Cancer in wildlife: patterns of emergence

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Abstract | Cancer is ubiquitous in wildlife, affecting animals from bivalves to pachyderms and cetaceans. Reports of increasing frequency demonstrate that neoplasia is associated with substantial mortality in wildlife species. Anthropogenic activities and global weather changes are shaping new geographical limitations for many species, and alterations in living niches are associated with visible examples of genetic bottlenecks, toxin exposures, oncogenic pathogens, stress and immunosuppression, which can all contribute to cancers in wild species. Nations that devote resources to monitoring the health of wildlife often do so for human-centric reasons, including for the prediction of the potential for zoonotic disease, shared contaminants, chemicals and medications, and for observing the effect of exposure from crowding and loss of habitat. Given the increasing human footprint on land and in the sea, wildlife conservation should also become a more important motivating factor. Greater attention to the patterns of the emergence of wildlife cancer is imperative because growing numbers of species are existing at the interface between humans and the environment, making wildlife sentinels for both animal and human health. Therefore, monitoring wildlife cancers could offer interesting and novel insights into potentially unique non-age-related mechanisms of carcinogenesis across species.

The prevalence and variety of neoplastic diseases in wildlife are likely under-reported and are certainly understudied. Phenotypically similar forms of cancer exist across disparate species, underscoring the universal nature of cancer. A better understanding of both shared and unique aspects of cancer across wildlife species will undoubtedly shed light on potential mechanisms of oncogenesis. This comparison may even untangle some of the complexities regarding human cancer. Certainly, the large number of animal populations inhabiting distinct environments provide many natural 'experiments' such as that examined by Møller et al.[1], where cancer in a broad spectrum of bird species was shown to be tightly linked to the natural history and immunity of each species. Wild animals are profoundly influenced not only by selective pressures within their own species but also by their interface with humans. Information gained from monitoring diseases in free-ranging wildlife is of paramount importance, as we often occupy the same habitat. A growing human population places increasing demand on many shared resources. For example, globally, water resources are being limited by both access (human development) and a shrinking supply, so that the demand for adequate wastewater treatment will become increasingly important over the coming decades (FIG. 1). Furthermore, an increasing human population will usher in global changes that wildlife already face, such as crowding, mixing of subpopulations and increased environmental complexity. How these changes modulate the pathophysiology of cancer in wildlife species will also be extremely important to identify, as the implications for wildlife and human health are likely to be similar.

This Review describes some of the cancers affecting wildlife populations and what we know about the role of infectious agents, environmental toxins and reproductive or metabolic disturbances in contributing to the oncogenic processes (TABLE 1). Although neoplasia occurs in nearly all multicellular organisms[2], this Review primarily addresses instances of such disease in wild vertebrates. We also describe new examples of spontaneous cancers that have been identified in both captive and wildlife species since the potential impact of cancer on wildlife was first reviewed by McAloose and Newton[3]. Such diseases are an increasing concern for protected and endangered species and are a unique frame of reference for pressures that drive neoplastic transformation.

Pathogen-driven cancer

Infections in humans are considered causal for approximately 15% of the global cancer burden[2]. Owing to a lack of vigilant screening, which is often applied to human cancer, the number of wildlife cancers caused by infection is not known, nor has it been possible to determine whether the number of cancers associated with pathogens is similar in humans and wildlife. However, there

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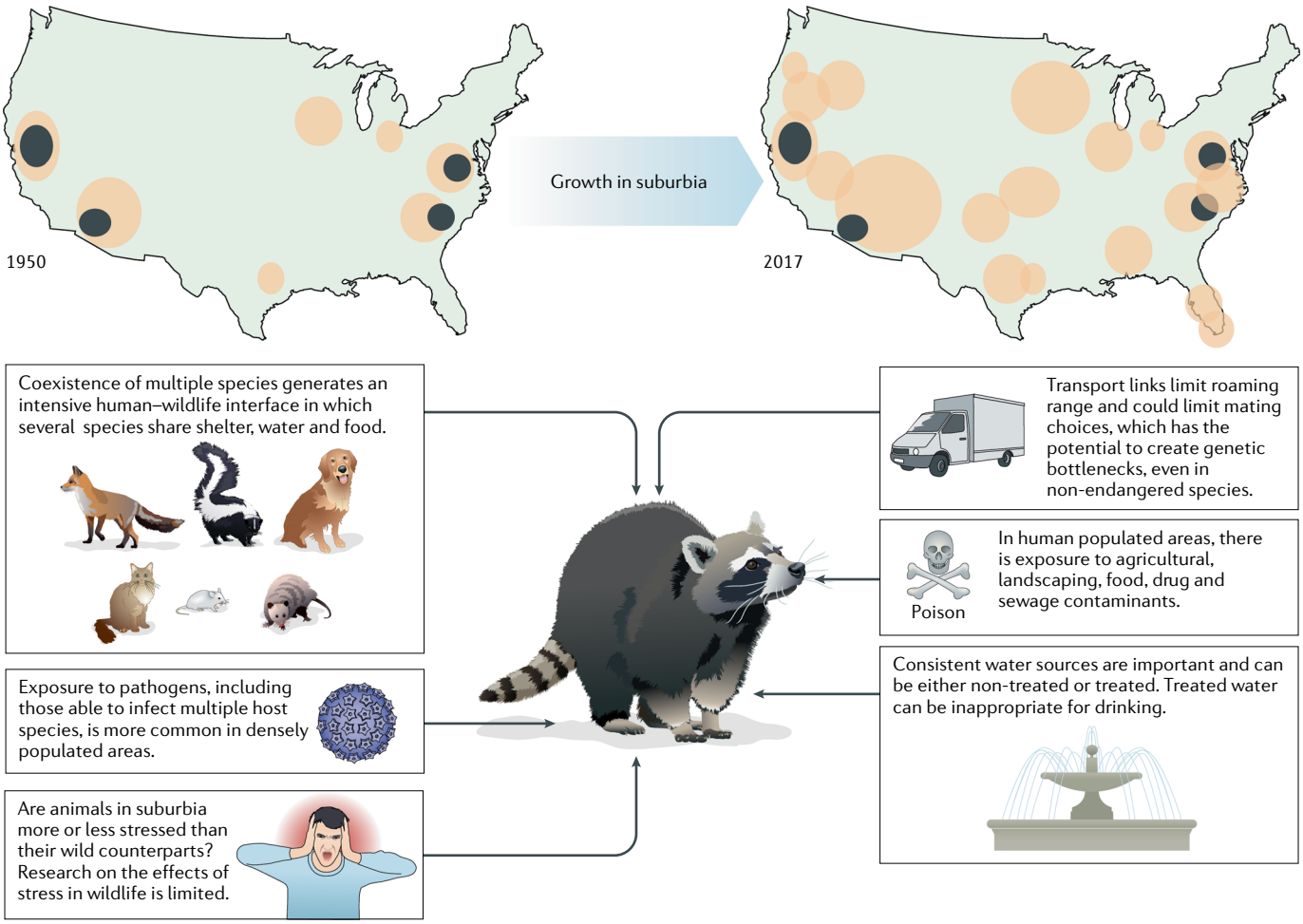


Fig. 1 | **Oncogenic pressures at the human–animal interface using suburbia as an example.** Suburbs or residential areas are an expanding and unique living niche for wildlife. The figure shows the USA, where there has been a large and rapid growth in suburbia from the 1950s until today. The pale orange areas depict the expansion from major and smaller cities (grey). Raccoons, foxes, opossums and other mesopredators are much denser in population in suburban areas than in any rural or wild landscape. Animals that live in suburbia share food and water sources, such as domestic waste, cat food, fountains, sprinklers and feeders, with domestic animals and humans. Access to food and water is dictated by man-made structures, such as roads, buildings or railways, that restrict natural roaming ranges. For example, raccoons in the wilderness range up to 12,000 acres, whereas in suburbia in the USA, their range is only 3–4 blocks (the smallest area that is surrounded by streets). Given these limitations in roaming, there is considerable potential for creating genetic islands or bottlenecks, even in this non-endangered species. Higher population densities (of animals and humans) can support pathogen exposure, stress, pathogen load and cross-species transmission. Pathogens that can jump species, for example, canine parvovirus and canine distemper virus, could hypothetically be very successful in this intensive housing situation. Infection with both of these pathogens can result in immunosuppression in the host and could, therefore, alter lifetime immunity to oncogenic pathogens.

is sound reasoning to hypothesize that wildlife might harbour an even greater burden of pathogen-associated cancer as a result of multiple factors, such as a lack of prophylaxis, higher burden of infectious disease, chronic stress and crowding. Despite research lagging in the identification of oncogenic microorganisms (viruses, bacteria or parasites) in domestic and non-domestic animal species, recent molecular strategies have been successful in revealing not only microorganism association with certain wildlife cancers but also interesting and novel patterns of pathogenesis.

Paradoxically, cancers associated with microorganisms were first described in animals, and subsequent research led the way for recognition of this common mechanism of oncogenesis in humans[4]. Studies of cancers with an infectious origin have provided insights into cell proliferation and pathogen lifestyles that challenged pre-existing dogmas of pathogen-driven diseases (BOX 1); however, proving transformation by a pathogen in the laboratory versus a naturally occurring infection in the wild is quite distinct[5,6]. Therefore, uncovering pathogen-driven oncogenesis is challenging, even with extensive epidemiology and considerable research investment. For example, documenting the role of human papillomavirus (PV) in cervical cancer beyond a reasonable doubt or as a necessary cause took almost 50 years of epidemiology, seroepidemiology, molecular investigation and pathogenesis studies[7]. Despite the sizeable challenges in demonstrating causality in wildlife disease, these types of studies provide valuable insight for global health.

Canine distemper virus
An enveloped single-stranded negative RNA virus of the family *Paramyxoviridae* related to the viruses that cause measles in humans. It is also referred to as carnivore distemper virus, as it causes systemic disease in a wide variety of animal families, including domestic and wild dogs, coyotes, foxes, pandas, wolves, ferrets, skunks, raccoons, large cats and pinnipeds.

Table 1 | **Notable examples of neoplasia in wildlife species and their associated aetiologies**

Species	Cancer type	Aetiology	Refs
Atlantic salmon (*Salmo salar*)	Leiomyosarcoma	Retrovirus (unknown species)	7,9,75
Beluga whale (*Delphinapterus leucas*)	Gastric papilloma	Organochlorine intoxication	90
Bighorn sheep (*Ovis canadensis*)	Nasal carcinoma and myxomatous fibromas	Unknown; suspected retrovirus	69,70
Bottlenose dolphin (*Tursiops truncatus*)	Lymphoma	Dioxins suspected	100
California sea lion (*Zalophus californianus*)	Urogenital carcinoma	Multifactorial; otarine herpesvirus 1 involvement; organochlorines, polyaromatic hydrocarbons and a genetic basis (loss of polymorphism at a single locus, the *HPSE2* gene) also suspected	49–56
Santa Catalina island fox (*Urocyon littoralis catalinae*)	Ceruminous gland tumours	*Otodectes cynotis* (ear mite; through chronic inflammation and epithelial hyperplasia)	14
Deer (*Capreolus* sp., *Odocoileus* sp. and *Ranger* sp.)	Cutaneous fibropapillomas and cutaneous fibromas	Deltapapillomavirus	46
Fallow deer (*Dama dama*)	Endometrial carcinoma, cervical carcinoma and leiomyomas	Presumed continuous hormonal stimulation in unbred geriatric individuals free from predation	D.A., unpublished data
Giraffe (*Giraffa camelopardalis*)	Fibropapillomas (sarcoids)	Deltapapillomavirus	46
Jaguar (*Panthera onca*)	Ovarian, endometrial and mammary carcinoma	Unknown pathogenesis: presumably heritable mutations	120–124
Koala (*Phascolarctos cinereus*)	Lymphoma	Koala retrovirus B	71–74
Mountain gorilla (*Gorilla beringei*)	B cell lymphoma	Gibbon lymphocryptovirus 1	64
Northern fulmar (*Fulmarus glacialis*)	Mesenchymal neoplasm	Papillomavirus	47
Raccoon (*Procyon lotor*)	Brain neuroglial tumours	Raccoon polyomavirus	24,25,29,30
Ring-necked pheasant (*Phasianus colchicus*)	Intestinal sarcoma (undetermined cell of origin)	Chronic typhlocolitis associated with *Heterakis gallinarum* (a nematode)	16
Sea turtle (All species; most prevalent in *Chelonia mydas*)	Fibropapillomas	Suspected alphaherpesvirus	57–63
Soft-shelled clam (*Mya arenaria*)	Clam leukaemia	Transmission of clonal malignant haemocytes	152
South American fur seal (*Arctocephalus australis*)	Urogenital carcinoma	Otarine herpesvirus 1	53
Tapir (*Tapirus* sp.)	Fibropapillomas (sarcoids)	Deltapapillomavirus	46
Tasmanian devil (*Sarcophilus harrisii*)	Devil facial tumour disease	Clonal transmissible tumour cells	146–151
Walleye fish (*Sander vitreus*)	Dermal sarcoma	Epsilon retrovirus	76,77
Water buffalo (*Bubalus arnee*)	Fibropapillomas (sarcoids)	Deltapapillomavirus	46
West Indian manatee (*Trichechus manatus*)	Uterine leiomyomas	Unknown	133
Western barred bandicoot (*Perameles bougainville*)	Papillomas and squamous cell carcinoma	Bandicoot papillomatosis carcinomatosis virus type 1	42,43
White rhinoceros (*Ceratotherium simum*) and Indian rhinoceros (*Rhinoceros unicornis*)	Uterine leiomyomas	Presumed continuous hormonal stimulation in unbred captive individuals	129,130
White suckers (*Catostomus commersonii*)	Hepatic and biliary neoplasia	EDCs suspected	101
White-tailed deer (*Odocoileus virginianus*)	Urothelial carcinoma	Unknown	157
Wolves, coyotes and jackals (*Canis* spp.)	Transmissible venereal tumour (oronasal and genital mucosa)	Clonal transmissible tumour cells	141–144
Zebra (*Equus* spp.)	Fibropapillomas (sarcoids)	Deltapapillomavirus	46

EDCs, endocrine-disrupting compounds; *HPSE2*, inactive heparanase 2.

There are multiple, non-mutually exclusive and potentially converging mechanisms by which pathogens can drive oncogenic transformation. These include chronic inflammation, with progression to hyperplasia and neoplasia; expression of viral proteins that orchestrate cell proliferation, cell death and/or metabolic pathways; and direct integration of the viral genome leading to mutagenesis. Examples of all these mechanisms occur among wildlife species.

Chronic inflammation to neoplasia

Chronic inflammatory responses as a result of pathogen infection can predispose a targeted tissue to cancer, and untreated persistent infections are common in wildlife[8]. This type of cellular transformation is considered to occur through a combination of DNA damage and pro-inflammatory factors[9]; however, this is likely to be an oversimplification. For example, genetic damage, exposure to carcinogens and chemokine expression during

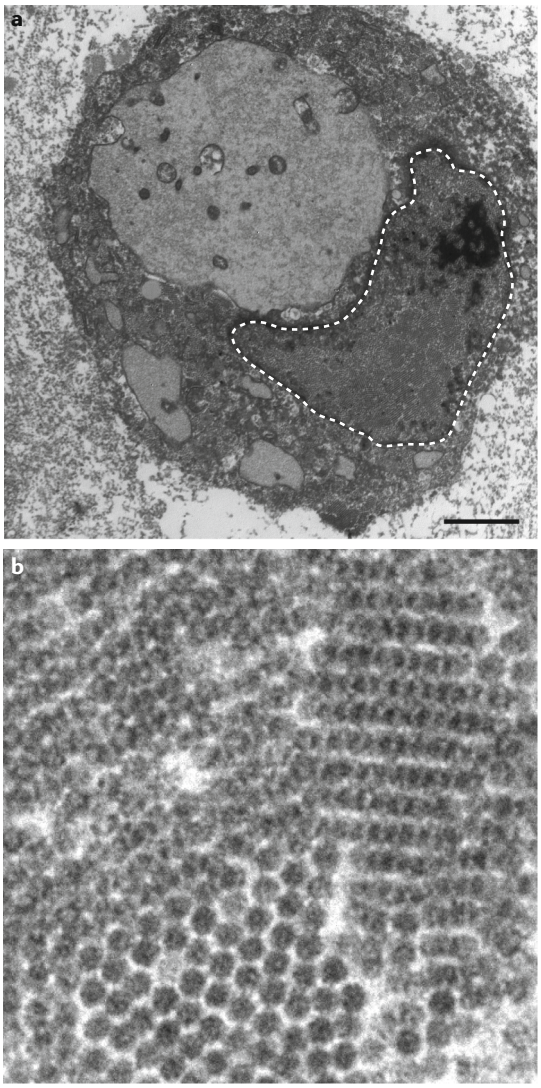
Box 1 | **Oncovirus–host co-evolution**

Viral taxonomists estimate that for most persistent oncogenic viruses, co-evolution with their host animal lineage has occurred slowly over millions of years. For example, papillomaviruses (PVs) are an ancient virus group containing 49 genera and over 300 virus species in animals ranging from fish to marine birds and mammals (http://pave.niaid.nih.gov/).

In the vast majority of PV infections, the infected host does not exhibit noticeable symptoms, but disruption of this apparently metastable coexistence can occur, for example, under conditions of immunosuppression. Unfortunately, a lack of widespread infection in healthy animals has limited our understanding of how persistent infections become oncogenic or have other potential sequelae. There is also no experimental model that can provide insights into the often decades-long metastable state of a potentially oncogenic viral infection.

Koch's postulates for establishing a relationship between a pathogen and a given disease are based upon the criteria that the pathogen should cause disease in all infected individuals and that the disease is not caused by other agents[168]. As PVs, polyomaviruses and herpesviruses typically infect the entire human population and cause cancer in, at most, only a small fraction of infected individuals, they cannot be explained by Koch's postulates. Cancer virology has instead utilized Hill's criteria for causation, whereby the more certain an association between a factor and an effect is, the greater the probability it is a causal relationship, an example of this being the finding that viral sequences are associated with particular forms of cancer[169]. Careful analysis of outbreaks and species-specific cancers can identify tumour-associated pathogens, and although we cannot infer causation lightly, they do provide insight into host susceptibility, the environment and the evolution of pathogens.

The image in part **a** shows the ultrastructure of a chondroblast surrounded by scant chondroid matrix from a seabird infected with an avian PV. In part **b**, a higher power magnification of part **a**, paracrystalline arrays of PV (virus diameter 46–48 nm) can be seen in the nucleus. Scale bar = 2 μm.



chronic gastritis in humans are all considered mechanisms for bacterial *Helicobacter*-associated gastric carcinoma and B cell lymphoma[10]. Yet, *H. pylori*-encoded cytotoxicity-associated immunodominant antigen (CagA) can directly manipulate host proliferation and apoptotic pathways[11,12]. Chronic gastritis associated with *Helicobacter* infection that results in adenocarcinoma has been reproduced under laboratory conditions in infected ferrets (*Mustela putorius furo*), gerbils (*Meriones unguiculatus*) and hamsters (*Mesocricetus auratus*), and there is some evidence to suggest that mucosa-associated lymphoid tissue (MALT) lymphoma is associated with *H. heilmannii* infection in big cats such as tigers (*Panthera tigris*) and cheetahs (*Acinonyx jubatus*)[13]. Taken together, the available data suggest that susceptibility to inflammation and subsequent neoplasia vary among different hosts as well as among different *Helicobacter* species.

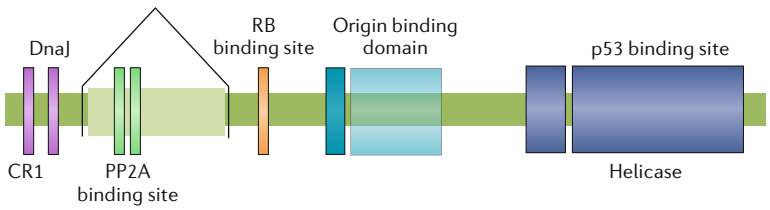
Wild animals commonly have a burden of macroparasites (such as helminths and arthropods). The consequences of infestation can be direct, such as tissue destruction, but chronic infestation can be associated with cancer. Inflammation associated with the ear mite (*Otodectes cynotis*) has been implicated in the development of ceruminous gland hyperplasia and carcinoma in feral, adult Santa Catalina Island foxes (*Urocyon littoralis catalinae*)[14]. This is an important discovery in the unique circumstance in which the fox population is isolated on a single island and can therefore be tracked and treated. Because these foxes are Near Threatened (International Union for Conservation of Nature (IUCN) Red List), a field trial was conducted to assess the impact of treatment of ceruminous gland hyperplasia with the pesticide acaricide, which kills ticks and mites[15]. Initially, these foxes had a 100% mite infestation rate, half of which developed ear tumours. Treatment significantly reduced hyperplasia compared with untreated controls[15]. The researchers proposed that the long-term presence of mites is associated with epithelial hyperplasia, and in support of causality, removal of the parasite burden resulted in reversal of tumour development. Ultimately, these findings have altered management decisions,

Box 2 | **Merkel cell polyomavirus**

Merkel cell polyomavirus (MCPyV) is a common, almost universal infection in humans[170]. In rare cases, MCPyV is found to be the cause of a very aggressive form of skin cancer called Merkel cell carcinoma, where viral DNA is integrated into the tumour genome[27].

Approximately half of the MCPyV genome encodes structural viral proteins (VPs), and the other half encodes viral tumour antigens (T antigens or T Ags). Among several established criteria for causality is the key finding that VP expression is uncoupled (absent) compared with the dysregulated or upregulated expression of T Ags. Expression of a T Ag alone is sufficient, in experimental models, to drive tumour formation[20]. Several viral T Ag–host protein interactions occur, among which are the binding and inhibition of the tumour suppressors RB, p53 and protein phosphatase 2A (PP2A) (see the figure).

Analyses of the genomes of polyomaviral-associated versus non-viral-associated Merkel cell tumours have demonstrated that virus-negative tumours have a high burden of somatic gene mutations, whereas MCPyV-positive tumours have few. Presumably, the T Ags of MCPyV are capable of efficiently hijacking cellular processes to drive tumorigenesis in a manner that is comparable to inducing somatic gene alterations[23].



with any fox caught during routine trapping now being treated with acaricide.

In another example, ring-necked pheasants (*Phasianus colchicus*) with intestinal nematode infestation (*Heterakis* spp.) frequently develop severe nodular typhlocolitis, a chronic inflammatory condition that can develop into local and metastatic sarcomas[16]. These have been primarily identified in captive pheasants, suggesting contributions from stress, higher parasite loads and altered diets[16].

Direct cell transformation

In tissue culture, cellular transformation can be achieved by disruption of a limited number of cellular regulatory pathways[17]. Some viruses encode proteins that can target regulatory pathways and disrupt cell cycle, metabolic or apoptotic control, which can all contribute to transformation. There are commonalities among oncogenic pathogens that directly transform cells and that have served as a guide for oncogenic viral discovery. These commonalities are that pathogens associated with cancer have been persistent (usually lifelong) infections, regardless of their host species; transformation is rare as a sequela of infection compared with the prevalence of infected hosts and is most likely to occur in immunosuppressed animals; and either tissue stem cells are the initial target cells of oncogenic viruses or 'stemness' results from infection. However, these are generalizations and not limited, among pathogens, to viruses, although viruses form the vast majority of oncogenic pathogens. The causal oncogenic viral families that have emerged, in all animals and humans, include *Papillomaviridae*, *Polyomaviridae*, *Retroviridae* and *Herpesviridae*. Reduced genetic diversity that arises when a new population is formed from a small number of individuals from a much larger population (known as the founder effect) appears to have implications for susceptibility to pathogens that can result in neoplasia. For example, more highly inbred California sea lions (*Zalophus californianus*) are susceptible to bacterial infection, helminthiasis, intoxication by harmful algal blooms and neoplasia; among these susceptibilities, the highest correlation was observed between the degree of genetic relatedness and the presence of urogenital carcinoma[18]. However, it should be noted that the overriding mechanism for urogenital carcinogenesis in California sea lions is not yet known, and development of these tumours could involve virus infection, environmental toxins or a combination of these and other factors.

Polyomaviruses and papillomaviruses. Polyomavirus (PyV) infections appear nearly ubiquitous in wildlife and have been identified in mammals, invertebrates, fish, amphibians, reptiles and birds[19]. Well-studied PyVs include the simian virus 40 (SV40) and murine PyV in laboratory animals and Merkel cell PyV (MCPyV), JC PyV and BK PyV in humans[20,21]. All PyVs encode the potentially oncogenic tumour antigen (T antigen or T Ag) proteins, which have a pivotal function in both virus replication and control of the host cell cycle[19,21]. On the basis of experimental studies, many viruses in this family cause tumours in immunosuppressed animals, but the vast majority of naturally occurring infections are clinically silent, with exceedingly rare transformation[20,21]. Examples of tumours caused by PyV infection include Merkel cell skin carcinomas in humans[22,23] (BOX 2), brain tumours in wild raccoons (*Procyon lotor*)[24,25] and a variety of tumours in laboratory animal species[26–28].

Raccoon polyomavirus (RacPyV) associated with the occurrence of cancer was first reported in 2013 (REF.[24]). There is now strong evidence that RacPyV causes a series of recently identified, naturally occurring neuroglial tumours in raccoons. Tumours in raccoons are not common, but to date, 23 cases of tumours have been recorded on the West Coast of the USA and Canada[29]. It is unlikely that these tumours occurred before 2013, because necropsy, including evaluation of the brain, is commonly performed on raccoons in many diagnostic laboratories in the USA because they are known to carry rabies on the East Coast. In 3 years (2013–2016), the number of raccoons with tumours represented 15% of the total number of raccoons that had necropsies performed regionally (northern California, USA). The number is heavily biased because animals submitted for necropsy evaluation are more likely to have clinical signs referable to the neurological system and to be unafraid of humans but is notably high nonetheless in the context of the previous and fairly consistent screening by necropsy. The tumours are invariably found crossing the nasal–brain barrier and affecting the olfactory tract and frontal brain lobes[24]. RacPyV has been detectable in all the identified tumours to date and is present in high copy number as measured by both quantitative PCR and in situ hybridization[25,30]. Metastases occurred in only a single case, and virus was detectable in all neoplastic cells, within all metastatic foci. Primary cell culture studies suggest that the target cell of transformation is the multipotent neuroglial stem cells of the subventricular zone of the brain[30] (FIG. 2).

Transcriptome analyses have revealed that T Ags are highly expressed in these tumours, but structural genes

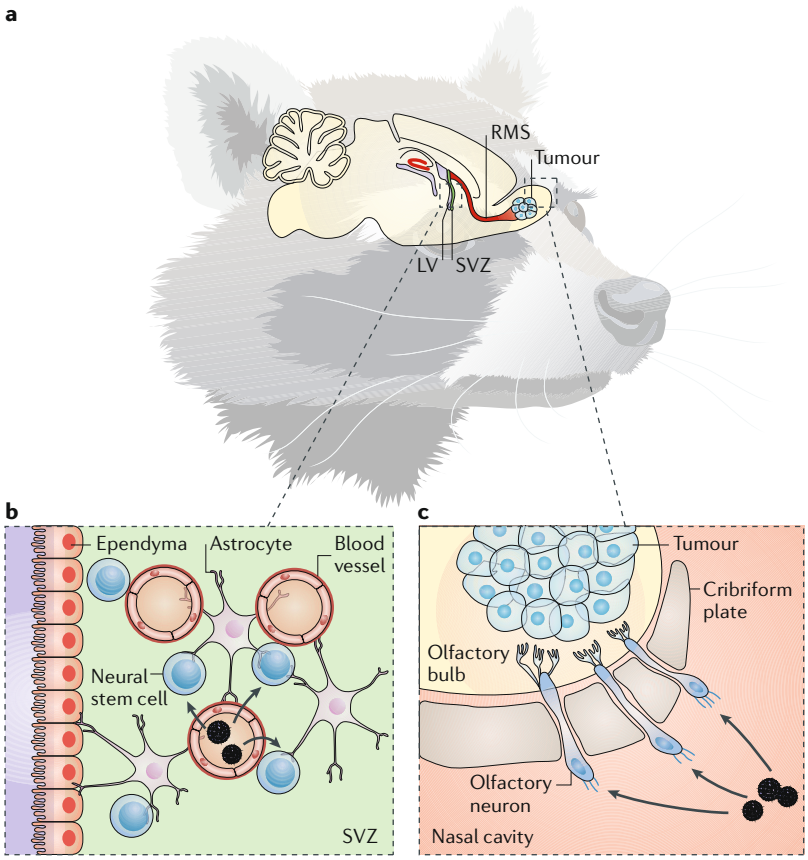


Fig. 2 | **Raccoon polyomavirus-induced cellular transformation. a** | Raccoon polyomavirus (RacPyV) transforms neural stem cells into neuroglial brain tumours along the rostral migratory stream (RMS) in the olfactory lobe. **b** | The route of entry for the virus into the host and the cellular events driving transformation are currently unknown. One possibility for the route of entry is through haematogenous spread of RacPyV into the neural stem cell niche of the subventricular zone (SVZ). **c** | Alternatively, airborne transmission may occur, with retrograde infection of olfactory nerves. Identifying how neural stem cells are infected will increase our understanding of the role tissue stem cells may play in persistent infections and neoplastic transformation. LV, lateral ventricle.

have exceptionally low expression[30]. This is highly relevant with regards to estimating viral causality because uncoupling of the oncogenic T Ag from capsid protein expression is a common prerequisite for transformation in known PyV-driven cancers[22]. In at least four of the raccoon tumours, RacPyV was episomal; therefore, exactly how capsid protein expression is suppressed is unknown, but the virome is both stable and abundant in the tumours analysed so far[25]. Among the many known PyV infections that have been identified in the animal kingdom, the reason why RacPyV infection in raccoons results in brain cancer is still enigmatic. Infections in raccoons, at least by serosurveillance, are widespread[29], but tumours have been detected only along the west coast of North America. Immunosuppression is very important in viral-induced human cancers[21], and it would be interesting to know whether affected raccoons were immunosuppressed either at the time of RacPyV infection or at another relevant timepoint during tumour progression. Possible mechanisms of immunosuppression range from co-infection(s) to a regional environmental toxin. Regardless, the association of brain cancer with RacPyV and its episomal status in neuroglial tumours highlight novel potential consequences of PyV infection.

Fibropapilloma
A condition characterized by the presence of proliferative benign neoplasms containing superficial epidermal and subjacent dermal tissue.

Although no other causal associations with cancer have been described, PyV infections have recently been detected in numerous wildlife species. The first carnivore PyV identified was extracted from a fibropapilloma on the tongue of a feral California sea lion[31,32]. In African great apes (chimps and gorillas), two new groups of PyVs were discovered that are most closely related to the oncogenic MCPyV, and ~30% (8/27) of the great ape populations tested carried detectable virus[33]. Wildlife-associated PyVs have also been identified in badgers[34], Weddell seals[35], sea otters[36], wild rodents[37], bats[38,39], penguins[40] and Black Sea bass[41]. Their relationship with cancer, if any, has not been uncovered.

PVs and PyVs are taxonomically distinct, but they share striking similarities in their viral lifestyles, including host persistence and their mechanisms of tumour induction. A demonstrative example of their close relationship is bandicoot papillomatosis carcinomatosis virus type 1 (BPCV1), which is a chimaera of structural and oncogenic elements of PyVs and PVs, respectively. The hybrid virus was discovered through its association with cutaneous hyperplasia and carcinomas in the Australian Western barred bandicoot (*Perameles bougainville*)[42]. A remarkable 57% of 127 captive and free-ranging Western barred bandicoots in the preliminary survey were affected with the hyperplasia and/or carcinoma syndrome[42,43]. The collective data suggest a causal relationship, but there is an unexpected anomaly in that the virus has not been detected in any clinically healthy individuals[42]. Given that PyVs and PVs are typically persistent, lifelong, innocuous infections widespread in the host species, it would be interesting to understand the recombination mechanism and to know whether BPCV1 persists in the host and, if so, in which cell type and bandicoot species. Alternatively, BPCV1 in the bandicoot may be a transient infection that can lead to transformation.

A sizeable number of 170 human PVs are currently recognized, and it is likely that all animals serve as hosts for a range of species-specific PVs. We largely assume, regardless of species, that PVs propagate exclusively in an epithelial niche. From a comparative standpoint to other types of virus, PVs can have a broader tissue tropism and host specificity[44,45]. Bovine deltapapillomavirus type 1 (BPV1) and BPV2, common in cattle, can also infect water buffalo, giraffe, tapirs, deer and zebras[44–46]. BPV1 and BPV2 can infect fibroblasts and can cause fibropapillomas[46]. Although little is known regarding recently identified avian and fish PVs, at least one avian PV (Fulmarus glacialis PV1 (FgPV1)) has been detected in mesenchymal cells of the northern fulmar (*Fulmarus glacialis*), a pelagic seabird[47].

Herpesviruses. Otarine (eared seals) herpesvirus type 1 (OtHV-1) is a gammaherpesvirus phylogenetically related to human herpesvirus 8 (HHV8; also known as Kaposi sarcoma herpesvirus (KSHV)), the causative agent of Kaposi sarcoma[48]. OtHV-1 may contribute to urogenital carcinomas in feral California sea lions[49–52] and has been detected in a single case of

urogenital carcinoma in a captive South American fur seal[53]. However, the criteria for causality remain limited to detection of the viral genome in tumour tissue. Like all persistent viruses, establishment of causality faces the obstacle that the virus is also detected in animals without cancer[54]. Environmental toxin exposure, a genetic basis and variation in hormone receptor expression are other factors that have also been identified as potential contributors to urogenital carcinoma occurrence in Californian sea lions[55,56].

Fibropapillomatosis found specifically in marine turtles is associated with variants of Chelonid alphaherpesvirus 5 (ChHV5)[57]. Dermal fibropapillomas and fibromas have been documented to various degrees in all marine turtle species, but the disease is most prevalent in green turtles (*Chelonia mydas*)[3,58]. Although most tumours appear benign, they can impair vision, obstruct the mouth or cloaca and impede swimming. Moreover, the formation of tumours in internal organs occurs in severe cases. Fibropapillomatosis is transmissible by experimental infection[59], suggesting that the associated herpesvirus plays a primary aetiological role; however, environmental cofactors have also been proposed to contribute[60–62]. Regardless of the role of the virus, ecology studies on ocean life have had to consider a new dimension in potential transmission routes because water immersion is such a uniquely shared space. Waterborne infection is possible, as herpesviruses can be stable in water[57], and ChHV5 DNA has been detected in marine leeches (genus *Ozobranchus*) in breeding grounds of the green turtle[63].

Infection of wild mountain gorillas with a specific strain of lymphocryptovirus 1 (GbbLCV-1) was recently discovered[64]. GbbLCV-1 is closely related to the human, oncogenic Epstein–Barr virus (EBV), thus explaining why previous reports detected ubiquitous EBV exposure, by serological assay, among gorillas[65]. Similar to EBV infection in humans, GbbLCV-1 primary infection occurs in infants, and latent infection was detected in peripheral white blood cells[64]. B cell lymphomas, a subset of which are caused by EBV infection in humans, were diagnosed in a single mountain gorilla within the group examined in this particular study, and GbbLCV-1 was detected by PCR in blood collected from this individual at the time of necropsy[64].

Viral integration

Both DNA and RNA viruses can disrupt the host genome by integration, but examples of integration causing cancer among wildlife are currently limited to retroviruses. Studies of transmissible exogenous retroviruses have led to the recognition that all animals carry a large number of integrated endogenous retroviruses (ERVs)[66]. ERVs make up 5% and 4.7% of the mouse and human genome, respectively, and many of these so-called fossil viruses retain transcriptional and (at least in mice) replication capacity[67]. Given the ability of ERVs to move within the genome, distinguishing them from exogenous viruses and identifying their potential contributions to cancer are vital. There are important examples of studies in wildlife species that have achieved a requisite combination of epidemiological, transmission and in vitro data supporting causality.

Jaagsiekte sheep retrovirus (JSRV) and enzootic nasal tumour virus (ENTV) are the causative agents of pulmonary and nasal carcinomas, respectively, in domestic sheep and goats[68]. Feral bighorn sheep spontaneously develop similar paranasal sinus tumours, and histological features and geographic clustering support an infectious aetiology[69,70]. The most convincing evidence for an infectious origin is that the tumours in bighorn sheep are transmissible through inoculation with a cell-free filtrate: within 18 months of inoculation, one of four bighorn sheep and, intriguingly, four of four domestic sheep developed tumours within ethmoid sinuses or nasal conchae[69]. However, PCR and immunohistochemistry failed to demonstrate the presence of ENTV or JSRV, so metagenomics, deep-sequencing and cell culture studies designed to uncover a viral cause are ongoing (S. L. Quackenbush, personal communication).

Gammaretroviruses (KoRVs) found in koalas (*Phascolarctos cinereus*) are in a unique state of evolutionary adaptation. At least three variants have been identified, KoRV-A, KoRV-B and KoRV-J, each with varying associations with cancer[71]. KoRV-A is endogenous and is rarely associated with cancer, while KoRV-B (a presently exogenous virus) is associated with lymphoma[72]. The lack of genetic diversity in the KoRV-A endogenous virus appears to be associated with its inability to induce tumours[73]. Whether KoRV-J is also associated with increased cancer incidence is still being investigated. Therefore, KoRVs might provide the opportunity to witness a retrovirus becoming embedded in the genome of its host, a phenomenon that has been only theorized in other species[74].

Herpesviridae, *Papillomaviridae* and *Retroviridae* are all associated with the development of tumours in fish, but retroviruses are particularly well represented, with suggested involvement in 13 different piscine tumours[75]. Compelling evidence (in the form of sequencing, isolation and transmission studies) for a causal role exists only for a few of these. Walleye dermal sarcoma virus (WDSV), an exogenous retrovirus that causes dermal sarcoma in walleye (*Sander vitreus*), encodes a cyclin-C-like homologue postulated to interfere with cell cycle regulation[76,77]. Experimental transmission with cell-free tumour filtrates has been successful by numerous transmission routes (including intramuscular, oral and topical)[78] and has expanded the potential host range of the virus to other fish species[79]. The study of fish oncogenic retroviruses has an interesting and potentially exploitable angle on host tumour immunity. Many of these retroviral-associated fish tumours develop seasonally, and their growth is linked to temperature-driven changes in the immune response of these fish (which are ectotherms), providing potentially valuable models of tumour regression[80].

Toxin-related cancer

Wildlife populations encounter numerous anthropogenic pollutants, including industrial and agricultural waste, radiation and, increasingly, pharmaceutical contaminants[81,82]. These pollutants coexist with biota in a complex ecosystem. As we move towards a more intensive agrarian and civic lifestyle worldwide, concentrated

Cloaca
The caudal opening in reptiles, amphibians and birds used for digestive, reproductive and urinary tract excretions.

Retroviruses
RNA viruses that utilize reverse transcriptase to generate a complementary DNA strand from the RNA template, which is then integrated into the genome of the infected cell.

Nasal conchae
Also called nasal turbinates. Convoluted, curled thin bones covered by respiratory epithelium that protrude into the breathing passage of animals.

Ectotherms
Animals dependent on exogenous heat to maintain body temperature.

Agrarian
Relating to farmland, agriculture or the cultivation of land for crops.

exposures are more likely for all. Ageing infrastructure, a global lack of governmental priority and regional water shortages may see the spread of environmental contaminants into water bodies or groundwater, affecting not only humans but also wildlife. Thus, studying the impact of environmental toxicology on cancer in wildlife has the potential not only to identify causal relationships that may affect humans but also to compare affected versus resistant species to identify evolutionary strategies inhibiting oncogenesis. Wildlife now frequently exist within changing environments, where large regions of mixed use (industrial, agricultural and residential) are increasingly becoming divided into more focused microenvironments, which reduce the ecosystem complexity and biodiversity. How this change will affect cancer incidence and how it relates to concentrated environmental pollution highlight the importance of disease surveillance in wild fauna.

Pollution may affect the cancer prevalence across wildlife species by diverse means. Historically, emphasis has been placed on the direct roles of xenobiotics or radiation-inducing somatic mutations that disrupt oncogenes or tumour suppressor genes[83]. While these are undoubtedly important, with mounting cases of documented contribution to wildlife cancer, these are perhaps over-represented because they are the easiest to identify as causal[84–86].

Organochlorines and cancer

Beginning in the 1980s, hundreds of stranded California sea lions have been examined by the marine stranding network[55]. These animals display a strikingly high prevalence of metastatic urogenital carcinomas, with up to 26% of adults having these tumours[55]. This aggressive and metastatic tumour appears to arise from the cervix and vagina in females and from the penis, prepuce and urethra in males. It exhibits similarities to human cervical intraepithelial neoplasia (CIN), with lesions that resemble human CIN grades I to III[55,87,88]. Organochlorines (OCs) and polycyclic aromatic hydrocarbons (PAHs) are putative endocrine disrupting compounds (EDCs) that have both been associated with the development of these tumours[89]. While the mechanism of cancer formation in these animals remains complex (including potential contribution from herpesvirus infection), OCs remain relevant as potential factors, as they are environmentally persistent molecules that bioaccumulate and biomagnify within predators[90].

Additional evidence for a contributory role of OCs in wildlife cancer can be found within beluga whales (*Delphinapterus leucas*) of the St. Lawrence Estuary, Quebec, Canada[3,90]. Over half of all cancers identified worldwide in toothed whales occur within this isolated population of approximately 900 beluga whales[90]. Cancers are most often of gastrointestinal origin, which is important given the whales propensity to feed within the benthic zone, which is associated with contaminated sediment[90]. While OCs have largely been banned in the USA since the 1980s, their environmental persistence, particularly in aquatic sediment, remains a threat to wildlife[91]. Furthermore, in many countries, OCs are continually used as pesticides owing to their low cost and efficacy. Sediment containing high levels of OCs from regional runoff is often identified within the gastric contents of beluga whales suffering from these malignancies[90]. These findings are of particular interest as many scientists have linked OC exposure to gastric cancer in humans[92,93]. Accumulated OCs and PAHs in sediment have also been associated with increased liver and skin tumours in a variety of fish, including English sole, European flounder and brown bullhead[90,94]. Identified and proposed mechanisms of carcinogenesis from OCs and PAHs are shown in FIG. 3.

Endocrine disrupting compounds

EDCs may mimic vertebrate sex hormones, functioning as either an agonist or antagonist within a particular hormonal pathway, or may alter hormonal action through perturbations in hormone production, receptor binding or metabolism[95]. The World Health Organization (WHO) has recognized EDCs as a widespread environmental contaminant owing to their multiple transmission routes — ingestion, inhalation, *trans*-dermal contact and *trans*-placental spread[96]. It has designated EDCs as a global emerging issue, with concern over the effects of these compounds on fertility, birth defects and cancer formation. The strongest link between EDCs and human cancer has been demonstrated with breast cancer, but potential involvement of biologically active EDCs in both male and female reproductive tumours is also a concern[97].

Wildlife encounter EDCs in much the same way that humans do — through ingestion, inhalation or skin contact. They are exposed to widely varying amounts of EDCs, and documentation of regional variation is important because, at nanomolar concentrations, EDCs primarily act through binding of nuclear receptors, but at millimolar concentrations, they may affect cell behaviour through epigenetic disruption[98]. EDCs implicated in wildlife cancer include dioxins, which are associated with an increasing prevalence of non-Hodgkin lymphoma in humans[99]. Dioxins have been detected from blubber and liver tissue in a single case of naturally occurring hepatosplenic lymphoma in a bottlenose dolphin and can drive dolphin lymphocyte proliferation in vitro[100]. In addition, examination of white suckers, a freshwater fish species in Lake Michigan tributaries, also indicates increased hepatic tumour prevalence associated with EDC levels[101].

Of increasing interest is the role of epigenetic disruption caused by EDCs. Indeed, this is now viewed as one possible explanation for their persistent biological effects. As endocrine hormonal mimics, EDCs principally act through binding of nuclear receptors, such as the oestrogen, androgen or thyroid receptors, to drive gene transcription[102]. Nuclear receptor activation may increase or decrease expression of key epigenetic pathways, including expression of DNA methyltransferases (DNMTs) and genes involved in the conversion of 5-methylcytosine (5-mC; such as tet methylcytosine dioxygenase 1 (TET1) and TET2) and in histone modifications (such as histone acetyltransferase KAT2A (also known as GCN5) and histone deacetylase 1 (HDAC1))[103,104]. Both nuclear receptors and EDCs may

Xenobiotics
Any substance (synthetic or natural) that is not naturally present in the body of an organism.

Endocrine disrupting compounds
(EDCs). A broad category of mostly man-made substances that are present in pesticides, plastics, personal care products, metals and pharmaceuticals, among many other items, which result in altered hormonal activity via agonistic and antagonistic receptor binding.

Bioaccumulate
When a substance becomes concentrated within the body of a living thing. If the source of the substance is from water, this is specifically referred to as bioconcentration.

Biomagnify
The increasing concentration of a substance within the tissues of an organism acquired through predatory acquisition (a food chain).

Benthic zone
The lowest ecological regions of a body of water, such as the sediment surface.

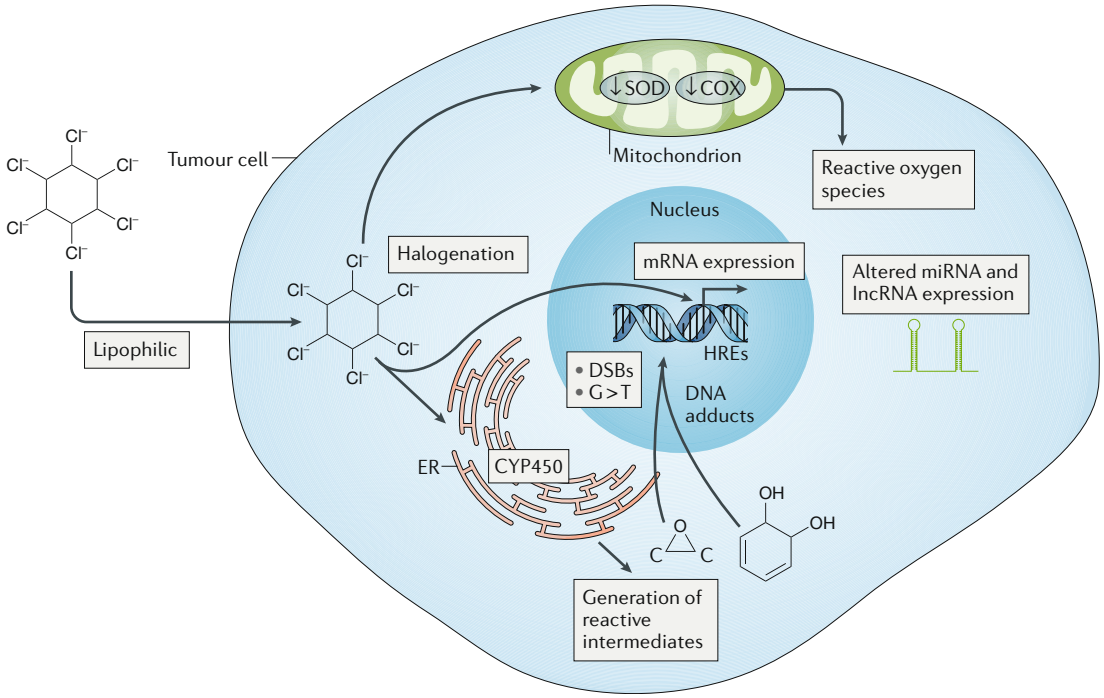


Fig. 3 | **Toxin-mediated oncogenesis.** This schematic depicts the molecular mechanisms of carcinogenesis induced by environmental contaminants. Organochlorines (OCs), polycyclic aromatic hydrocarbons (PAHs) and many endocrine disrupting compounds (EDCs) are lipophilic and, thus, are easily absorbed across the plasma membrane of cells[171]. OCs and PAHs may directly damage biomolecules, but most require bioconjugation by the cytochrome P450 (CYP450) system to generate reactive intermediates[172]. These are then capable of inducing DNA damage, including G > T transversions during DNA replication characteristic of some PAHs[173,174]. OCs and EDCs alter mitochondrial function, decreasing the activity of cytochrome *c* oxidase (COX) subunits and superoxide dismutase (SOD), leading to reactive oxygen species production and cellular damage[175]. Additionally, many of these compounds are hormonal mimics, resulting in altered gene expression[176]. Finally, many EDCs have been shown to modulate the expression of regulatory long non-coding RNAs (lncRNAs) and microRNAs (miRNAs) both in vitro and in vivo, including several candidate oncomiRs (miRNAs associated with cancer)[177]. DSBs, double-strand breaks; ER, endoplasmic reticulum; HREs, hormonal response elements.

regulate non-coding RNA expression, including long non-coding RNA, such as HOX transcript antisense RNA (HOTAIR), which is implicated in the development and progression of human cancers[105,106]. This complex interplay explains in part why one would expect EDCs to alter the epigenetic environment of a cell, potentially promoting carcinogenesis, but mechanistic studies in specific cancers are still lacking[107]. As these pathways are highly conserved across mammals, more research effort should be funded to evaluate the impact of epigenetic alterations on oncogenesis in environmental contaminant-associated wildlife disease. Studies that may be difficult to perform in disparate human populations may be easily achieved through looking at relative population bottlenecks in wildlife, such as the beluga.

It is unlikely that environmental contaminants function solely as mutagens within cancer development; rather, they operate through multiple mechanisms. One such mechanism may be immunosuppression. While research into environmental toxicants often centres on their non-communicable disease status, it is a mistake to dissociate them from any impact on the host immune system or potential role in the acquisition of infectious disease. Through either direct or indirect means (whereby increased organismal energy expenditure must be spent to overcome the deleterious effects of pollution), environmental toxins may predispose animals to infection by oncogenic pathogens (viral, bacterial or parasitic). Many of the same compounds that are associated with tumour formation in humans and wildlife, such as OCs (including polychlorinated biphenyls (PCBs)), dioxins and other EDCs, may be immunosuppressive or alter the immune reaction to infectious disease[108,109]. Furthermore, environmental pollutants likely act throughout cancer initiation, promotion and progression to assert changes in biological function in addition to increasing genomic stress. A zebrafish model indicates that the OC pentachlorophenol may produce Warburg-like effects by interfering with oxidative phosphorylation in cells, mimicking the altered cellular metabolism commonly identified in human tumours[110].

Reproduction-related cancers

The remarkable proliferative capacity of the reproductive tract makes it a common site for cancer, and this susceptibility creates risks beyond the overall fitness of the animal, such as impaired fecundity. Poaching, habitat destruction, competition for resources with humans and invasive species play a more evident role in the decline of populations. However, reduced populations are more susceptible to any additional negative factors, and decreased fecundity due to neoplasias affecting the

reproductive system may have increased impact for small populations. Smaller populations of free-ranging animals replicate, to some degree, the limitations of zoo populations. Captive animals receive medical treatment, are on standardized diets and are held in high population densities, and their reproduction is often controlled medically or by separation; however, increasingly, wild populations are being more individually managed than in the past, making the differences between wild populations and captive animals less disparate.

Limited genetic diversity in small gene pools can lead to decreased fitness in populations but can also allow the rapid increase in prevalence of deleterious genes[111]. Small populations can also limit breeding opportunities, leading to abnormal social structures, fewer pregnancies, as well as pregnancies that occur later in the animal's life, and a corresponding decrease in overall reproductive health[112,113]. The concept of evolutionary mismatch provides a model for these types of population effects and can be likened to the neoplastic diseases associated with nulliparity in women[114,115]. Many fragmented populations are also exposed to environments contaminated with toxins affecting reproduction, making it difficult to tease out the relative impact each factor might have. Furthermore, rates of potentially cancer-causing pathogen transmission might be anticipated to be different between smaller, denser populations and larger, free-ranging populations. There might also be a greater exposure to zoonotic agents as humans impinge on these populations.

An example of the effects of limited genetic diversity is seen in the Florida panther (*Puma concolor coryi*), an Endangered (U.S. Fish and Wildlife Service Endangered Species) and inbred species, with one study showing that 11 of 17 (65%) individuals had cryptorchidism[116]. Cryptorchidism is a highly heritable trait that is also associated with exposure to endocrine disruptors, such as 1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene (p,p'-DDE), a breakdown product of dichlorodiphenyltrichloroethane (DDT), mercury and PCBs[117]. In addition to the negative effects on spermatogenesis, cryptorchidism is linked to the development of seminomas and Sertoli cell tumours, although no testicular cancer has been specifically identified in the limited surveys so far carried out on Florida panthers[116,118]. A similar high rate of cryptorchidism has been reported in a population of Sitka black-tailed deer (*Odocoileus hemionus sitkensis*) restricted geographically to Kodiak Island (Alaska, USA), although reproductive system cancers were also not identified in this limited observational study[119].

A Near Threatened (IUCN Red List) species, the jaguar (*Panthera onca*), whose population is carefully managed in captivity, has shown an alarmingly high incidence of ovarian carcinoma in USA captive populations, leading to death or euthanasia[120–124]. These findings are reminiscent of women with mutations in *BRCA1* or *BRCA2* genes[125], and although a large number of candidate genes have now been found in jaguars, further analysis will be required to identify specific mutations in the genes correlating with tumorigenesis[123]. Similar cancers have been only anecdotally reported in free-ranging jaguars, highlighting the challenges of such investigations in the field and the value of zoo collections in better understanding the interactions of genetics, environment and disease. Furthermore, while genetic analyses are possible from small samples of skin, blood, hair or even faeces, substantial political impediments to sharing biological materials across international borders make it difficult or impossible to effectively collaborate with conservation scientists in countries where these species are free-ranging. Laws intended to protect endangered species can often make the science required to effect such protection unfeasible[126].

A more subtle effect of less frequent pregnancy is a reduction in future fertility, an increasingly recognized phenomenon of evolutionary mismatch seen in captive populations of wild mammals and often described as 'use it or lose it'[115,127]. Hormonal stimulation, particularly by oestrogen, can produce marked proliferative responses from the uterine, cervical, vaginal and mammary epithelium and smooth muscle[128]. Such stimulation would be infrequent in the wild, as females would become pregnant on their first estrous cycle, spend a considerable time span being pregnant or lactating and would then become pregnant again shortly after they began to cycle again. One study of the reproductive pathology of white rhinoceros estimates that a free-ranging female would have 30–90 estrous cycles in a typical lifetime, with the majority of its adult lifespan spent in lactation or pregnancy[129]. However, females held in captivity in a non-reproductive state (that is, separated from a fertile male) would experience greater than 300 cycles, exposing the reproductive tract to an oestrogen-rich, proliferative hormonal milieu up to ten times more frequently. This leads to progressively decreased fertility and an increase in proliferative and neoplastic diseases, collectively described as asymmetric reproductive ageing[129] (FIG. 4).

An example highlighting how pregnancy can provide a natural protective mechanism against asymmetric reproductive ageing processes is the observation that leiomyomas and cystic endometrial hyperplasia have been reported in nearly all nulliparous captive white rhinos yet are very rare in multiparous reproductively active animals[129]. This scenario is poignantly demonstrated by the critically endangered northern white rhino (*Ceratotherium simum cottoni*), in which such lesions have been described in nearly all remaining females, making this species functionally extinct[129]. A similar prevalence of these lesions has also been reported in the Indian rhinoceros (*Rhinoceros unicornis*)[130]. Captive, aged chimpanzees, largely kept in non-reproductive conditions, have a leiomyoma incidence of 40–62% (4/10 in one study and 20/32 in another)[131,132], yet the number in wild populations has not been accurately estimated. In addition to environmental toxins, the incidence of reproductive system cancers in manatees may also be associated with increasing urban encroachment and fragmentation of their range, leading to isolation of individuals and difficulty in finding mates[133]. The continued monitoring of a wild population of mountain gorillas in central Africa provides one of the few opportunities to compare free-ranging and captive populations: interestingly, no leiomyomas have been

Evolutionary mismatch
A concept in evolutionary biology referring to the presence of once beneficial traits in a population that, owing to rapid environmental change, are no longer beneficial but harmful.

Cryptorchidism
The absence of one or both testes from the scrotum, usually resulting from a failure to descend during development.

Seminomas
A type of germ cell tumour of the testicle.

Sertoli cell tumours
A sex cord-gonadal stromal tumour composed of Sertoli cells, which line the seminiferous tubules and help in the development of sperm. These are typically benign and often hormonally active.

Estrous cycle
The recurring cyclic variation in reproductive hormones (for example, oestrogen and progesterone) in the mammalian female that controls behaviour, reproductive organ morphology, ovulation and conception.

Leiomyomas
When present in the reproductive tract (vagina, cervix, uterus, oviduct or ovary), these are hormonally responsive benign smooth muscle tumours. In humans, these are also known as fibroids.

Cystic endometrial hyperplasia
A condition of excessive proliferation of the glandular epithelium of the uterus, typically associated with excessive progesterone and/or oestrogen stimulation.

Nulliparous
An animal that has never given birth.

Multiparous
An animal that has given birth multiple times.

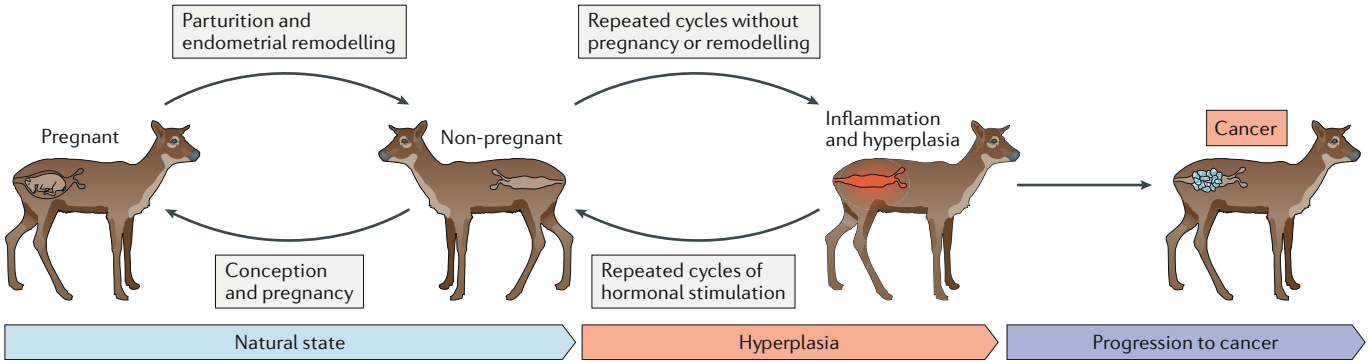


Fig. 4 | **Reproductive system cancers in wildlife.** In the normal, natural state, adult wild animals are typically pregnant or lactating. During brief non-pregnant states, animals have short hormonally driven estrous cycles, which typically result in another pregnancy. Pregnancy, parturition and post-partum involution result in extensive remodelling of the uterine endometrium and removal of hyperplastic tissue. However, if pregnancy does not occur regularly owing to factors such as skewing of sex ratios, captivity or other abnormal pressures on a population, repeated estrous cycles may occur with elevated and prolonged hormonal exposure, leading to hyperplasia without remodelling as might occur during parturition and involution. This phenomenon of asynchronous reproductive ageing can lead to inflammation, infertility and hormonally driven cancers, such as leiomyomas.

reported in the free-ranging population of approximately 900 individuals, while one of nine reproductive tracts available for evaluation from captive gorillas had leiomyomas[131]. Similar effects have been seen in women, where early pregnancy and numbers of pregnancies significantly decrease the risk of some subtypes of breast cancers later in life, and multiparous women have a greatly reduced risk of leiomyomas than nulliparous women[134–136].

In sexually intact domestic dogs and cats, when they cycle but do not conceive, they are exposed not only to high levels of oestrogen but also to high endogenous levels of progesterone during diestrus. In these species, and in wildlife species with similar cycles such as African painted dogs or lions, the endogenous high hormonal levels are also suspected to predispose these animals to increased mammary cancer[137,138]. The use of progestin contraceptives in zoos only increases this effect, resulting in many mammary cancers in tigers as well as other carnivores, unless animals are periodically allowed to breed and carry a fetus to term[139]. While contraceptives are not commonly used in free-ranging populations, similar effects might be expected in some species if breeding opportunities are less frequent.

Another manifestation of human impact on animal populations may be the loss of predators in many ecosystems; large predators are often targeted by humans as a result of hunting for sport, out of fear for personal safety or to protect livestock[140]. It is likely that in these cases, prey animals will have longer lifespans, with corresponding increases in cancer, similar to humans when the reduction of infectious diseases and modern health care increased life expectancies. An example of this is a semi-wild population of fallow deer managed in an urban park island effectively free from predation for over 100 years where population control was finally achieved following sterilization of all the males (D. A., unpublished observations). Ten to 12 years after this population control, many females were found to be nulliparous or had only produced fawns much earlier in their lifetime, and most had developed endometrial hyperplasia, endometrial carcinoma, cervical carcinomas and leiomyomas. However, as might be expected, multiple factors are likely to play a role, including age, prolonged hormonal stimulation without pregnancy (asymmetric reproductive ageing), potential toxins in an urban environment and genetics (inbreeding).

Diestrus
A non-receptive phase of the estrous cycle dominated by progesterone production.

Transmissible cancer

One of the most unique cancers in the animal and human world is transmissible venereal tumour (TVT) of the dog, which is also seen in other canids[3,141]. In this disease, a neoplastic population of cells is transmitted during coitus, upon which the cells implant on the mucosa of the new host and persist until a vigorous host immune response causes tumour regression[142,143]. Recent work shows that the tumour regression (either spontaneous or following vincristine chemotherapy) is sequential and dependent on host innate immunity[144]. After tumour development, the host innate immune system is activated, leading to remodelling of host epithelium, immune cell infiltration of the tumour, cell cycle arrest within the tumour cells and, finally, repair of host tissue damage. Specific cytokines (especially C-C motif chemokine ligand 5 (CCL5; also known as RANTES)) were identified as key players, in addition to changes in gene expression associated with methylation of tumour cell DNA[144]. Since 1876 when it was first described[145], TVT was thought to be the only naturally transmissible tumour in nature; however, in 1996, a new transmissible tumour was identified, affecting the already endangered Tasmanian devil (*Sarcophilus harrisii*), known as devil facial tumour disease (DFTD)[146]. This tumour is transmitted between devils during social interactions, including mating. Such interactions are often violent and may result in oral and facial wounds where the tumour cells are implanted. Subsequent proliferation of the tumours leads to disfigurement and facial damage sufficient to cause starvation and death[147]. Intriguingly, tumours affect the most reproductively fit animals,

thus spreading more rapidly through the population[147]. This tumour clone (known as DFTD1) and a similar but distantly related tumour clone (DFTD2) also identified in Tasmanian devils indicate that transmissible tumours may not be as rare as was once thought and that these diseases threaten to make this species extinct in a matter of a few short generations[148]. Tasmanian devils have experienced a succession of population crashes or bottlenecks, which have greatly limited their genetic diversity[149]. The inability of Tasmanian devils to reject implanted tumour cells was proposed to be the catastrophic event of a reduction in major histocompatibility complex (MHC) diversity in the Tasmanian devil population[150]; however, more recent work suggests that tumour cells downregulate the expression of MHC proteins via epigenetic mechanisms[149]. Further, DFTDs show no evidence of exposure to exogenous mutagens or viruses and despite being allogeneic grafts, DFTDs need to escape the host immune system. This requires hemizygous loss of β2-microglobulin (*B2M*), which encodes a component of MHC class I in DFTD1, suggesting that there is selection to escape immune detection[151]. This work has also shown sensitivity of both tumour clones to tyrosine kinase inhibitors[151].

Similarly, once-flourishing populations of soft-shelled clams (*Mya arenaria*) are now at risk of extinction as a result of horizontally transmitted neoplastic haemocytes derived from a single clonal origin, likely spread from clam to clam by currents[141,152]. Furthermore, four independent disseminated cancer lineages have since been identified in three other bivalve species[152]. Collectively, while these transmissible tumours are relatively rare events in the overall incidence of cancer in natural wildlife populations, the rapid endangerment of species, such as the Tasmanian devil, highlights the potential for such an event to have a catastrophic effect.

With respect to the potential relevance of transmissible cancers to human health, a recent report demonstrated that malignant, genetically altered stem cells from the cestode *Hymenolepis nana*, which normally infects and inhabits the intestines, had spread to other organs in an immunocompromised human infected with HIV[153]. The infection resulted in the death of the patient. This phenomenon may not be novel but simply under-reported or misreported, as earlier descriptions of similarly abnormal transformed cells from parasites disseminating in multiple species of hosts, including humans, were labelled with different terminology, such as "aberrant" or "anomalous" infections[154].

Challenges

There are many reasons the occurrence of cancer in various wildlife populations could be underestimated. With a few exceptions, surveillance programmes are limited and are often targeted to specific diseases or pathogens. Neoplasia that has not yet resulted in substantial morbidity may go unrecognized, particularly if lesions are small or affect only internal organs. If neoplasia does result in mortality, carcass attrition may limit discovery. Caution is also warranted in interpreting the data that are available. Recently, researchers noted the apparent lack of cancer in elephants and suggested a possible association with the presence of additional copies of the *TP53* gene (pseudogenes)[155]. However, others have noted that cancer is likely under-reported in elephants[156].

Long-term mortality investigations in wildlife are rare, but they provide valuable insights into the potential impacts of cancer. Neoplasia might have limited impact on some populations, but other studies indicate a substantial rate of cancer. As discussed above, the long-term investigation of beluga mortality in the St. Lawrence Estuary revealed the potential impacts of cancer in that population[90]; the focused examination of Santa Catalina Island foxes led to recognition of aural neoplasms[14]; and systematic collection of pinnipeds (aquatic fin-footed mammals) on the California coast resulted in the documentation of genitourinary carcinomas among California sea lion[49]. Susceptibility could be increased in a given population owing to genetic background, oncogenic viruses or other agents. Looking at taxa inclusive of multiple species could easily result in a lack of statistical significance for a given species. Many mortality reports look at broader taxa, for example, all reptiles in a given region, and it is unlikely that individual species are sufficiently represented to assess the potential impacts of neoplasia.

Animals with occult lesions may be overlooked without detailed examinations by trained professionals, but the large, destructive tumours of DFTD are easily recognized[141,147]. However, cases of urothelial carcinoma in the bladders of feral, white-tailed deer (*Odocoileus virginianus*) were difficult to identify without a thorough examination of the mucosa at necropsy and confirmation by histopathology, and it is likely that under-reporting of such lesions has resulted from inadequate examination (M.K.K., unpublished observations)[157].

Estimates of morbidity and mortality in wildlife due to spontaneous disease are generally very difficult, and much of the problem lies in the challenges of detecting affected individuals. If a particular type of cancer affects a small percentage of the population, it could easily be missed owing to the inherent difficulty in detecting carcasses. For animals as small as passerine birds, more than 75% of the carcasses may disappear owing to scavenging or decay within the first day after death[158]. Even carcasses of large ungulates can be surprisingly difficult to find. An outbreak of haemorrhagic disease in one white-tailed deer population resulted in 8% mortality that was confirmed by tracking radio-collared individuals. However, the state wildlife department did not receive any reports of sick or dead deer during that outbreak[159]. Without systematic surveillance, smaller animals dying of cancer at a less dramatic rate are likely to be undiscovered.

More thorough examination of mortality events is warranted to document disease threats to wild populations. Many of the forerunners of modern wildlife biology felt that disease was secondary to habitat, and mortality due to disease did not place populations (or species) at undue risk. However, wildlife diseases with unmitigated impacts on populations have begun to emerge at an alarming rate. Anthropogenic factors may be a factor in such disease emergence and have been confirmed in many cases (for example, toxins, dissemination of infectious agents and genetic bottlenecks).

In other cases, the origins are less certain. Regardless, disease threats, including cancer, continue to place our wild populations at risk.

Future directions and conclusions

Owing to the difficulty in acquiring case material during an outbreak and the relative rarity of recognized disease outbreaks in wild animals (both captive and free-ranging), support for archiving of biological specimen collections is critical. This is important for animals collected during mortality events, as well as collections of samples from unaffected animals, as the latter can provide very important baseline data. Potential disease outbreaks are often identified only after anecdotal reports accumulate to a critical level and valuable biological material has not been collected, discarded or lost. Continuous monitoring of cancers in wild animals is needed, as well as collation and archiving of tissues (biobanks) to test the potential cause or causes of those cancers[160]. In addition, documentation of the wide diversity of endocrine and reproductive patterns, development of tools to estimate stress and studies of the genetic or environmental associated immunosuppression in the animal kingdom will improve our ability to correlate disturbances in the natural history of individual species with increased incidences of cancer.

The study of how evolutionary bottlenecks affect cancer predisposition and outcome in wildlife also has ramifications for human cancers. Founder effects have been identified that predispose ethnic populations to breast, ovarian, prostate and colorectal cancers[161–164]. As our ability to interrogate complex data sets in the age of 'big data' grows, it is possible to evaluate how cancer is affected by ancestral and spontaneous genetic polymorphisms as well as the environment. Favé et al.[165] recently published an intriguing method for the computational analysis of genetic and environmental interactions in determining disease. Performing similar analyses across wildlife cancer would undoubtedly reveal more information regarding the role of putative tumour suppressors and oncogenes and how our changing environment dictates outcomes like cancer.

Tumour prevalence varies greatly across the wide variety of animals, and studying wildlife cancer can provide us with an appreciation of the varied mechanisms of oncogenesis. The so-called Peto's paradox asks why cancer incidence is not directly related to the number of cells in an organism and lifespan[166]. If we believe that cancer exists as a result of the combined influences of endogenous and exogenous genomic stressors, chronic inflammation and infectious disease, the immune system, and inherent variation in cell biology, assessing the contribution of multiple factors, such as pathogen infection and environmental pollutants on cancer formation, is a prime example of how wildlife oncology stands to address the question of Peto's paradox. An example highlighting this is why California sea lions are susceptible to urogenital carcinoma, but other marine mammals that share exposure to the same (or similar) environment are not. Therefore, examining several animal species within a particular ecosystem is likely to help reveal both mechanisms of cancer resistance as well as species-specific biological processes that are requisite for cancer formation[167].

The role wildlife can play as both a sentinel for novel threats to humankind and as models for as yet unrecognized or poorly understood mechanisms of cancer development cannot be underestimated. Wild populations provide clues to the very basic questions regarding the origin, evolution and likely consequences of cancer on a population level. Studies of cancers in wild populations due to the interplay between host defences and infectious agents, environmental toxins (natural and man-made) and the disturbed proliferative capacity of the reproductive tract can provide useful information for human health and make the challenges associated with this research worth the effort. Furthermore, the benefit such a study provides for the preservation of the wildlife in our shared world is all the more reason to turn our investigative resources away from the bench and towards the wilderness.

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