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PERSPECTIVE

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Human activities might influence oncogenic processes in wild animal populations

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Based on the abundant studies available on humans showing clear associations between rapid environmental changes and the rate of neoplasia, we propose that human activities might increase cancer rate in wild populations through numerous processes. Most of the research on this topic has concentrated on wildlife cancer prevalence in environments that are heavily contaminated with anthropogenic chemicals. Here, we propose that human activities might also increase cancer rate in wild populations through additional processes including light pollution, accidental (for example, human waste) or intentional (for example, bird feeders) wildlife feeding (and the associated change of diet), or reduction of genetic diversity in human-impacted habitats. The human species can thus be defined as an oncogenic species, moderating the environment in the way that it causes cancer in other wild populations. As human impacts on wildlife are predicted to increase rather than decrease (for example, in the context of urbanization), acknowledging the possible links between human activity and cancer in wild populations is crucial.

Cancer incidence is currently increasing worldwide, becoming one of the leading causes of death for humans in today's world[1,2]. This surge in cancer incidence is mostly caused by the characteristics of our modern life, including a recent change of diet, alcohol consumption or smoking and lack of physical activity, but also an increased exposure to pollutants[3].

Our species is not the only one exposed to environmental modifications caused by human activities. Many wildlife species are also experiencing anthropogenic changes in their environment. As these environmental modifications, as well as other characteristics of the modern world, have increased cancer prevalence in humans, similar effects can also be expected for wild animals living in human-modified habitats. In line with this hypothesis, several studies have now shown that many animal species can develop cancer (see ref. [4]), and that exposure to pollution is associated with neoplasia development in wild populations[5–7]. The human species can thus be defined as an oncogenic species or agent, moderating the environment in the way that it causes cancer in wild populations. Although predator species have previously been shown to be able to modulate immune responses in prey species[8] with potential consequences on their ability to defend themselves against neoplasia development, our species is the first to have such a general and worldwide reach that can affect most of the wild habitats and populations.

Despite the expectation that increased cancer rates in wild animals might result from anthropogenic modifications of the environment, wildlife cancer research is in its infancy. This might seem surprising as oncogenic phenomena are expected to influence fitness-related traits of individuals such as competitive abilities, susceptibility to pathogens, vulnerability to predation and ability to disperse; ultimately influencing population dynamics and ecosystem functioning[9]. Here, we propose that the impact of cancer in wild populations is currently underestimated and that cancer prevalence should be exacerbated by rapid environmental changes caused by human activities. We propose several pathways to explain how human activities contribute to cancer in wild animal populations, as well as provide details on the underlying molecular and cellular mechanisms associated with them (Fig. 1).

Pollution and cancer in wild populations

Relationships between environmental contaminants and tumour development are strongly supported by scientific data from the human literature and a large body of work from captive animals as well as laboratory experiments using animal models[10,11]. Based on this well-established link between toxicology and cancer biology, researchers are now interested in assessing how pollutants affect the development of neoplasia in wild animals[12]. An emblematic study on beluga whales (*Delphinapterus leucas*) from the Saint Lawrence Estuary (a highly polluted habitat due to effluents from aluminium smelting facilities[13]) found cancer (mostly intestinal adenocarcinoma) in 27% of examined adult animals[5], potentially preventing this beluga population from recovering after a strong decline due to hunting pressures. Similarly, cancer epizootics have been extensively studied in freshwater, marine and estuarine fishes in strongly polluted areas[14]. More recently, cancer prevalence has been associated with organochlorine contaminants in California sea lions (*Zalophus californianus*)[7]. These pollutants increase the rate of neoplasia through numerous mechanisms including induction of somatic mutations[15], unrepaired DNA damage[16], immunotoxic effects[17], and/or through interference with the production, release, metabolism and elimination of natural hormones[18]. Pollutants may also contribute to infection-induced oncogenesis by causing mutations or through immune suppression. Polychlorinated biphenyls, for example, are carcinogens but also have immunosuppressive effects[19], and the levels of these pollutants have been shown to be elevated in the blubber of genital carcinomas of sea lions associated with the gammaherpesvirus[12,20].

Another type of contamination that has received some attention over the past few years is the accidental release of artificial radio-

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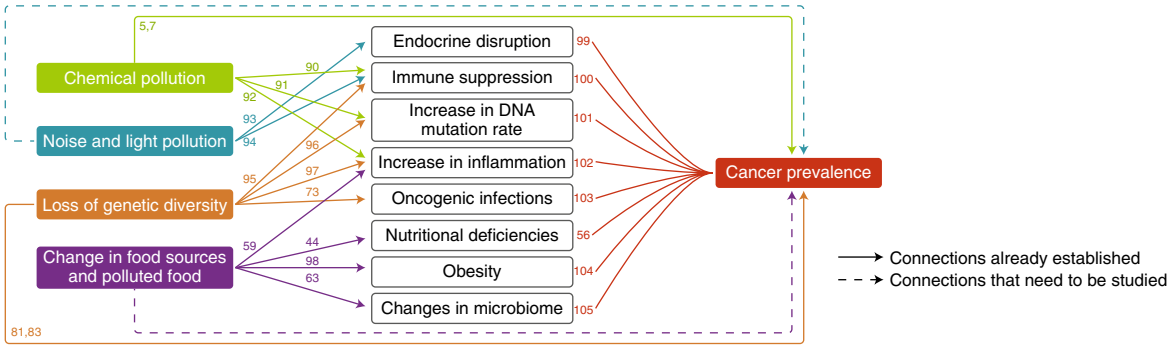

Fig. 1 | Summary of the relationships between human activities and the physiological and molecular pathways impacted that might affect cancer prevalence in wild populations. Refs [5,7,44,56,59,63,73,81,83,90–105] are sample references for established connections.

nuclides into the atmosphere. For example, one study found a significant positive effect of background radiation on the occurrence of external tumours in birds in Chernobyl[6]. These findings confirm the results obtained in humans showing an increased risk of childhood leukaemia in Ukraine[21] or an increased incidence of all malignancies in Sweden (the fallout was deposited in northern Europe in rain during the first week following the accident[22]). However, the incidence of cancer in wild animals inhabiting the Chernobyl and Fukushima contaminated areas has so far not been estimated, as the few studies published on this topic have focused on specific forms of tumour. For example, thyroid cancer drastically increased in Ukraine after the Chernobyl nuclear accident[21,23], but this form of cancer has never been considered in radioactively contaminated wild animals. Therefore, it is likely that the rate of neoplasia is largely underestimated in habitats exposed to the fallout after the nuclear disasters in Ukraine and Japan.

Apart from the types of pollutant discussed above, many other anthropogenic agents (so far not considered) might influence carcinogenesis in wild populations. For example, the worldwide accumulation of micro-plastics in terrestrial and aquatic environments is a problem of growing importance. Micro-plastics are ingested by a wide range of species, potentially causing serious health threats and increasing cancer prevalence through their intrinsic toxicity (they contain organic contaminants) and their ability to adsorb organic contaminants onto their surface[24]. For example, one of these contaminants (bisphenol A) possesses endocrine disruption properties and may contribute to the development of breast cancer[25] and prostate carcinoma in adult humans[26], as well as hepatic tumours in rodents[27]. It remains to be tested if plastics and their constituents have similar carcinogenic effects on wildlife and at levels of exposure found in 'natural' environments, but plastic pollution might be an unstudied candidate contributing to the general increase in spontaneous benign and malignant tumours in marine environments[12,28].

Similarly, wild animals and especially farmland species are exposed to high levels of pesticides and herbicides with a potential negative impact on their rate of hormone-dependant neoplasia. In humans, observational studies have repeatedly found an increase in the rate of breast and prostate cancers in populations occupationally or professionally exposed to these pollutants[29–31]. The mechanisms at play are not yet clear and are still debated but might involve perturbation of the homeostatic redox level(s) of biological compartments, disruption of the endocrine system and epigenetic effects[32].

Although the impact of chemical pollutants has been the most studied topic of wildlife cancer, this field is only at its infancy, as the impact of most of the pollutants found in natural or human-modified habitats on cancer development is still mostly ignored. More importantly, scientists have never considered how interactions between pollutants might influence cancer prevalence in wild populations. In 'natural' habitats, wild animals are in fact often exposed to a mixture of several pollutants and a probable consequence is therefore a modulation of the toxicity of individual components.

Light pollution in urban environments

Artificial lighting is a common characteristic of human settlement and transport networks. The link between artificial light at night (ALAN) and cancer was first established in female employees working a rotating night shift for whom elevated breast cancer risk was associated with occupational exposure to ALAN[33]. This increase in breast cancer risk has been postulated to result from the suppression of pineal melatonin production[34]. Melatonin is a hormone with anti-tumour properties, present in all vertebrates, that is rhythmically secreted by the pineal gland, peaking at night and being suppressed by light, and involved in regulation of circadian rhythms[35]. Even a minimal light contamination is known to disrupt normal circadian production of melatonin and promote tumour growth in rats in captivity[36]. The underlying mechanisms of the cancer suppression effects of melatonin include antioxidant activity, modulation of melatonin receptors, stimulation of apoptosis, regulation of pro-survival signalling and tumour metabolism, inhibition of angiogenesis, metastasis, and induction of epigenetic alteration[37].

Several studies have now also shown changes in levels of hormones that are related to cancer in humans (melatonin, oestrogen, testosterone, stress hormones) in wild animals exposed to ALAN, leading to ALAN being considered as an environmental endocrine disruptor for wildlife[38]. Finally, light pollution can also obviously affect sleep in wild animals[39], and increase in sleep duration has been described as a mechanism that helps to decrease cancer burden[40]. Sleep duration is associated with the strength of immune system. Lower immune capacity resulting from sleep deprivation might therefore limit the ability to control cancer appearance and elimination of cancer cells at an early stage (reviewed in ref. [40]).

It should be noted, however, that in natural populations the health costs of ALAN might be compensated by a stronger investment in cancer defence mechanisms due to a slower pace of life. Light pollution is mostly associated with the urban environment, a habitat with low extrinsic mortality and more predictable resources compared with rural habitats. These conditions tend to favour a slower pace of life[41] with a higher investment in self-maintenance, including stronger immune defences[42]. A potential change of neoplasia risk in urban environments should thus be the result of complex interactions between an adjustment of pace of life (and the associated life history modifications), disruption of the endocrine system and alteration of the sleep pattern with immunological consequences.

Anthropogenic food and cancer in wildlife

Humans currently live in a nutritional environment that differs from that for which our genetic constitution was selected[43], and

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the same is increasingly true for wild animals. In today's changing world, animals eat anthropogenic food items they did not previously eat through two main pathways: supplementary feeding to enhance an animal's survival or to create aggregations of individuals for recreational monitoring, hunting or tourism; and unintentional food provisioning, which usually involves refuse sites (garbage, harvest and fishing discards).

When provisioned, food might contain toxic contaminants with severe negative health consequences[44]. One of the most common causes of wildlife feed contamination is fungal growth, which can produce toxic metabolic by-products known as mycotoxins, secondary metabolites of moulds[44]. For example, food contaminated with aflatoxin has been used as bait for white-tailed deer[45] and in supplemental feeders of northern bobwhite (*Colinus virginianus*)[46]. This mycotoxin is associated with carcinogenicity in human and animal populations[47], and has been shown to cause hepatic lesions in white-tailed deer[48]. Veterinary pharmaceuticals can pose an additional problem for wildlife, as livestock carcasses are often disposed of in supplementary feeding stations for avian scavengers. For example, 92% of tested Eurasian griffon vultures (*Gyps fulvus*) showed variable concentrations of residues of antibiotic fluoroquinolone[49], which is considered to be a photochemical carcinogen[50].

Although supplementary food provided by humans may cover the energetic needs of wild animals, the low quality of such food may potentially impact the risk of developing cancer[51]. A recent review on nutritional effects of supplementary food on wildlife demonstrated that nearly half of the studies (42%) found negative effects of provisioning on protein or micronutrient deficiencies[44]. In addition, higher sugar content and lower fibre content often describes anthropogenic food provided for animals[52]. All of these dietary characteristics have been associated with different types of cancer in humans[53–56]. Inappropriate nutrition can also lead to the deterioration of body condition with an associated decrease in innate and acquired immune responses[57,58], potentially impacting cancer defences. Finally, the low levels of antioxidants in processed anthropogenic foods may also contribute to the development of cancer through DNA damage by reactive oxygen and nitrogen species[59].

Studies on wild species are now also indicating that anthropogenic effects can alter the microbiome community of wild animals with changes in gut microbiota composition, for example in response to urbanization in birds[60], pesticide exposure in honey bees[61], climate change in lizards[62] and habitat fragmentation in African primates[63]. Although a wide range of factors can affect microbiome communities (that is, changes in social group composition[64] stress hormone levels[65]), change in diet is probably one of the most likely causes. Although the study of wildlife microbiome is relatively new, the effects of change in wildlife diet on microbiome in response to anthropogenic activities have already started to accumulate[66–68]. The link between microbiome and cancer is now becoming one of the most intensively studied directions in human cancer research in the search for cancer therapies[69], and it is now established that large numbers of malignancies are associated with an altered composition of gut commensal microbiota[70]. Depending on its composition, gut microbiota can be either oncogenic (by affecting immune system or producing genotoxic substances), or tumour suppressive[70]. The existence of a link between cancer in wildlife and anthropogenic changes in microbiome composition is therefore very likely, and in addition to anthropogenic foods we can expect that pollution or habitat fragmentation may also affect microbiome composition.

Finally, there are also other, indirect pathways related to supplementary feeding that can affect oncogenic processes in wild populations. For example, feeding stations can attract large numbers of animals, and this crowding effect can cause stress with immunesuppressive effects[44]. In addition, feeding stations can facilitate intra- and inter-specific transmission of pathogens[71], including oncogenic viruses.

Loss of genetic diversity, inbreeding and cancer

Environmental and anthropogenic perturbations can directly and indirectly affect the genetic diversity of populations and therefore influence the capacity of individuals to respond to extrinsic and intrinsic challenges. Apart from the clear reciprocal link between genetic diversity and vulnerability to pathogens, more and more evidence supports an association between reduced genetic diversity, inbreeding and cancer both in humans and animals (reviewed in ref. [72]). Cancer being a multifactorial disease, loss of genetic diversity can induce malignant transformations through the accumulation of oncogenic homozygous mutations (direct effect) and via increased susceptibility to oncogenic pathogens (indirect effect). For example, reduced genetic diversity has been associated with increased susceptibility of endangered wildlife species to cancer-causing pathogens, such as papillomatosis and carcinomatosis syndrome in western barred bandicoots (*Perameles bougainville*)[73], and viral papilloma and squamous cell carcinomas in snow leopards (*Uncia uncia*)[74].

Reduction of population size, increased likelihood of close-kin mating and natural selection purging deleterious alleles or favouring certain haplotypes can all contribute to a higher frequency of long stretches of consecutive homozygous regions in the genome (runs of homozygosity (ROH))[75]. ROH harbour disproportionately more deleterious homozygotes than other parts of the genome[75] and the presence of homozygous alleles can give rise to recessive disorders[76]. Reduced genetic diversity amplifies the impact of deleterious homozygous mutations[75] and human genomic studies have shown strong association between homozygosity of some germline low-penetrance oncogenes and cancers[77].

Evidence from both domesticated animals and wildlife further demonstrates that reduction in genetic diversity can directly impact oncogenic processes. For example, although domestic dogs and cats show exceptional phenotypic diversity, they have significantly lower genetic diversity compared with their wild ancestors[78,79], and this has been linked to the observed relatively high cancer prevalence in our closest animal companions[80]. Furthermore, high prevalence of urogenital carcinoma of California sea lions (*Z. californianus*) has been linked to loss of polymorphism at a single locus, the *heparanase 2* gene (*HPSE2*)[81]. Additionally, two recent studies have observed associations between low genetic diversity and high cancer prevalence in Santa Catalina Island foxes (*Urocyon littoralis catalinae*)[82,83] and the South African Cape mountain zebra (*Equus zebra zebra*)[84]. Furthermore, overall loss of genetic diversity may indirectly increase cancer prevalence by reducing immune potential or by creating chronically inflamed cancer-supportive environments[85].

There is thus a strong interplay between exposure to taxing environmental perturbations and anthropogenic impacts, reduction in population size, loss of genetic diversity and cancer. The complex interaction of these extrinsic and intrinsic factors may generate a biological vortex where the impact of oncogenic (direct and indirect) drivers becomes amplified, and thus may further imperil the long-term survival of the numerous species suffering from low genetic diversity.

Concluding remarks and perspectives

Owing to their ubiquitous distribution, animals are on the front lines of environmental changes and of exposure to toxic hazards. While it is well accepted that these processes affect pathogen dynamics and hence the impacts of infectious disease[86], much less is known about non-communicable diseases such as cancer due to the difficulty of detecting and measuring oncogenic processes in wild species. Here, we review the information available on processes for which the connections with cancer have been established (that is, pollutants, toxins). In addition, we propose that other environmental perturbations (that is, light pollution, factors associated with urban-

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izations, for example, food), for which the direct link with cancer has not yet been studied but that are known to impact physiological pathways involved in cancer development, might also influence the rate of neoplasia in wild populations. Thus, cancer is undoubtedly an underestimated health consequence of modern anthropogenic changes, but we must not limit ourselves to the over-simplified prediction that human activities will lead to catastrophic conservation scenarios due to an increased prevalence/severity of oncogenic phenomena in natural populations. Oncogenic phenomena should not be considered in isolation from other biological players in ecosystem functioning, and most ecological impacts are sooner or later followed by evolutionary responses that lead to new equilibria.

The majority of cancers originate from cancer-causing mutant alleles that are somatically acquired throughout life. This peculiarity has at least two major implications: (1) environmental conditions that are directly or indirectly mutagenic are likely to significantly influence cancer prevalence in natural populations; and (2) natural selection is limited in its purging effect (as most individuals possess healthy genes at birth). It is therefore predicted that natural selection, in a world increasingly exposed to oncogenic contexts, should mostly favour adaptations that (1) prevent malignant progressions during an individual's reproductive period; and/or (2) alleviate by one way or another (for example, tolerance, adjustments of life history traits) their detrimental effect on fitness.

While it is biologically possible to select high levels of cancer resistance[87] and/or tolerance, decades of research have illustrated that the evolution of defences against one natural enemy affects the individual's ability to defend itself against other enemies and/or to optimally express other fitness-related traits[88]. For instance, natural defences against cancer (typically the immune system) are costly to maintain, and individuals that are constantly challenged by malignant proliferation may lack sufficient energy to mount an effective defence against opportunistic infections. Thus, even though anthropogenic mutagenic pressures may increase slowly enough to permit the selection of adaptations to cope with the cancer burden, the enhanced presence of malignant cells in an organism's body could, because of trade-offs, have numerous and very complex consequences on the evolutionary ecology of species and on ecosystem functioning.

Theoretical approaches are now needed to predict these ecological and evolutionary changes, considering enemy (malignant cells, predators, parasites, competitors) encounter rates, defence costs and mechanistic interactions among defence mechanisms. This also suggests that — more than ever — malignant cell communities (oncobiota[89]) should be considered as key members of ecosystems, and that any ecological variables (for example, pollution, inbreeding) that exacerbate their prevalence and dynamics are indirectly relevant and must also be considered. It is therefore urgent to develop and conduct more research in this direction because — more than ever — ecosystems are being altered by human activities, and this tendency is unlikely to decrease in the future.

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Competing interests

The authors declare no competing interests.

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