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Infection and cancer in multicellular organisms

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Evolutionary considerations suggest that oncogenic infections should be pervasive among animal species. Infection-associated cancers are well documented in humans and domestic animals, less commonly reported in undomesticated captive animals, and rarely documented in nature. In this paper, we review the literature associating infectious agents with cancer to evaluate the reasons for this pattern. Non-malignant infectious neoplasms occur pervasively in multicellular life, but oncogenic progression to malignancy is often uncertain. Evidence from humans and domestic animals shows that non-malignant infectious neoplasms can develop into cancer, although generally with low frequency. Malignant neoplasms could be difficult to find in nature because of a low frequency of oncogenic transformation, short survival after malignancy and reduced survival prior to malignancy. Moreover, the evaluation of malignancy can be ambiguous in nature, because criteria for malignancy may be difficult to apply consistently across species. The information available in the literature therefore does not allow for a definitive assessment of the pervasiveness of infectious cancers in nature, but the presence of infectious neoplasias and knowledge about the progression of benign neoplasias to cancer is consistent with a widespread but largely undetected occurrence.

1. Introduction to pervasiveness of cancer: evolutionary considerations

Cancer is responsible for approximately 13% of human deaths worldwide [1]. It is also a common cause of mortality in domestic animals [2]. Estimates of overall incidence in humans, dogs, cattle and horses are roughly similar, with estimated rates ranging from about 0.2 to 0.8% per year [3]. Although benign tumours are common in nature, malignant tumours (i.e. cancer) have been reported relatively rarely and often anecdotally. In this paper, we provide an overview of infectious cancers and assess whether the knowledge about neoplasms among humans, domestic animals and captive undomesticated animals provides insight into the pervasiveness of cancer in nature. Following standard definitions, we consider tumours and neoplasias to be synonyms for cells within a tissue that are characterized by abnormally elevated growth, and cancer to be malignant neoplasias, with malignancy being characterized by invasiveness and/or metastasis.

Cancer has been reported relatively rarely from wild populations. One hypothesis to account for this paucity is that cancer is indeed rare in nature relative to its frequency in domestic animals and humans. An alternative hypothesis is that cancer is common among multicellular organisms but its paucity is more apparent than real. We review the literature with the goal of evaluating these hypotheses.

Cancer could be difficult to find in nature for several reasons: a low frequency of oncogenic development to malignancy, short survival after malignancy and reduced survival prior to malignancy [4,5]. Evidence from captive, undomesticated animals, primarily in zoo populations, suggests that cancer may be responsible for about 1–5% of deaths [6–9]. But exposure to oncogenic agents and mortality from other causes likely differs between wild, captive and domestic populations. Contributing factors may include diet, population density, predation, hormonal status, selective breeding and exposures to infections and non-infectious hazards.

Table 1. Infectious causes of human cancer.

infectious agent	taxonomic affiliation	cancer
Epstein–Barr virus = human herpes virus 4 (EBV)	gamma herpes virus	nasopharyngeal, gastric cancers; post-transplant proliferative disease, Hodgkin's lymphoma, Burkitt's lymphoma
human papillomavirus (HPV)	alpha papillomavirus	cervical, penile, oropharyngeal, rectal cancers
human T-lymphotropic virus type 1 (HTLV-1)	deltaretrovirus	adult T-cell leukaemia and lymphoma
Merkel cell polyomavirus (MCPyV)	polyomavirus	Merkel cell cancer
hepatitis B virus (HBV)	hepadnavirus	liver (hepatocellular) cancer
hepatitis C virus (HCV)	flavivirus	liver (hepatocellular) cancer
Kaposi sarcoma-associated herpes virus = human herpes virus 8 (KSHV = HHV-8)	gamma herpes virus	Kaposi's sarcoma
<i>Helicobacter pylori</i>	Helicobacteraceae	gastric, mucosal-associated lymphoid tumours
<i>Clonorchis sinensis</i>	Opisthorchiidae (trematodes)	liver cancer (cholangiocarcinoma)
<i>Schistosoma haematobium</i>	Schistosomatidae (trematodes)	bladder cancer

Evolutionary considerations can be invoked to explain why cancer might be rare in nature. Specifically, if cancer is presumed to be a late manifestation of organismal senescence, it could be interpreted as a by-product of selection acting at younger ages [10]. By this argument, animals in nature rarely survive to ages normally associated with cancer and cancer therefore could be rare in nature.

Conversely, evolutionary logic can also be invoked to suggest that cancer may be common in nature. If the low prevalence of cancer results largely from anti-cancer adaptations, then natural selection would be expected to increase their frequency or effectiveness until the rarity of cancer makes the selection pressure against cancer too weak for further reductions. Because larger, longer lived organisms should have a greater potential for accumulation of oncogenic mutations, such organisms are expected to acquire more effective adaptations for preventing or controlling cancer. By this argument (one resolution of Peto's paradox), the prevalence of cancer could be similar among species regardless of body size and longevity with stronger selection for anti-cancer adaptations occurring in organisms that are large and long-lived [5,11]. The end result could be low incidences of cancer throughout nature in large and small organisms alike.

A complementary evolutionary argument arises from consideration of infectious causation of cancer. (We define infectious causation broadly to include any cancer caused by a subcellular, unicellular or multicellular parasite.) Infection may contribute to cancer indirectly, for example, when inflammatory responses increase mutations or proliferative signals [12–15]. Alternatively, infectious agents may contribute to cancer directly by encoding proteins that compromise cellular barriers to oncogenesis, such as cellular regulation of telomerase, apoptosis, cellular adhesion or cell-cycle arrest; or cellular restraints on oncogenesis, such as control of proliferation rate [16]. These characteristics evolve particularly in intracellular pathogens not because cancer is beneficial to infectious agents but apparently because these attributes increase the ability of these pathogens to reproduce within hosts with reduced exposure to immunological destruction [17]. As obligately intracellular pathogens, viruses often replicate their genomes by stimulating host cells to proliferate as an alternative to formation and release of virions. Accordingly, the

known infectious causes of human cancers are disproportionately viral (table 1). Oncogenicity has arisen independently in different viruses, which invoke different molecular mechanisms to abrogate the same cellular barriers to oncogenesis; these mechanisms and their effects of cellular proliferation and immortalization are understood in great detail (reviewed by Ewald & Swain Ewald [17]). The oncogenicity of these viruses therefore appears to result from natural selection acting on the viruses to force host cell replication, thereby enhancing the propagation of the viral genomes under the constraint of immune surveillance [16].

From the pathogens' perspective, cancer is generally a negative outcome because host death from cancer, or from cancer-induced vulnerability to other causes of mortality, generally eliminates chances of future transmission. For virtually all well-studied infectious cancers, these fitness costs affect only a small portion of the viral population because the proportion of infected individuals that develop cancer is generally small, probably because additional mutations in the host are generally necessary to complete the transition from benign tumour to cancer. The evolution of viral oncogenicity therefore relies on a trade-off: the positive effects of oncogenic characteristics of pathogens on reproduction and survival outweigh the negative effects of cancer on transmission, which arise in a small number of infected hosts. As is the case with cancers that are not caused by infection, natural selection acting on pathogens will tend to curb but not entirely eliminate oncogenic effects, because as oncogenicity evolves to lower levels, selection pressure to dampen it declines; however, selection pressure favouring increased proviral replication selects for viruses that have some oncogenic attributes across the spectrum of host body size and longevity.

This evolutionary perspective also indicates that natural selection could act on oncogenic pathogens of short-lived hosts to cause cancer in periods of time that are much shorter than the years to decades that are required for human oncogenic pathogens. When the lifespan of the host is short or options for transmission become frequent, the trade-off mentioned above should favour increased viral-induced proliferation of host cells and hence increased oncogenicity. The intervals between the onset of infection and the onset of cancer suggest that viral-induced cancers can vary greatly in response to this

trade-off. For example, Rous's sarcoma can be transmitted frequently among chickens in agricultural settings; it has evolved to cause cancer very soon after the onset of infection as a result of the actions of an *src* genetic element [18]. At the other extreme, for human T-lymphotropic virus type 1 (HTLV-1) in Japan, the first opportunity for transmission is often delayed: decades may elapse between the infection of a baby and the first transmission opportunity, which occurs after the baby grows to sexual maturity. The time between infection and HTLV-1 induced cancer is also very long, typically several decades [19,20].

In light of these considerations, we integrate knowledge from humans, domestic animals, and undomesticated animals in captive and natural settings to draw implications about the general presence of cancer across species. We focus on pathogens with accepted oncogenicity, insights from interspecific comparisons of neoplasias caused by the same or similar pathogens, relationships between non-cancerous (or precancerous) neoplasias and cancer, and the extent to which infectious causation has been studied.

2. Infectious cancers in vertebrates

(a) Historical trend

Recognition that parasites can cause cancer in vertebrates developed slowly over the past century. Most of the known infectious causes of cancer in vertebrates are viruses. Rous [21,22] showed that a non-filterable agent, now known as Rous's sarcoma virus, caused a cancer of chickens. This finding led to discoveries of an oncogenic papillomavirus in rabbits [23], mouse mammary tumour virus (MMTV) in mice [24], murine leukaemia virus in mice [25] and simian virus 40 in hamsters [26]. Over the past half-century, many other tumour viruses were associated with malignant and non-malignant neoplasias of domestic and wild animals, mostly in poultry, rodents, cats, rodents, ungulates and primates [27,28].

Epstein–Barr virus was the first generally accepted viral cause of a human cancer: endemic Burkitt's lymphoma [29]. *Plasmodium falciparum* has been broadly accepted as an aetiological cofactor for endemic Burkitt's lymphoma, though with some reservations [30–36]. Over the same decades during which infectious correlates of endemic Burkitt's lymphoma were being recognized, trematode infections were implicated in causing bladder and liver cancer ([31,37–39]; table 1). Since then, cellular and especially viral agents have been increasingly implicated ([40–48]; table 1). Currently, infectious causation is accepted for 15–20% of human cancer [49,50]. This percentage may grossly underestimate the true extent of infection-induced cancers, however, because infectious causation has not been adequately evaluated for most human cancers and can be ruled out for only a very small portion.

Seven viruses are now generally accepted infectious causes of human cancers (table 1). The selection for increased propagation through host cell proliferation does not apply to extracellular parasites. In this regard, the mechanism by which *Helicobacter pylori* contributes to human cancer (table 1) is still unclear, although it does involve the compromising of host barriers to cancer to some extent [51]. The means by which trematode parasites contribute to human cancer have been presumed to be through induction of inflammation [52]. Recent work suggests, however, that the two human cancers caused by trematodes (table 1) may involve joint infectious

causation with viruses: hepatitis B and C viruses for cholangio-sarcoma and human papillomaviruses for bladder cancer (reviewed by Ewald & Swain Ewald [51]). The trematode infections may thus be exacerbating viral causation in these cancers through oncogenic effects of inflammation.

The predominant role of viruses among infectious cancers of humans is paralleled by the current state of knowledge about infectious cancers in other vertebrates. This knowledge is best developed in the veterinary literature on domestic animals, for which virtually all examples of infectious causes of cancer involve viral aetiologies [2]. Although the literature on cancer in wild vertebrates is much less complete, the current state of knowledge implicates a disproportionate involvement of viruses relative to other pathogens ([53,54]; table 2).

(b) Related oncogenic pathogens in humans, domesticated and undomesticated species

The literature on cancers of humans, domestic animals and wildlife suggests that closely related viruses can cause infectious cancers in these groups. Much of this evidence involves transfer of viruses between hosts that are closely related phylogenetically. In such cases, cancer-causing proclivities in one host species may carry over to the other. The literature on humans and domestic animals provides the most detailed confirmation of this connection. The few viruses that are accepted causes of cancer in wildlife tend to have phylogenetically related viruses that are oncogenic in humans (table 2). The literature on undomesticated animals, however, consists largely of anecdotal observations, but these too accord with the idea that some of these cancers are caused by infectious agents that are closely related to those known oncogenic pathogens of humans and domesticated animals.

The comparisons between T-lymphotropic viruses in humans and simians provide an illustration. These deltaretroviruses are referred to as human T-lymphotropic viruses when isolated from human hosts and simian T-lymphotropic viruses (STLVs) when isolated from simian hosts. Phylogenetic analyses indicate that STLVs have been introduced into humans from simians several times over recent millennia [62]. STLV infections of non-human primates are generally asymptomatic but have been associated with anecdotal reports of leukaemia or lymphoma mostly in captive individuals of several primate species: African green monkeys, baboons, macaques and gorillas [63–66]. These associations suggest that oncogenicity may occur in simian hosts but may be less apparent due to host death and insufficient study. In humans, adult T-cell leukaemias and lymphomas occur in about 5% of infections with HTLV-1, but almost always after several decades of infection; death then occurs within several months after the onset of the cancer [20]. The vast majority of time during which humans are infected with HTLV-1 therefore would not involve a cancerous state. If cancer comprises a similarly small proportion of time when simian hosts are infected with STLVs, any cancer caused by these viruses would be difficult to detect except in captivity, especially if the cancer made the individuals vulnerable to other sources of mortality.

Domestic cats have an unusually high rate of lymphoma [67]. Cats infected with feline leukaemia virus (FeLV), a gammaretrovirus, are 60 times more likely than uninfected cats to develop lymphoma or leukaemia [68,69]. Prior to introduction of the FeLV vaccine, the annual incidence of lymphoma was 0.2%; as many as 70% of diagnosed lymphomas were

Table 2. Oncogenic viruses in wildlife.

virus	host	references	taxonomic group of viruses	human oncogenic viruses in same taxonomic group	
				virus	transmission
various retroviruses	walleye pike (<i>Sander vitreus</i>) Atlantic salmon (<i>Salmo salar</i>) Attwater's prairie chicken (<i>Tympanuchus cupido attwateri</i>)	[55–57]	Retroviridae	HTLV-1	sex, milk, blood
woodchuck hepatitis virus	woodchuck (<i>Marmota monax</i>)	[58]	Hepadnaviridae	HBV	sex, blood
Otarine herpesvirus-1	California sea lion (<i>Zalophus californianus</i>)	[59]	gamma herpes virus	EBV, KSHV	sex, saliva
bandicoot papillomatosis carcinomatosis virus-1	western barred bandicoots (<i>Perameles bougainville</i>)	[60]	papillomavirus – polyomavirus mosaic	(1) HPV (2) MCPyV	(1) sexual contact, (2) probably saliva
ranavirus-1	leopard frog (<i>Rana pipiens</i>)	[61]	Iridoviridae	none	

associated with FeLV infection [67]. Despite a major reduction in FeLV infection among vaccinated populations of domestic cats, reported cases of leukaemia/lymphoma may not have decreased accordingly, suggesting that other non-viral or unidentified viruses may be playing an increasing role in the development of this cancer [67–69].

Another retrovirus, the lentivirus feline immunodeficiency virus (FIV), is similar to HIV regarding immune manifestations, course and cell tropism. Like HIV, it is associated with increased risk of cancer in domestic cats [70,71], including lymphomas, leukaemias and squamous cell carcinoma (SCC) [68]. FIV co-infection with FeLV confers about 80 times the risk for lymphoma development relative to cats that are negative for both [70]. As is the case with HIV, the association of FIV with cancer appears to be through decreased immune surveillance of nascent cancer rather than direct cellular transformation [69]. Although species-specific FIV infections in large, non-domestic cats have historically been considered mild, recent investigation of non-captive African lions found indicators of FIV-associated immune depletion [72]. Three out of four of the sampled lion populations had greater than 95% positivity for FIV [72]—such high prevalences along with signs of immune suppression in some non-captive African lions suggest that viral-associated lymphoma might be a problem for wild cat populations as well. A captive lion showing wasting, periodontitis and lymphadenopathy (similar to the wild lion findings of Roelke *et al.* [72]) was found at autopsy to have lymphoma and was FIV positive [73]. However, a retrospective study in US zoos of captive-born African lions with lymphoma found no FIV in tumour samples; nor were any of the lions serologically positive for FIV, according to zoo records [74]. The lower rates of positivity in zoo populations draw attention to the possibility that infectious causes of cancer might sometimes be more prevalent in nature because pathogens may be less prevalent in small, isolated zoo populations.

The difficulty in detecting cancer in wild populations could be assessed by comparing the detailed knowledge of cancers in domestic animals with findings in feral

populations of the same species. A comparison of FIV infection rates, for example, reported positivity in 23% of stray urban cats, 5% of feral cats and 6% in client-owned cats [75]. A comparison of FIV-associated cancers observed in feral cats with client-owned cats could therefore provide a sense of the extent to which cancer detection is decreased in feral settings.

Bovine papillomavirus (BPV) is a cause of cancers in cattle. Oncogenic BPVs have been found in other species, both captive and wild [76,77]. This presence illustrates the potential for oncogenic viruses to be transmitted among species, although the oncogenicity is likely to vary among host species. Phylogenetic analyses indicate that BPV has been transmitted from cows to horses, causing the most common equine neoplasm: sarcoids—locally invasive skin tumours, one form of which is malignant. Sarcoids appear to be caused by an ‘equine-specific’ BPV-type variant [78]. Both prophylactic and therapeutic vaccines against BPV have been developed for cattle and a therapeutic vaccine that has been tested in horses shows promise for sarcoid regression and control [77,78].

The papillomavirus *Equus caballus* papillomavirus-2 (EcPV-2) is associated with another cancer of horses: equine penile SCC. EcPV-2 is more closely related to the oncogenic human papillomavirus type 16 than it is to the cause of the benign equine cutaneous papilloma (EcPV-1) [79,80].

Oncogenic papillomaviruses of cats show similar cross species transfers. In domestic cats, feline papillomaviruses cause tumours and are associated with invasive SCCs [81,82]. The type of cancer that is often positive for this virus has also been found in a wild lion [83], and benign tumours and SCCs positive for feline papillomaviruses have been found in snow leopards [84]. Efforts to identify hallmarks for PV-infected versus uninfected SCCs [85] and to, for example, develop PCR testing for PV positivity in non-domestic cat species [86] should help to further determine the role and scope of PV oncogenicity in felids.

Although oncogenic viruses of humans and other vertebrates are often phylogenetically related (table 2), the human

oncogenic viruses are diverse (table 1). Moreover, closely related members of a viral group, human papillomaviruses for example, can vary greatly in their oncogenicity [87]. Oncogenicity therefore appears to be strongly subject to evolutionary modification. Investigating the oncogenic potential of pathogens on the basis of demonstrated oncogenicity of a viral group may therefore lead to rapid identification of new oncogenic infections, but runs the risk of missing portions of the spectrum of infectious causation.

Some cancers in domestic animals are caused by viruses from groups that are not known to cause cancer in humans. For example, Jaagsiekte Sheep Retrovirus causes lung cancer in sheep [28]. It is classified within the beta retroviruses, a group for which no virus has been accepted as a cause of human cancer; moreover, no infectious cause of human lung cancer has yet been generally accepted.

The betaretrovirus MMTV is a well-established cause of mammary tumours in mice [88]. Although the status of these tumours as malignant or non-malignant neoplasias was debated for a century, the metastatic potential of the tumours indicates that MMTV is a cancer-causing virus [89]. Mammary neoplasms are common in both canines and domestic cats, with malignancy rates in dogs at approximately 50% [90,91] and cats closer to 90% [92]. Possible viral aetiology in these domestic animal mammary cancers have been reviewed or investigated [90,93,94]. In one study, MMTV-like sequences were identified in malignant mammary tumours of dogs (18.6% positivity) and cats (22.2% positivity) [95]. Similar rates have been found in some studies of human breast cancer [96].

A similar line of enquiry has been taken with human papillomavirus (HPV). Because HPV has been isolated from human breast tumours, researchers recently looked for papillomaviruses in canine mammary tumours. PCR results were negative, however, for virus in all tested tumours [97].

(c) Associations between benign and malignant neoplasias

Insights into the pervasiveness of infectious cancers among species can be gained from assessing developmental links between non-malignant tumours and cancers. This idea builds on the recognition that oncogenicity generally begins with non-malignant growth. Terminology can be confusing, however, because once the transition to a cancer is established, the non-malignant growths are often considered to be precancerous rather than benign neoplasias.

This view of non-malignant neoplasms may be especially relevant to an understanding of the broader presence of cancer in undomesticated animals. In wildlife settings, neoplasias that sometimes give rise to cancers should be more readily observable than the associated cancers because non-malignant neoplasias are more numerous and persist for a longer time. As knowledge about cancers in humans and domestic animals has developed over the past century, it has become apparent that early 'benign' neoplasias have been developmentally associated with cancer. This process has linked actinic keratosis and benign papillomas with SCCs in several domestic species, haematopoietic dysplasia with acute myelogenous leukaemias in dogs and cats, endometrial hyperplasia with adenocarcinoma in rabbits and benign mammary tumours to malignant carcinomas in dogs [98,99]. These findings parallel analogous associations

in human cancer, for example, between cervical intraepithelial neoplasia and cervical cancer and between colorectal polyps and colorectal cancer.

Non-malignant neoplasms are common in the phyla of wild and domesticated vertebrates and are often associated with infection [2,61]. As with human cancers, recognition of infectious causation in domestic animals and links between benign and malignant infectious tumours are still expanding (e.g. [100,101]).

Feline papilloma viruses provide an illustration. Feline PVs have been isolated from rare neoplasias in domestic cats, referred to as benign viral plaques. These plaques have been shown to transform into *in situ* carcinoma [102]; in one instance, a metastatic SCC apparently arose from a PV positive *in situ* carcinoma [103]. Further investigation into PV association with more common feline cancers has revealed significant positivity in both oral and cutaneous domestic cat SCCs [101,104].

The establishment of the connection between benign neoplasia and cancer has often been prolonged. BPVs, for example, generally cause benign tumours in cattle. They were eventually associated with SCCs of the alimentary tract and bladder over a half-century after evidence of infectious causation of bovine papillomas was first published [27,105,106]. The association of BPV with bovine cancer was identified among cattle grazing on bracken fern in the Scottish Highlands, which were found to have papillomas co-occurring with alimentary cancer and transforming to SCC [105,106]. Bracken fern causes immune suppression in cows and appears to have carcinogenic properties [78,106]. A similar process of BPV infection plus immune suppression and mutagenic effects is associated with bovine urinary bladder cancer [78].

In horses, SCC is the most prevalent form of penile cancer, comprising 44–88% of surveyed cases [107]. Until recently, attention focused on possible oncogenic effects of chronic inflammation, UV exposure and smegma accumulation [80]. The discovery of a novel papilloma virus, EcPV-2 [79] and its association with equine penile SCC [79,80] along with the histopathological finding that benign penile papillomas (from which EcPV-2 has also been isolated) can transition to SCC [107–109] suggest a causal role for papillomavirus in this cancer.

The possible link between benign tumours and unrecognized cancer is further compounded by ambiguities in defining the boundary line between the two categories. Although clearly metastatic or invasive tumours can be distinguished from tumours that have no capacity to spread from the original site, the dividing line between malignant and benign tumours, that is, cancer as opposed to non-cancerous or precancerous growths, is not as distinct as the language would imply. This ambiguity is present histologically within an accepted transition from precancerous to cancerous neoplasia [91,99] and becomes even more problematic for defining the boundary of benign neoplasias that are not yet linked to a malignancy. Cutaneous fibromas, for example, frequently occur in wild populations of deer and elk and are caused by papillomaviruses [110,111]. Between about 1 and 10% of white-tailed deer killed by hunters in the northeastern USA had fibromas, the range probably resulting from variation in degree to which small tumours were noted [112]. An infectious aetiology was first reported in 1955 [27]. These neoplasias are often referred to as benign [113] but can be lethal when present at many

cutaneous sites in an animal as well as in the lungs [7,8,113], where they have been interpreted as metastatic by some investigators [7,8,114].

3. Oncogenic viruses in reptiles and fishes

Among reptiles, recognition of cancers has been developing slowly. During the middle of the twentieth century, cancer in reptiles was thought to be rare [115], but over the past half-century a variety of cancers have been documented mostly from captive animals in different reptile groups [9]. Studies of captive lizards report rates of neoplasias from 1 to 6% [9]. The dataset reporting 6% indicated that about three-quarters of the neoplasias occurred in non-geriatric animals and involved haematopoietic cells, the musculoskeletal system, liver or skin [9]. In an investigation of autopsied snakes from a zoo, neoplasias were implicated in 23% of the deaths [116]. A large variety of neoplasms were reported in many snakes species, about three-quarters of which were considered malignant. The neoplasm rate increased greatly over about one-third of the 10-year duration of the study, indicating some sort of environmental exposure [116].

The aetiologies of neoplasias in reptiles are largely unknown, but associations between viruses and neoplasias have been reported in at least two species each of snakes, lizards and turtles (reviewed by Hernandez-Divers & Garner [9]). Fibropapillomatosis in sea turtles, caused by a herpes virus, are generally considered to be benign, but tumours can be present in many different areas of the body and potentially fatal [117]. Although the scope of knowledge among reptiles is limited and subject to the caveats about generalizations from captive animals, these studies draw attention to the possibility that infectious cancers could be prevalent but largely unreported in reptiles in nature.

Non-malignant neoplasias are common in fish species. They have been associated with viral infections [61,118,119], but, for reasons mentioned above, determining whether these apparently benign tumours sometimes progress to malignancy will require studies specifically directed to address this question.

4. Infectious neoplasias in plants and invertebrates

Although pathogen-associated tumours have long been recognized in plants and algae [120,121], cancer appears to be absent. Doonan & Sablowski [122] suggest that this paucity results from the constraints on cell mobility imposed by the plant's cell wall matrix. The cell wall matrix, however, can be altered in ways that would allow for plant cells to be unconstrained (e.g. plant cells in pollen tubes). We therefore suggest a modification of their hypothesis. In animal cells, specialized cell types have evolved to be mobile and invasive as part of their normal functioning. Immune cells, for example, maintain abilities to move throughout the body and invade tissues. The genetic instructions for mobility, spread throughout the body, and invasion of tissues is therefore maintained in the genomic information for virtually all animals. From an evolutionary perspective, most cells within a body are moulded by natural selection to inhibit these processes and thereby enhance the fitness of the organism to which they belong. In this context, oncogenesis is

largely the breaking of this regulation so that individual cells can replicate themselves and spread, increasing their numbers at the expense of the fitness of the organism [16]. If the genetic instructions for mobility, spread and invasion are not already present in plant genomes (because plants do not have mobile, invasive cells as components of their defences and development), then agents of cancer (whether infectious or non-living) cannot unmask these instructions. Removal of the inhibition of these instructions, whether by infection, mutation and/or epigenetic modification, can therefore make normal cells into cancerous cells in animals but not plants. By contrast, agents of non-cancerous neoplasias need only unmask instructions for cellular reproduction and therefore should be common among plant species.

This explanation for the absence of cancer in plants leads to two general predictions. If plant or plant-like species are discovered with mobile, invasive cells as part of their normal development or maintenance, then these species should sometimes develop cancer. The reciprocal prediction is that any multicellular organisms that do not have mobile, invasive cells as normal aspects of their developmental or maintenance should not experience cancers. Because virtually all animals normally have mobile, invasive cells as part of their life histories, this logic suggests that virtually all animal species will experience some form of cancer (under the assumption that the low levels of cancer are maintained by adaptations to control cancer regardless of body size and longevity). Natural selection acting on intracellular pathogens would be especially likely to compromise these regulatory mechanisms to allow long-term persistence and spread within multicellular animals (as discussed above).

In contrast with these expectations, there are few reported examples of cancers in invertebrate animals; however, there appears to have been relatively little effort to investigate this possibility. Moreover, observed invertebrate neoplasms tend to be difficult to categorize as to malignancy in part because criteria for recognizing malignancy in vertebrates may not be directly transferrable. The dividing line separating cancer from non-cancerous neoplasias may therefore often be ambiguous in invertebrates [119].

Some neoplasias in invertebrates have cancer-like characteristics and some have been associated with pathogens. Tumours that are malignant or have cancer-like characteristics have been reported in cnidarians, flatworms, roundworms, crustaceans and insects [119,123–126]. In shrimp, a lymphoma-like neoplasm of lymphoid organs, and abnormal growth and metastases have been associated with viral infection [119,125,127,128]. These malignancies in short-lived invertebrates support the view that infection-induced cancers are not limited to larger, longer lived organisms. A cancer of shrimp, for example, occurs in embryos [125], in which the number of cells is small and the duration of life prior to the cancer is short. These shrimp had intra-nuclear inclusion bodies typical of viral infections [125].

These invertebrate cancers are consistent with the trade-off hypothesis, which proposes that infectious agents are selected to increase proliferation rates of infected cells until the average costs incurred through neoplasial pathologies outweigh the benefits of viral proliferation (see Introduction). They also accord with the hypothesis that natural selection for defences against cancer restricts cancer to low incidences per lifetime rather than low levels per cell per unit time (see Introduction).

5. Transmissible cancer cells

In Tasmanian devil facial tumour disease (TDFD) and canine transmissible venereal tumour (CTVT), the infecting agent of the cancer is known to be the cancer cell itself [129]. TDFD results from cancer cells that are transmitted among Tasmanian devils (*Sarcophilus harrisi*) by biting during aggressive interactions; CTVT is similarly transmitted among dogs by licking and biting [129]. Attention to the possibility of additional examples of transmissible cancer cells has been inadequate to determine whether transmissible cancer cells are widespread in nature.

Their occurrence may be limited by constraints on mitochondrial maintenance. Without repair mechanisms found in multicellular organisms [130], mitochondrial function may disintegrate through accumulation of mutations. Canine transmissible venereal tumour cells diverged from canine cells approximately 11 000 years ago [131]. Sequences of mitochondrial genomes suggest that CTVT cells have more recently acquired mitochondria from dog cells [132], thereby allowing these tumour lineages to avoid fitness losses that arise from progressive genetic deterioration of mitochondria. If new transmissible cancer cell lineages do not acquire such mechanisms for dealing with mitochondrial deterioration, they may arise and become extinct without being noted. In this regard, it is noteworthy that Tasmanian facial tumour cells have arisen recently, diverging from Tasmanian devils only about 20 years ago [133,134].

TDFD and CTVT are conspicuous cancers because they are external and associated with grossly apparent tissue damage. Other transmissible cell cancers may therefore be present but not yet recognized because they are less apparent and associated with a short duration in species in natural settings, for the reasons mentioned above. More pervasive phylogenetic comparisons of neoplastic cells with normal cells in the host species should help resolve this issue.

6. Environmental pollutants, infection and control of cancer

The belief that cancer is rare in nature has led to concern that cancer in nature may generally result from an unnatural contamination of the environment. Contaminants that increase mutations can be expected to increase the incidence of cancer. But pollutants could also contribute to cancer through immune suppression. This mechanism could be especially important for infection-induced cancers because intact immune systems are particularly effective at combatting infection. Sea turtle fibropapillomatosis, which is caused by an alpha herpesvirus, for example, is more prevalent in areas subject to pollution from human activities [135,136], although a variety of correlates of human activity could be causally involved [135]. Levels of polychlorinated biphenyls are elevated in the blubber of genital carcinomas of sea lions induced by a gammaherpesvirus [53,137]. Polychlorinated biphenyls have been classified as carcinogens but also have immunosuppressive effects [138]. These infection-associated tumours emphasize the need to consider infectious causation when the tumours are linked to immunosuppressive pollutants, or more generally with human activities (e.g. increased incidences of cancers in whales and fish that are exposed to such pollutants; [139,140]).

The associations between industrial pollutants, immune suppression and infectious animal tumours, parallel the increased incidence of papillomavirus-induced bovine cancers in response to immune suppression by bracken fern [105] and the increased incidence of human cancers in response to immunosuppressive therapy and HIV-induced immunosuppression [141].

The discovery of pollution-associated cancers suggests obvious environmental interventions that may reduce the frequency of such cancers. Similarly, the discovery of infectious contributions to oncogenesis offer analogous opportunities for intervention. Specifically, because infectious agents provide targets that are different from human cells, discoveries of infectious causation of cancer offer important opportunities for relatively safe interventions. Prophylactic vaccines are now in use to prevent infectious causes of cervical and liver cancer [142,143]. Anti-infective drugs are useful therapeutically for liver cancer and stomach cancer [142,144–146]. These successes provide further evidence of the importance of infectious agents in initiating and maintaining cancers; but they also serve as a model for controlling other infectious cancers in humans, domesticated and captive wild animals, and perhaps even animals in nature where vaccines or anti-infective compounds can be administered or pathogen transmission controlled.

7. Conclusion

Evolutionary considerations suggest that cancer may be pervasive in animal species. The literature reviewed here illustrates the prevalence of infectious cancers in humans and domestic animals. In captive and wild animals, the limited amount of research has documented a widespread presence of infectious neoplasms but relatively few examples of infectious cancers. This paucity, however, does not mean that infectious cancers are rare in undomesticated animals, for a variety of reasons: the lack of systematic investigation, the long amount of time that has been needed to determine whether 'benign' neoplasias sometimes develop malignancy, the difficulty in adapting diagnostic criteria for malignancy to different species, additional sources of other mortality in nature and the difficulty in determining whether infectious associations are causal. Evolutionary considerations suggest that additional research will not lead to discoveries of cancer in plants even though infectious tumours are widespread, because the normal functioning of plants does not involve cell mobility and invasion.

Knowledge about infectious causation of cancer is still expanding across the spectrum of animals, paralleling improved knowledge about oncogenic effects of pathogens. In undomesticated felids, for example, FIV used to be considered benign but is now associated with immunological pathologies [147]. Considering the immunopathology of FIV in domestic cats and observed increases in the incidence of cancer, it is reasonable to expect that the similar immunopathology in wild cats will be associated with increased oncogenic pathologies as well. Viruses with well-established oncogenic capabilities such as FeLV or papillomaviruses may have been underestimated with regards to their potential for zoonotic spread as well as degree of pathogenicity in both their original and new hosts [147,148]. This problem highlights the importance of integrating the study of oncogenic viruses across a broad spectrum of host species.

The evidence from wild and captive undomesticated animals emphasizes the need for more detailed studies to specifically address sources of ambiguity. One useful approach would involve repeated sampling to evaluate whether non-cancerous neoplasms undergo oncogenic transitions. Frequent sampling may be necessary because survival may decline more precipitously in nature as oncogenesis proceeds. Skin and blood cancers seem the most amenable to repeat testing of individuals in nature to allow detection of precancerous states and early stages of cancer.

The pervasiveness of infectious causation of cancer is not known even for the best studied species. In humans, for example, infection is known to be responsible for about 20% of cancers, but viruses with oncogenic capacities have been reported for most human cancers. The traditional view of oncogenesis is that it results mostly from accumulation of mutations. Because larger animals with longer lifespans have more somatic cells that are exposed to mutagens for longer periods of time, this traditional view interpreted cancer as being largely a problem of large, long-lived organisms. Probably as a consequence, researchers have not been motivated to search carefully for cancer among the entire spectrum of living organisms. Applying an evolutionary perspective to cancer questions this traditional view by suggesting that natural selection can favour two outcomes: imperfect defences against cancer that lower cancer rates across a broad spectrum of multicellular animals (disproportionately in large, long-lived animals) and selection for levels of oncogenicity in pathogens that can raise the probability of oncogenesis, usually to low frequencies.

This shift in thinking emphasizes the need for more comprehensive and focused investigations of the contribution of infection to oncogenesis among animal species. Studies designed for the purpose of discovering the presence and prevalence of cancers in wildlife are needed to avoid the

interpretive ambiguities that arise when anecdotal observations are reported from studies designed for other purposes. Large study populations are needed in natural settings to detect cancers that may be present for a short period of time in a small proportion of the individuals. Longitudinal studies of particular individuals need to be conducted to determine whether benign neoplasms progress to cancer in natural populations. If so, the benign neoplasms would serve as an indication of the pervasiveness of the less common and more ephemeral cancers to which they progress. Studies across the spectrum of living organisms need to be conducted with the knowledge that we still do not have a clear benchmark for the occurrence of infection-induced cancers in any species. Even in the most thoroughly studied species, *Homo sapiens*, the overall prevalence of infection-induced cancer relative to all cancer could be anywhere from 20 to nearly 100%. This uncertainty arises because demonstration of infectious causation of cancer can be extremely difficult, especially when experiments are constrained by ethical and logistical considerations, and because the discovery of a non-infectious cause of cancer (e.g. tobacco smoke for lung cancer) does not rule out a causal contribution by an infectious agent. The first step for any species is finding an association between an infectious agent and a neoplasm. This association then needs to be evaluated, experimentally if possible, to assess whether the association indicates infectious causation and whether it progresses to cancer.

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