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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 tumorigenesis³²[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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649 • Authors' contributions

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.

1118

1119

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.

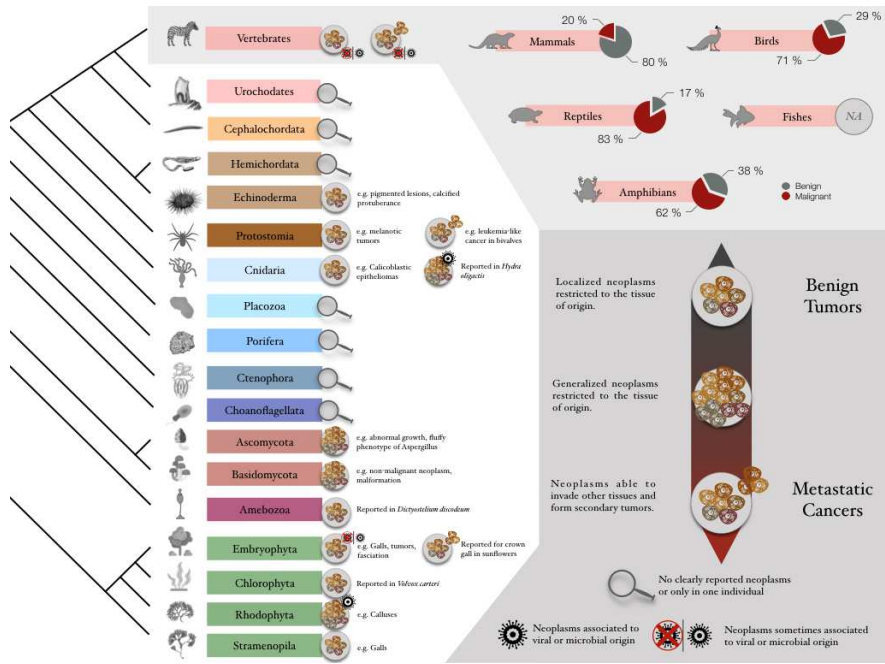
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1158 **Figure 1 : Benign and malignant neoplasm diversity across the eukaryotic tree of life**

1159 *(using the tree in Aktipis et al. 2015 as a starting point).*

1160 Symbols on the right of the taxon label represent the different neoplasm types reported in that
1161 group (or in specific species when reports are limited to a specific lineage). The names of
1162 common tumors in non-vertebrate taxa are given as examples. Inside the continuum between
1163 benign and malignant tumors, three different tumor types are indicated with diagrams (see
1164 inset): localized neoplasms restricted to a tissue (benign tumors), neoplasms able to invade the
1165 majority of their tissue of origin (their status between benign and malignant tumors is
1166 intermediate), and tumors able to spread to distant organs (metastatic cancers). Tumors
1167 associated with viral or microbial origin are indicated by a black virus symbol, while the taxa
1168 harboring tumors occasionally associated with pathogens are represented by two virus
1169 symbols, one crossed out in red. The absence of neoplasms (or reports based upon only one
1170 individual) is symbolized by a magnifying glass. The proportion of benign and malignant
1171 neoplasms in vertebrates is estimated from zoo datasets and veterinary reports taken from
1172 Madsen et al. 2017 for birds and reptiles, Boddy et al. 2020 for mammals, and Balls &
1173 Clothier 1975 for amphibians.