Urban environment and cancer in wildlife: available evidence and future research avenues

Tuul Sepp, Beata Ujvari, Paul W. Ewald, Frédéric Thomas, Mathieu Giraudeau

Urban environment and cancer in wildlife: available evidence and future research avenues

Sepp, Tuul[1], Ujvari, Beata[2], Ewald, Paul W.[3], Thomas, Frédéric [4*] and Giraudeau, Mathieu[4]*

* These authors contributed equally to this review

[1]Institute of Ecology and Earth Sciences, University of Tartu, Vanemuise 46, 51014 Tartu, Estonia

[2]School of Life and Environmental Sciences, Centre for Integrative Ecology, Deakin University, Waurn Ponds, Vic, Australia

[3]Department of Biology, University of Louisville, Louisville, KY, 40292, USA

[4]CREEC, 911 Avenue Agropolis, BP 6450134394 Montpellier Cedex 5, France, and MIVEGEC, UMR IRD/CNRS/UM 5290, 911 Avenue Agropolis, BP 6450134394 Montpellier Cedex 5, France

Abstract

While it is generally known that the risk of several cancers in humans is higher in urban areas compared to rural areas, cancer is often deemed a problem of human societies with modern lifestyles. At the same time, more and more wild animals are affected by urbanization processes and are faced with the need to adapt or acclimate to urban conditions. These include, among other things, increased exposure to an assortment of pollutants (e.g., chemicals, light, noise), novel types of food, and new infections. According to the abundant literature available for humans, all of these factors are associated with an increased probability of developing cancerous neoplasias; however, the link between the urban environment and cancer in wildlife has not been discussed in the scientific literature. Here, we describe the available evidence linking environmental changes resulting from urbanization to cancer-related physiological changes in wild animals. We identify the knowledge gaps in this field and suggest future research avenues, with the ultimate aim of understanding how our modern lifestyle affects cancer prevalence in urbanizing wild populations. In addition, we consider the possibilities of using urban wild animal populations as models to study the association between environmental factors and cancer epidemics in humans, as well as to understand the evolution of cancer and defence mechanisms against it.

Keywords: urbanization, neoplasia, wild animals, pace-of-life, senescence, anthropogenic effects

Introduction

The impact of urbanization (defined the process by which humans form dense settlements constructed of buildings, roads, and supporting infrastructure; Johnson & Munshi-South, 2017) on the diversity, ecology, and health of wild animals has been a focus of the studies in the field of ecology for the last few decades. These studies have led to an understanding that cities are functional ecosystems and experience the same biological processes as wild ecosystems, including evolution (Donihue & Lambert, 2014). Accumulation of knowledge in the field of urban ecology has built a solid foundation for a new burgeoning field of study, urban evolutionary biology, which aims to understand how urbanization influences genetic changes within populations (Santangelo *et al*., 2018). Rapidly expanding urban areas act as alternative selection pressures, to which some species are able to adapt via allele frequency variations and potentially mutations (Johnson & Munshi-South, 2017). At the same time, other species rarely seen in cities historically are currently colonizing developed areas by becoming more tolerant of living near humans (Lehrer *et al*., 2016). The causes of this change in tolerance and the genetic basis of adaptive evolution of the urban environment are not known. Selective pressures acting on wild animals living within city borders or near urban development include an increased exposure to high human disturbance (Soulsbury & White, 2016), elevated noise levels (Kight & Swaddle, 2011), increased chemical pollution (Sanderfoot & Holloway, 2017), artificial light at night (Dominoni *et al.*, 2016), novel food sources (Murray *et al.*, 2016, Birnie-Gauvin *et al.*, 2017), and changes in infection patterns (Hassel *et al.*, 2017). The effects of these factors on human health and wellbeing are relatively well studied (e.g., Gong *et al.,* 2012, Prasad *et al*., 2016), but we still know very little about the health, life-history strategies and causes of mortality of wild animals living in the cities, or about the mechanisms through which wild animals adapt to urban conditions.

One adverse health effect of urban environments that has received a lot of attention in humans is cancer, which has become one of the leading causes of human mortality. This is mostly due to characteristics of our modern lifestyle, including recent changes in diet, alcohol consumption and smoking, and increased exposure to a mixture of pollutants (Soto & Sonnenschein, 2010, Vucenik & Stains, 2012, Chaturvedi *et al*., 2013, Vineis & Husgafvel-Pursiainen, 2005). In addition, an increasing proportion of cancer deaths may be ascribed to the decrease in mortality due to other factors like accidents, hunger, or infectious diseases, resulting in an increasing proportion of human populations reaching old age (Ahmad *et al*., 2015).

Wild animal populations can be compared to prehistoric human populations, in which fossil data indicates a low prevalence of cancer (David and Zimmerman, 2010). It is clear that the characteristics of a modern lifestyle and the urbanizing environment have brought along a change in cancer prevalence in humans, but so far little attention has been given to similar changes in wild animals. It has only recently been proposed that human activities might increase the cancer rate in wild populations (Giraudeau *et al*., 2018, Pesavento *et al*., 2018). In this article, we identify characteristics of the urban environment that have been associated with cancer in humans, and review the literature on the known health effects of these factors on wild animals, thereby describing the available direct and indirect evidence linking environmental changes resulting from urbanization to cancer-related physiological changes in wild animals. We also discuss the possibilities of changed mortality patterns in urban wild animals, including reduced predation pressures, increased resource availability, and changes in host–parasite dynamics, which—like in humans—could lead to a larger proportion of populations reaching old age, and accordingly potentially developing cancer. By identifying the knowledge gaps in this field, we suggest future research avenues, with the ultimate aim of understanding the magnitude of how human modern lifestyle affects cancer prevalence in urbanizing wild populations as well as the possibilities of using urban wild animal populations as models to study the association between environmental factors and cancer epidemics in humans.

Urban nutrition and cancer

In humans, cancer is related to dietary choices and to changes in diet over our evolutionary history (Ducasse *et al.,* 2015). The major changes that have taken place in our diet concern glycemic load, fatty acid and macronutrient composition, micronutrient density, acid–base balance, sodium–potassium ratio, and fibre content (Cordain *et al.,* 2005). An example of a population suffering increased cancer prevalence as a result of diet change is the Inuit population, where malignant diseases, including cancers, were thought to be virtually non-existent at the end of the 19th century but have become increasingly frequent during the 20th century (Friborg and Melbye, 2008). Wild animals that are in contact with humans live in a disturbed, resource-rich environment, and these environmental properties favour the emergence and proliferation of profiteering/cheating cells, namely, carcinogenesis (Ducasse *et al.,* 2015). Wild animals in urban environments routinely eat anthropogenic food items (e.g., bread, processed foods, sugar-rich foods) that they did not previously eat (Birnie-Gauvin *et al.,* 2017), through supplementary feeding (reviewed by Sorensen *et al*., 2014) and/or unintentional food provisioning. At the global level, regions with the highest human densities and per capita food losses are most affected by those anthropogenic subsidies, which have shaped the architecture of many ecosystems (Oro *et al.,* 2013).

In some cases, supplementary feeding could aid in the maintenance of body condition, especially in wintering animals (reviewed in Gil & Brumm, 2014, but see also Clausen *et al.* 2015 for no positive effects). By reducing deaths caused by famine, human food can increase the survival of wild animals (e.g., Robb *et al.*, 2008), with the proportion of individuals reaching older age and therefore (like human populations) being more vulnerable to developing cancer. Alternatively, in some instances, supplementary feeding could also increase the ability of an animal to suppress tumour growth due to better body condition. So far, however, there is no evidence for this latter possibility. Despite the increasing popularity of wildlife feeding, the literature on health effects of these practices are sparse and site- or species-specific (Burgin & Hardiman, 2015), mainly concentrating on food quantity rather than food quality (Birnie-Gauvin *et al.*, 2017) and general fitness effects rather than specific physiological pathways. Inappropriate nutrition (e.g., high levels of processed fat, suboptimal levels of protein, vitamins, antioxidants, and other essential nutrients) can lead to depletion of fat reserves, poor body condition, and decrease in innate and acquired immune responses in wildlife (reviewed by Becker *et al.*, 2015, Birnie-Gauvin *et al.*, 2017). We can expect the possible link between poor nutrition and cancer to be mediated at least partly by lowered immunity, which results from poor-quality anthropogenic food. In addition, a review of the nutritional effects of supplementary food on wildlife demonstrated the negative effects of provisioning on protein or micronutrient deficiencies (Murray *et al.*, 2016), which have been suggested to increase cancer risk in humans (Ames and Wakimoto, 2002).

In humans, obesity is one of the most important known causes of cancer, and about 10% of all cancer deaths among non-smokers are related to obesity (Haslam and James, 2005). The underlying mechanisms can be related to changes in metabolic and physiological pathways involved in oncogenesis, including hormone concentrations, growth factors, inflammatory cytokines, and oxidative stress (Haslam & James, 2005, Ducasse *et al.*, 2015). The link between anthropogenic food, obesity, and cancer is so far virtually unexplored in wild animals, although obesity has been acknowledged as a problem resulting from wildlife feeding (Beckmann & Lackey, 2008, Marechal *et al*., 2016). We suggest that tourist-fed small mammals (e.g., squirrels in urban parks) are a good place to start looking for links between anthropogenic food, obesity, and cancer in wildlife.

Infections, urban habitat alterations, and cancer

The urban environment can break down the existing host–parasite relationships, thereby allowing hosts to "escape" their natural parasite communities (Calegaro-Marques & Amato, 2014). However, increased population densities and contact between different species in urban areas can create opportunities for increased disease transmission and act as a proliferation source of novel diseases (Hassel *et al.*, 2017). Infectious agents have been increasingly recognized as causes of cancer; they are presently accepted as etiologic agents for about 20% of human cancer (Zur Hausen & De Villiers, 2015). Candidate pathogens have been correlated with most of the remaining 80% of human cancers, but their causal role has not yet been determined. Known human tumor viruses have very different genomes, life cycles, and represent a number of virus families (Liao, 2006), indicating that oncogenicity could be a characteristic of a wide range of viruses. While it is known that urbanization can increase the prevalence of viral infections in wild animals (e.g. Bradley *et al*., 2008), the studies on virus prevalence in wildlife in the context of urbanization have so far mainly focused on potential zoonotic diseases, and data on potentially oncogenic viruses in wild animals is largely missing.

In all well-studied examples of infection-induced oncogenesis in humans and wildlife, infectious agents probably act jointly with noninfections environmental factors, such as those discussed in the other sections of this article. Infectious agents typically abrogate the major barriers to cancer, and noninfectious agents further compromise these barriers by generating mutations, altering host defences, and stimulating cell proliferation (Ewald & Swain Ewald, 2015). Pollutants may contribute to infection-induced oncogenesis by causing mutations or through immune suppression. Sea turtle fibropapillomatosis, for example, is caused by an alpha herpes virus and is more prevalent in areas subject to pollution from human activities (Foley *et al.,* 2005), and levels of polychlorinated biphenyls are elevated in the blubber of genital carcinomas of sea lions induced by a gamma herpes virus (Ylitalo *et al.,* 2005). Another example is increased retroviral (feline immunodeficiency virus) infections in feral cats in urban settings with high host densities, which is associated with increased risk of cancer in domestic cats (Magden *et al*., 2011, Hartmann, 2012). These infection-associated tumours emphasize the need to consider infectious causation when the tumours are linked to immunosuppressive pollutants, or more generally with human activities.

Another mechanism that links urban habitat alteration, infections and cancer, is habitat fragmentation and changes in connectivity between populations. Urbanization often results in reduced population sizes or greater isolation (reviewed by Johnson & Munshi-South, 2017). While this may facilitate infection transmission among urban populations, it may also facilitate the escape of uninfected individuals from populations that overcome with infection. Restriction of gene flow between populations due to barriers such as roads and buildings can lead to lower genetic diversity (i.e. Wilson *et al.*, 2015*)*. In addition to the clear reciprocal link between genetic diversity and vulnerability to pathogens, accumulating evidence supports an association between reduced genetic diversity, inbreeding and cancer (Ujvari *et al*., 2018).

Urban chemical pollution and cancer

Urban pollution can act as a mutagen, increasing mutation rates in the germline or within somatic tissues (Johnson & Munshi-South, 2017). For example, both proximity to cities and to steel mills increased germline mutation rate in herring gulls (Yauk *et* al., 2000) and air filtration reduced heritable mutation rates in laboratory mice housed outdoors near major highways and steel mills (Somers *et al*., 2004). This process can accelerate adaptation to urban environment. For example, a recent study demonstrated the independent evolution of tolerance to polychlorinated biphenyls (PCBs) in four Atlantic Killifish populations in urban estuaries (Reid *et al*., 2016). At the same time, mutations in DNA are considered the proximate cause of cancer (Tomassetti *et al*., 2017). Environmental pollutants are known to cause cancer in humans, and evidence that similar pathways are also affecting the health of wild animals has been accumulating. Classical examples include the effects of water pollution with polycyclic aromatic hydrocarbons (PAH), PCB-s, and dichlorodiphenyltrichloroethanes (DDT) on cancer epidemics in several fish species (Sakamoto & White, 2002) as well as mammals (Ylitalo *et al.,* 2005, Randhawa *et al.,* 2015). However, surprisingly, most of the numerous pollutants found in urban environments are unexplored in this context.

One of the possible research directions to pursue would be to study the mixture of pollutants found in the air of cities. This pollution comes predominantly from local vehicular traffic in urban areas with emission of gases, particles, volatile organic compounds, and polycyclic aromatic hydrocarbons (PAHs), many of which are considered as carcinogens. An increased risk of lung cancer associated with exposure to outdoor air pollutants has been consistently found in several studies on humans (Raaschou-Nielsen *et al*., 2013). Other agents present in air pollution have been shown to be associated with mammary carcinomas in rodents (i.e. benzene, kerosene, toluene, and xylenes, Huff *et al.*, 1989, Maltoni *et al.*, 1997) and human breast cancer (i.e. nitrogen dioxide, benzene, PAHs, Labrèche *et al.*, 2010, Petralia *et al.*, 1999, Crouse *et al.*, 2010). At the mechanistic level, this relationship between carcinogenesis and air pollution is due to an increase of chromosome aberrations and micronuclei in lymphocytes (Sram *et al.*, 2007, DeMarini, 2013), changes in the expression of genes involved in DNA damage and repair, epigenetic effects (DNA methylation), inflammation, as well as telomere shortening, immune response and oxidative stress (Loomis *et al.*, 2013).

So far, only a handful of studies have been published on the relationship between air pollution and cancer incidence in captive animals and no studies have, to the best of our knowledge, ever studied this topic in wild populations. In captive mice, for example, an increase in the incidence of lung adenoma and tumor multiplicity of urethane-induced adenomas was associated with traffic related air pollution (Reymao *et al.*, 1997). As an indirect link between air pollution and oncogenic processes in wild populations, exposure to volatile organic compounds is correlated with an up-regulation of intra-cellular antioxidants (i.e. gluthatione), suggesting an increased production of reactive oxygen species, a factor known to influence cancer development (North *et al.*, 2017). Future studies should thus take advantage of new technologies available to measure exposure to air pollution at the individual level (North *et al.*, 2017) to study the dose at which animals are exposed in the wild and the impact of this contamination on cancer incidence.

Light and noise pollution in urban environments

In humans, the link between artificial light at night (ALAN) and cancer was first established in female employees working rotating night shifts (reviewed by Chepesiuk, 2009), and was lately also confirmed in the context of urbanization (Keshet-Sitton *et al.*, 2017). The increased breast cancer risk in female night shift workers has been postulated to result from the suppression of pineal melatonin production (Blask *et al.*, 2005). Melatonin, a hormone present in all vertebrates and also in bacteria, protozoa, plants, fungi, and invertebrates, is involved in the regulation of circadian rhythms; it peaks at night and is suppressed by light (Hardeland *et al.*, 2006). In a laboratory experiment, it was shown that even minimal light contamination (0.2 lux) disrupted normal circadian production of melatonin and promoted tumour growth in rats (Dauchy *et al.*, 2010). Direct links between ALAN, melatonin, and cancer prevalence have not been established for wild animals so far. However, there are several examples of ALAN–wildlife studies showing changes in the levels of hormones that have been related to cancer in humans (e.g., testosterone in Siberian hamster *Phodopus sungorus*, Aubrecht *et al*., 2014; corticosterone in social voles *Microtus socialis*, Zubidat *et al.*, 2011; melatonin in mouse lemurs *Microcebus murinus*, Le Tallec *et al.*, 2016; and European blackbirds *Turdus merula*, Dominoni *et al*., 2013).

Although hormonal effects might be the most important pathway in linking light pollution to cancer prevalence, other possibilities should also be considered. Among them, obesity and metabolic disruption are well-studied consequences of ALAN in humans (Renehan *et al.*, 2008) and should also be considered in wild animals. Light pollution can also affect sleep in wild animals. For example, great tits slept significantly less and woke up earlier when a light-emitting diode was placed in their nestbox (Raap *et al.*, 2015). An increase in sleep duration has been postulated as a mechanism that helps to decrease cancer burden, since sleep duration is associated with immune system strength (Roche *et al*., 2017). Because studies on the effects of

ALAN on the health of wild animals have so far concentrated largely on hormonal changes, the next steps would be to expand these studies to (1) characterize the specific cancer-related physiological pathways affected by ALAN and to (2) analyze neoplasia prevalence in animals subjected to ALAN. As the clearest link with ALAN in humans is to breast cancer, more studies on light pollution effects on wild mammals are needed, considering that the main focus of studies on ALAN to wildlife has so far been on birds and insects.

In addition to light pollution, anthropogenic noise pollution is an important environmental stressor that is rapidly gaining attention among biologists and can, among other effects, disrupt the normal sleep–wake cycle of animals (Francis & Barber, 2013). In laboratory rats, noise stress increased plasma levels of stress hormones and oxidative stress (Said & El Gohari, 2016). Continued oxidative stress can lead to chronic inflammation, which in turn could exacerbate most chronic diseases including cancer (Reuter *et al.,* 2010). Studies on humans have cautiously linked noise pollution levels to higher risks of non-Hodgkin lymphoma (Sørensen *et al.*, 2015) and an increased risk of estrogen-receptor-negative breast cancer (Sørensen *et al*., 2014). As expected, nothing is so far known about the effects of noise pollution on cancer prevalence in wild animals. Nevertheless, house sparrow (*Passer domesticus*) nestlings reared under traffic noise had reduced telomere length when compared with their unexposed neighbours, an effect that could be mediated by oxidative stress (Meillere *et al.,* 2015). Shorter telomeres have been linked to increased vulnerability of several types of cancer (e.g. Zhu *et al.*, 2016). In addition, noise exposure increased stress hormone levels and suppressed cellular immunity in tree frogs (*Hyla arborea;* Troianowski *et al*., 2017), and both of these effects are generally considered to be cancer risk factors (e.g. Antoni *et al*., 2006) . Because it is so difficult to disentangle the effects of noise from other anthropogenic stress sources such as traffic pollution, disturbance, or light pollution in the field, experimental studies on the physiological effects of noise pollution on wild animals are needed.

Changes in survival and life-history strategies

In humans, increased survival and the consequent increased proportion of the population reaching old age has been suggested to be one of the causes of current cancer epidemics since cancer is an age-related disease (White *et al*., 2014). A meta-analysis on birds indicated that the urban environment may enhance survival (Sepp *et al*., 2018), possibly through increased resource availability or lower predation pressure. Lower rates of predation and resultingly higher survival in urban habitats has also been shown in small mammals (e.g., Lehrer *et al*., 2016). Age structures of urban wild animal populations have rarely been studied, but there are some data supporting the hypothesis that there are more old animals in urban populations than in rural populations (e.g., Evans *et al*., 2009). While senescence effects are shown to be common in wild animals (Nussey *et al*., 2013), cancer demography data are lacking for wild populations, and more research is needed to elucidate if cancer rates are higher in aged wild animals (Rozhok & DeGregori, 2016). However, numerous studies in zoo animals (e.g., Chu *et al*., 2012) have indicated that, like in humans, survival to old age can lead to increased cancer mortality in a wide range of animal species.

While age can be a risk factor for cancer development, increased survival prospects can also lead to changes in life-history strategies and physiological investment patterns, with higher investments in self-maintenance over reproduction (Rozhok & DeGregori, 2016). For example, it has been shown that reduced predation alone can substantially slow the rates of physiological aging in mammals, leading to a “slower” life strategy (delayed reproduction and longer somatic maintenance; Austad, 1993). A slower paced life with increased investment in self-maintenance (with a trade-off in lower reproductive investment) has been suggested for birds living in urban habitats (Sepp *et al*., 2018, see also Brans *et al.* 2018 for the emergence of a life-history-physiology syndrome in urban *Daphnia*). This can result in stronger cancer defence mechanisms in animals in more stable, resource rich, and less risky habitats, as cities are for some species. Accordingly, comparing urban and rural populations of wild animals could help to identify physiological mechanisms related to tumour suppression. These types of studies would hugely benefit if the age of the study subjects was known. We are therefore in urgent need of establishing longitudinal research projects including urban and rural animal populations that would allow us to take into account the age of the animal as well as distinguish the causes of mortality in urban and rural wild animal populations.

Conclusions and future directions

Urbanization affects an ever-increasing number of wild animals and their habitats. Our responsibility is to ensure that the development of human societies does not come at the expense of wild animal diversity and health. At the same time, urbanizing wild animal populations could be a promising model system for understanding the evolution of cancer and physiological defences against it, and help to define the factors of the urban environment that have the strongest potential to increase cancer risk. Studying cancer prevalence and defence mechanisms in urban wild animals could therefore lead to a better understanding of how to develop an urban environment with minimal negative health effects for both humans and wild animals. At the same time, urban areas could be considered as natural laboratories for studying the evolution of cancer. This is a promising research avenue, considering the notion that the fastest measured rates of evolution are associated with human altered environments (Donihue & Lambert, 2014).

Species likely vary in their susceptibility to cancer due to variation in tolerance to environmental oncogenic factors (Vittecoq *et al*., 2018) and variation in cancer defense mechanisms (Harris *et al*., 2017). Interspecific variation in cancer risk may depend on life-history characteristics such as body size, growth rate, and investment in sexual signal traits, but also on physiological mechanisms such as wound healing or the presence or depth of placentation (reviewed by Harris *et al., 2017*). While the existence of these internal species-specific differences in cancer defense have to be acknowledged, investment in cancer defenses still exhibits considerable amount of plasticity depending on extrinsic factors such as mortality risk and resource predictability (Rozhok & DeGregori, 2016). Accordingly, if we want to extrapolate the impact of urban environment on cancer probability from wildlife to humans, we must take these species-specific differences into account. The best way to do that would be to compare cancer prevalence and cancer defenses between populations of the same species living in habitats that are more or less affected by urbanization. Considering that cities tend to be more similar to one another than they are to nearby non-urban ecosystems, studying cancer susceptibility and resistance in the context of urbanization would also contribute to understanding of how common is convergent evolution in these physiological processes across different species, traits, and genes (see also Rivkin *et al*., 2018 for key questions in urban evolutionary ecology).

By acknowledging the diversity of cancer aetiologies, there is the possibility of detecting the ecological conditions where anthropogenic impacts on the environment should increase or decrease cancer prevalence. While most urban environmental factors (pollution, low-quality food, infections) should increase cancer prevalence, some characteristics of the urban environment can be considered cancer suppressive. For example, urbanization can affect oncogenic pathogens more than their hosts, leading to fewer cancers caused by infection. Similarly, increased resource availability can lead to better body condition and immune defences. Urban environmental factors can act as selection pressures that may cause new mutations or act on standing genetic variation within populations leading to both higher cancer probability through DNA mutations, and to higher probability for genome-based cancer defence mechanisms to arise (Johnson & Munshi-South, 2017).

Given that advancing age is indisputably the most significant risk factor for cancer, a higher prevalence of cancer (or oncogenic processes) is expected in the prey population under such conditions. In predator–prey relationships, different ecosystem consequences are expected depending on which protagonist—the prey or the predator—is the most affected by human-induced oncogenic processes. Because these issues in turn differentially affect the frequency of genes involved in cancer resistance, numerous and complex reciprocal feedbacks are expected (Roche *et al.* 2017). Thus, while urbanization and other anthropogenic changes in the environment are expected to increase the frequency/severity of oncogenic processes in wildlife species (Giraudeau *et al*., 2018), there are currently no simple answers to the questions about how this will influence biodiversity and ecosystem functioning in urban habitats.

It has been suggested that urban settings unintentionally provide an experimental macrocosms for studying the ability of organisms to adapt to rapid changes in their habitats due to intense human land use (“The urban Petri dish”, Donihue & Lambert, 2014). For testing evolutionary hypotheses in urban settings, a three-tiered program has been suggested, including (1) identification of traits that vary with ecological context; (2) studying the genetic basis of those traits and (3) experimental manipulation to directly identify drivers of those trait differences (Donihue & Lambert, 2014).

Accordingly, the first steps should be comparing traits related to cancer prevalence and cancer defences between urban and rural populations (Figure 1). As a first step, we need a better understanding of age structures and causes of death in urban wild animal populations compared to their rural counterparts. As a second step, minimally invasive methods for assessing cancer prevalence in wild populations need to be developed. And third, we need methods for assessing the investment in cancer defenses, both on the level of immune system functioning and gene expression. Since the link between pollution in aquatic environments and cancer in wildlife has been convincingly established, a good starting point would be ponds and canals in city parks in highly urbanized areas, which are important habitats for fish and a wide variety of wild and semi-domesticated wild birds.

The second step would be to study differences in genes related to tumorigenesis or tumor suppression between wild animals from urban and rural habitats. As an example, a study in the flounder (*Platichthys flesus*) found higher polymorphism of the known tumor suppressor gene p53 in populations living in highly contaminated versus reference estuaries (Marchand et al., 2010). As a third step, experimental evolutionary approaches using urban environmental characteristics (i.e., the use of laboratory or controlled field manipulations to investigate evolutionary processes) are needed, since they may not only intensify the selection of already known suppressive mechanisms, but could also lead to the discovery of novel tumour suppressor mechanisms (Vittecoq *et al*., 2018). Both field and experimental evolutionary studies have demonstrated that organisms exposed to environmental oncogenic factors can - sometimes rapidly - evolve specific adaptations to cope with pollutants and their adverse effects on fitness

(Reid *et al.*, 2016). It is suggested that the fastest rates of evolution globally take place in human-impacted habitats (Hendry & Kinnilison, 1999), and there is strong evidence of adaptive evolution in urban systems (reviewed by Donihue & Lambert, 2014). From an applied perspective, Vittecoq *et al.*, (2018) suggested that studying these species could inspire novel cancer treatments by mimicking the processes allowing these organisms.

Although this area now commands the attention of a variety of researchers, a broad predictive framework is lacking, mainly because the links between urbanization, oncogenic processes, and biodiversity are complex. One single method or model cannot thoroughly reveal how organisms challenged by an urban context resist cancer progression, or how ecosystems will react to an increase in cancer prevalence in resident species. A focused interdisciplinary research effort combining the work of urban ecologists, cancer biologists, animal physiologists and geneticists will be rewarded with an understanding of how modern lifestyles affect cancer prevalence in urbanizing wild populations and how animals cope with this selection pressure, possibly allowing us to use urban wild animal populations as models to study the association between environmental factors and cancer epidemics in humans.

Authors' contributions

TS and MG conceived the idea, TS and FT coordinated the article writing, all authors participated in writing and editing the manuscript, and gave final approval for publication.

Acknowledgements

We are grateful to Laure Devine for language editing. This work was supported by ANR TRANSCAN to FT and BU, Horizon 2020 research and innovation program under the Marie

Sklodowska-Curie grant agreement No 746669 to MG, and grant agreement No 70174 to TS. The publication reflects only the authors' views, and the Research Executive Agency is not responsible for any use that may be made of the information it contains. The authors declare that they have no conflicts of interest.

References

Ahmad, A.S., Ormiston-Smith, N. & Sasieni, P.S. (2015). Trends in the lifetime risk of developing cancer in Great Britain: Comparison of risk for those born in 1930 to 1960, British Journal of Cancer 112, 943–947. doi.org/10.1038/bjc.2014.606

Ames, B.N. & Wakimoto, P. (2002). Are vitamin and mineral deficiencies a major cancer risk? Nature Reviews Cancer 2, 694–704. doi.org/10.1038/nrc886

Antoni, M.H., Lutgendorf, S.K., Cole, S.W., Dhabhar, F.S., Sephton, S.E., McDonald, P.G., Stefanek, M., & Sood, A.K. (2006). The influence of bio-behavioural factors on tumour biology: pathways and mechanisms. Nature Reviews Cancer 6, 240–248. doi.org/10.1038/nrc1820

Aubrecht, T.G., Weil, Z.M. & Nelson, R.J. (2014). Dim light at night interferes with the development of the short-day phenotype and impairs cell-mediated immunity in Siberian hamsters (Phodopus sungorus). Journal of Experimental Zoology Part A-Ecological Genetics and Physiology 321, 450–456. doi.org/10.1002/jez.1877

Austad, S.N. (1993). Retarded senescence in an insular population of Virginia opossums (Didelphis virginiana). Journal of Zoology 229, 695–708. doi.org/10.1111/j.1469-7998.1993.tb02665.x

Becker, D.J., Streicker, D.G. & Altizer, S. (2015). Linking anthropogenic resources to wildlife-pathogen dynamics: a review and meta-analysis. Ecology Letters 18, 483–495. doi.org/10.1111/ele.12428

Beckmann, J.P. & Lackey, C.V. (2008). Carnivores, urban landscapes, and longitudinal studies: a case history of black bears. Human–Wildlife Conflicts 2, 168-174 doi.org/10.1111/ddi.12666

Birnie-Gauvin, K., Peiman, K.S., Raubenheimer, D. & Cooke, S.J. (2017). Nutritional physiology and ecology of wildlife in a changing world. Conservation Physiology 5, cox030. doi.org/10.1093/conphys/cox030

Blask, D.E., Brainard, G.C., Dauchy, R.T., Hanifin, J.P., Davidson, L.K., Krause, J.A., Sauer, L.A., Rivera-Bermudez, M.A., Dubocovich, M.L., Jasser, S.A., Lynch, D.T., Rollag, M.D. & Zalatan F. (2005). Melatonin-depleted blood from premenopausal women exposed to light at night stimulates growth of human breast cancer xenografts in nude rats. Cancer Research 65, 11174–11184. doi.org/10.1158/0008-5472.can-05-1945

Bradley, C. A., Gibbs, S. E. J., & Altizer, S. (2008). Urban land use predicts West Nile Virus exposure in songbirds. Ecological Applications 18, 1083–1092. doi.org/10.1890/07-0822.1

Brans, K.I., Stoks, R. & De Meester, L. (2018) Urbanization drives genetic differentiation in physiology and structures the evolution of pace-of-life syndromes in the water flea *Daphnia magna*. Proceedings of the Royal Society B 285, 20180169. doi.org/10.1098/rspb.2018.0169

Burgin, S. & Hardiman, N. (2015). Effects of non-consumptive wildlife-oriented tourism on marine species and prospects for their sustainable management. Journal of Environmental Management 151, 210–220. doi.org/10.1016/j.jenvman.2014.12.018

Calegaro-Marques, C., & Amato, S. B. (2014). Urbanization breaks up host-parasite interactions:

A case study on parasite community ecology of rufous-bellied thrushes (Turdus rufiventris) along a rural-urban gradient. PLoS ONE, 9(7), e103144. doi.org/10.1371/journal.pone.0103144

Chaturvedi, A.K., Anderson, W.F., Lortet-Tieulent, J., Curado, M.P., Ferlay, J., Franceschi, S., Rosenberg, P.S., Bray, F. & Gillison, M.L. (2013). Worldwide trends in incidence rates for oral cavity and oropharyngeal cancers. Journal of Clinical Oncology 31, 4550–4559. doi.org/10.1200/jco.2013.50.3870

Chepesiuk, R. (2009). Missing the dark: Health effects of light pollution. Environmental Health Perspectives 117, A20–A27. doi.org/10.1289/ehp.117-a20

Chu, P.Y., Zhuo, Y.X. & Wang, F.I. (2012). Spontaneous neoplasms in zoo mammals, birds, and reptiles in Taiwan—a 10-year survey. Animal Biology 62, 95–110. doi.org/10.1163/157075611x616941

Clausen, K.K., Madsen, J. & Tombre, I.M. (2015). Carry-over or compensation? The impact of winter harshness and post-winter body condition on spring-fattening in a migratory goose species. PLoS ONE 10, e0132312. doi.org/10.1371/journal.pone.0132312

Cordain, L., Eaton, S.B., Sebastian, A., Mann, N., Lindeberg, S., Watkins, B.A., O'Keefe, J.H. & Brand-Miller, J. (2005). Origins and evolution of the Western diet: health implications for the 21st century. American Journal of Clinical Nutrition 81, 341–354. doi.org/10.1093/ajcn.81.2.341

Crouse, D.L., Goldberg, M.S., Ross, N.A., Chen, H. & Labrèche, F. (2010). Postmenopausal breast cancer is associated with exposure to traffic-related air pollution in Montreal, Canada: a case–control study. Environmental Health Perspectives 118, 1578. doi.org/10.1289/ehp.1002221

Dauchy, R. T., Dauchy, E. M., Tirrell, R. P., Hill, C. R., Davidson, L. K., Greene, M. W. & Blask, D. E. (2010). Dark-phase light contamination disrupts circadian rhythms in plasma measures of endocrine physiology and metabolism in rats. Comparative Medicine 60, 348–356. doi.org/10.1371/journal.pone.0102776

David, A.R. & Zimmerman, M.R. (2010). Cancer: an old disease, a new disease or something in between? Nature Reviews Cancer 10, 728. doi.org/10.1038/nrc2914

Dominoni, D.M., Goymann, W., Helm, B. & Partecke, J. (2013). Urban-like night illumination reduces melatonin release in European blackbirds (Turdus merula): implications of city life for biological time-keeping of songbirds. Frontiers in Zoology 10, 60. doi.org/10.1186/1742-9994-10-60

Dominoni, D.M., Borniger, J.C. & Nelson, R.J. (2016). Light at night, clocks and health: from humans to wild organisms. Biology Letters 12, 20160015. doi.org/10.1098/rsbl.2016.0015

Donihue, C. M., & Lambert, M. R. (2014). Adaptive evolution in urban ecosystems. Ambio 44, 194-203. doi.org/10.1007/s13280-014-0547-2

Ducasse, H., Arnal, A., Vittecoq, M., Daoust, S. P., Ujvari, B., Jacqueline, C., Tissot, T., Ewald, P., Gatenby, R. A., King, K. C., Bonhomme, F., Brodeur, J., Renaud, F., Solary, E., Roche, B. & Thomas, F. (2015), Cancer: an emergent property of disturbed resource-rich environments? Ecology meets personalized medicine. Evolutionary Applications 8, 527–540. doi.org/10.1111/eva.12232

Ewald, P.W. & Swain Ewald, H.A. (2015). Infection and cancer in multicellular organisms. Philosophical Transactions of The Royal Society B Biological Sciences 370, 20140224. doi.org/10.1098/rstb.2014.0224

Evans, K. L., Gaston, K. J., Sharp, S. P., Mcgowan, A., & Hatchwell, B. J. (2009). The effect of urbanisation on avian morphology and latitudinal gradients in body size. Oikos 118, 251–259. doi.org/10.1111/j.1600-0706.2008.17092.x

Foley, A.M., Schroeder, B.A., Redlow, A.E., Fick-Child, K.J. & Teas, W.G. (2005). Fibropapillomatosis in stranded green turtles (Chelonia mydas) from the eastern United States (1980-98): trends and associations with environmental factors. Journal of Wildlife Diseases 41, 29–41. doi.org/10.7589/0090-3558-41.1.29

Francis, C.D. & Barber, J.R. (2013). A framework for understanding noise impacts on wildlife: an urgent conservation priority. Frontiers in Ecology and the Environment 11, 305–313. doi.org/10.1890/120183

Friborg, J.T. & Melbye, M. (2008). Cancer patterns in Inuit populations. Lancet Oncology 9, 892–900. doi.org/10.1016/s1470-2045(08)70231-6

Gil, D., & Brumm, H. (2014). Avian urban ecology. Behavioural and physiological adaptations. Oxford University Press. doi.org/10.1650/condor-15-75.1

Giraudeau, M., Sepp, T., Ujvari, B., Ewald, P.W. & Thomas, F. (2018). Human activities might influence oncogenic processes in wild animal populations. Nature Ecology & Evolution, 2, 1065–1070.

Gong, P., Liang, S., Carlton, E.J., Jiang, Q.W., Wu, J.Y., Wang, L. & Remais, J.V. (2012). Urbanisation and health in China. Lancet 379, 843–852. doi.org/10.1016/s0140-6736(11)61878-3

Hardeland, R, Pandi-Perumal, S.R. & Cardinali, D.P. (2006). Melatonin. International Journal of Biochemistry & Cell Biology 38, 313–316. doi.org/10.1016/j.biocel.2005.08.020

Hartmann, K. 2012. Clinical aspects of feline retroviruses: a review. Viruses 4, 2684-2710. doi.org/10.3390/v4112684

Haslam, D.W. & James, W.P.T. (2005). Obesity. Lancet 366, 1197–1209. doi.org/10.1016/s0140-6736(05)67483-1

Hassell, J. M., Begon, M., Ward, M. J., & Fèvre, E. M. (2017). Urbanization and Disease Emergence: Dynamics at the Wildlife–Livestock–Human Interface. Trends in Ecology & Evolution, 32, 55–67. doi.org/10.1016/j.tree.2016.09.012

Hendry, A.P. & Kinnison, M.T. (1999). The pace of modern life: Measuring rates of contemporary microevolution. Evolution 53, 1637–1653. doi.org/10.2307/2640428

Huff, J.E., Haseman, J.K., Demarini, D.M., Eustis, S., Maronpot, R.R., Peters, A.C., Persing, R.L., Chrisp, C.E., Jacobs, A.C. (1989). Multiple-site carcinogenicity of benzene in Fischer 344 rats and B6C3F1 mice. Environmental Health Perspectives 8, 125–163. doi.org/10.1289/ehp.8982125

Johnson, M.T.J. & Munshi-South, J. (2017) Evolution of life in urban environments. Science 358, eaam8327. doi.org/10.1126/science.aam8327

Keshet-Sitton, A., Or-Chen, K., Yitzhak, S., Tzabary, I. & Haim, A. (2017). Light and the city: breast cancer risk factors differ between urban and rural women in Israel. Integrative Cancer Therapies 16, 176–187. doi.org/10.1177/1534735416660194

Kight, C. R., & Swaddle, J. P. (2011). How and why environmental noise impacts animals: an integrative, mechanistic review. Ecology Letters 14, 1052–1061. doi.org/10.1111/j.1461-0248.2011.01664.x

Labrèche, F., Goldberg, M.S., Valois, M.F. & Nadon, L. (2010). Postmenopausal breast cancer and occupational expo¬sures: results of a case-control study in Montreal, Quebec, Canada. Occupational and Environmental Medicine 67, 263–269. doi.org/10.1136/oem.2009.049817

Lehrer, E.W., Schooley, R.L., Nevis, J.M., Kilgour, R.J., Wolff, P.J. & Magle, S.B. (2016).

Happily ever after? Fates of translocated nuisance woodchucks in the Chicago metropolitan area. Urban Ecosystems 19, 1389. doi.org/10.1007/s11252-016-0560-2

Liao, J.B. (2006). Viruses and human cancer. Yale Journal of Biology and Medicine 79, 115–122. doi.org/10.1111/j.1467-9736.2006.00214.x

Le Tallec, T., Thery, M. & Perret, M. (2016). Melatonin concentrations and timing of seasonal reproduction in male mouse lemurs (Microcebus murinus) exposed to light pollution. Journal of Mammalogy 97, 753–760. doi.org/10.1093/jmammal/gyw003

Loomis, D., Grosse, Y., Lauby-Secretan, B., El Ghissassi, F., Bouvard, V., Benbrahim-Tallaa, L., ... & Straif, K. (2013). The carcinogenicity of outdoor air pollution. Lancet Oncology 14, 1262. doi.org/10.1016/s1470-2045(13)70487-x

Magden, E., Quackenbush, S. L. & VandeWoude, S. (2011). FIV associated neoplasms--a mini-review. Veterinary Immunology and Immunopathology 143, 227-234. doi.org/10.1016/j.vetimm.2011.06.016

Maltoni, C., Ciliberti, A., Pinto, C., Soffritti, M., Belpoggi, F. & Menarini, L. (1997). Results of long-term experimental carcinogenic¬ity studies of the effects of gasoline, correlated fuels, and major gasoline aromatics on rats. Annals of the New York Academy of Sciences 837(1), 15–52. doi.org/10.1111/j.1749-6632.1997.tb56863.x

Marchand, J., Evrard, E., Guinand, B., Cachot, J., Quiniou, L., & Laroche, J. (2010). Genetic polymorphism and its potential relation to environmental stress in five populations of the European flounder *Platichthys flesus*, along the French Atlantic coast. Marine Environmental Research 70, 201‑209. doi.org/10.1016/j.marenvres.2010.05.002

Marechal, L., Semple, S., Majolo, B. & Maclarnon, A. (2016). Assessing the effects of tourist provisioning on the health of wild barbary macaques in Morocco. PLoS ONE 11, e0155920.

doi.org/10.1371/journal.pone.0155920

Meillere, A., Brischoux, F., Ribout, C. & Angelier, F. (2015). Traffic noise exposure affects telomere length in nestling house sparrows. Biology Letters 11, 20150559. doi.org/10.1098/rsbl.2015.0559

Murray, M.H., Becker, D.J., Hall, R.J. & Hernandez S.M. (2016). Wildlife health and supplemental feeding: A review and management recommendations. Biological Conservation 204, 163–174. doi.org/10.1016/j.biocon.2016.10.034

North, M.A., Kinniburgh, D.W., & Smits, J.E. (2017). European starlings (Sturnus vulgaris) as sentinels of urban air pollution: A comprehensive approach from noninvasive to post Mortem Investigation. Environmental Science & Technology 51, 8746–8756. doi.org/10.1021/acs.est.7b01861

Nussey, D.H., Froy, H., Lemaitre, J.F., Gaillard, J.M. & Austad, S.N. (2013). Senescence in natural populations of animals: widespread evidence and its implications for bio-gerontology. Ageing Research Reviews 12, 214–225. doi.org/10.1016/j.arr.2012.07.004

Oro, D., Genovart, M., Tavecchia, G., Fowler, M.S. & Martínez-Abraín, A. (2013). Ecological and evolutionary implications of food subsidies from humans. Ecology Letters 16, 1501–1514. doi.org/10.1111/ele.12187

Petralia, S.A., Vena, J.E., Freudenheim, J.L., Dosemeci, M., Michalek, A., Goldberg, M.S., Brasure, J. & Graham, S. (1999). Risk of premeno¬pausal breast cancer in association with occupational exposure to polycyclic aromatic hydrocarbons and ben¬zene. Scandinavian Journal of Work Environment and Health 25, 215–221. doi.org/10.5271/sjweh.426

Pesavento, P.A., Agnew, D., Keel, M.K. & Woolard, K.D. (2018). Cancer in wildlife: patterns of emergence. Nature Reviews Cancer 18, 646–661. doi.org/10.1038/s41568-018-0045-0

Prasad, A., Gray, C.B., Ross, A., Kano, M. (2016). Metrics in urban health: current developments and future prospects. Annual Review of Public Health 37, 113–133. doi.org/10.1146/annurev-publhealth-032315-021749

Raap, T., Pinxten, R. & Eens, M. (2015). Light pollution disrupts sleep in free-living animals. Scientific Reports 5, 13557. doi.org/10.1038/srep13557

Raaschou-Nielsen, O., Andersen, Z.J., Beelen, R., Samoli, E., Stafoggia, M., Weinmayr, G., Hoffmann, B., Fischer, P., Nieuwenhuijsen, M.J., Brunekreef, B., Xun, W.W., Katsouyanni, K., Dimakopoulou, K. & Forsberg, B. (2013). Air pollution and lung cancer incidence in 17 European cohorts: prospective analyses from the European Study of Cohorts for Air Pollution Effects (ESCAPE). Lancet Oncology 14, 813–822. doi.org/10.1016/s1470-2045(13)70279-1

Randhawa, N., Gulland, F., Ylitalo, G.M., Delong, R., & Mazet, J.A. (2015). Sentinel California sea lions provide insight into legacy organochlorine exposure trends and their association with cancer and infectious disease. One Health 1, 37–43. doi.org/10.1016/j.onehlt.2015.08.003

Reid, N.M., Proestou, D.A., Clark, B.W., Warren, W.C., … Whitehead, A. (2016). The genomic landscape of rapid repeated evolutionary adaptation to toxic pollution in wild fish. Science 354, 1305-1308. doi.org/ 10.1126/science.aah4993

Renehan, A.G., Tyson, M., Egger, M., Heller, R.F. & Zwahlen, M. (2008). Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. Lancet 371, 569–578. doi.org/10.1016/s0140-6736(08)60269-x

Reuter, S., Gupta, S.C., Chaturvedi, M.M. & Bharat, B.A. (2010). Oxidative stress, inflammation, and cancer. How are they linked? Free Radical Biology and Medicine 49, 1603–1616. doi.org/10.1016/j.freeradbiomed.2010.09.006

Reymao, M.S., Cury, P.M. & Lichtenfels, A.J. (1997). Urban air pollution enhances the formation of urethane-induced lung tumours in mice. Environmental Research 74, 150–158. doi.org/10.1006/enrs.1997.3740

Rivkin, L.R., Santangelo, J.S., Alberti, M., Aronson, M.F.J., … Johnson, M.T.J. (2018). A roadmap for urban evolutionary ecology. Evolutionary Applications, in press. doi.org/10.1111/eva.12734

Robb, G.N., McDonald, R.A., Chamberlain, D.E. & Bearhop, S. (2008). Food for thought: Supplementary feeding as a driver of ecological change in avian populations. Frontiers in Ecology and the Environment 6, 476–484. doi.org/10.1890/060152

Roche, B., Møller, A.P., Degregori, J. & Thomas, F. (2017). Cancer in animals: Reciprocal feedbacks between evolution of cancer resistance and ecosystem functioning. In Ujvari, B., Roche, B., Thomas, F. (Eds.) Ecology and Evolution of Cancer. London Academic Press. doi.org/10.1016/b978-0-12-804310-3.00013-2

Rozhok, A.I., & DeGregori, J. (2016). The evolution of lifespan and age-dependent cancer risk. Trends in Cancer 2, 552–560. doi.org/10.1016/j.trecan.2016.09.004

Said, M.A. & El-Gohary, O.A. (2016). Effect of noise stress on cardiovascular system in adult male albino rat: implication of stress hormones, endothelial dysfunction and oxidative stress. General Physiology and Biophysics 35, 371–377. doi.org/10.4149/gpb_2016003

Sakamoto, K. & White, M. (2002). Dermal melanoma with schwannoma-like differentiation in a brown bullhead catfish (Ictalurus nebulosus). Journal of Veterinary Diagnostic Investigation 14, 247–250. doi.org/10.1177/104063870201400311

Sanderfoot, O.V., Holloway, T. (2017). Air pollution impacts on avian species via inhalation exposure and associated outcomes. Environmental Research Letters 12, 083002. doi.org/10.1088/1748-9326/aa8051

Santangelo, J.S., Rivkin, L.R. & Johnson, M.T. J. (2018). The evolution of city life. Proceedings of the Royal Society B 285, 20181529. doi.org/10.1098/rspb.2018.1529

Sepp, T., McGraw, K. J., Kaasik, A. & Giraudeau, M. A review of urban impacts on avian life-history evolution: does city living lead to slower pace of life? Global Change Biology 24, 1452–1469. doi.org/10.1111/gcb.13969

Somers, C.M., McCarry, B.E., Malek, F. & Quinn, J.S. (2004). Reduction of particulate air pollution lowers the risk of heritable mutations in mice. Science 14, 1008-10. doi.org/10.1126/science.1095815

Sorensen, A., Van Beest, F.M. & Brook, R.K. (2014). Impacts of wildlife baiting and supplemental feeding on infectious disease transmission risk: a synthesis of knowledge. Preventive Veterinary Medicine 113, 356–363. doi.org/10.1016/j.prevetmed.2013.11.010

Sørensen, M., Ketzel, M., Overvad, K., Tjonneland, A. & Raaschou-Nielsen, O. (2014). Exposure to road traffic and railway noise and postmenopausal breast cancer: A cohort study. International Journal of Cancer 134, 2691–2698. doi.org/10.1002/ijc.28592

Sørensen, M., Poulsen, A.H., Ketzel, M., Dalton, S.O., Friis, S. & Raaschou-Nielsen, O. (2015). Residential exposure to traffic noise and risk for non-hodgkin lymphoma among adults. Environmental Research 142, 61–65. doi.org/10.1016/j.envres.2015.06.016

Soto, A.M. & Sonnenschein, C. (2010). Environmental causes of cancer: endocrine disruptors as carcinogens. Nature Reviews Endocrinology 6, 363–370. doi.org/10.1038/nrendo.2010.87

Soulsbury, C.D., White, P.C.L. (2016). Human-wildlife interactions in urban areas: a review of conflicts, benefits and opportunities. Wildlife Research 42, 541–553. doi.org/10.1071/wr14229

Sram Rj, Beskid O, Rossnerova A, Rossner, P., Lnenickova, Z., Milcova, A., Solansky, I. &

Binkova, B. (2007). Environmental exposure to carcinogenic polycyclic aromatic hydrocarbons-the interpretation of cytogenetic analysis by FISH. Toxicology Letters 172, 12–20. doi.org/10.1016/j.toxlet.2007.05.019

Tomasetti, C., Li, L. & Vogelstein, B. (2017). Stem cell divisions, somatic mutations, cancer etiology, and cancer prevention. Science 355, 1330-1334. doi.org/10.1126/science.aaf9011

Troïanowski, M., Mondy, N., Dumet, A., Arcanjo, C. & Lengagne, T. (2017). Effects of traffic noise on tree frog stress levels, immunity and color signaling. Conservation Biology 28074559. doi.org/10.1111/cobi.12893

Ujvari, B., Roche, B. & Thomas, F. (2017). Ecology and evolution of cancer. London: Academic Press. doi.org/10.1016/b978-0-12-804310-3.00012-0

Ujvari, B., Klaassen, M., Raven, N., Russell, T., Vittecoq, M., Hamede, R., Thomas, F., … Madsen, T. (2018). Genetic diversity, inbreeding and cancer. Proceedings of the Royal Academy of Sciences B 285, 20172589. doi.org/10.1098/rspb.2017.2589

Vineis, P. & Husgafvel-Pursiainen, K. (2005). Air pollution and cancer: biomarker studies in human populations. Carcinogenesis 26(11), 1846-55. doi.org/10.1093/carcin/bgi216

Vittecoq, M., Giraudeau, M., Sepp, T., Marcogliese, D., Klaassen, M., Ujvari, B., Thomas, F. (2018). Turning oncogenic factors into an ally in the war against cancer. Evolutionary Applications 11, 836-844. doi.org/10.1111/eva.12608

Vucenik, I. & Stains, J.P. (2012). Obesity and cancer risk: evidence, mechanisms, and recommendations. Annals of the New York Academy of Sciences 1271, 37–43. doi.org/10.1111/j.1749-6632.2012.06750.x

White, M.C., Holman, D.M., Boehm, J.E., Peipins, L.A., Grossman, M., & Henley, S.J. (2014). Age and cancer risk: A potentially modifiable relationship. American Journal of Preventive

Medicine 46, 7–15. doi.org/10.1016/j.amepre.2013.10.029

Wilson, A., Fenton, B., Malloch, G., Boag, B., Hubbard, S. & Begg, G. (2015) Urbanisation versus agriculture: A comparison of local genetic diversity and gene flow between wood mouse *Apodemus sylvaticus* populations in human-modified landscapes. Ecography 39, 87–97. doi.org/10.1111/ecog.01297

Yauk, C.L., Fox, G.A., McCarry, B.E. & Quinn, J.S. (2000). Induced minisatellite germline mutations in herring gulls (*Larus argentatus*) living near steel mills. Mutation Research 452, 211-218. doi.org/10.1016/S0027-5107(00)00093-2

Ylitalo, G.M. Stein, J.E., Hom, T., Johnson, L.L., Tilbury, K.L., Hall, A.J., Rowles, T., Greig, D., Lowenstine, L.J., Gulland, F.M. (2005). The role of organochlorines in cancer-associated mortality in California sea lions (Zalophus californianus). Marine Pollution Bulletin 50, 30–39. doi.org/10.1016/j.marpolbul.2004.08.005

Zhu, X., Han, W., Xue, W., Zou, Y., Xie, C., Du, J. & Jin, G. (2016) The association between telomere length and cancer risk in population studies. Scientific Reports 6, 22243. doi.org/10.1038/srep22243

Zubidat, A.E., Nelson, R.J. & Haim, A. (2011). Spectral and duration sensitivity to light-at-night in 'blind' and sighted rodent species. Journal of Experimental Biology 214, 3206–3217. doi.org/10.1242/jeb.058883

Zur Hausen, H. & De Villiers, E.M. (2014). Cancer "causation" by infections--individual contributions and synergistic networks. Seminars in Oncology 42, 207–222. doi.org/10.1053/j.seminoncol.2015.02.019

Figure 1. Flow chart of possible experimental designs for studying cancer in wild populations. Steps proposed here are based on the suggestions for studying evolution in urban environments by Donihue and Lambert (2014).