consequence of a tumor on the organism's health, it
555 is important in an evolutionary perspective that these effects are expressed before or during
556 the reproductive life of the organism. However, conventional wisdom holds that most
557 oncogenic manifestations occur in the post-reproductive period, because natural selection is
558 weak during that stage. Even if this argument is questionable given that even cancer at
559 subclinical levels may be important to consider[189], it does not apply to the majority of
560 benign tumors. Benign tumors often occur earlier than malignant ones, particularly when the
561 benign stage is a precursor of malignant lesions (e.g. as seen before, this is the case in
562 adenoma-to-carcinoma, where successive benign stages occur earlier in life[190–192]). In
563 addition, some human benign tumors largely occur early in life and in a significant portion of

564 the population (e.g., benign nevi or hemangioma)[193]. While studies are more scattered in
565 non-human animals, there are a few examples: a higher prevalence of fibropapillomatosis is
566 observed in juvenile and sub-adult green turtles[108,194], and dermal sarcomas in walleye are
567 benign lesions observed exclusively during the spawning season in 20% to 30% of the
568 reproductive population[104]. These examples show that benign tumors can potentially affect
569 the reproductive life of their host, at least because of their timing of occurrence. Measuring
570 their reproductive impact is a promising way to further our understanding of the fitness
571 consequences of benign tumors.

572 Finally, selection for mechanisms preventing neoplasm initiation and progression is
573 likely to depend on the environmental context in which species evolve, which is not constant
574 over time and/or space. Fluctuations in the effective size of a population are acknowledged to
575 shift adaptive values and can make neutral or even detrimental phenotypes predominant and
576 then selected in populations[195]. These phenomena are amplified in domestication, when
577 mutations involved in neoplasms having little or only a slightly detrimental impact on an
578 organism can be selected. It is assumed that cancer incidence is higher in domestic species
579 than in their wild counterparts[139] as a potential result of different genetic drift forces.
580 However, the proportion of benign tumors selected by the same processes has yet to be
581 determined. An illustration of such a problem is the variation in mast-cell tumor prevalence
582 among dog breeds. Because artificial selection on dog breeds has radically shaped their
583 genomes[196], different genes have been identified as responsible for these tumors depending
584 on the breed[197]. However, their grade can vary from benign to malignant among different
585 breeds, and some, like the pug, have a significantly higher risk of developing benign mast
586 tumors than other dogs[198]. Comparing the occurrence of tumors, their malignant potential,
587 and the strength of the genetic drift may help us understand the evolutionary history of
588 domesticated species or fragmented populations.

589 Given the ubiquity of non-malignant neoplasms among metazoans, it is surprising that
590 they have until now received so little attention. We would like to argue here that they are
591 probably much more than asymptomatic neoplasia that can be neglected. In the same way that
592 oncogenic processes have been neglected as potential factors influencing the ecology and the
593 evolution of multicellular organisms[13,199], benign neoplasms represent a fascinating
594 research direction that remains to be explored to complete our understanding of metazoan
595 evolution. Evolutionary oncology needs to consider both benign and malignant neoplasms as
596 a continuum to fully understand their impact at every scale of living entities—from cells to
597 ecosystems.

598 # Concluding remarks

599 Benign neoplasms have received less attention than malignant tumors in medical sciences,
600 undoubtedly because an understandable focus on malignant forms, which have more often
601 obvious and serious impacts on the patient/host (e.g., metastatic cancers). Concerning
602 evolutionary biologists and ecologists, it is only recently that they started to consider
603 oncogenic processes as phenomena possibly important to understand animal ecology and
604 evolution[14]. Even now, when performance in fitness-related traits varies between
605 individuals in wildlife species, reasons are most often attributed to intraspecific variability,
606 infectious diseases, or bad genes *sensu lato*, and rarely to tumor-related processes, especially
607 benign ones. Here, we argue that benign neoplasms deserve to be better studied both by
608 oncologists and evolutionary ecologists. Indeed, the use of the term "benign" has obfuscated
609 the importance of tumors that can be severe but not (or not yet) cancerous. Benign tumors can
610 be the cause of a range of manifestations from a complete benignancy to lethality. From an
611 evolutionary point of view, it is inappropriate to neglect benign tumors until they have a
612 substantial effect on host fitness. This consideration should bring new insight into oncogenic
613 processes because cancer is only the tip of the iceberg among an incredibly wide diversity of

614 neoplastic manifestations. It is thus important to go beyond the benign/malignant dichotomy
615 in order to integrate all the variety of processes governing these communities of neoplastic
616 cells, as well as the multiplicity of their manifestations at the individual level.
617
618

List of abbreviations used in the manuscript and their meanings

ALV: avian leukosis virus

APC: *adenomatous polyposis coli*

DNA: deoxyribonucleic acid

FeLV: feline leukemia virus

FP: fibropapillomatosis

HBV: hepatitis B virus

HIF-1: hypoxia-inducible factor 1

HPV: human papillomavirus

HTLV: human T-Lymphotropic virus

ITH: intra-tumor heterogeneity

PV: papillomavirus

TA: telomerase activity

TME: tumor microenvironment

VEGF: vascular endothelial growth factor

Declarations Section

- Ethics approval and consent to participate

  NA

- Consent for publication

The manuscript has been read and approved by all authors

- Availability of data and material

  NA

- Competing interests

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- Authors' contributions

JB wrote the manuscript and create the figure, BOX2 and BOX3. AMN write the BOX1. FT, AMN and BU conceptualized the original idea of the manuscript and all authors significantly contributed to all revisions.

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Box 1: The evolution of multicellularity and disparities in malignancy risks

Multicellularity evolved multiple times, independently, in distinct lineages from all major taxonomic groups (e.g., bacteria, red/green/brown algae, fungi, animals, amoebae)[200]. In all cases, the fitness and evolutionary success of the newly evolved multicellular phenotypes were dependent on the ability to control cellular proliferation in response to group cues (as opposed to environmental signals – such as in unicellular individuals). This fundamental capability was achieved differently in different taxa, as a function of each lineage's ancestral genetic background as well as cytological and developmental constraints. Nevertheless, various intrinsic (e.g., mutations) and extrinsic (e.g., viruses or other pathogens) factors can trigger uncontrolled proliferation and the formation of tumors, and tumors have been reported in all multicellular lineages[201]. However, the propensity to form tumors will be dependent on many aspects, including how the control of cell proliferation was established in each lineage – both evolutionarily (e.g., in plants vs animals; or among animals with different developmental programs) and during development (e.g., in stem cells vs terminally differentiated cells). The impact of tumors on the fitness of the individual will also depend on many factors including their location and the functional organization of the organism. For instance, plants are thought to be less affected by tumors as they do not possess "vital organs", and functional redundancy is generally high in plants (i.e., multiple roots, branches, leaves, flowers)[151,202].

But tumors can pose a higher fitness cost to the individual if they spread locally or disseminate globally – that is, are malignant. This difference in their impact on fitness reflects in the generally increased research focus on cancer, as cancer is, by definition, associated with the expression of malignancy. Nevertheless, assessing the potential for malignancy is not always easy, both in a clinical setting and in an evolutionary framework. In the latter context,

the terms cancer or “cancer-like phenomena” are often applied to situations in which invasion and/or migration have not been observed[201] (see discussion in the main text). However, as with uncontrolled proliferation, the propensity of cells to acquire the ability to invade, migrate and disseminate is also likely dependent on the evolutionary history of the lineage and the involvement of such processes in the normal development. That is because, although cancer progression is an evolutionary process within the individual, the genetic/epigenetic changes that result in fitness-increasing traits at the cell level are mainly manifestations of the dysregulation of normal/existing processes associated with the evolutionary history and functionality of the individual. That is, the malignant phenotype is a novel expression of previously evolved traits. Consequently, malignancy risk (or the degree of malignancy) is likely dependent on the traits that each multicellular lineage expresses during its normal development and life history. In this context, for instance, plants are unlikely to develop cancers as cell migration is not part of the repertoire of traits that plants express. Conversely, among mammals, species with more invasive placenta are thought to be more vulnerable to malignancy (the Evolved Levels of Invasibility hypothesis[203]). Overall, the propensity of lineages to develop benign or malignant tumors should be understood not only in terms of the evolution of tumor/cancer suppressing mechanisms, but also in the context of existing traits that can be affected by, or be co-opted into, oncogenic processes. Consequently, it might be possible to predict how (and to what degree) the two types of tumors could affect the fitness of individuals in different lineages.

Box 2: Can intra-tumor competition prevent malignancy?

In evolutionary biology, the fittest strategy is a relative notion: it must always be considered with other strategies displayed by the other population members and their frequencies[204,205]. In other words, in an evolutionary arms race, going faster is as useful as making competitors go slower. In a tumor population, a clone with a reduced mitotic rate but with the ability to reduce competitor fitness will have a benefit and can be selected. In addition, density-dependent mechanisms can favor the maintenance of heterogeneous populations through time. The selection of such clones at the intra-tumor level could result in the evolution and maintenance of benign tumors. In 1997, Tomlinson[206] illustrated this problem with a mathematical model in which a cell produces a cytotoxin that harms sensitive cells nearby, but production of the cytotoxin also reduces the cell's mitotic rate. He demonstrated that this cell can increase in number in the population if it decreases the fitness of other clones (sensitive cells). This game theory model also supports the existence of stable equilibrium, with a mixed population of cytotoxin-producing, sensitive, and resistant cells. The emergence of such a strategy in a cell population can sustain or even reduce tumor growth, sometimes to extinction. Freischel et al.[208] recently provided the first experimental proof that competition alters the growth dynamics of some breast cancer cells because of frequency-dependence fitness. This approach applied to benign tumor cell lineages could reveal whether interactions between cells can prevent malignant progression.

Box 3: Can Peto's Paradox be resolved by benign tumors?

All else being equal, animals with more cells should suffer from a higher risk of cancer, considering that all cells have the same risk of accumulating mutations and initiating oncogenic processes. However, a rather similar rate of cancer was observed in most animals independently of their body size or longevity[209]. This paradoxical finding, named Peto's paradox, can be explained by the evolution of increased anti-cancer defenses in large long-lived animals [210,211]. Because of their cost to the organism, life-threatening benign tumors should also promote the evolution of such defense mechanisms. Thus, although this question has to our knowledge not been addressed, we predict that a similar paradox will also be observed for benign tumors that can negatively impact the fitness of their bearers. Conversely, for benign tumors that have no or little impact on their host fitness, we expect a positive correlation between the size and/or the longevity of organisms and the frequency of these asymptomatic neoplasia. This, however, remains to be carefully tested because biological similarities between benign and malignant tumors may induce anti-cancer defenses to also act on benign tumors and affect their occurrence risk. For instance, it is usually assumed that four basic barriers must be compromised for oncogenesis to generate cancer: apoptosis, telomerase regulation, cell cycle arrest, and cell adhesion, allowing for invasiveness[152]. Anticancer adaptations relying on an enhanced investment in the three first barriers should also prevent the progression of benign tumors. It is also possible that some anticancer defenses rely on some functional trade-offs, and that activating defenses against malignant tumors in return favors benign tumor occurrence and/or growth. These hypotheses illustrate the need of considering benign neoplasms as members of a benign/malignant continuum when investigating Peto's Paradox.

Table 1: Definitions

Tumors	Group of genetically and/or epigenetically aberrant cells that have abnormally proliferated
Dysplasia	Proliferation of abnormal cells within a tissue which can lead to malformations or tumors.
Malignant tumor	Type of tumor that has already invaded nearby surrounding tissues.
Metastasis	A malignant tumor that has migrated away from its primary site.
Benign tumor	Type of tumor composed of cells unable to invade nearby tissues and/or distant organs, in opposition to malignant ones.
Cancer	Disease in which abnormal cells harboring the hallmarks of cancer lead to the formation of tumors able to spread and invade nearby tissues (malignant tumors).
Adenoma	Benign tumor composed of epithelial cells.
Carcinoma	Malignant tumor composed of epithelial cells.
In situ carcinoma	Malignant tumor composed of epithelial cells restricted to the originating tissue, i.e. without penetration of the basement membrane.

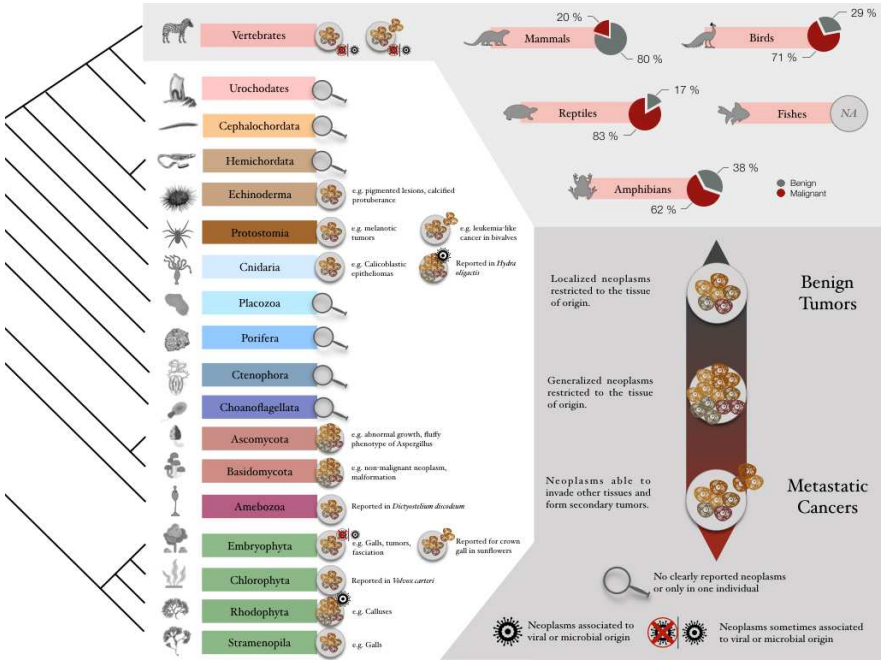

Figure 1 : Benign and malignant neoplasm diversity across the eukaryotic tree of life *(using the tree in Aktipis et al. 2015 as a starting point).*

Symbols on the right of the taxon label represent the different neoplasm types reported in that group (or in specific species when reports are limited to a specific lineage). The names of common tumors in non-vertebrate taxa are given as examples. Inside the continuum between benign and malignant tumors, three different tumor types are indicated with diagrams (see inset): localized neoplasms restricted to a tissue (benign tumors), neoplasms able to invade the majority of their tissue of origin (their status between benign and malignant tumors is intermediate), and tumors able to spread to distant organs (metastatic cancers). Tumors associated with viral or microbial origin are indicated by a black virus symbol, while the taxa harboring tumors occasionally associated with pathogens are represented by two virus symbols, one crossed out in red. The absence of neoplasms (or reports based upon only one individual) is symbolized by a magnifying glass. The proportion of benign and malignant neoplasms in vertebrates is estimated from zoo datasets and veterinary reports taken from Madsen et al. 2017 for birds and reptiles, Boddy et al. 2020 for mammals, and Balls & Clothier 1975 for amphibians.