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

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► To cite this version:

Tuul Sepp, Beata Ujvari, Paul W. Ewald, Frédéric Thomas, Mathieu Giraudeau. Urban environment and cancer in wildlife: available evidence and future research avenues. *Proceedings of the Royal Society B: Biological Sciences*, 2019, 286 (1894), pp.20182434. 10.1098/rspb.2018.2434 . hal-02469172

HAL Id: hal-02469172

<https://hal.umontpellier.fr/hal-02469172>

Submitted on 19 Nov 2020

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16 **Abstract**

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

33

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

35 **Introduction**

36 The impact of urbanization (defined the process by which humans form dense settlements
37 constructed of buildings, roads, and supporting infrastructure; Johnson & Munshi-South, 2017)
38 on the diversity, ecology, and health of wild animals has been a focus of the studies in the field
39 of ecology for the last few decades. These studies have led to an understanding that cities are
40 functional ecosystems and experience the same biological processes as wild ecosystems,
41 including evolution (Donihue & Lambert, 2014). Accumulation of knowledge in the field of
42 urban ecology has built a solid foundation for a new burgeoning field of study, urban
43 evolutionary biology, which aims to understand how urbanization influences genetic changes
44 within populations (Santangelo *et al.*, 2018). Rapidly expanding urban areas act as alternative
45 selection pressures, to which some species are able to adapt via allele frequency variations and
46 potentially mutations (Johnson & Munshi-South, 2017). At the same time, other species rarely
47 seen in cities historically are currently colonizing developed areas by becoming more tolerant of
48 living near humans (Lehrer *et al.*, 2016). The causes of this change in tolerance and the genetic
49 basis of adaptive evolution of the urban environment are not known. Selective pressures acting
50 on wild animals living within city borders or near urban development include an increased
51 exposure to high human disturbance (Soulsbury & White, 2016), elevated noise levels (Kight &
52 Swaddle, 2011), increased chemical pollution (Sanderfoot & Holloway, 2017), artificial light at
53 night (Dominoni *et al.*, 2016), novel food sources (Murray *et al.*, 2016, Birnie-Gauvin *et al.*,
54 2017), and changes in infection patterns (Hassel *et al.*, 2017). The effects of these factors on
55 human health and wellbeing are relatively well studied (e.g., Gong *et al.*, 2012, Prasad *et al.*,
56 2016), but we still know very little about the health, life-history strategies and causes of

57 mortality of wild animals living in the cities, or about the mechanisms through which wild
58 animals adapt to urban conditions.

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

67 Wild animal populations can be compared to prehistoric human populations, in which
68 fossil data indicates a low prevalence of cancer (David and Zimmerman, 2010). It is clear that
69 the characteristics of a modern lifestyle and the urbanizing environment have brought along a
70 change in cancer prevalence in humans, but so far little attention has been given to similar
71 changes in wild animals. It has only recently been proposed that human activities might increase
72 the cancer rate in wild populations (Giraudeau *et al.*, 2018, Pesavento *et al.*, 2018). In this article,
73 we identify characteristics of the urban environment that have been associated with cancer in
74 humans, and review the literature on the known health effects of these factors on wild animals,
75 thereby describing the available direct and indirect evidence linking environmental changes
76 resulting from urbanization to cancer-related physiological changes in wild animals. We also
77 discuss the possibilities of changed mortality patterns in urban wild animals, including reduced
78 predation pressures, increased resource availability, and changes in host–parasite dynamics,
79 which—like in humans—could lead to a larger proportion of populations reaching old age, and

80 accordingly potentially developing cancer. By identifying the knowledge gaps in this field, we
81 suggest future research avenues, with the ultimate aim of understanding the magnitude of how
82 human modern lifestyle affects cancer prevalence in urbanizing wild populations as well as the
83 possibilities of using urban wild animal populations as models to study the association between
84 environmental factors and cancer epidemics in humans.

85

86 **Urban nutrition and cancer**

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

103 In some cases, supplementary feeding could aid in the maintenance of body condition,
104 especially in wintering animals (reviewed in Gil & Brumm, 2014, but see also Clausen *et al.*
105 2015 for no positive effects). By reducing deaths caused by famine, human food can increase the
106 survival of wild animals (e.g., Robb *et al.*, 2008), with the proportion of individuals reaching
107 older age and therefore (like human populations) being more vulnerable to developing cancer.
108 Alternatively, in some instances, supplementary feeding could also increase the ability of an
109 animal to suppress tumour growth due to better body condition. So far, however, there is no
110 evidence for this latter possibility. Despite the increasing popularity of wildlife feeding, the
111 literature on health effects of these practices are sparse and site- or species-specific (Burgin &
112 Hardiman, 2015), mainly concentrating on food quantity rather than food quality (Birnie-Gauvin
113 *et al.*, 2017) and general fitness effects rather than specific physiological pathways. Inappropriate
114 nutrition (e.g., high levels of processed fat, suboptimal levels of protein, vitamins, antioxidants,
115 and other essential nutrients) can lead to depletion of fat reserves, poor body condition, and
116 decrease in innate and acquired immune responses in wildlife (reviewed by Becker *et al.*, 2015,
117 Birnie-Gauvin *et al.*, 2017). We can expect the possible link between poor nutrition and cancer to
118 be mediated at least partly by lowered immunity, which results from poor-quality anthropogenic
119 food. In addition, a review of the nutritional effects of supplementary food on wildlife
120 demonstrated the negative effects of provisioning on protein or micronutrient deficiencies
121 (Murray *et al.*, 2016), which have been suggested to increase cancer risk in humans (Ames and
122 Wakimoto, 2002).

123 In humans, obesity is one of the most important known causes of cancer, and about 10%
124 of all cancer deaths among non-smokers are related to obesity (Haslam and James, 2005). The
125 underlying mechanisms can be related to changes in metabolic and physiological pathways

126 involved in oncogenesis, including hormone concentrations, growth factors, inflammatory
127 cytokines, and oxidative stress (Haslam & James, 2005, Ducasse *et al.*, 2015). The link between
128 anthropogenic food, obesity, and cancer is so far virtually unexplored in wild animals, although
129 obesity has been acknowledged as a problem resulting from wildlife feeding (Beckmann &
130 Lackey, 2008, Marechal *et al.*, 2016). We suggest that tourist-fed small mammals (e.g., squirrels
131 in urban parks) are a good place to start looking for links between anthropogenic food, obesity,
132 and cancer in wildlife.

133

134 **Infections, urban habitat alterations, and cancer**

135 The urban environment can break down the existing host–parasite relationships, thereby
136 allowing hosts to “escape” their natural parasite communities (Calegario-Marques & Amato,
137 2014). However, increased population densities and contact between different species in urban
138 areas can create opportunities for increased disease transmission and act as a proliferation source
139 of novel diseases (Hassel *et al.*, 2017). Infectious agents have been increasingly recognized as
140 causes of cancer; they are presently accepted as etiologic agents for about 20% of human cancer
141 (Zur Hausen & De Villiers, 2015). Candidate pathogens have been correlated with most of the
142 remaining 80% of human cancers, but their causal role has not yet been determined. Known
143 human tumor viruses have very different genomes, life cycles, and represent a number of virus
144 families (Liao, 2006), indicating that oncogenicity could be a characteristic of a wide range of
145 viruses. While it is known that urbanization can increase the prevalence of viral infections in
146 wild animals (e.g. Bradley *et al.*, 2008), the studies on virus prevalence in wildlife in the context
147 of urbanization have so far mainly focused on potential zoonotic diseases, and data on potentially
148 oncogenic viruses in wild animals is largely missing.

149 In all well-studied examples of infection-induced oncogenesis in humans and wildlife,
150 infectious agents probably act jointly with noninfectious environmental factors, such as those
151 discussed in the other sections of this article. Infectious agents typically abrogate the major
152 barriers to cancer, and noninfectious agents further compromise these barriers by generating
153 mutations, altering host defences, and stimulating cell proliferation (Ewald & Swain Ewald,
154 2015). Pollutants may contribute to infection-induced oncogenesis by causing mutations or
155 through immune suppression. Sea turtle fibropapillomatosis, for example, is caused by an alpha
156 herpes virus and is more prevalent in areas subject to pollution from human activities (Foley *et*
157 *al.*, 2005), and levels of polychlorinated biphenyls are elevated in the blubber of genital
158 carcinomas of sea lions induced by a gamma herpes virus (Ylitalo *et al.*, 2005). Another example
159 is increased retroviral (feline immunodeficiency virus) infections in feral cats in urban settings
160 with high host densities, which is associated with increased risk of cancer in domestic cats
161 (Magden *et al.*, 2011, Hartmann, 2012). These infection-associated tumours emphasize the need
162 to consider infectious causation when the tumours are linked to immunosuppressive pollutants,
163 or more generally with human activities.

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

171 diversity and vulnerability to pathogens, accumulating evidence supports an association between
172 reduced genetic diversity, inbreeding and cancer (Ujvari *et al.*, 2018).

173

174 **Urban chemical pollution and cancer**

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

190 One of the possible research directions to pursue would be to study the mixture of
191 pollutants found in the air of cities. This pollution comes predominantly from local vehicular
192 traffic in urban areas with emission of gases, particles, volatile organic compounds, and
193 polycyclic aromatic hydrocarbons (PAHs), many of which are considered as carcinogens. An

194 increased risk of lung cancer associated with exposure to outdoor air pollutants has been
195 consistently found in several studies on humans (Raaschou-Nielsen *et al.*, 2013). Other agents
196 present in air pollution have been shown to be associated with mammary carcinomas in rodents
197 (i.e. benzene, kerosene, toluene, and xylenes, Huff *et al.*, 1989, Maltoni *et al.*, 1997) and human
198 breast cancer (i.e. nitrogen dioxide, benzene, PAHs, Labrèche *et al.*, 2010, Petralia *et al.*, 1999,
199 Crouse *et al.*, 2010). At the mechanistic level, this relationship between carcinogenesis and air
200 pollution is due to an increase of chromosome aberrations and micronuclei in lymphocytes (Sram
201 *et al.*, 2007, DeMarini, 2013), changes in the expression of genes involved in DNA damage and
202 repair, epigenetic effects (DNA methylation), inflammation, as well as telomere shortening,
203 immune response and oxidative stress (Loomis *et al.*, 2013).

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

215

216 **Light and noise pollution in urban environments**

217 In humans, the link between artificial light at night (ALAN) and cancer was first
218 established in female employees working rotating night shifts (reviewed by Chepesiuk, 2009),
219 and was lately also confirmed in the context of urbanization (Keshet-Sitton *et al.*, 2017). The
220 increased breast cancer risk in female night shift workers has been postulated to result from the
221 suppression of pineal melatonin production (Blask *et al.*, 2005). Melatonin, a hormone present in
222 all vertebrates and also in bacteria, protozoa, plants, fungi, and invertebrates, is involved in the
223 regulation of circadian rhythms; it peaks at night and is suppressed by light (Hardeland *et al.*,
224 2006). In a laboratory experiment, it was shown that even minimal light contamination (0.2 lux)
225 disrupted normal circadian production of melatonin and promoted tumour growth in rats
226 (Dauchy *et al.*, 2010). Direct links between ALAN, melatonin, and cancer prevalence have not
227 been established for wild animals so far. However, there are several examples of ALAN–wildlife
228 studies showing changes in the levels of hormones that have been related to cancer in humans
229 (e.g., testosterone in Siberian hamster *Phodopus sungorus*, Aubrecht *et al.*, 2014; corticosterone
230 in social voles *Microtus socialis*, Zubidat *et al.*, 2011; melatonin in mouse lemurs *Microcebus*
231 *murinus*, Le Tallec *et al.*, 2016; and European blackbirds *Turdus merula*, Dominoni *et al.*, 2013).

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

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

246 In addition to light pollution, anthropogenic noise pollution is an important
247 environmental stressor that is rapidly gaining attention among biologists and can, among other
248 effects, disrupt the normal sleep–wake cycle of animals (Francis & Barber, 2013). In laboratory
249 rats, noise stress increased plasma levels of stress hormones and oxidative stress (Said & El
250 Gohari, 2016). Continued oxidative stress can lead to chronic inflammation, which in turn could
251 exacerbate most chronic diseases including cancer (Reuter *et al.*, 2010). Studies on humans have
252 cautiously linked noise pollution levels to higher risks of non-Hodgkin lymphoma (Sørensen *et*
253 *al.*, 2015) and an increased risk of estrogen-receptor-negative breast cancer (Sørensen *et al.*,
254 2014). As expected, nothing is so far known about the effects of noise pollution on cancer
255 prevalence in wild animals. Nevertheless, house sparrow (*Passer domesticus*) nestlings reared
256 under traffic noise had reduced telomere length when compared with their unexposed
257 neighbours, an effect that could be mediated by oxidative stress (Meillere *et al.*, 2015). Shorter
258 telomeres have been linked to increased vulnerability of several types of cancer (e.g. Zhu *et al.*,
259 2016). In addition, noise exposure increased stress hormone levels and suppressed cellular
260 immunity in tree frogs (*Hyla arborea*; Troianowski *et al.*, 2017), and both of these effects are
261 generally considered to be cancer risk factors (e.g. Antoni *et al.*, 2006) . Because it is so difficult
262 to disentangle the effects of noise from other anthropogenic stress sources such as traffic

263 pollution, disturbance, or light pollution in the field, experimental studies on the physiological
264 effects of noise pollution on wild animals are needed.

265

266 **Changes in survival and life-history strategies**

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

281 While age can be a risk factor for cancer development, increased survival prospects can
282 also lead to changes in life-history strategies and physiological investment patterns, with higher
283 investments in self-maintenance over reproduction (Rozhok & DeGregori, 2016). For example, it
284 has been shown that reduced predation alone can substantially slow the rates of physiological
285 aging in mammals, leading to a “slower” life strategy (delayed reproduction and longer somatic

286 maintenance; Austad, 1993). A slower paced life with increased investment in self-maintenance
287 (with a trade-off in lower reproductive investment) has been suggested for birds living in urban
288 habitats (Sepp *et al.*, 2018, see also Brans *et al.* 2018 for the emergence of a life-history-
289 physiology syndrome in urban *Daphnia*). This can result in stronger cancer defence mechanisms
290 in animals in more stable, resource rich, and less risky habitats, as cities are for some species.
291 Accordingly, comparing urban and rural populations of wild animals could help to identify
292 physiological mechanisms related to tumour suppression. These types of studies would hugely
293 benefit if the age of the study subjects was known. We are therefore in urgent need of
294 establishing longitudinal research projects including urban and rural animal populations that
295 would allow us to take into account the age of the animal as well as distinguish the causes of
296 mortality in urban and rural wild animal populations.

297

298 **Conclusions and future directions**

299 Urbanization affects an ever-increasing number of wild animals and their habitats. Our
300 responsibility is to ensure that the development of human societies does not come at the expense
301 of wild animal diversity and health. At the same time, urbanizing wild animal populations could
302 be a promising model system for understanding the evolution of cancer and physiological
303 defences against it, and help to define the factors of the urban environment that have the
304 strongest potential to increase cancer risk. Studying cancer prevalence and defence mechanisms
305 in urban wild animals could therefore lead to a better understanding of how to develop an urban
306 environment with minimal negative health effects for both humans and wild animals. At the
307 same time, urban areas could be considered as natural laboratories for studying the evolution of

308 cancer. This is a promising research avenue, considering the notion that the fastest measured
309 rates of evolution are associated with human altered environments (Donihue & Lambert, 2014).

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

328 By acknowledging the diversity of cancer aetiologies, there is the possibility of detecting
329 the ecological conditions where anthropogenic impacts on the environment should increase or
330 decrease cancer prevalence. While most urban environmental factors (pollution, low-quality

331 food, infections) should increase cancer prevalence, some characteristics of the urban
332 environment can be considered cancer suppressive. For example, urbanization can affect
333 oncogenic pathogens more than their hosts, leading to fewer cancers caused by infection.
334 Similarly, increased resource availability can lead to better body condition and immune defences.
335 Urban environmental factors can act as selection pressures that may cause new mutations or act
336 on standing genetic variation within populations leading to both higher cancer probability
337 through DNA mutations, and to higher probability for genome-based cancer defence mechanisms
338 to arise (Johnson & Munshi-South, 2017).

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

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

354 those traits and (3) experimental manipulation to directly identify drivers of those trait
355 differences (Donihue & Lambert, 2014).

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

366 The second step would be to study differences in genes related to tumorigenesis or tumor
367 suppression between wild animals from urban and rural habitats. As an example, a study in the
368 flounder (*Platichthys flesus*) found higher polymorphism of the known tumor suppressor gene
369 p53 in populations living in highly contaminated versus reference estuaries (Marchand et al.,
370 2010). As a third step, experimental evolutionary approaches using urban environmental
371 characteristics (i.e., the use of laboratory or controlled field manipulations to investigate
372 evolutionary processes) are needed, since they may not only intensify the selection of already
373 known suppressive mechanisms, but could also lead to the discovery of novel tumour suppressor
374 mechanisms (Vittecoq *et al.*, 2018). Both field and experimental evolutionary studies have
375 demonstrated that organisms exposed to environmental oncogenic factors can - sometimes
376 rapidly - evolve specific adaptations to cope with pollutants and their adverse effects on fitness

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

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

392

393 **Authors' contributions**

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

396

397 **Acknowledgements**

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

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

404

405

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697 Figure 1. Flow chart of possible experimental designs for studying cancer in wild populations.

698 Steps proposed here are based on the suggestions for studying evolution in urban

699 environments by Donihue and Lambert (2014).

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