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## Title

Cancer and mosquitoes – an unsuspected close connection

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## 1 **Introduction**

2 Cancer is a major public health problem, with an estimated 18.1 million new cases and 9.6  
3 million deaths in 2018 (Bray et al., 2018). Moreover, high population growth, aging, and  
4 increased exposure to pollutants are causing a rapid worldwide increase in cancer incidence  
5 and mortality in countries with different levels of economic wealth (Bray et al., 2018; Torre et  
6 al., 2015). The predicted burden is so high that cancer is thought to be the only important  
7 obstacle to an increase of life expectancy during the 21<sup>st</sup> century (Torre et al., 2015), and it is  
8 expected to become the leading cause of death worldwide.

9 Meanwhile, mosquitoes represent a global public health problem because they act as  
10 vectors for viruses, bacteria and protozoa (Mehlhorn et al., 2012), including, among others,  
11 agents of malaria, filariasis, encephalitis, yellow fever, dengue, West Nile fever, chikungunya,  
12 and, more recently, Zika. Mosquito-borne infectious diseases cause significant morbidity and  
13 mortality worldwide, with more than 700 million people infected and more than a million  
14 deaths annually (Caraballo and King, 2014). They represent a growing problem, with  
15 mosquito invasions occurring throughout the world and affecting every continent but  
16 Antarctica (Masterson, 2019).

17 Regarding the dramatic global impacts of these two concerns for humans, it is crucial to  
18 investigate whether they have a reciprocal connection. Indeed, cancers and mosquito-borne  
19 pathogens are both globally distributed, therefore affecting the same populations and can co-  
20 occur within the same individuals. Knowing whether there is a connection between cancers  
21 and mosquito-borne pathogens could also be helpful not only for forecasting the net impact of  
22 the different control strategies on human health, but also for envisioning integrative strategies  
23 targeting the two problems at the same time. Unfortunately, very few studies (Benelli et al.,  
24 2016) have examined the link between these two threats, and the existing ones have generally

25 focused only on the transmission of oncogenic pathogens through mosquitoes (Marcondes and  
26 Benelli, 2019; Ward et al., 2016).

27 In this review, we provide an overview of the possible links between mosquitoes and  
28 cancer. To do so, we focus on (i) the impact of mosquitoes on carcinogenesis in humans, (ii)  
29 the impact of cancer development in humans on mosquito behaviour, and (iii) the  
30 consequences of cancers in mosquitoes and on their disease transmission potential (see  
31 Figure). We will then discuss the most promising research avenues on this topic and the  
32 public health strategies that could be envisioned in this context.

33

#### 34 **Impact of mosquitoes on carcinogenesis**

35 We first focus on how mosquitoes can promote the risk of developing cancer in humans. In  
36 this part, we show that this risk could result from the (i) transmission of oncogenic pathogens,  
37 (ii) inflammatory reactions following mosquito blood meals, (iii) non-inflammatory effects of  
38 indirectly oncogenic mosquito-borne pathogens, and (iv) direct transmission of cancer cells.

39

#### 40 *Oncogenic pathogen transmission.*

41 Over the last decades, an increasing number of infections have been linked to the  
42 development of human and animal cancers (Ewald and Swain Ewald, 2015; McAloose and  
43 Newton, 2009; Parkin, 2006; Zur Hausen, 2009). The frequency of cancers with an infectious  
44 causation has certainly been underestimated because cancer symptoms generally occur after  
45 years of development, therefore making the identification of a causal link extremely  
46 challenging. Nevertheless, current estimates are that 20% of cancer cases have an infectious  
47 causality (Parkin, 2006; Zur Hausen, 2009), and it has been suggested that underlying  
48 infectious agents can only actually be strictly excluded in 5% of cancer cases (Ewald, 2009).  
49 Epidemiological studies suggest that the current increase in emerging pathogen transmission

50 (Jones et al., 2008) could have a substantial effect on the future burden of cancer worldwide  
51 (currently around two million cancer cases annually are known to be caused by an infectious  
52 agent) (De Martel et al., 2012).

53 An infectious agent is considered as an oncogenic pathogen when the infection is a  
54 prerequisite for the occurrence and/or the development of cancer (Zur Hausen, 2009).  
55 Oncogenic pathogens may make a direct contribution to cancer development, most commonly  
56 through integration of their DNA into the host genome (*e.g.* Epstein-Barr virus (Moormann et  
57 al., 2011)). According to Ward et al. (2016), many of the pathogens that are likely to promote  
58 cancer development (Ewald and Swain Ewald, 2012; Plummer et al., 2016) could possibly be  
59 transmitted through mosquitoes because they can be found in blood (Ward et al., 2016). This  
60 category of pathogens includes *Plasmodium* species, Epstein–Barr virus, Kaposi sarcoma  
61 herpesvirus, Hepatitis B virus and Hepatitis C virus (Ward et al., 2016). Moreover, it has also  
62 been suggested that mosquitoes may be able to transmit unknown viruses that could be linked  
63 with cancer (Benelli et al., 2016; Lehrer, 2010a).

64 The International Agency for Research on Cancer has recently mentioned malaria, which is  
65 caused by the mosquito-borne protozoan *Plasmodium* and produces 228 millions new  
66 infections every year, as a probable oncogenic pathogen (WHO, 2019). This parasite can have  
67 a direct action on carcinogenesis because analogies at the cellular level have been reported for  
68 malaria and gastrointestinal tumours (Suresh et al., 2005). The association between malaria  
69 and the risk of developing cancer could be explained by the ability of *Plasmodium* parasites to  
70 induce the immune response towards the destruction of plasmodium-infected cells (Degarege  
71 et al., 2009), which could decrease the immune system's ability to target cancer cells. This  
72 action could also be indirect, especially through reactivation of oncogenic viruses. For  
73 instance, endemic Burkitt lymphoma occurs at higher incidences in areas where malaria is  
74 endemic because *Plasmodium falciparum* fuels transmission of Epstein Barr virus that is

75 associated with more than 95% of cancer cases (Burkitt, 1961). Burkitt lymphoma is an  
76 aggressive B-cell malignancy (Brady et al. 2007). The B-cells are the primary targets of  
77 Epstein Barr virus (a known oncogenic pathogen) infection (Shannon-Lowe et al., 2017). By  
78 stimulating the proliferation of B-cells, *Plasmodium falciparum* could enhance oncogenic  
79 effects of the Epstein Barr virus on these target cells (Ewald and Swain Ewald 2014).  
80 Knowing that mosquito-borne pathogens could stimulate antibody production (*e.g.*,  
81 stimulating B-cell replication), there is good reason to think that other pathogens might  
82 similarly contribute to amplified the oncogenic effect of Epstein Barr virus.

83 This connection is supported by the fact that several studies have found a significant  
84 relationship between malaria cases and mortality across all cancers in all 50 states of the USA  
85 (Lehrer, 2010a, 2010b). More specifically, relationships between malaria outbreaks in the  
86 USA and reports of brain tumour incidence have also been observed (Lehrer, 2010a, 2010b).  
87 While these results strongly suggest an association between malaria and cancer, they do not  
88 provide a direct proof of causality between these two pathologies.

89 It is worth pointing out that other studies found that the stimulation of the host immune  
90 system could also limit cancers development and progression. For example, malaria infection  
91 can reduce the growth of lung tumours via the induction of innate and adaptive anti-tumour  
92 responses in a mouse model (Chen et al., 2011; Faure, 2016). Therefore, the interaction  
93 between *Plasmodium* parasites and cancer might be complex and needs much more  
94 investigation.

95

96 *Immune reaction following the mosquito blood meal.*

97 Mosquito blood meals are characterised by an edema and an inflammatory influx of  
98 neutrophils that yield localised innate immune reactions (Pingen et al., 2016). This  
99 inflammation induces different immune responses, which are different for each mosquito

100 species (Donovan et al., 2007; Fontaine et al., 2011; Schneider et al., 2011, 2004), and  
101 accompanied by tissue damage, which could increase the risk of developing cancer (Coussens  
102 and Werb, 2002; Hanahan and Weinberg, 2011; Johansson and Ward, 2017). Moreover, it is  
103 now becoming clear that the tumour's microenvironment, which is largely organised by  
104 inflammatory cells, is driving the neoplastic process by fostering the proliferation, survival,  
105 and migration of cancer cells (Coussens and Werb, 2002). Therefore, in areas where humans  
106 are particularly exposed to mosquito bites, the risk of developing cancer should rise following  
107 exposure to multiple mosquito blood meals. To the best of our knowledge, this has never been  
108 investigated.

109

#### 110 *Mosquito-borne transmission of indirectly oncogenic pathogens*

111 Each mosquito-borne pathogen can also indirectly contribute to carcinogenesis by inducing  
112 changes in the microenvironment via inflammation or the immunomodulation they produce  
113 (Dalton-Griffin and Kellam, 2009; Jacqueline et al., 2018; Zur Hausen, 2009). In this case,  
114 their diversity of action ranges from chronic inflammation (*Helicobacter pylori*, which is  
115 associated with 65% of stomach cancers (Sepulveda, 2013)) to immunosuppression (HIV  
116 (Gopal et al., 2014)). Moreover, pathogen persistence within the host induces successive  
117 genetic, epigenetic, and/or immune changes that facilitate cancerous development (Ewald and  
118 Swain Ewald, 2012; Ewald and Swain Ewald, 2013).

119

#### 120 *Direct transmission of cancer cells.*

121 While not observed in natural conditions, a study has shown that a hamster reticulum cell  
122 sarcoma, named TM, can be transmitted by the mosquito species *Aedes aegypti* through a  
123 direct transfer of cancer cells (Banfield et al., 1966, 1965). When passed by subcutaneous  
124 transplantation within the hamsters, cancer cells appear in their blood after five days and

125 increase constantly until reaching a high density just before host death (greater than 100,000  
126 per mm<sup>3</sup>). TM cancer cells remained viable for up to eight hours after ingestion by the adult  
127 mosquito, and only 1 to 2% of the mosquitoes tested had viable cancer cells after several  
128 days, which could be due to the digestion processes in the mosquito gut. Mosquitoes carrying  
129 cancer cells were able to implant these cells into 5 to 10% of other hamsters (Banfield et al.,  
130 1966, 1965).

131

### 132 **Consequences of cancers in humans on mosquitoes**

133 A variety of changes in mosquito behaviour have been reported when they are exposed to  
134 people infected with pathogens (Busula et al., 2017; Emami et al., 2017; Lacroix et al., 2005;  
135 Robinson et al., 2018). Infection induces a change in host odour, CO<sub>2</sub> blood concentration,  
136 and many other physiological factors (Cummins et al., 2014; Shirasu and Touhara, 2011),  
137 which could impact the attractiveness of mosquitoes for infected hosts. Since cancer can  
138 influence many aspects of host physiology, it could similarly influence attraction of  
139 mosquitoes.

140 Malignant cancers are often associated with a higher iron level in blood (Kwok, 2002).  
141 This surplus of iron is needed during early steps of tumour development, *i.e.*, enhanced  
142 survival (Bauckman et al., 2015) and proliferation of transformed cells (Steedmann-  
143 Olmedillas, 2011), as well as during late stages to promote the metastatic cascade (Jung et al.,  
144 2019). Moreover, iron is required for optimal egg development and viable offspring in  
145 mosquitoes (Zhou et al., 2007), suggesting that blood meal with higher iron concentration  
146 may impact mosquito behaviour and reproduction (hence vector population dynamics and  
147 infectious disease transmission intensity).

148 Some cancers can change human odour (Shirasu and Touhara, 2011). For example,  
149 patients with gynaecological tumours also complain of heavy vaginal discharge with an

150 offensive odour resulting from the production of acetic, isovaleric, and/or butyric acids (Kuge  
151 et al., 1996). Matsumura et al. have shown that the urine from mice with artificially induced  
152 cancerous lung tumours could be clearly discriminated from non-affected (control) mice by  
153 the detection of volatile biomarkers in their urine (Matsumura et al., 2010). Dogs are also able  
154 to detect these odour modifications and so can be used as potential detectors of different  
155 cancers, such as melanoma, bladder cancer, ovarian cancer, and colorectal cancer (Horvath et  
156 al., 2008; McCulloch et al., 2006; Pickel et al., 2004; Sonoda et al., 2011; Willis et al., 2004).  
157 Other study have investigated the potential of using the *Drosophila*'s olfactory system to  
158 recognise cancer cells by their scent (Strauch et al., 2014).

159 Cancer can also change the CO<sub>2</sub> concentration in the blood (major driver of mosquito host  
160 seeking behaviour). Lung cancer is often associated with dyspnea (shortness of breath) or  
161 previous respiratory disease including chronic bronchitis, emphysema, or pneumonia, all of  
162 which can alter the CO<sub>2</sub> concentration in the blood (Brenner et al., 2012). Dyspnea was also  
163 observed for other cancers (e.g., breast cancer, lymphoma) but could be linked to risk factors  
164 such as a history of smoking, asthma, or chronic obstructive pulmonary disease or a history of  
165 exposure to asbestos (Dudgeon et al., 2001).

166 Since cancer can modify many physiological factors in humans, we would expect that their  
167 attractiveness to mosquitoes could also be altered. This suggests that individuals with cancer  
168 could be more or less actively targeted for the transmission of mosquito-borne pathogens.

169

### 170 **Consequences of cancers in mosquitoes on humans**

171 No study has yet detected natural cancer in mosquitoes, so the impact of cancer on  
172 mosquito life history traits is highly speculative at the moment. Nevertheless, several types of  
173 tumours occurring naturally (Robert, 2010; Salomon and Rob Jackson, 2008; Scharrer and  
174 Lochhead, 1950) or triggered by genetic engineering (Mirzoyan et al., 2019), including

175 neuroblastoma, ovarian, and imaginal disk tumours, have been reported in different insect  
176 species, especially in *D. melanogaster* (Mirzoyan et al., 2019; Salomon and Rob Jackson,  
177 2008). It is therefore possible that natural cancers exist in mosquitoes and have significant  
178 effect on traits such as longevity, fecundity, or feeding-behaviour.

179 Changes in an organism's life-history traits may be an adaptive response to a parasitic  
180 infection (Adamo, 1999; Minchella and Loverde, 1981; Polak and Starmer, 1998). One  
181 solution developed by many animal species against biotic aggressors (such as parasites) is the  
182 adjustment of life-history traits to compensate for their negative effects on fitness (Forbes,  
183 1993; Hochberg et al., 1992; Michalakis and Hochberg, 1994; Thomas et al., 2000). An  
184 example is the work by Vézilier and colleagues, which shows that mosquitoes infected by  
185 *Plasmodium* species lay their eggs two days earlier than non-infected ones (Vézilier et al.,  
186 2015) to compensate for the rapid decrease in egg quality observed in infected mosquitoes.  
187 This type of adaptive response can have consequences on mosquito communities and  
188 indirectly on the evolution of pathogen communities.

189 Because malignancies usually also reduce survival, and hence potentially host fitness, a  
190 similar process could also exist in this context. Indeed, it has been shown that *Drosophila*  
191 *melanogaster* harbouring an early gut cancer adjust their life-history traits by having their  
192 egg-laying period peak two days earlier than normal, which would maximise their immediate  
193 reproductive effort and therefore compensate for the reduced survival (Arnal et al., 2017).

194

## 195 **Conclusion and perspectives**

196 Despite the significant impact of cancers and mosquito-borne diseases on human health,  
197 there is little documented evidence of a relationship between these two concerns for humans.  
198 Briefly, we know that the direct transmission of cancer cells is mechanistically possible based  
199 on a single experimental model and that mosquitoes can transmit oncogenic pathogens or

200 induce immune reactions, which could favour carcinogenesis. In addition, we have seen  
201 evidence that cancer in humans or in insect can alter the insect's life history traits, hence  
202 pathogen transmission dynamics. Nevertheless, the impact of these connections *in natura*  
203 needs to be quantified, especially in populations affected by these two threats.

204 First, we need to determine if there are more oncogenic pathogens transmitted by  
205 mosquitoes than are currently observed, especially by refining our knowledge on the  
206 oncogenic capacities of malaria. Identifying such connections between pathogens and cancer  
207 could have a strong impact on prevention strategies, as exemplified by the papillomavirus  
208 vaccine that avoids cases of cervical cancer by protecting against its infectious causation.  
209 Moreover, this interaction could be more complicated because mosquito bites can create  
210 immunosuppression, which can favor proliferation of oncogenic pathogens but also directly  
211 cancer development (so called "promoter arthropods" hypothesis (Coluzzi et al., 2003, 2002)).  
212 In the case of mosquito-borne pathogens, identifying such connections could create an  
213 unprecedented synergy between vector control programs and the prevention of numerous  
214 cancer cases, with paying much attention on using insecticides to avoid increasing cancer risk.

215 It is worth pointing out that the vast majority of blood feeding events will be by  
216 mosquitoes engaging in their first (*i.e.* mosquitoes are non-infectious) blood meal or by  
217 mosquitoes that do not carry infectious agents from previous blood meals. Thus, while all  
218 feeding events will cause inflammatory reactions and possibly impact cancer dynamics, only a  
219 small proportion of feeding events will involve the vectoring of infectious agents.

220 Regarding the huge number of people living in areas affected by mosquitoes, investigating  
221 the link between the rate of mosquito bites and the probability of developing cancer through  
222 local inflammation could also be very informative. Experimental studies are first required to  
223 evaluate the immunomodulation effect after exposure to mosquito saliva (therefore mosquito  
224 blood meal) on cancer development and to characterise interactions between the inflammatory

225 process involved following mosquito blood meals and the one involved in cancer initiation.  
226 Second, large-scale statistical analyses are now possible due to improved both cancer  
227 surveillance in tropical countries and mosquito surveillance in the North hemisphere  
228 (Sankaranarayanan, 2014).

229 Importantly, experiments on mosquito transmission of cancer cells must be repeated with  
230 different host species, different mosquito species, and different types of cancer cells. While  
231 very promising, these experiments cannot conclusively prove the existence of such  
232 transmission in the field, and most importantly to humans. Once mosquito transmission has  
233 been quantified experimentally in a more robust way, the question of the importance of this  
234 transmission route *in natura* can be addressed.

235 Experiments on odour modification in people affected by cancer and its correlation with  
236 mosquito attractiveness can quantify the impact of human cancer development on mosquito  
237 behaviour. The technical tools are available today (Vantaux et al., 2018) to perform such  
238 experiments, and the integration of such information to epidemiological models could provide  
239 a first estimation of the impact of human cancers on the epidemiology of mosquito-borne  
240 pathogens (Roux et al., 2015).

241 Finally, the potential consequences of natural cancers in mosquitoes on human health  
242 could be also important. We first need to identify natural cases of cancer in mosquitoes, even  
243 if the prevalence is low. Once this has been quantified, we can expose mosquitoes to  
244 radiation, pesticides or other xenobiotic agents. We can also use genetic engineering to create  
245 cancerous mosquitoes in order to design experiments to study the evolution of mosquito life  
246 history traits when a cancer affects them.

247 To conclude, it is essential to develop integrative strategies considering both cancers and  
248 mosquito-borne pathogens. Such a research avenue will require inter-disciplinary  
249 collaborations from evolutionary biologists, entomologists, experts in chemical ecology,

250 oncologists, immunologist, epidemiologists, and public health experts. Considering the  
251 potentially huge impact of such connections, quantifying them to forecast the impact of  
252 different control strategies for human health should lead to promising benefits.

253

#### 254 **Figure list**

255 **Figure 1.** Schematic representation of the possible connections between mosquitoes,  
256 mosquito-borne diseases, and cancer. (A) The impact of mosquitoes on carcinogenesis in  
257 humans, including the mosquito transmission of oncogenic pathogens (symbolized here by a  
258 human herpesvirus 8), the mosquito transmission of cancer cells from a cancerous person to  
259 another susceptible person, and the possible immune reactions following mosquito blood  
260 meals. All these processes could increase the risk of developing cancer in the human  
261 population. (B) The possible negative or positive impact of cancer on human attractiveness to  
262 mosquitoes, and therefore on the transmission intensity of mosquito-borne diseases, and (C)  
263 the possible negative or positive impacts that natural cancers could have on mosquito  
264 phenotype (lifespan, fecundity, feeding behaviour) and therefore on their vector capacity.

265

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