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IDEA AND PERSPECTIVE

A framework for how environment contributes to cancer risk

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Abstract

Evolutionary theory explains why metazoan species are largely protected against the negative fitness effects of cancers. Nevertheless, cancer is often observed at high incidence across a range of species. Although there are many challenges to quantifying cancer epidemiology and assessing its causes, we claim that most modern-day cancer in animals – and humans in particular – are due to environments deviating from central tendencies of distributions that have prevailed during cancer resistance evolution. Such novel environmental conditions may be natural and/or of anthropogenic origin, and may interface with cancer risk in numerous ways, broadly classifiable as those: increasing organism body size and/or life span, disrupting processes within the organism, and affecting germline. We argue that anthropogenic influences, in particular, explain much of the present-day cancer risk across life, including in humans. Based on a literature survey of animal species and a parameterised mathematical model for humans, we suggest that combined risks of all cancers in a population beyond *c*. 5% can be explained to some extent by the influence of novel environments. Our framework provides a basis for understanding how natural environmental variation and human activity impact cancer risk, with potential implications for species ecology.

Keywords

Ageing, anthropogenic impact, body size, cancer risk, environment, epidemiology, evolutionary mismatch, global change, longevity, modern lifestyles, mutagens, pathogens.

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INTRODUCTION

Cancer is a pervasive threat to many multicellular organisms, and vulnerable populations are expected to evolve cancer prevention and suppression (hereafter 'resistance'). Indeed, a large array of resistance mechanisms exist, including tissue architecture, cell cycle regulation and differentiation, DNA mismatch repair, apoptosis, immune responses, and replicative ageing (Greaves 2000; DeGregori 2011; Reinhardt & Schumacher 2012; Campisi 2013). Despite the likely deep evolutionary history in the establishment and reinforcement of these processes, cancers occur across the tree of life, and sometimes at high incidence (Aktipis *et al*. 2015). These contradictory observations beg for explanation, specifically regarding the role of environments in promoting or suppressing cancer, and the implications of dynamic cancer risks for species ecology and evolution.

Much of our understanding of cancer comes from human tumour cells, either isolated *de novo* from biopsies, or studied on well-characterised cell lines *in vitro* or as allografts in immunodeficient laboratory mice. Only recently has increased emphasis been given to investigating cancers over a broad range of taxa [comparative oncology, see Glossary (Schiffman *et al*. 2015; Nunney *et al*. 2015)]. Although our knowledge remains largely restricted to humans, most cancers are thought to obtain through a stepwise mutational process, resulting in the Hallmarks of Cancer (Hanahan & Weinberg 2000, 2011). A central prediction emerging from the multistage theory of carcinogenesis (Glossary) is that lifetime risk of any form of cancer (hereafter 'cancer risk'; Glossary) should correlate with the lifetime number of stem cell divisions (Box 1). Perhaps surprisingly, cancer risk across mammal species shows no significant trend with longevity or with body mass (Peto *et al*. 1975; Peto 1977). There are numerous explanations for what has come to be known as Peto's paradox (Glossary) (e.g. Nunney 1999, 2013; Leroi *et al*. 2003; Nagy *et al*. 2007; Caulin & Maley 2011; DeGregori 2011; Maciak & Michalak 2015), most being based on differential selection for phenotypic traits that reduce cancer risk in more massive and/or longer-lived species.

However, whereas considerable study addresses Peto's paradox, few authors have recognised an additional feature of the cancer risk data: most surveyed species and taxonomic groups have lifetime cancer risks of less than *c*. 5%, and for many, cancer is very rarely observed, if at all (e.g. Effron *et al*. 1977; Varki 2000; Abegglen *et al*. 2015). To the best of our knowledge, when sufficiently investigated, high lifetime cancer risk (conservatively defined here as greater than *c*. 5% of a population suffering cancer-related negative effects on performance, health, survival, and/or fitness during their lifetimes) is observed only in populations that live in captivity or in polluted areas, or that are subject to cancer-promoting infections, founder effects, inbreeding, or selective breeding. Even in the human population where cancers account for *c*. 11–25% of mortality (Ferlay *et al*. 2015), as will be described below, the majority of cases are associated with present-day human ecology, including survival to older ages, unhealthy lifestyles, parasitic infections, and mutagenic exposure.

Previous study has discussed how evolutionarily novel environments (Glossary) are a likely source of many human

Box 1 Relative contributions of life span and body mass to cancer risk

The multistage theory of carcinogenesis as envisaged by Armitage & Doll (1954) posits that several independent mutations are typically required to initiate cancer. This process implies that, all else being equal, the more stem cell divisions occurring over a lifetime, the higher the probability of a given cancer obtaining (Albanes & Winick 1988), since cells are most vulnerable to mutation during the cell cycle (Cairns 2002; Branzei & Foiani 2005). The lifetime number of stem cell divisions (and therefore cancer risk) is expected to correlate with stem cell number (body size), stem cell division rate, and life span (Nunney 1999; Noble *et al.* 2015). Focusing on body size and life span, theory predicts that the former should have a smaller effect on cancer risk than the latter (Nunney 1999). To see this, consider a very simple multi-stage model for cancer risk, R

$$R \propto s(ud)^M \quad (1)$$

where s is the number of stem cells, u is the rate at which each stem cell acquires any one of M mutations necessary for cancer, and d is the number of divisions per stem cell over a lifetime. This simple model assumes that $u \ll 1$ and $(ud)^k \ll 1$, and that cells with fewer than M mutations have no fitness advantage. Interestingly, these cellular processes can be reinterpreted as life history traits, whereby s correlates with body mass and d with life span. To see the difference in the relative importance of body size (s) and life span (d), consider a cancer requiring three mutations ($M = 3$) (Tomasetti *et al.* 2015). Here, increasing d by a factor of 10 changes R as much as multiplying s by a factor of 1000.

Equation 1 and related formulae (e.g. Calabrese & Shibata 2010; Kokko & Hochberg 2015) characterise R as cellular transformation to invasive carcinoma (Glossary), and do not include probabilities of subsequent tumour growth, metastasis and impacts on performance or health (the definition of cancer risk employed here). A more complete model would incorporate these phenomena, as well as both environmental and age-related effects, the latter of which has been hypothesised to explain differences in cancers typically occurring early in life with those typically associated with the ageing process (e.g. Rozhok & DeGregori 2016).

diseases (Gluckman & Hanson 2004; Gluckman *et al.* 2011), and has examined associations between environments and cancer across species (e.g. Newman & Smith 2006; McAloose & Newton 2009) and in humans (Irigaray *et al.* 2007). We go significantly further by proposing a framework for how environments, and specifically novel environments, affect cancer risk across species and in the human population. We argue that many, probably most cancers across animal species, and particularly in humans, result from environmental states that increase cancer risk above baseline levels occurring in native habitats (Fig. 1). These baseline levels reflect long-term adaptations to prevailing exogenous (e.g. temperature, physical habitat and biotic interactions) and endogenous (e.g. behaviour and physiology) environmental conditions. Environments obviously vary over different spatial and temporal scales, and evolutionary theory predicts how a species adapts to varying selection pressures (e.g. Chevin *et al.* 2010). Importantly, trait evolution can be slow relative to the time scales of environmental variation and behavioural responses (Tuomainen & Candolin 2011), meaning that the fitness associated with a trait may vary considerably without a significant evolutionary response (so called 'evolutionary mismatches'). This is particularly relevant to cancers, where specific costly adaptations are unlikely to obtain in response to the diversity of possible transient and spatially limited environmental insults. Moreover, due to the (1) complexity of cancer genetics (Blekhman *et al.* 2008; Hindorff *et al.* 2011), (2) weak selection against certain cancer sensitivity mutations and/or the costs of reinforced cancer resistance (Nunney 2003; Frank 2004a, b), or (3) the tolerance of low probabilities of cancers that pleiotropically trade-off with traits under positive selection

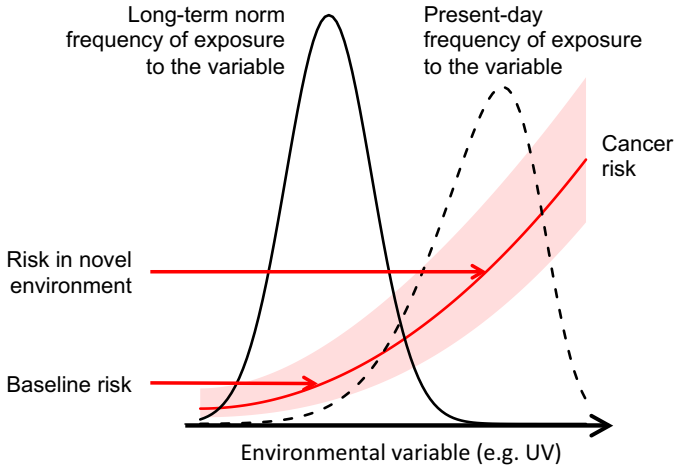

Figure 1 Schematic representation of how a novel environmental variable is associated with increases in cancer risk above levels established by long-term evolution. The long-term exposure to a 'native' environmental variable (e.g. UV radiation) is expected to select for adaptations (see Introduction in main text) that form a reaction norm in cancer risk (red line) across the distribution of the environmental variable (black solid line). Baseline risk (lower red arrow) is the expected lifetime cancer risk under native environmental conditions. Novel environments correspond to a shift in the frequency distribution of the environmental variable (black dashed line) and associated cancer risks (upper red arrow). Shaded red area around mean risk line may either indicate variability among individuals within a population, or between populations of a given species. In the case of a qualitatively novel environment (e.g. a pollutant, not shown), the black solid line would be replaced by a point at $x,y = 0,0$ with a corresponding mean and variance in baseline risk. Note that, alternatively, novel environments may result in *decreases* in cancer risk, as for example, following the invasion of a predator or parasite, resulting in shifts in species demography to younger (less cancer prone) ages.

(Crespi & Summers 2006), the fixation of resistance across all cancer-risk loci is unlikely, even in the long term (Maher *et al*. 2013).

Deviations from native habitat conditions may take the form of idiosyncratic pulses, sustained temporal variation, directional trends, or shifts to new states. Given heterogeneity at different spatial and temporal scales, environmental exposure and associated cancer risk are expected to vary within a population. Although it is difficult to accurately estimate baseline cancer risks and the environments under which these prevailed, we *can* identify putative environmental drivers of increased risk by focussing on species (or populations) showing unexpectedly high overall levels of cancer (i.e. greater than the conservative benchmark of 5%). Humans have influenced ecosystems since the Late Pleistocene (Boivin *et al*. 2016), and we claim that as a result of the intensification and globalisation of these effects, the environments experienced by many present-day metazoan species differ significantly from their pre-anthropogenic states (Eriksson 2013), and consequently many, possibly most instances of high cancer risk are attributable to human impacts.

We begin by reviewing the theoretical and empirical basis for how evolutionary adaptations limit cancer as a life threatening and fitness reducing disease. This sets the stage for understanding how environmental deviations from native conditions, typically acting on shorter time scales than significant evolutionary responses, affect individual biology and ecology, which in turn impacts individual cancer risks. There are nevertheless numerous hurdles in quantifying cancer epidemiology and assessing relationships between environment and cancer, and we discuss five such limitations. We then present a framework where novel environments impact cancer risk on one or more of three basic biological levels: those altering body size and/or longevity, those disrupting within-organism processes, and those resulting in heritable genetic change. We finally develop and analyse an empirically parameterised mathematical model to deduce overall cancer incidence in recent and ancient humans, which also allows estimation of how different components of modern (novel) environments have increased cancer risk in our species. Our framework provides a basis for understanding the relevance of environments to cancer across life, uncovers a number of important questions regarding the implications of cancer dynamics for ecological communities and evolutionary change, and makes predictions for future research.

EVOLUTIONARY THEORY AND CANCER RESISTANCE

Somatic cells in metazoans exhibit an array of cooperative behaviours that contribute to the fitness of the whole organism. Obtaining the benefits of cooperation without paying the costs would have provided the context for cells to cheat (Glossary). Cancer is a prime example of cheating in the metazoa (Aktipis *et al*. 2015), whereby somatic cells grow and invade local and distant tissues (invasive carcinoma and metastasis, respectively). Failure of higher-level physiological systems to prevent this process or keep it in check would have had substantial fitness consequences for the host organism, resulting in selection for costly cancer resistance mechanisms (Crespi & Summers 2005; Merlo *et al*. 2006; Casás-Selves & Degregori 2011; Greaves & Maley 2012; Aktipis *et al*. 2015). The evolution of some of these processes appears to have occurred deep in the metazoan phylogeny, where cancer risk and its reduction were associated with the emergence of 'gatekeeper' genes (Domazet-Lošo & Tautz 2010), possibly accompanied (and followed) by purifying selection against cancer-prone genotypes (Thomas *et al*. 2003) (but see Blekhman *et al*. 2008). With subsequent selection for larger body plans and longer life spans, additional, sometimes apparently species-specific, mechanisms have emerged (Gorbunova *et al*. 2014).

Evolutionary theory makes two central predictions relating to interspecific and intraspecific process and pattern. First, *taxonomic-group or species-specific* cancer suppression has evolved in response to environmental challenges (e.g. UV radiation, temperature, diet, and exposure to competitors, predators and parasites) and coevolved with metabolic processes, mutation rates, characteristics of cell and tissue microenvironments (Glossary), and life history traits such as body size and life span. Theory suggests that if there is positive selection acting on traits that also render individuals more susceptible to disease, then the positive trait is more likely to evolve if the marginal fitness costs of augmented disease (cancer) resistance are sufficiently low (Hochberg *et al*. 1992; Boddy *et al*. 2015; Kokko & Hochberg 2015).

Most empirical support for this first prediction comes from studies on the body size or longevity extremes that generate Peto's paradox. For example, carcinoma in long-lived captive naked mole rats has been observed in only a few individuals out of thousands examined (Buffenstein 2008; Delaney *et al*. 2016; Taylor *et al*. 2016), and it remains to be determined whether inbreeding or laboratory conditions may have contributed to these cases, which were exclusively middle-aged and older individuals. Study indicates that this species has reinforced resistance against various diseases, including cancers (e.g. Tian *et al*. 2013), and that occasional cancer may have both an evolutionary and ecological basis (Hochberg *et al*. 2016). Work on captive African and Asian elephants reveals that they have 20 copies of the TP53 tumour suppressor gene, suggesting that the total stem cell population in an elephant can tolerate numerous mutations with little risk of any single stem cell lineage transforming into a neoplasm (Abegglen *et al*. 2015; Sulak *et al*. 2016). Lifetime cancer risk in captive elephants is estimated at 3–5% (Elephant Encyclopedia 1995–2012; www.elephant.se) (Abegglen *et al*. 2015).

Although the evolutionary theory of cancer resistance is consistent with observations of low incidence across species and with reinforced protective mechanisms in those species that tend to generate Peto's paradox (i.e. the most massive and longest lived; Seluanov *et al*. 2009; Gorbunova *et al*. 2014; Abegglen *et al*. 2015; MacRae *et al*. 2015; but see e.g. Rozhok & DeGregori 2016), complementary approaches such as phylogenetic analyses are uncommon (Gomes *et al*. 2011; Keane *et al*. 2015). For example, Gomes and colleagues (Gomes *et al*. 2011) compared and contrasted telomere length and telomerase activity across more than 60 mammal species. They propose that the capacity of ancestral adult mammals to suppress telomerase has been lost in certain short-lived, small mammal species. Their results are consistent with the

prediction that replicative ageing (shorter telomeres and repressed telomerase activity) tends to protect the organism from the fitness-reducing effects of cancer as a correlated response to larger body sizes and longer life spans (Weinstein & Ciszek 2002; but see Seluanov *et al*. 2007; Eisenberg 2011).

The second prediction of evolutionary theory is that, whereas no correlation is expected between species over the full range of metazoan taxa, variation *within a species* should reveal positive associations between life history traits (particularly longevity) and cancer risk (Box 1). This is because (1) selection on trade-offs between life history and cancer resistance is expected to be too weak (due, for example, to cancer emerging late in life) over ecological time scales of a few generations or less, (2) there is little or no additive genetic variation upon which selection can work, and/or (3) the phenotypic variation has little or no genetically heritable component. Limited support for this prediction comes from the correlation of cancer incidence with body mass across dog breeds (Fleming *et al*. 2011) and with human height (Shors *et al*. 2001; Green *et al*. 2011; Kabat *et al*. 2014; Jiang *et al*. 2015). An alternative, untested explanation for these patterns is that life history traits are in linkage disequilibrium with specific mutations that increase (or decrease) cancer risk.

Similar to body size within a species, cancer incidence and mortality tend to correlate with age (in humans, Martincorena & Campbell 2015; in dogs, Fleming *et al*. 2011; for limitations, see Li *et al*. 1996; Pompei & Wilson 2001). This is not surprising since classic theory of the evolution of ageing and senescence (Medawar 1952; Williams 1957; Hamilton 1966) leads to the prediction that cancer resistance will be generally favoured in an inverse age-dependent manner (e.g. DeGregori 2011; Hochberg *et al*. 2013), but this effect (increasing cancer risk for longer lived individuals within a species) is also predicted to be a straightforward consequence of more time for (multistage) cancer to obtain, and for emerging tumours to grow and constitute risks to individual performance and survival. Another explanation for within-species patterns is that cancer risk is somehow pleiotropically associated with genetically heritable differences in height or longevity (e.g. Cournil & Kirkwood 2001), although we are not aware of any supporting evidence.

CHALLENGES IN HOW WE PERCEIVE AND QUANTIFY CANCER

Despite a plethora of anecdotal observations of cancer in animals and, more rarely, epidemiological studies in natural populations, the actual importance of cancers (altered behaviours, reduced reproduction, synergisms with other diseases, morbidity, mortality) to demography, population dynamics, intra- and interspecific interactions, spatial distributions, and/or genomic evolution has seldom been demonstrated for any species in the wild.[1] When cancer is assessed in wild animals, the data is usually semi-quantitative, recorded from individuals spending time in captivity (Ratcliffe 1933), and/or represents only one sampled population at a single time point (but see Lair *et al*. 2015).

We present five non-mutually exclusive factors that limit our ability to accurately assess the causes of cancer, and the importance of cancer to the performance, survival or Darwinian fitness of the individual, and by extension to the ecological and evolutionary dynamics of populations.

SAMPLING

Numerous biases exist in interpreting epidemiological data on cancer (e.g. for humans see Doll & Peto 1981), which also limit our ability to generalise findings about cancer in the wild. First and foremost, accurate field sampling in natural, near-pristine habitats is highly unusual (McAloose & Newton 2009), and may even be infeasible should individuals harbouring a cancer have altered behaviours (Vittecoq *et al*. 2013, 2015). In addition, quantification of epidemiological parameters such as incidence, morbidity and mortality is potentially biased by (1) small sample sizes (eTable 1 in Abegglen *et al*. 2015), (2) reports with no follow-up or concurrent study of hypothetical explanations (Daoust *et al*. 1991), (3) the underreporting of studies revealing little or no observed cancer, (4) oversampling of species that are relatively easy to sample and examine (e.g. humans, domestic and captive mammals), (5) oversampling of emblematic species (Aguirre & Lutz 2004), (6) populations suspected to be exposed to carcinogens (Hueper 1963), (7) oversampling of species showing unexpectedly high (Lair *et al*. 2015) or low (Buffenstein 2008) cancer incidence, (8) oversampling of animals attracting attention through aberrant behaviours, external signs of cancer, or found in atypical locations (e.g. Newman & Smith 2006), and (9) observations of high incidence, but that cannot accurately ascribe associated health impacts (Nerlich *et al*. 2006).

Another form of sampling bias stems from potentially irrelevant phylogenetic and ecological comparisons, such as between mice, humans, naked mole rats and whales. A more insightful approach is to make comparisons within phylogenetic groups, ecological niches, or life histories (Abegglen *et al*. 2015; Faulkes *et al*. 2015; Keane *et al*. 2015; Sanchez *et al*. 2015). Thus, for example, rather than compare mice and naked mole rats, which have little in common excepting body size, comparisons should begin within their taxonomic groups, e.g. Hystricomorpha (including *Heterocephalus glaber*) and Myomorpha (including *Mus musculus*). Although some examples of elevated cancer risk in captivity involve phylogenetically-related taxa (e.g. Canfield *et al*. 1990; Owston *et al*. 2008), it is unknown to what extent these patterns are related to similar types of environmental forcing, similar ecology or biology, or to other as of yet unexplained factors.

THE DIFFERENCES BETWEEN DISEASE, INDIVIDUAL CONDITION, POPULATION LIMITATION AND NATURAL SELECTION

Establishing benchmarks for studying cancer (i.e. presence/absence, stages in progression, importance to the functioning of

[1]The most notable exception is transmissible facial tumours in Tasmanian devils (e.g. McCallum *et al*. 2009; Epstein *et al*. 2016; Hollings *et al*. 2016). However, transmissible cancers differ importantly from endogenously emerging cancers, in that the population and evolutionary dynamics of the former are more akin to certain infectious diseases.

the host organism) is highly challenging. Even should stem cells obtain one or more cancer driver mutations (Glossary), the affected tissue may not become invasive (Martincorena *et al*. 2015), and should a lesion progress to invasive cancer, it may never present health (Greaves 2014) or fitness (DeGregori 2011; Hochberg *et al*. 2013) consequences. It is often difficult to determine whether an early-stage neoplasm will progress to have future performance or survival consequences. This means that early cancer detection without subsequent reassessment is likely to overestimate impact.

Moreover, as with highly virulent microparasitic diseases, the symptoms associated with many cancers – especially those producing external tumours – elicit the intuitive reaction that they are likely to have individual health and population consequences. However, the severity of a disease for individuals does not necessarily predict how the disease will affect population size (Anderson 1979), and disease-driven population limitation need not be associated with strong selection for disease resistance (Holt & Hochberg 1997). Rather, the strength of selection integrates reduced fitness, allelic dominance (in diploids), the frequency of alternative fitter genotypes, and population structure over spatiotemporally heterogeneous environments (e.g. Orr 2009).

Cancer emergence, health effects, and fitness consequences are each sequentially probabilistic. This means that adaptations to minimise the fitness impacts of cancers should increase with extended pre-reproductive and reproductive life spans (Kokko & Hochberg 2015), but also that cancer will be expressed more often with longer periods of ageing and senescence, as is the case, for example, in humans (DeGregori 2011; Hochberg *et al*. 2013). Thus, cancer morbidity and mortality at older, post-reproductive ages are generally not expected to produce a substantial evolutionary response (Kirkwood 2005; but see Brown & Aktipis 2015). Species with short pre-reproductive and reproductive life spans and little senescence (e.g. Ricklefs 1998) will tend to perish before succumbing to a threatening neoplasm, and are expected to have less adaptation to preventing cancer. Limited data concur with these basic predictions. For example, elephants have long pre-reproductive and reproductive life spans, show little senescence (Promislow 1991), have reinforced cancer suppression, and their lifetime cancer rates in captivity are < 5% (Abegglen *et al*. 2015); field mice show high cancer rates, but only when reared beyond their short, natural life spans (Andervont & Dunn 1962; Schug *et al*. 1991; Pompei *et al*. 2001); naked mole rats have long reproductive life spans, show little senescence (e.g. Buffenstein 2008), and have augmented cancer protection (e.g. Tian *et al*. 2013).

REAL ANTAGONISTIC PLEIOTROPY?

Positive selection on certain phenotypic traits due, for example, to antagonistic coevolution may be associated with increased cancer risks (Crespi & Summers 2006). Antagonistic pleiotropy (Glossary) is often advanced as an explanation for correlations between positively selected traits and the occurrence of diseases (Carter & Nguyen 2011), but evidence for its specific role in cancer is largely indirect, particularly in humans (Leroi *et al*. 2005; Grimes & Chandra 2009; Giaimo & d'Adda di Fagagna 2012). For example, studies of human female breast cancers suggest pleiotropy between fecundity and the presence of BRCA1/2 mutations (Smith *et al*. 2012; Kwiatkowski *et al*. 2015). Although many factors may be involved, da Silva (da Silva 2012) used mathematical models to show that considerable augmentations in fecundity associated with weak negative impacts on fitness (resource transfers or the 'grandmother effect'; Croft *et al*. 2015; Brown & Aktipis 2015; see also Pavard & Metcalf 2007) could explain the current low frequencies of BRCA alleles, but only in conjunction with low general female fertility in our distant ancestors (by which time much of the evolution leading to the present-day frequencies would have occurred). Alternatively, the association between BRCA mutations and increased fecundity may be real, but not genetically linked. This could occur, for example, if there are associations between the mutated BRCA gene and particular ethnic groups (e.g. Fackenthal & Olopade 2007) or families (Kwiatkowski *et al*. 2015).

Perhaps the most convincing evidence for positive selection on a trait linked with cancer susceptibility comes from male swordtail fish (*Xiphophorus*). Hybrid males harbouring the *Xmrk* oncogene are more susceptible to melanomas in later life, but are also larger and better at competing for mating opportunities (Fernandez & Morris 2008). Limited evidence comes from two additional sources. First, in free-living populations of *X. variatus* subsequently reared in the laboratory, older, non-hybrid males express melanosis or nodular melanomas (e.g. Schartl *et al*. 1995; Fernandez & Bowser 2010). Second, Fernandez and Bowser (2010) observed that 8 out of 52 non-hybrid males of *X. cortezi* at one field site showed signs of melanoma stemming from *Xmrk* genes. However, closer examination of these fish did not reveal adverse impacts of the neoplasms, and the authors did not note whether the remaining field sites were similarly inspected. Nevertheless, the fact that not all fish harbour the *Xmrk* gene suggests some form of frequency dependent or fluctuating habitat selection (for discussion, see Fernandez & Bowser 2010), indicative of antagonistic pleiotropy.

INFERRING AND UNTANGLING CAUSAL FACTORS

In species where cancer epidemiology has been quantified, there is almost invariably a hypothesised contributing novel environment (e.g. cases listed by Vittecoq *et al*. 2015; Ujvari *et al*. 2016a). However, inferring environmental influence is often based on probable or possible cause. For example, Daoust *et al*. (1991) notes the stark contrast in multicentric mesenchymal tumour incidence between samples of white-fronted geese (*Anser albifrons*), (23%, $n = 30$) and three other goose species: *Branta canadensis* (0.9%, $n = 117$), *Chen caerulescens caerulescens* (0%, $n = 594$), and *Chen rossii* (0%, $n = 77$). The cause(s) of these striking differences, although suggestive of environmental impacts on white-fronted geese, would be difficult if not impossible to either retrospectively evaluate or retest should present-day populations show little or no cancer.

Indeed, determining contribution and causality in disease and mortality is notoriously difficult (Rothman & Greenland 2005). Cancers are no exception, in part because one or more aetiological agents may contribute (for certain bivalves, see Carballal *et al*. 2015) and interact in a complex causal web (for humans Galea *et al*. 2010). Moreover, cancer may be only

one of a myriad of diseases and dysfunctions affecting the organism. This means that it will often be difficult to establish the causal and/or contributing role of cancer in individual health, reproduction and survival, and by extension, whether *cancer itself* will impact, and be impacted by, natural selection. Consider the following hypothetical but realistic scenario. In studying samples of a population over many generations it is discovered that individuals exposed to a toxin show one or more cellular and tissue abnormalities (including cancers) that are statistically associated with mortality risk. Should resistance evolve, will it (1) detoxify the chemical, and/or (2) result in the avoidance of habitats where the chemical is found, and/or (3) act downstream and suppress cancers and/or other diseases caused by toxin exposure? Assuming that a unique set of cancer driver mutations are obtained sequentially, different environmental (causal) factors may each differentially be responsible for each driver mutation as part of a multistage process (Noble *et al*. 2016). How natural selection proceeds in such complex situations is largely unexplored.

THE 'PRIMACY OF MORTALITIES'

All else being equal, changes in the incidence of factors that contribute to mortality over a given age range will (obviously) alter the incidence of other factors that act at the same or at later ages. In contrast, changes in the incidence of late acting factors are typically less likely to affect the dynamics of those acting at younger ages. This well-known demographic effect is potentially important for cancer risks that increase precipitously with age (e.g. human prostate cancers). For example, improvements in preventing and treating early-onset cardiovascular diseases have not only increased life span, but also appear to have shifted deaths to other later-occurring causes, including cancer (e.g. Davis 1994). Moreover, different diseases show contrasting age-specific patterns in multi-stage acceleration (Frank 2004c), suggesting that complex patterns in age-specific cancer risk may emerge due to changes in the probabilities of other diseases occurring (e.g. through more effective prevention or individual treatment). As discussed in more detail below, many cancers observed in captive animals and in humans are an indirect consequence of reducing mortality in young and mid-aged individuals through, for example, animal protection in households and zoos, and, for humans in particular, improved sanitation and health care.

A FRAMEWORK FOR HOW ENVIRONMENTS CONTRIBUTE TO CANCER

Despite biases in quantification and difficulties in ascribing cause there is considerable evidence that novel environments contribute to explaining the high levels of present-day cancer in many animal species, and the majority of cancer risk in humans. What is currently lacking is a framework for understanding the underlying causal web. We take first steps towards a more general theory of cancer risk by proposing how environments influence one or more of three distinct biological levels (*The organism*, *Within-organism processes*, *The genome*; Fig. 2) and how this, in turn, leads to cancer (Fig. 3). We then illustrate how our framework can be used to gain quantitative insights into overall cancer risk in the human population.

The organism: longer life span and larger body size

Many cancers in humans and the few other animal species studied in detail can be ascribed to ageing and longevity (Campisi 2013; de Magalhães 2013). Whereas survival to ages at which

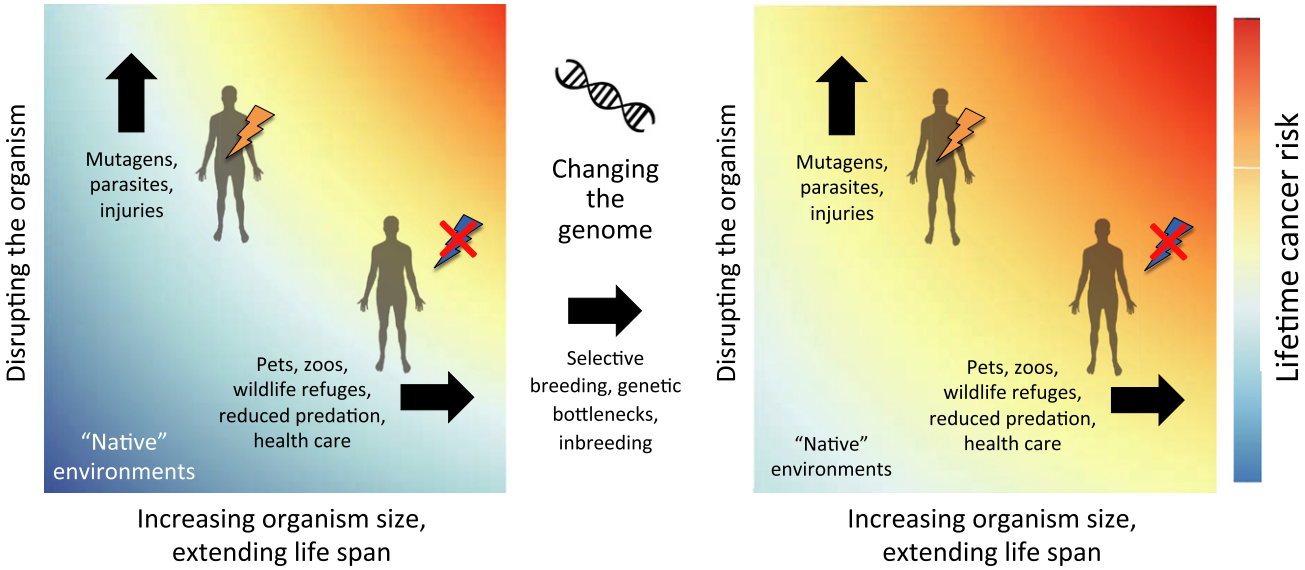

Figure 2 Hypothetical effects on cancer risk of one or more of three biological levels: *The Organism*, *Within-Organism*, and *The Genome*. Specific abiotic and biotic environment variables (including lifestyle behaviours) will alter one or more of these biological levels and in so doing, increase cancer beyond baseline risks associated with environments experienced over evolutionary time ('native' environments) (see Fig. 1). Although we expect interactions between whole organism and within-organism effects (left panel) on cancer risk, the interactive effects of changes to genomes (right panel) will depend, in part, on whether genetic effects selectively increase cancer risk in young individuals (e.g. mutations in *RB* and retinoblastoma in humans), or rather, are (partially) age related (e.g. *BRCA1* mutations and breast cancer in humans).

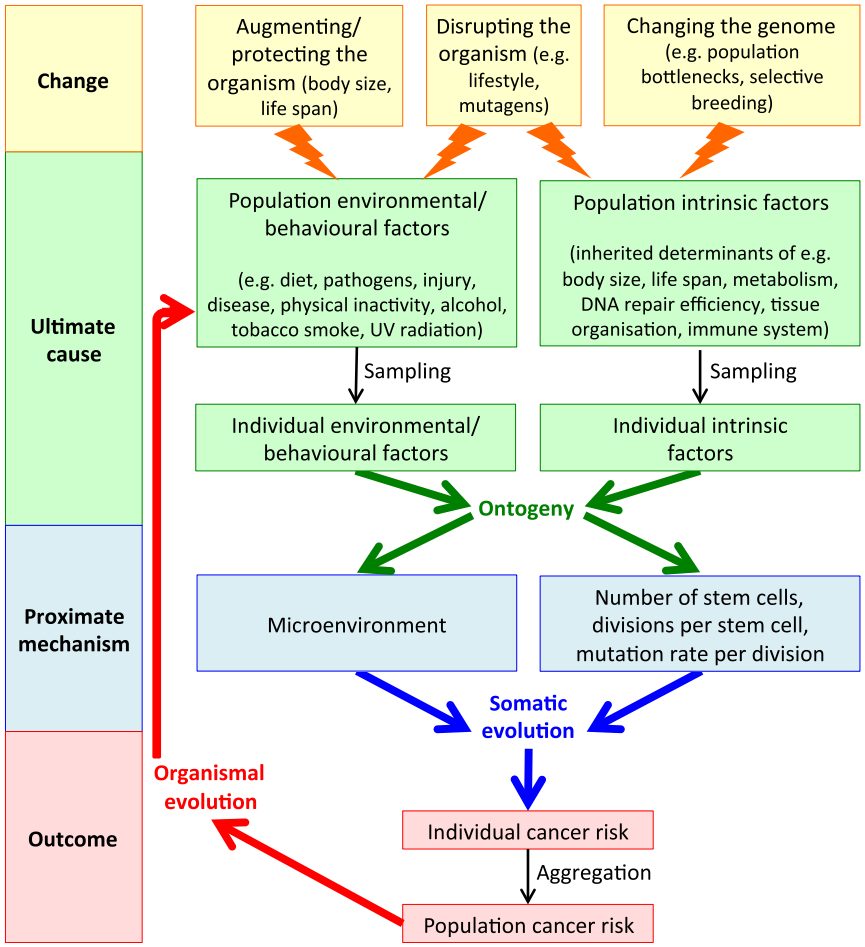

Figure 3 A framework for how environmental factors influence cancer risk over ecological and evolutionary timescales. Intrinsic and environmental/behavioural factors (green boxes) ultimately determine cancer risk (red boxes) through their effects on the proximate mechanism of somatic evolution (blue boxes). In general, a population of stable size in a stable environment is expected to evolve low cancer risk, because cancer-affected individuals have lower fitness. Environmental change or variation (yellow boxes) can increase cancer risk if it outpaces the evolutionary response. Within-species variation in cancer risk results from genetic diversity, environmental heterogeneity, and from stochasticity in the mutational process ('bad luck'; see also Box 3).

cancer is a health threat is probably rare in natural habitats (Finch 1990; Kirkwood 2005), modern-day transformations have made survival to cancer-prone ages the rule for many species living in protected environments, particularly humans.

Improved survival increases cancer risk in three interactive ways. First, because cancer is a multi-stage mutational process, longer life means *more time to obtain* all necessary mutations to produce a cancer and for the cancer to grow, spread, and impact performance and health. Second, the *ageing process itself* favours both genomic instability (Vijg & Suh 2013) and the likelihood that tissue microenvironmental conditions will be hospitable to the expression of deleterious mutations leading to tumour development and invasion (DeGregori 2011, 2012; Campisi 2013). Third, longer life means *more potential exposure* to environmental factors (e.g. mutagens) that increase the probability of multi-stage carcinogenesis obtaining (see *Within-organism processes* below).

One prime example of increases in health and longevity is the confinement of wildlife in protected habits (e.g. laboratories, nature reserves, zoos, homes; but see Clubb & Mason 2003). As alluded to above, studies from zoo animals indicate that most species have cancer incidences lower than 5% (Effron *et al.* 1977; Abegglen *et al.* 2015), though according to the data compiled by Abegglen *et al.* (2015) a significant minority (30% or 11/37 species) exhibit incidences (based on necropsied animals) above 5%. Beyond the reasonable hypothesis that many observed cancers in laboratory and captive populations are associated with longer life spans compared to field situations, and notwithstanding potential biases due to small sample sizes, to the best of our knowledge, all cases greater than *c.* 5% lifetime risk reported in the literature can be explained by other novel environmental effects as contributing factors, for example, viral infections or the use of chemical contraceptives (e.g. McAloose *et al.* 2007; Ewald & Swain Ewald 2015; see also *Within-organism processes* below).

The life spans of modern humans and their ancestors have increased over time scales of millions (Caspari & Lee 2004; Finch 2007), tens of thousands and thousands (Kaplan *et al.* 2000; Caspari & Lee 2004; Burger *et al.* 2012), and hundreds and tens (Fogel 2012; Burger *et al.* 2012; NCD Risk Factor Collaboration (NCD-RisC) 2016) of years. Modern medicine promotes longevity (increasing cancer risk), but also lowers

cancer mortality at younger ages and shifts some cancer effects on health and survival to older ages. The net overall pattern is that overall cancer risk in Western society is < 1% by age 20, about 2% by age 40, and < 10% at 50 (Martincorena & Campbell 2015). These low figures (mortality estimates are evidently even lower), despite numerous mutagenic exposures (e.g. smoking, UV radiation), can be explained by (1) treatment advances of modern medicine, (2) highly effective, evolved, natural cancer prevention mechanisms functioning at younger ages, and (3) the many years typically required for a nascent cancer to emerge, progress, and present health consequences (Jones *et al*. 2008; Yachida *et al*. 2010).

Similar to life span, body mass is expected to correlate with the lifetime number of stem cell divisions in the organism, and therefore cancer risk (Peto 1977; Nunney 1999; Noble *et al*. 2015). Although body mass itself is correlated with life span between species, the correlations differ between taxa (Healy *et al*. 2014), and the within species correlation is complex (Speakman 2005). Indirect evidence for associations between increased body size and cancer comes from how improved nutrition and health care have contributed to general increases in human stature and life span over recorded history (Floud *et al*. 2011; but see e.g. Formicola & Giannecchini 1999 for variation over much longer time spans). Human height is correlated with the masses of many tissues and organs, such as the liver, kidneys and the heart (Heymsfield *et al*. 2007). Height is therefore also expected to correlate with the number of cell divisions required to establish these organs and maintain their function (Floud *et al*. 2011; Zhao *et al*. 2011), which in turn is expected to correlate with cancer risk (Albanes & Winick 1988; Noble *et al*. 2015). Limited support for this complex chain of causality comes from studies showing that human height (Shors *et al*. 2001; Green *et al*. 2011; Kabat *et al*. 2014; Jiang *et al*. 2015) and certain organ sizes (Silva *et al*. 2011) correlate with cancer risk.

Within-organism processes: disrupted cells, tissues and support systems

Even with the establishment of highly effective cancer resistance mechanisms, natural selection is not expected to achieve zero risk (see above and, more generally Lynch 2012). A straightforward prediction is that sufficient deviations from the native distribution of environmental variables that affect cancer risk will increase the probability of obtaining somatic mutations leading to cancer. This may be associated with, for example, injury, disease, or exposure to mutagens (e.g. Grivennikov *et al*. 2010; Dang 2015). Gluckman & Hanson (2004) have argued that environmental conditions during periconceptual, foetal and infant periods of life can also have significant impacts on disease risk, but the implications of these effects for cancers are little understood.

There are numerous examples in humans and other metazoans of suspected or demonstrated associations between environmental impacts on individual physiology and cancer (Newman & Smith 2006; McAloose & Newton 2009), such as chemical exposure (Martineau *et al*. 2002; Lerebours *et al*. 2014), contraceptives (Harrenstien *et al*. 1996), and UV radiation (Fernandez *et al*. 2012; Leiter *et al*. 2014). Although humans often have a causal role in cancers stemming from these and other abiotic or physical environmental variables, human implication is usually more difficult to demonstrate in the many cancers associated with extra- and intracellular organisms. Indeed, extra- and intracellular organisms are widely considered to be a major factor in certain cancers in animals and in humans (Ewald 2009; zur Hausen 2009; McAloose & Newton 2009; Coffee *et al*. 2013; Ewald & Swain Ewald 2015) (Box 2). This may involve changes to the microbiome (Dalmasso *et al*. 2014; Vogtmann & Goedert 2016), but is more usually associated with parasitic infections. According to de Martel and colleagues (de Martel *et al*. 2012) pathogens are estimated to account for 16.1% of human cancer globally, with considerable variation between cancer types and geographical regions. Evaluating causality between pathogens and cancer is challenging, in part because of potential delays between the presence of the parasite and cancer detection (Ewald & Swain Ewald 2015). An alternative approach to linking infection with cancer is to study temporal correlations in parasite infection dynamics and cancer. Examples include the spread of HPV (e.g. Baseman & Koutsky 2005; Ramqvist & Dalianis 2010; Chaturvedi *et al*. 2011), HIV (Robbins *et al*. 2014) and Hepatitis C virus (Perz *et al*. 2006).

In addition to impacts mediated by the external environment, humans, in particular, influence their own cancer risks through certain lifestyle behaviours. These include alcohol consumption, UV radiation exposure, smoking (Irigaray *et al*. 2007), certain foods (Soto & Sonnenschein 2010), and lack of physical activity and obesity (Vucenik & Stains 2012). Such effects are expected to be multifactorial as suggested, for example, by study comparing cancers in the Japanese living in Japan and Hawai'i (Doll & Peto 1981; Maskarinec & Noh 2004). Moreover, there is some evidence that other behaviours such as sleep patterns (Blask 2009), reproductive biology (Aktipis *et al*. 2014), and psychological states (Reiche *et al*. 2004), stresses and trauma (Reiche *et al*. 2004; Antoni *et al*. 2006) influence cancer risk.

The genome: the emergence of cancer sensitivity genes

Changes to the heritable genome can have impacts on cancer. These range from very simple to highly complex predispositions (for humans, see Frank 2004a). Certain cancers are associated with the emergence of rare variants or homozygosity stemming from genetic bottlenecks, selective breeding, or founder effects. For instance, in humans, founder effects and preferential association within groups may favour the persistence of cancer sensitivity genes (de la Chapelle & Wright 1998; Rudan *et al*. 2003; Fackenthal & Olopade 2007).

The emergence and persistence of some cancers in animals, in particular transmissible cancers (Box 2), may be promoted by low genetic diversity or heritable sensitivity genes (Fredrickson 1987; Siddle *et al*. 2007; Miller *et al*. 2011; Murchison *et al*. 2012, 2014; Browning *et al*. 2014). For example, the Santa Catalina Island fox shows a cancer rate of *c*. 50%, and this elevated level could be explained by some combination of mite infections often associated with these cancers, and the accumulation of deleterious mutations in this highly inbred, low genetic diversity population (Vickers *et al*. 2015; Robinson *et al*. 2016). Related fox populations on two

Box 2 Cancer and parasites

Although cancer cells are comparable to some parasitic organisms in that they grow and may spread and multiply within the host, a fundamental difference is that unlike parasites, cancer emerges from self, and is not transmitted between individual hosts (but see exceptions below). Somatically emerging cancer is therefore an evolutionary dead end. Cancer genes, however, can evolve (and be positively selected (Crespi & Summers 2006)) beyond the host individual as vertically transmitted allelic variants within the genome. Evolutionary theory predicts conditions under which selection on initially virulent, vertically transmitted parasites may result in in lowered virulence (Lipsitch *et al*. 1996). Virulence in the context of cancer genes (i.e. rates of tumour progression, metastasis and associated impacts on health) would reduce the survival and reproduction of hosts, resulting in purifying selection on such genes and/or positive selection on other genes contributing to cancer suppression.

In contrast, transmissible cancers share features with certain horizontally transmitted parasites (Ostrander *et al*. 2016; Ujvari *et al*. 2016b), including intraspecific (Murgia *et al*. 2006; Siddle *et al*. 2007; Metzger *et al*. 2015) and interspecific (Metzger *et al*. 2016) infection. Transmissible cancers are also similar to some parasites (Lafferty & Kuris 1999) in that emergence and spread may depend on environmental conditions. For cancers, this includes pollutants in molluscs [J. Sherry, pers. comm.: St-Jean *et al*. 2005; Muttray *et al*. 2012; but see (Barber 2004) for both examples and counterexamples], and as of yet unknown causes of population bottlenecks and low genetic diversity in Tasmanian devils and in dogs (Murgia *et al*. 2006; Siddle *et al*. 2007; Miller *et al*. 2011).

Moreover, similar to many parasites, there is recent evidence that canine transmissible cancers may have evolved via recombination (Strakova *et al*. 2016). However, it is not known for this or other transmissible cancers whether evolutionary rates are similar to parasitic species with comparable life cycles and life histories. Although not experimentally demonstrated, the low virulence of transmissible cancers in dogs (evolved over thousands of years) and the high virulence of facial tumours in Tasmanian devils (tens of years) (Murgia *et al*. 2006; Siddle & Kaufman 2013; but see Epstein *et al*. 2016) are consistent with predictions under certain conditions of the evolutionary attenuation of initially high virulence (e.g. Day & Proulx 2004).

other of the Channel Islands are also inbred, also subject to mite infections, but show no cancer (Vickers *et al*. 2015). Thus, mites and genetic effects may be causal, but additional contributors appear necessary to explain why cancers are restricted to Santa Catalina Island.

Human-induced population bottlenecks and selective breeding appear to contribute to many cancers in domestic animals (Vail & MacEwen 2000; Dobson 2013). For example, some cancers in domestic dogs have a genetic basis, stemming from selective breeding (Dobson 2013; Karyadi *et al*. 2013; Davis & Ostrander 2014; Schiffman & Breen 2015). Similarly, strong selection for specific traits may increase cancer risk, such as more frequent egg laying in farmed chickens leading to increased age-related incidence of ovarian cancer (Johnson *et al*. 2015). Finally, a recent study on *Hydra* suggests that prolonged breeding in captivity fostered the emergence of tumours after *c*. 50 asexual generations (Domazet-Lošo *et al*. 2014; Alexander Klimovich, pers. comm.), suggestive of epigenetic alterations, emerging pleiotropy, or mutation accumulation.

CANCER RISK IN PAST AND PRESENT HUMAN POPULATIONS

As indicated above, cancer risk in the human population is subject to alterations at all three biological levels. Not surprisingly, many if not most of these effects are associated with impacts from humans themselves, and in particular extended life spans, environmental mutagens, and lifestyle behaviours. These risks (and by extension, their environmental drivers) are the basis for the current debate of the relative importance of random mutation and environmental drivers in human cancers (Box 3). Here, we take initial steps towards understanding the roles of environment in cancer risk by considering some of the general features of human life history and demography past and present. In particular, we employ information about hunter-gatherers currently and in the recent past to calibrate a mathematical model and conduct a sensitivity analysis with the goal of predicting what overall cancer risks may have been in our recent and more distant ancestors.

Estimates vary, but generally indicate expected hunter-gatherer life spans of 30–40 years (Gurven *et al*. 2007). Tuljapurkar *et al*. (2007) used demographic models of men and women to estimate the relative force of selection (Glossary) as a function of age. Their results indicate that the fitness effect of a mutant allele expressed beyond 40 years of age is 20% of what it would be if it were expressed beyond 20 years of age. Selection on an individual at 50 and 60 years of age is 5 and 1%, respectively, of selection on a 20-year-old. If this applies generally to pre-modern humans, then it suggests that there would have been selection against germline cancer sensitivity, but with a pronounced decline for those cancers with health effects after *c*. 40 years of age. Supporting this prediction, modern day age-specific cancer risk (e.g. Howlader *et al*. 2016) approximately recapitulates the inverse of the predicted force of selection in early *Homo sapiens* (Tuljapurkar *et al*. 2007) and in modern hunter-gatherers (Lee 2003).

Additional evidence for the hypothesis of less cancer in our recent and distant ancestors comes from mortality data in hunter-gatherer groups prior to outside contact. Data from pre-contact (before 1960) Hiwi indicate low levels (4/86 or 5% of young and older adult deaths) of 'other organic/pathological' causes of mortality (including cancers), whereas post-contact was considerably higher (26/69 or 38%) (Hill *et al*. 2007). However, it is not known with certainty how cancers may have contributed to these or other mortalities. Similar

Box 3 Cancer and 'bad luck' in humans

Tomasetti & Vogelstein (2015) compiled data on 31 cancer types in humans to assess the relative contributions of a random factor ('bad luck') and environmental and inherited factors to cancer incidence. They proposed that the random factor should correlate with the total lifetime number of stem cell divisions per tissue or organ, assuming that cancer-causing mutations have a fixed probability of emerging per stem cell division. Stem cells divide during ontogeny and in tissue repair, the latter occurring in conjunction with, for example, injury, parasitism, mutagenic exposure, cellular ageing and cellular diseases other than cancer. Their analysis uncovered a strong positive association between cancer incidence and the lifetime number of stem cell divisions, which they interpreted as indicating that random mutations due to replication and repair errors ('bad luck') explain much of the variance in risk among cancer types in humans. In a subsequent study, Wu *et al*. (2016) claimed, on the contrary, that extrinsic environments play a much larger role in human cancer risk than does 'bad luck'. Such contrasting results highlight the challenges in untangling the effects of intrinsic processes and extrinsic environments on cancer risk (Noble *et al*. 2015, 2016). In the more complete framework proposed here, environmental and intrinsic factors interactively determine the parameters of somatic evolution, which, in turn, contributes to cancer risk (Fig. 2). Some of these factors (e.g. those due to lifestyle) are preventable, and account for many, possibly the majority of present-day human cancers (Doll & Peto 1981; Schottenfeld *et al*. 2013; White *et al*. 2014; Colditz & Sutcliffe 2016; Song & Giovannucci 2016), whereas others (e.g. inherited cancer risks, old age) magnify within-organism disruption (shape of risk isoclines in Fig. 2), and together with particular risks of certain cancers across ethnic groups and geographical regions (Vineis & Wild 2014), should be taken into account in determining risk status.

assessments (lower life expectancy and lower risks for certain cancers compared to Western society) hold for the Tsimané Amerindians (excluding deaths from unknown causes, 1.3% (16/1276) of deaths attributable to cancers for all ages, and 7.8% (7/90) for individuals 60 years old or greater) (Gurven *et al*. 2007), and Inuits (Boysen *et al*. 2008; Wilkins *et al*. 2008) for which rapid social and environmental changes may explain why the incidence of many cancers has recently increased (Boysen *et al*. 2008; Young *et al*. 2016), whereas high incidence, endemic nasopharyngeal cancers appear to be linked to infectious agents (Friborg & Melbye 2008).

A MATHEMATICAL MODEL OF CANCER RISK IN HUMANS

To examine the relationship between longevity and cancer risk, we use a simple mathematical model (Supplementary methods) that accounts for the probability of acquiring cancer for the first time, the mortality rate due to cancer, and the rate of background mortality (i.e. death from causes other than cancer).

In human populations, the observed risk of acquiring cancer increases exponentially with age, coinciding with a decline in the force of selection (Fig. 4a). Incorporating this cancer risk curve and standard background mortality functions, our model accurately reproduces empirical post-infancy survivorship curves for the US in 2011 (Arias 2015), Sweden in 1861 [The human mortality database. University of California, Berkeley (USA), and Max Planck Institute for Demographic Research (Germany). Accessed 2 August 2016; www.mortality.org] and a composite hunter-gatherer survivorship curve (Gurven *et al*. 2007) (Fig. 4b). If cancer incidence and the cancer death rate remain fixed, the shape of the survivorship curve strongly depends on relative cancer risk, but only when background mortality is relatively low (Fig. 4b, rightmost curves in each panel).

However, in reality, populations vary in cancer risk and cancer death rate, as well as background mortality. Based on modern US life expectancy and cancer incidence curves, our model predicts, as expected, a lifetime cancer risk of *c*. 40% (Fig. 4c). A population that is identical except that it has 30% lower cancer incidence in adults is predicted to have *c*. 30% lower lifetime risk of cancer (Fig. 4c). In pre-modern humans, the model estimates a lifetime cancer risk between 0.6 and 10% (for those alive and cancer-free at age 5). The higher estimate (Fig. 4c) assumes that background mortality in pre-modern humans was similar to what is observed in modern hunter-gatherers (Gurven *et al*. 2007), and that adult cancer risk per year was 30% lower in pre-modern humans than in the modern US population (based on epidemiological studies that estimate 30–50% of risk in modern Western populations is attributable to lifestyle (Doll & Peto 1981; Parkin *et al*. 2011; Song & Giovannucci 2016; see also Fig. S1). The lower estimate assumes a much higher background mortality rate deduced from prehistoric skeletal remains (Gage 1998) – which most likely overestimates adult mortality (O'Connell *et al*. 1999) – and assumes that cancer risk per year was 80% lower than in the US currently (due to changes in both environment and stature). The model results indicate that most of the difference in lifetime cancer risk between pre-modern humans and the modern US population is due to lower background mortality in the latter, which enables more individuals to attain the advanced ages at which cancer risk is substantially increased. If modern US cancer incidence were applied to modern-day hunter-gatherers and to Sweden in 1861, then lifetime cancer risks in the latter populations would be 13 and 24%, respectively (in individuals alive and cancer-free at age 5, assuming the same stature and environmental contributors as in the US currently).

Contrasting patterns emerge when we examine cancer risk over the age range 5–40 years old, which is when the force of selection is expected to be strongest (Fig. 4a). The model indicates that cancer risk by 40 years old was between 0.4 and 1% in pre-modern humans, whereas it is *c*. 2% currently in the US population (Fig. 4d). Most of this difference is predicted to be due to increased environmental forcing in the modern population. In particular, once life expectancy reaches 75 years, the background mortality rate before age 40

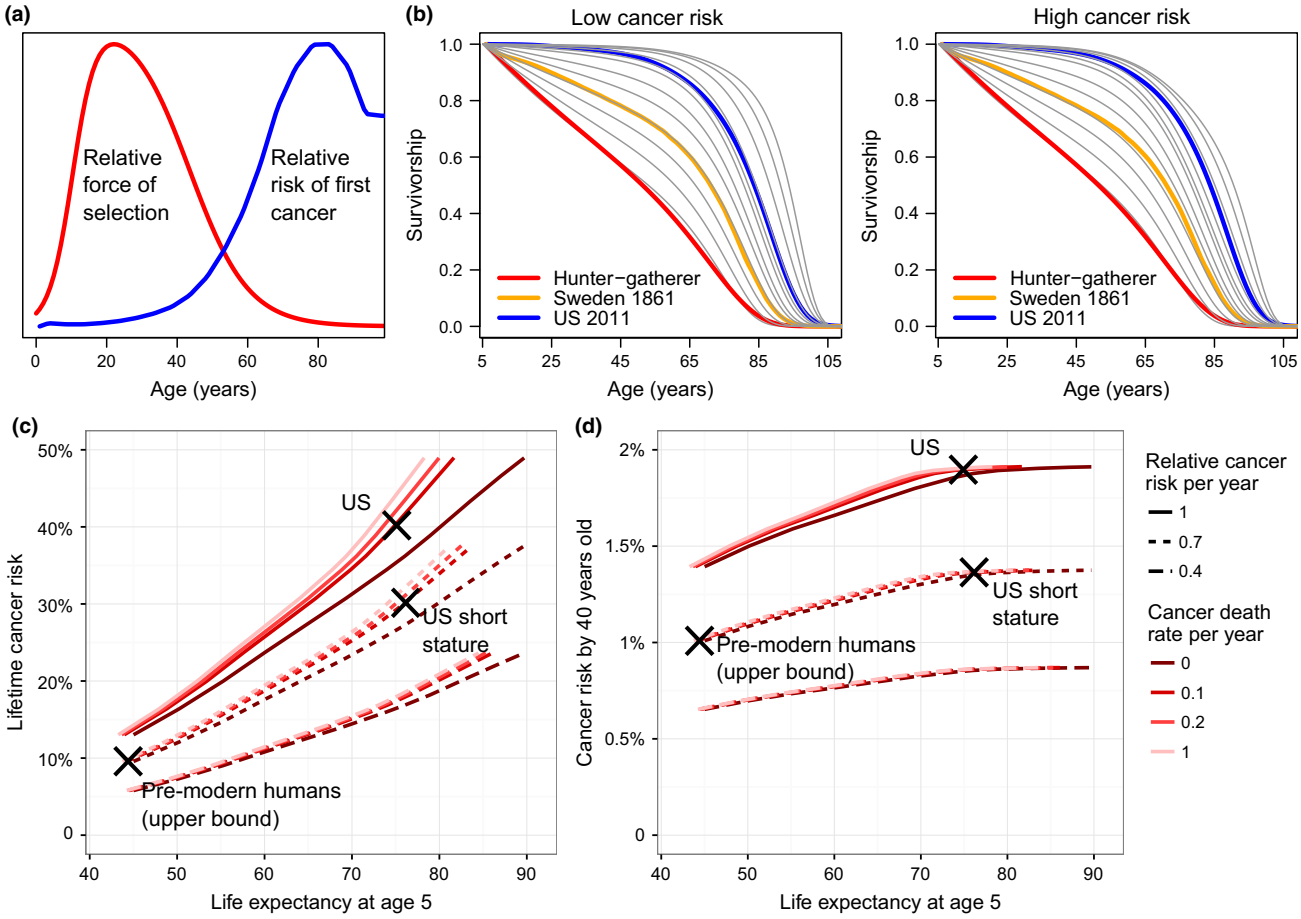

Figure 4 Relationship between longevity and cancer risk in humans, based on a mathematical model using empirical data. (a) Relative force of selection (red line, qualitative approximation based on Lee (2003); for illustrative purposes; not used in the model) and relative risk of acquiring cancer for the first time (blue line, used as model input, estimated using the DevCan software package based on US data for 2010–2012 (Fay 2004; [DevCan: Probability of Developing or Dying of Cancer Software, Version 6.7.3. Statistical Research and Applications Branch, National Cancer Institute (2005). Accessed 1 August 2016; http://srab.cancer.gov/devcan]. (b) Survivorship curves generated by the model (thin lines), with empirical curves for hunter-gatherers, Sweden in 1861, and the US in 2011 (thick lines) for comparison. Mortality in children < 5 years old is excluded so as to better reflect typical life expectancy among individuals who are at substantial risk of cancer. Model results are shown for low cancer risk (left panel, using as input the US cancer incidence curve rescaled by 0.4 for adults) and high cancer risk (right panel, using as input the US cancer incidence curve). In both cases, the death rate of individuals with cancer in the model is assumed to be 0.1 per year. (c) Lifetime cancer risk (for those alive and cancer-free at age 5) vs. life expectancy at age 5, according to the model. Each lifetime risk curve shows the effect of varying the parameters of background mortality, such that the survivorship curve varies within a family of curves resembling those shown in the previous panel. Crosses mark model predictions for the modern US population; a population identical to the modern US population except that the incidence of cancer per year is 30% lower in adults; and a population with the background mortality of hunter-gatherers and with 30% lower incidence of cancer per year in adults, which is assumed to provide an upper bound for cancer risk in pre-modern humans. A 30% difference in cancer incidence can be accounted for by lifestyle factors, or by a difference in stature of *c.* 19 cm (Supplementary methods). (d) Cancer risk by age 40 (for those alive and cancer-free at age 5) vs. life expectancy at age 5, according to the model. Crosses are as in the previous panel. When cancer incidence and the cancer death rate remain constant, cancer risk by age 40 is positively correlated with life expectancy. This is because higher life expectancy corresponds to less background mortality, which results in more individuals being alive and susceptible to cancer.

is already very low. Therefore, further reductions in background mortality (which will increase life expectancy beyond 75 years) are predicted to have almost no effect on cancer risk by 40 years of age (Fig. 4d), whereas not surprisingly they have a dramatic effect on cancer risk over a lifetime (Fig. 4c).

Note that these results for the human population concern the lifetime risk of acquiring cancer, irrespective of possible effects on health or survival. Thus, the age-specific incidence data used in the model is likely to overestimate actual cancer risks, in part due to advances in detecting cancers, many of which have no subsequent effects on health or survival. In populations with high background mortality rates (e.g. ancient hunter-gatherers), cancer would less often have negative consequences due to the 'primacy of mortalities'.

DISCUSSION

We argue that elevated cancer risks across the tree of life – particularly observations of greater than *c.* 5% lifetime risk – are largely attributable to novel environments, that is deviations in certain environmental conditions from those

Box 4 Questions for future research

Beyond the obvious need for more studies explaining cancer risks in free-living species, both in near-pristine systems and in those perturbed either naturally or by human activity, a number of important questions merit attention.

1 To what extent are cancers distinct from infectious and non-infectious diseases in how they are affected by environments (Eisenberg *et al*. 2007) and, inversely, in how they affect species ecology and evolution (Vittecoq *et al*. 2013; Ujvari *et al*. 2016a)?
2 For the many cancers associated with viral or parasitic infections, will selection for resistance be directed at the parasite or at the subsequent induction of cancer? Is the epidemiology of cancer-associated parasites distinct from other parasitic organisms?
3 Can we detect contemporary signals of selection on cancer genes (either directly or linked to other traits under selection) due to novel environments?
4 We actually do not know cancer risks as a function of environmental conditions (Fig. 1) for any species in the wild. On the basis of the tissues they affect, how sensitive are different cancer types on the basis of the tissues they affect to different (quantitative/qualitative) environmental drivers?
5 Our study considered the risk of *any* cancer emerging and affecting individual performance, health, survival and fitness. How do the risk levels of different cancer types (e.g. cancer cell phenotype; tissues or organs affected) vary with environments?
6 Are there phylogenetic signals of cancer resistance evolution and natural cancer risk? That is, to what extent do novel genes associated with cancer risk appear in species lineages, or rather is most evolution due to modifications of existing genes (e.g. copy number Abegglen *et al*. 2015)?
7 To what extent can cancer be employed as an indicator of more general environmental impacts resulting from, e.g. climate change, species invasions or disease epidemics? Linking specific cancers with a small number of causal factors could be useful in certain wildlife conservation efforts (McAloose & Newton 2009) and in cancer prevention in the human population.

experienced over evolutionary time scales in native habitats (Fig. 1). This does not mean that resistance to certain cancers does not continue to evolve, but rather that over ecologically relevant time spans of less than a few generations, environmental drivers and not evolutionary responses dominate variation in cancer epidemiology. We stress that *c*. 5% is a proposed benchmark,[2] based on our literature survey showing no indisputable examples of cancer beyond this level where novel environments cannot be invoked as an explanation, and our case study of ancient humans suggestive of similar levels. Inversely, *c*. 5% is a prediction associated with constraints on selective evolution in limiting cancer risks across life, and we expect that the actual figure may be considerably lower for many species. Supporting this, Abegglen *et al*. (2015) found that 51% of the captive species in their data set showed *no* cancer. Although these cases may be explained by other factors such as small sample sizes – taken at face value they indicate that baseline levels in native habitats are likely to be extremely low as well. We therefore suggest that an interesting unsolved question is the extent to which evolution prevents cancer (and other diseases), revealed as baseline risks, as a function of spatio-temporal environmental variation. Additional important questions for future research are presented in Box 4.

Our proposal that anthropogenic influences explain much of the novel environmental variation responsible for present-day cancer risk is in line with previous study suggesting that cancer was of lower importance in free-living animal populations and in humans in the past (e.g. Greaves 2000; Capasso 2005; David & Zimmerman 2010; Greaves & Aktipis 2016). We contend, nevertheless, that cancer has been and still is occasionally important for certain populations in the wild that are relatively untouched by human activity. Arguably the most prevalent contributors are parasitic infections (Ewald 2009; Ewald & Swain Ewald 2015), but more research is needed to evaluate the extent to which these deviate from evolutionary norms (Fig. 1), and if so, the potential indirect causal role of humans (e.g. contaminants increase parasitic infection and cancer).

Although environmental impacts on cancer epidemiology are attracting increased interest, the relevance for ecological and evolutionary dynamics remains underexplored. Similar to certain parasites, transmissible cancers and cancers associated with parasitic infections can have significant population and evolutionary impacts (Box 2), and possibly epidemic-like behaviour (McCallum *et al*. 2009; Ramqvist & Dalianis 2010). Epidemic-like phenomena could also occur in species vulnerable to endogenously emerging cancers, but the influences of environment – via increased cancer risk – on species ecology are unknown. The relative and absolute influences of cancer on behaviour, intra- and interspecific competition, survival, and/or reproduction could have contrasting implications for population ecology and merit further study. Nevertheless, the ecological impacts of cancers will be challenging to study (Vittecoq *et al*. 2013, 2015), in particular, given the likely delays between environmental causes and the effect of disease on individual performance and survival (e.g. Ewald & Swain Ewald 2015; Lair *et al*. 2015).

The framework presented here focuses on how deviations from native environmental conditions increase cancer risk at (1) the whole-organism level, by enabling larger body size and longer life span, (2) the within-organism level, by disrupting intraindividual physiology and contributing to multi-stage carcinogenesis, and (3) the germline level, by altering genomes and cancer sensitivity. Supporting the generality of this approach, each of these three levels can be linked to more distal contributions of species ecology (e.g. environmental change leads to heightened susceptibility to a pathogen associated with cancer, or to population contraction and a genetic bottleneck; the removal of a predator results in longer life spans), and to the

[2]Obtaining an estimate based on statistical analyses would be difficult if not impossible, given study-to-study differences (and biases) in methodology for assessing cancer risk and its aetiology.

more proximal process of multistage carcinogenesis. Nevertheless, given the complexity of the causal network proposed here (Fig. 3), testing predictions and dissecting impacts of the various contributors to cancer will be challenging, requiring theoretical, comparative and experimental approaches. For example, more rigorous tests of the effects of captivity on cancer in zoo animals (Ratcliffe 1933), or proposals that reductions in predation or parasite pressure should result in increased cancer risk (Vittecoq *et al*. 2013), would require contrasts with data from natural habitats and communities with predators/parasites, respectively. This could be accomplished for some model species by employing field enclosures to monitor individuals and control community composition (Legrand *et al*. 2012).

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DEDICATION

This article is dedicated to the memory of our friend and colleague Isabelle Olivieri.

AUTHORSHIP

MEH conceived the study, wrote the manuscript, designed the figures and contributed to the figures and boxes; RJN performed the modelling work and wrote the mathematical modelling section, designed and produced the figures and contributed to the boxes revisions.

DATA ACCESSIBILITY STATEMENT

We confirm that, should our manuscript be accepted, the data supporting our results will be archived in an appropriate public repository.

GLOSSARY

Antagonistic pleiotropy. Expression of a single gene affecting two or more phenotypic traits, where at least one trait is beneficial to fitness, and another trait has negative fitness consequences.

Cancer driver mutations. Epigenetic alterations or mutations to key genes that result in the Hallmarks of Cancer (Hanahan & Weinberg 2000, 2011), including unchecked cellular proliferation, tissue invasion and metastasis. In addition to those necessary for the Hallmarks of Cancer, other driver mutations may increase the selective growth advantage of cancer subclones resulting in tumour growth and invasion (Bozic *et al*. 2010) (but see Sottoriva *et al*. 2015).

Cancer risk. The probability over an individual's lifetime of cancer emerging and having consequences for performance, health, survival or reproduction.

Cellular cheating. Achieving the Hallmarks of Cancer, resulting in deregulation of proliferation inhibition, cell death, division of labour, resource allocation and extracellular environment maintenance (Aktipis *et al*. 2015). Somatic cheating in the context of cancer is an evolutionary dead end.

Comparative oncology. The study of cancer defences and carcinogenesis between species, between individuals within a species, or between tissues within individuals.

Force of selection. The fitness of an allele expressed at age x, measured as remaining fecundity and contributions (e.g. resource transfers) to the survival and fecundities of close kin.

Invasive carcinoma. A growing population of epithelial cells that exhibit all of the Hallmarks of Cancer, infiltrate or destroy surrounding tissue, and possibly metastasize.

Microenvironment. The immediate environment of a cell or group of cells (e.g. a tumour), including other tissue structures (e.g. epithelial cells), the vascular system, nutrients, immune factors, and chemical signals.

Multistage theory of carcinogenesis. The theory that cancers proceed through successive stages, corresponding to one or more mutations (or epigenetic alterations) activating oncogenes and disabling tumour suppressor genes (Armitage & Doll 1954; Frank 2007). Some of these mutations may be inherited, increasing the risk of certain cancer types obtaining.

Novel environment. The full set of environmental conditions, including those stemming from behaviour and ecology, that tend to differ from the conditions under which a species evolved and continues to evolve, and (in the context of this study) that result in a significant effect on cancer risk (Fig. 1). Novel environments can be either quantitative (e.g. temperatures, caloric intake), or have both qualitative (e.g. pollutants, infectious disease, selective breeding) and quantitative components. They may also be distal in causation, for example life in captivity, healthcare or habitat fragmentation. We hypothesise that novel environments will usually increase overall cancer risk, but it is possible that some cancers will decrease (e.g. the invasion of a generalist predator that tends to kill older individuals before cancer typically obtains).

Peto's paradox. The empirical observation that neither species longevity nor body size correlates with cancer risk. The same observation has been identified for tissue families within organisms (Noble *et al*. 2015).

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