REVIEW ARTICLE

Cancer and life-history traits: lessons from host–parasite interactions

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SUMMARY

Despite important differences between infectious diseases and cancers, tumour development (neoplasia) can nonetheless be closely compared to infectious disease because of the similarity of their effects on the body. On this basis, we predict that many of the life-history (LH) responses observed in the context of host–parasite interactions should also be relevant in the context of cancer. Parasites are thought to affect LH traits of their hosts because of strong selective pressures like direct and indirect mortality effects favouring, for example, early maturation and reproduction. Cancer can similarly also affect LH traits by imposing direct costs and/or indirectly by triggering plastic adjustments and evolutionary responses. Here, we discuss how and why a LH focus is a potentially productive but under-exploited research direction for cancer research, by focusing our attention on similarities between infectious disease and cancer with respect to their effects on LH traits and their evolution. We raise the possibility that LH adjustments can occur in response to cancer via maternal/paternal effects and that these changes can be heritable to (adaptively) modify the LH traits of their offspring. We conclude that LH adjustments can potentially influence the transgenerational persistence of inherited oncogenic mutations in populations.

Key words: Cancer, evolutionary ecology, life-history traits, parasites, plasticity.

INTRODUCTION

Cancer, a leading cause of human death worldwide, occurs across phylogenetical lineages, suggesting that cancer may have been present throughout the evolutionary history of multicellular organisms (Merlo *et al.* 2006; Aktipis and Nesse, 2013; Nunney, 2013). Despite the widespread existence of cancer in the animal kingdom, oncology and other sciences have until very recently developed in relative isolation. This is unfortunate given that links between these disciplines have the reciprocal potential to reveal new directions for research and perspectives as well as proposing new therapeutic solutions. For example, it is increasingly acknowledged that applying ecological and evolutionary theory to cancer allows researchers to improve techniques to control malignant progression and prevent therapeutic failures (Aktipis and Nesse, 2013; Thomas *et al.* 2013; Rozhok and DeGregori, 2015). In addition, considering the ecological contexts in which cancers occur in wildlife improves our understanding of the evolution of the pathology itself, as well as to its theoretical potential to shape organism traits (Kokko and Hochberg, 2015). Ecologists have also proposed that oncogenic

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phenomena have important influences on shaping animal behaviour, life history and even ecosystem functioning (Vittecoq *et al*. 2013, 2015).

Here, we propose a research direction deserving of more attention concerning life-history (LH) responses displayed by animals in the face of cancer risks and/or malignant progression. The primary reasons this topic has until now been poorly investigated are because it is often assumed that: (i) cancer in wildlife is rare; and (ii) adaptive responses against cancer are unlikely to evolve because cancer is a post-reproductive disease (see Vittecoq *et al*. 2013). However, evidence increasingly indicates that cancer is in fact likely to be common in wildlife, and has been documented in a diverse array of taxa from invertebrates to large mammals (Table 1). Furthermore, cancer can increase the risk that animals die early in life due to predation or parasitism (Martineau *et al*. 2002; McAloose and Newton, 2009). For example, oncogenic phenomena in wildlife (as in humans) encompass a large range of more or less malignant tumours, ranging from benign neoplasms to metastatic malignancies that induce various consequences on health and vigour, such as early death and decreased reproductive potential (Table 1; see also Vittecoq *et al*. 2013). As a result of these negative effects, animals can become more susceptible to interspecific interactions (especially predation and parasitism) that result in death *prior* to the end of the reproductive period. Together, these observations suggest that natural selection should favour adaptations that prevent cancer-induced reductions in fitness, just as we would expect for any other infections (Thomas *et al*. 2009). Thus, we draw on the literature related to parasitism and its effects on LH traits to guide us towards profitable avenues for cancer research. Whereas proximate mechanisms guarding against cancer, such as lower somatic mutation rates and redundancy of tumour suppressor genes, are currently being extensively studied in some wildlife species (Caulin and Maley, 2011; Roche *et al*. 2012), thus far much less attention has been paid to other traits, such as LH adaptations.

Infection and cancer in multicellular organisms

Importantly, cancer cells not only act similarly to parasites by diverting energy and resources from other vital functions of the host, but also a substantial proportion of malignancies are caused by infections (ca. 20% of human cancers; Ewald and Swain Ewald, 2015). Thus, infections could contribute to cancer directly or indirectly. Direct initiation results from pathogens (particularly intracellular parasites) altering cellular regulatory mechanisms (e.g. apoptosis and cell-cycle arrest) and cell proliferation rates, and therefore breaking down cellular barriers that would otherwise prevent oncogenesis. Infection-induced inflammatory responses may also result in increased mutation rates and compromised proliferation signals, and concomitantly indirectly initiate malignant transformations (reviewed in Ewald and Swain Ewald, 2012, 2013). Although protozoans (e.g. *Plasmodium falciparum*, Molyneux *et al*. 2012), bacteria (e.g. *Helicobacter pylori*, Mager 2006; Ewald and Swain Ewald, 2014) and trematodes (e.g. *Schistosoma haemotobium*, Mostafa *et al*. 1999; Ewald and Swain Ewald, 2014) have all been shown to directly or indirectly cause malignancies, viruses are the most frequent sources of infection-induced cancers (reviewed by Ewald and Swain Ewald, 2015). While oncogenic pathogens and their induced malignancies are well documented in humans and domestic animals, they are less well recorded in undomesticated captive animals, and are largely undetected in nature. Ewald and Swain Ewald (2015) have proposed several explanations for why cancer is rarely found in natural populations: (1) although benign neoplasms occur pervasively in multicellular organisms they rarely transition to detectable malignant tumours; (2) reduced survival due to malignancy [as a direct (detrimental to health) or indirect (increased predation) consequence of cancer] hinders detectability; and (3) diagnostics and evaluation of malignancy are inconsistent across species. The full scope of infection-induced cancers is still not known for any multicellular species, but interestingly infection-induced cancers are known to occur at young ages (e.g. cervical cancer in humans).

Cancer, being induced by pathogens or acting analogously to parasites, or both, clearly has a major impact on host' LH traits. We next discuss cancer as selective force on host LH traits.

Why should cancer influence LH traits?

Cancer, both solid tumours and blood cancers, can be thought of as a developing species that behaves in a manner akin to parasites (Duesberg *et al*. 2011). As far as host LH traits are concerned, parasites likely play an important role in their evolution because they often impose important selective pressures on the host (Michalakis and Hochberg, 1994). Similarly, cancer cells depend on their hosts for sustenance, proliferating inside their bodies, exploiting them for energy and resources, and thereby impairing their health and fitness. Based on these similarities, it is predicted that several of the responses that have evolved in the context of host–parasite interactions should also be relevant in the context of cancer (Vittecoq *et al*. 2013). Evolutionary theory on host–parasite interactions postulates that host species should also be under selective pressures to avoid the source of the pathology in the first instance (e.g. Hart, 1994), then prevent its progression once infected, and finally alleviate the fitness costs if further development is not preventable (Thomas *et al*. 2009).

Table 1. Examples of cancers observed in different metazoan groups and their potential impacts on host LH traits (modified from Vittecoq *et al*. 2015).

Common name	Latin name	Context and prevalence	Cancer type	Factors favouring cancer	Potential impact on host LH traits	Reference
Invertebrate						
Hydra	*Pelmatohydra robusta*	Laboratory population, unknown	Undetermined	Genetic predisposition	Reduced population growth rate, reduced capacity of egg production. Tumour-bearing polyps have significantly reduced fitness	Domazet-Loso *et al*. (2014)
Blue mussel	*Mytilus trossulus*	Cultured and wild populations, up to 40% in northeast Pacific	Haemic neoplasia	Unknown	Increased mortality. Haemocytes showing significantly less phagocytic capacity leading to reduced immune function and mortality	Ciocan *et al*. (2006); Ciocan and Sunila (2005); Galimany and Sunila (2008)
Soft-shell clam	*Mya arenaria*	East coast of North America, up to 100% in affected areas	Haemic neoplasia	Retrotransposon (Steamer)	Increased mortality. Haemocytes showing significantly less phagocytic capacity leading to reduced immune function and mortality	Metzger *et al*. (2015)
Common fruit fly	*Drosophila melanogaster*	Laboratory population, 19% in 5-week old males	Gut and testis tumours	Unknown	Altered egg production, females with cancer reach peak oviposition earlier than healthy females	Salomon and Jackson (2008)
Fish						
Yellow sea horse & weedy sea dragon	*Hippocampus kuda* & *Phyllopteryx taeniolatus*	Captive (zoo), 9 out of 172 syngnathids analysed, mostly adult males	Cardiac rhabdomyosarcoma, renal adenocarcinoma, renal adenoma, lymphomas, exocrine pancreatic carcinoma, intestinal carcinoma	Unknown	Cancer potentially impacts feeding and predator evasion, as well as might reduce reproductive output by primarily affecting males (male sea horses being the carers of eggs)	LePage *et al*. (2012)
Coral trout	*Plectropomus leopardus*	Free-living, 15% in part of the Great Barrier Reef	Melanomas	Genetic predisposition – potentially associated with hybridization with another Plectropomus species	Fish with cancer are potentially less active and feed less	Sweet *et al*. (2012)
Amphibians						
African clawed frog	*Xenopus laevis*	Laboratory population, 5% in the studied population	Various forms the most common being hepatomas, ovarian tumours and teratomas	Various, e.g. virus, bacterium (*Myocobacterium marinum*)	In some cases diseased individuals stop feeding and die. Ovarian tumours might impair reproduction	Balls (1962); Goyos and Robert (2009); Hardwick and Philpott (2015)
Reptiles						
Green turtle	*Chelonia mydas*	Free-living, up to 58% in the Hawaiian archipelago	Tumours of the skin, flippers, periocular tissues, carapace and plastron; nodules can also be found in all internal organs	Herpes virus infection	High mortality rates, impaired movements. Rapidly growing tumours disrupt the turtle's biologic functions (swimming, diving), predator evasion and feeding	Brill *et al*. (1995); Chaloupka *et al*. (2009); Page-Karjian *et al*. (2014)

Table 1. (*Cont.*)

Common name	Latin name	Context and prevalence	Cancer type	Factors favouring cancer	Potential impact on host LH traits	Reference
Egyptian mastigure	*Uromastyx aegyptius*	Captive (zoo), 53% in the studied population	Multicentric lymphomas	Unknown	High mortality rate. Lymphomas impair feeding, increase parasite burden and cause organ failure	Gyimesi *et al.* (2005)
Birds						
Rock dove	*Columba livia*	Laboratory population, 34% in the studied population	Various forms, the three most frequent cancers are seminomas, thyroid adenomas and lymphomas	Unknown	Adenocarcinomas of the female reproductive tracts and seminomas of testicles might impair reproduction	Shimonohara *et al.* (2012)
Domestic chicken	*Gallus gallus*	Breeding stocks, tumour commonly causes ⩾1%–2% mortality of birds, with occasional losses of ⩾20%	Lymphoid leucosis	Avian leucosis virus	Subclinical infection decreases egg production and quality, and hence reproduction	Dunn (2013)
Mammals						
Tasmanian devil	*Sarcophilus harrisii*	Free-living, up to 80% in 2–3 year-old individuals	Tasmanian DFTD	Low genetic variation	High mortality rates, tumours on head impair vision and feeding. DFTD spreads via social interactions, primarily during mating. High mortality rates at reproductive age caused shift in reproductive strategy to semelparous from iteroparous	McCallum *et al.* (2007)
Santa Catalina Island fox	*Urocyon littoralis catalinae*	Population living on Santa Catalina Island, 48·9% of dead foxes examined from 2001 to 2008, 52·2% randomly sampled live mature animals	Ceruminous gland dysplasia and hyperplasia	Indirectly caused by ear mite (*Otodectes cynotis*) infection	The gross proliferative lesions and invasive carcinomas infiltrating adjacent bones may impair hearing and hence the hunting ability of the animals	Vickers *et al.* (2015); Moriarty *et al.* (2015)
Beluga	*Delphinapterus leucas*	Free-living, 27% of the adults found dead in St. Lawrence estuary	Various forms, most frequent cancers are adenocarcinoma of the intestine and stomach. Ovarian cancers in females	Probable role of the polycyclic aromatic hydrocarbons found in beluga's prey	High mortality rates. Intestinal carcinomas alter nutrition absorption, ovarian tumours might impair reproduction	Martineau *et al.* (2002)
California sea lion	*Zalophus californianus*	Free-living, 18–25% of animals examined post-mortem	Genital tract carcinomas	Genotype, persistent organic pollutants and herpesvirus	Since the urogenital carcinoma affects sub-adult and adult animals of both sexes (cervix and vagina of females and the penis, prepuce and urethra of males) it could potentially alter reproduction and LH strategies of seals	Browning *et al.* (2015)

Costs on LH traits

Parasitic organisms exploit their host for resources that could otherwise be used for maintenance, growth and/or reproduction (Poulin, 2007; Schmid-Hempel, 2011). Direct costs resulting from this exploitation can cause inter-individual (or inter-population) variation in LH traits such as fecundity and survival (Thomas *et al.* 2000). At the same time, inter-individual differences in physiology and LH productivity may 'drive' or encourage consistent variation in behaviour (Biro and Stamps, 2008; Biro *et al.* 2014), and differences in behaviour can in turn affect the likelihood of encounter rates with parasites and transmission of them between one another (Boyer *et al.* 2010; Dunn *et al.* 2011; Bull *et al.* 2012; Seaman and Briffa, 2015). Thus, inter-individual (or inter-population) variation in LH traits could at the same time be both causes and consequences of parasitism. Additionally, direct modifications of the host's LH traits may also result from toxic products of the parasite's metabolism (Michalakis, 2009). Finally, the complex machinery constituting the immune system often incurs metabolic costs that indirectly generate modifications of the host's LH traits as a result of trade-offs (Sorci *et al.* 2009). The extent to which these trade-offs are manifest are likely to differ among individuals that differ in their energetic and productive capacities (van Noordwijk and de Jong, 1986; Reznick *et al.* 2000; Biro and Stamps, 2008).

In the context of malignancies, the time elapsing from the appearance of the first cancerous cells to the development of a metastatic cancer may vary from weeks to years, or even decades, depending on individuals and types of cancer. The shape of the relationship between health/fitness-related traits and tumour development is not precisely known for most species and most cancers (see Vittecoq *et al.* 2015). Nonetheless, individuals harbouring tumours are likely to be, sooner or later, in a worse condition than healthy individuals on average, even if individuals differ in their intrinsic energetic and LH capacities. Frequent symptoms of cancer are extreme tiredness (fatigue) or weight loss, resulting from cancer cells using up much of the body's energy supply, or releasing substances that modify the way the body derives energy from food (Wagner and Cella, 2004; Ryan *et al.* 2007). Although cancer-related fatigue is one of the most prevalent symptoms in cancer sufferers, the precise aetiology of this distressing and debilitating symptom remains poorly understood. Given that energy allocation relative to energy acquisition is at the heart of predictions for how competing LH traits might be affected by such energy 'drains' (van Noordwijk and de Jong, 1986), a research focus on energetics might thus be very informative for understanding LH responses to cancer.

Plastic adjustments of LH traits

Host LH traits can undergo flexible and adaptive responses to parasitism in order to compensate for the negative costs exerted by parasites on host fitness (Hochberg *et al.* 1992; Michalakis and Hochberg, 1994). For instance, hosts unable to resist infection by other means (e.g. immunological resistance, inducible defences or long-distance migration) are theoretically favoured by selection if they partly compensate the parasite-induced losses by reproducing earlier (Forbes, 1993) or if their behaviour impedes the transmission of the parasite in spatially structured contexts (Débarre *et al.* 2012). Infected individuals may, for instance, increase their reproductive activities before dying or being castrated by parasites (Minchella and Loverde, 1981; Sorci *et al.* 1996; Polak and Starmer, 1998; Adamo, 1999), or simply increase their fitness through kin selection-mediated effects (Débarre *et al.* 2012; Iritani and Iwasa, 2014). Among recent examples, Vézilier *et al.* 2015 demonstrated that female mosquitoes parasitized by *P. falciparum* begin laying their eggs two days earlier, thereby compensating the loss of fecundity due to their reduced lifespan. In the context of cancer, preliminary results (Arnal *et al.* unpublished data) suggest that females in *Drosophila* harbouring early stages of tumours tend to reach the peak of oviposition earlier than healthy females before concomitantly dying sooner. As compelling as these recent studies are, clearly additional studies of this kind are necessary before generalizations can be made.

Parental 'programming' and inheritance of LH traits

The influence of parental (non-genetic) effects on their offspring's phenotype is increasingly acknowledged as an important adaptive mechanism in animals (Mousseau *et al.* 2009; Wolf and Wade, 2009). There is a growing body of evidence indicating that parasitic exploitation of a host can lead to changes in the phenotype of the hosts' offspring, though the latter are not parasitized (reviewed by Poulin and Thomas, 2008). For instance, animals infected with harmful parasites often produce smaller offspring because parents cannot allocate sufficient energy to reproduction (e.g. Hakkarainen *et al.* 2007; Gallizzi *et al.* 2008). Additionally, paternal stress can affect offspring phenotype by altering sperm phenotype and affecting post-zygotic development and performance (Crean *et al.* 2012, 2013; Rando, 2012; Bromfield *et al.* 2014; Zajitschek *et al.* 2014). Several proximate mechanisms have been put forward to explain parental effects due to infections, most involving hormonal or other physiological pathways, as well as epigenetic phenomena, and ultimately leading to offspring that are pre-adapted to the parasites they are most

likely to encounter based on their parent's experience (Sorci and Clobert, 1995).

Are there consequences of having 'cancerous' parents? Given that most if not all individuals among metazoan species accumulate precancerous lesions and *in situ* tumours in many organs as they age (Folkman and Kalluri, 2004), this question is relevant to virtually all multicellular organisms. Few cancers are directly transmissible, so the risk of offspring contagion is often not applicable. However, because of the health consequences associated with tumourigenesis, parents with more or less advanced malignancies are likely to be affected in their ability to provide adequate resources/parental care to their offspring. To our knowledge this question has never been empirically addressed. As for parasites, deeper trans-generational effects probably exist, as suggested by several studies indicating that epigenetic modifications that influence cancer risk can be inherited through the germline across multiple generations (reviewed in Fleming *et al.* 2008). Similar to infections, cancer risk could be correlated within families across generations. This should presumably be the case in species with low dispersal, living in areas (naturally or artificially) contaminated by mutagenic substances, because both parents and offspring experience the same ecological contexts. Similarly, the same should apply to cancer caused by inherited oncogenic vulnerabilities. At the moment there is little evidence available on the consequences of having parents harbouring tumours and/or oncogenic mutations on offspring phenotype, in terms of costs and adaptive (non-genetic) transgenerational effects.

Although parent-to-offspring transmission of cancer cells may be uncommon, parent-to-offspring transmission of infections that induce cancer appear to be moderately common (Ewald and Swain Ewald, 2015). For example, in humans, T-lymphotropic virus type 1 (Coovadia *et al.* 2007) and potentially hepatitis B virus are transmissible to offspring in milk (but see Chen *et al.* 2013) and cause cancer in a substantial proportion of those offspring (Ewald and Swain Ewald, 2015). In captive wildlife, vertical transmission of simian T-lymphotropic viruses in apes (Parrish *et al.* 2004; d'Offay *et al.* 2007), feline immunodeficiency virus in cats (O'Neil *et al.* 1995) and mouse mammary tumour virus in mice (Bentvelzen *et al.* 1970) is known, but their occurrence in the wild requires further study.

Evolutionary change in the host population

Whenever there is a genetic basis to LH traits, or trade-offs between them, evolutionary change in the host population can occur in response to 'infection' by cancer just as it would with parasites. For instance, selection may favour early sexual maturity when the risk of future infection and mortality is high. Indeed, snails from localities with a high prevalence of castrating trematodes become sexually mature earlier than conspecifics living in areas of low prevalence (Lafferty, 1993; Fredensborg and Poulin, 2006). One of the best examples of altered LH strategies in response to exposure to cancer involves the Tasmanian devils (*Sarcophilus harrisii*) and their transmissible cancer, the devil facial tumour disease (DFTD). Following the appearance of DFTD, devils have responded to the cancer-induced mortality by rapidly transitioning from a late maturing iteroparous (multiple reproductive cycles) to an early maturing semelparous (single breeding) reproductive strategy (Jones *et al.* 2008).

Concluding remarks

Is it justifiable to ignore LH traits when studying oncogenic phenomena? In the light of this discussion, we suggest that the answer is clearly no. Cancer can directly affect LH traits by imposing costs and/or indirectly by triggering plastic adjustments and evolutionary responses, just as parasites are well known to do. Reciprocally, these effects can potentially influence cancer risks, through the evolution of differential cancer vulnerabilities in populations (e.g. Kokko and Hochberg, 2015). For instance, BRCA1 and BRCA2 mutations are inherited and predispose women to breast and ovarian cancer, but even though carriers of these mutations have a reduced survival, they also have enhanced fertility (Easton *et al.* 1995; Smith *et al.* 2012). This result may indicate antagonistic pleiotropy (i.e. when one gene controls more than one trait, at least one of these traits is beneficial to the organism's fitness and at least one is detrimental to fitness). However, since the adaptive response by the host also favours the transmission of BRCA1 and BRCA2 to the next generations, this suggests that the existence of LH trait adjustments could influence the persistence of oncogenic mutations in certain populations. In addition, such adjustments would be, in our opinion, a potentially more parsimonious alternative to the antagonistic pleiotropy hypothesis classically invoked to explain why oncogenic mutations persist at a higher frequency than expected by the mutation-selection balance (e.g. Bodmer, 2006; Risch *et al.* 2006).

To understand the evolution of LH traits in a cancer context, one must consider the complete ecological context in which individuals developing tumours live. Unfortunately, there is only limited data to date, supporting the hypotheses we have outlined above (Table 1). Clearly more data and research, including on the assumptions of cancers potentially affecting fitness related traits, are needed to draw a more substantiated parallel between cancer and infectious diseases. Because one single method or model cannot thoroughly integrate all the complexity of

the processes we have discussed, researchers interested in these adaptive responses must engage in greater exchanges and collaborations involving scientists from different disciplines. Finally, we strongly encourage researchers to systematically explore the myriad of symptoms displayed by cancerous patients in order to discover those that could be LH trait responses, *vs* those that illustrate pathological costs without adaptive value.

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