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1 **The evolution and ecology of benign tumors**

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## 22 **Abstract**

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

## 40 **Introduction**

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

61 As a scientific field, oncology has until recently developed in relative isolation from  
62 evolutionary and ecological sciences. Despite pioneering papers during the mid-seventies[9–  
63 11], it has only been during the last decade that evolutionary biology and ecology started to  
64 profoundly transform our understanding of malignant tumor biology, cancer initiation,

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

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

76

77

## 78 **Tumors as evolutionary and ecological processes**

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

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

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

## 110 **Benign vs malignant tumor cells**

### 111 **Genetic, epigenetic and transcriptomic profiles**

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

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

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

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

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

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

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



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

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

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

## 187 **Cellular state, activities and metabolic profiles**

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

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

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

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

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

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

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

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

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

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

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

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

## 284 **Infectious causation**

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

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

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

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

331

## 332 **The ecology of benign and malignant tumors**

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

338

339 **Cell turnover and intra-tumor heterogeneity (ITH)**

340

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

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



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

371

### 372 **Cell-cell interactions**

373

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

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

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

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

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

400

#### 401 **The role of the tumor microenvironment**

402

403 Tumor growth requires strong support from the tumor microenvironment (TME)[54], and this  
404 strong dependency means that the TME in turn exerts a selective influence on tumor  
405 development trajectories[128]. In malignant tumors, it is increasingly acknowledged that  
406 cancer development is orchestrated by dynamic and reciprocal interactions between tumor  
407 and TME cells (i.e., cancer-associated fibroblasts, bone marrow-derived cells, leukocytes,  
408 blood, and lymphatic vascular endothelial cells)[129–131]. As pointed out by Amini et al.  
409 [132], studies comparing the microenvironment of benign tumors to that of malignant tumors  
410 are lacking. Even in the transition from benign to malignant, the role of tumor-associated  
411 stromal cells is only partly understood; the specific assemblage in the benign neoplasm is still  
412 unknown.

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

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

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

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

437

438

## 439 **The evolutionary and fitness impact of benign tumors**

### 440 **Benign tumors in the tree of life**

441 While it is well established that tumors are widespread across multicellular lineages[3],  
442 cancer studies face many biases in non-human species. First, there is the ambiguity of tumor  
443 categorization (i.e., cancerous, pre-malignant, benign) for non-vertebrate species. For  
444 example, assessing the invasiveness of cells in an animal without distinctly localized organs  
445 or with very little differentiated tissues is often a matter of debate (i.e., hydras[137]). This  
446 problem led Aktipis et al. in 2015[3] to use the term "cancer-like" to describe neoplasms in  
447 some phyla (i.e., fungi, plants, corals), which may imply that these manifestations are  
448 malignant (see Box 1 and Figure 1). In addition, tumor sampling in natural populations is  
449 biased toward metazoan species, leading to an underestimation and a lack of knowledge  
450 concerning possible tumors occurring in other phyla. Besides these taxonomic disparities,  
451 benign neoplasms are less often reported than cancer cases in veterinary reports (1,398 versus  
452 6,022; Web of Science 19/02/2021). Finally, organisms harboring symptomatic tumors should  
453 be more prone to the development of health problems, like infections, that increase mortality  
454 risks, even by extrinsic causes such as higher predation risks[138], increasing their  
455 detectability because of symptoms but in the same way reducing their frequency in the natural  
456 population.

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

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

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

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

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

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

### 497 **The impact of benign tumors on fitness**

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

512         However, symptomatic benign tumors can also have detrimental effects on host  
513 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

619 **List of abbreviations used in the manuscript and their meanings**

620 **ALV:** avian leukosis virus

621 **APC:** *adenomatous polyposis coli*

622 **DNA:** deoxyribonucleic acid

623 **FeLV:** feline leukemia virus

624 **FP:** fibropapillomatosis

625 **HBV:** hepatitis B virus

626 **HIF-1:** hypoxia-inducible factor 1

627 **HPV:** human papillomavirus

628 **HTLV:** human T-Lymphotropic virus

629 **ITH:** intra-tumor heterogeneity

630 **PV:** papillomavirus

631 **TA:** telomerase activity

632 **TME:** tumor microenvironment

633 **VEGF:** vascular endothelial growth factor

634

635 **Declarations Section**

636

637 • Ethics approval and consent to participate

638 NA

639 • Consent for publication

640 The manuscript has been read and approved by all authors

641 • Availability of data and material

642 NA

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650 JB wrote the manuscript and create the figure, BOX2 and BOX3. AMN write the  
651 BOX1. FT, AMN and BU conceptualized the original idea of the manuscript and all  
652 authors significantly contributed to all revisions.  
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1052 Box 1: The evolution of multicellularity and disparities in malignancy risks

1053 Multicellularity evolved multiple times, independently, in distinct lineages from all major  
1054 taxonomic groups (e.g., bacteria, red/green/brown algae, fungi, animals, amoebae)[200]. In all  
1055 cases, the fitness and evolutionary success of the newly evolved multicellular phenotypes  
1056 were dependent on the ability to control cellular proliferation in response to group cues (as  
1057 opposed to environmental signals – such as in unicellular individuals). This fundamental  
1058 capability was achieved differently in different taxa, as a function of each lineage’s ancestral  
1059 genetic background as well as cytological and developmental constraints. Nevertheless,  
1060 various intrinsic (e.g., mutations) and extrinsic (e.g., viruses or other pathogens) factors can  
1061 trigger uncontrolled proliferation and the formation of tumors, and tumors have been reported  
1062 in all multicellular lineages[201]. However, the propensity to form tumors will be dependent  
1063 on many aspects, including how the control of cell proliferation was established in each  
1064 lineage – both evolutionarily (e.g., in plants vs animals; or among animals with different  
1065 developmental programs) and during development (e.g., in stem cells vs terminally  
1066 differentiated cells). The impact of tumors on the fitness of the individual will also depend on  
1067 many factors including their location and the functional organization of the organism. For  
1068 instance, plants are thought to be less affected by tumors as they do not possess “vital  
1069 organs”, and functional redundancy is generally high in plants (i.e., multiple roots, branches,  
1070 leaves, flowers)[151,202].

1071

1072 But tumors can pose a higher fitness cost to the individual if they spread locally or  
1073 disseminate globally – that is, are malignant. This difference in their impact on fitness reflects  
1074 in the generally increased research focus on cancer, as cancer is, by definition, associated with  
1075 the expression of malignancy. Nevertheless, assessing the potential for malignancy is not  
1076 always easy, both in a clinical setting and in an evolutionary framework. In the latter context,



1077 the terms cancer or “cancer-like phenomena” are often applied to situations in which invasion  
1078 and/or migration have not been observed[201] (see discussion in the main text). However, as  
1079 with uncontrolled proliferation, the propensity of cells to acquire the ability to invade, migrate  
1080 and disseminate is also likely dependent on the evolutionary history of the lineage and the  
1081 involvement of such processes in the normal development. That is because, although cancer  
1082 progression is an evolutionary process within the individual, the genetic/epigenetic changes  
1083 that result in fitness-increasing traits at the cell level are mainly manifestations of the  
1084 dysregulation of normal/existing processes associated with the evolutionary history and  
1085 functionality of the individual. That is, the malignant phenotype is a novel expression of  
1086 previously evolved traits. Consequently, malignancy risk (or the degree of malignancy) is  
1087 likely dependent on the traits that each multicellular lineage expresses during its normal  
1088 development and life history. In this context, for instance, plants are unlikely to develop  
1089 cancers as cell migration is not part of the repertoire of traits that plants express. Conversely,  
1090 among mammals, species with more invasive placentas are thought to be more vulnerable to  
1091 malignancy (the Evolved Levels of Invasibility hypothesis[203]). Overall, the propensity of  
1092 lineages to develop benign or malignant tumors should be understood not only in terms of the  
1093 evolution of tumor/cancer suppressing mechanisms, but also in the context of existing traits  
1094 that can be affected by, or be co-opted into, oncogenic processes. Consequently, it might be  
1095 possible to predict how (and to what degree) the two types of tumors could affect the fitness  
1096 of individuals in different lineages.

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1099 Box 2: Can intra-tumor competition prevent malignancy?

1100 In evolutionary biology, the fittest strategy is a relative notion: it must always be considered  
1101 with other strategies displayed by the other population members and their  
1102 frequencies[204,205]. In other words, in an evolutionary arms race, going faster is as useful as  
1103 making competitors go slower. In a tumor population, a clone with a reduced mitotic rate but  
1104 with the ability to reduce competitor fitness will have a benefit and can be selected. In  
1105 addition, density-dependent mechanisms can favor the maintenance of heterogeneous  
1106 populations through time. The selection of such clones at the intra-tumor level could result in  
1107 the evolution and maintenance of benign tumors. In 1997, Tomlinson[206] illustrated this  
1108 problem with a mathematical model in which a cell produces a cytotoxin that harms sensitive  
1109 cells nearby, but production of the cytotoxin also reduces the cell's mitotic rate. He  
1110 demonstrated that this cell can increase in number in the population if it decreases the fitness  
1111 of other clones (sensitive cells). This game theory model also supports the existence of stable  
1112 equilibrium, with a mixed population of cytotoxin-producing, sensitive, and resistant cells.  
1113 The emergence of such a strategy in a cell population can sustain or even reduce tumor  
1114 growth, sometimes to extinction. Freischel et al.[208] recently provided the first experimental  
1115 proof that competition alters the growth dynamics of some breast cancer cells because of  
1116 frequency-dependence fitness. This approach applied to benign tumor cell lineages could  
1117 reveal whether interactions between cells can prevent malignant progression.

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1120 Box 3: Can Peto's Paradox be resolved by benign tumors?

1121 All else being equal, animals with more cells should suffer from a higher risk of cancer,  
1122 considering that all cells have the same risk of accumulating mutations and initiating  
1123 oncogenic processes. However, a rather similar rate of cancer was observed in most animals  
1124 independently of their body size or longevity[209]. This paradoxical finding, named Peto's  
1125 paradox, can be explained by the evolution of increased anti-cancer defenses in large long-  
1126 lived animals [210,211]. Because of their cost to the organism, life-threatening benign tumors  
1127 should also promote the evolution of such defense mechanisms. Thus, although this question  
1128 has to our knowledge not been addressed, we predict that a similar paradox will also be  
1129 observed for benign tumors that can negatively impact the fitness of their bearers. Conversely,  
1130 for benign tumors that have no or little impact on their host fitness, we expect a positive  
1131 correlation between the size and/or the longevity of organisms and the frequency of these  
1132 asymptomatic neoplasia. This, however, remains to be carefully tested because biological  
1133 similarities between benign and malignant tumors may induce anti-cancer defenses to also act  
1134 on benign tumors and affect their occurrence risk. For instance, it is usually assumed that four  
1135 basic barriers must be compromised for oncogenesis to generate cancer: apoptosis, telomerase  
1136 regulation, cell cycle arrest, and cell adhesion, allowing for invasiveness[152]. Anticancer  
1137 adaptations relying on an enhanced investment in the three first barriers should also prevent  
1138 the progression of benign tumors. It is also possible that some anticancer defenses rely on  
1139 some functional trade-offs, and that activating defenses against malignant tumors in return  
1140 favors benign tumor occurrence and/or growth. These hypotheses illustrate the need of  
1141 considering benign neoplasms as members of a benign/malignant continuum when  
1142 investigating Peto's Paradox.

1143

1144 **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.
<i>In situ</i> carcinoma	Malignant tumor composed of epithelial cells restricted to the originating tissue, i.e. without penetration of the basement membrane.

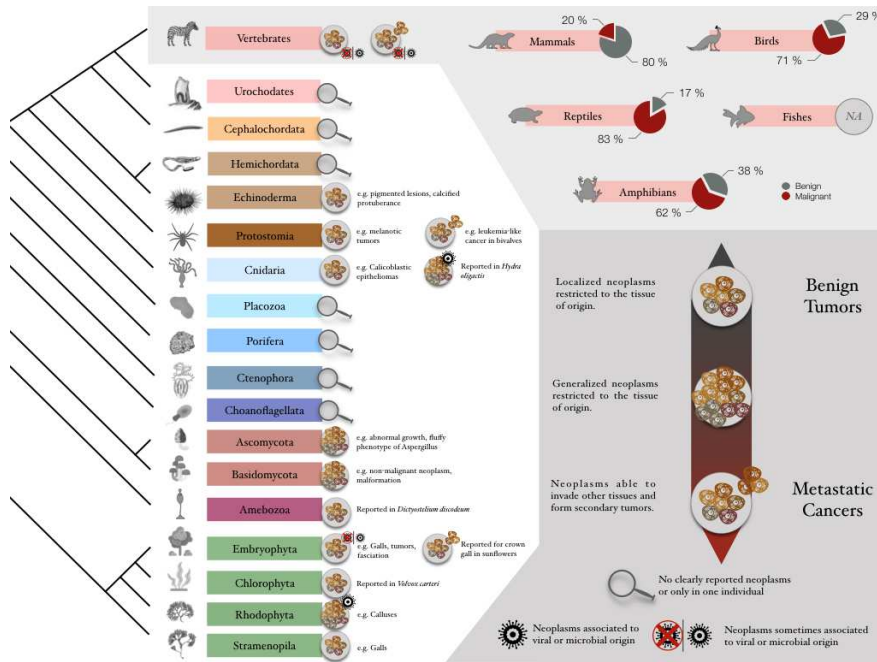
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**Figure 1 : Benign and malignant neoplasm diversity across the eukaryotic tree of life**

(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.