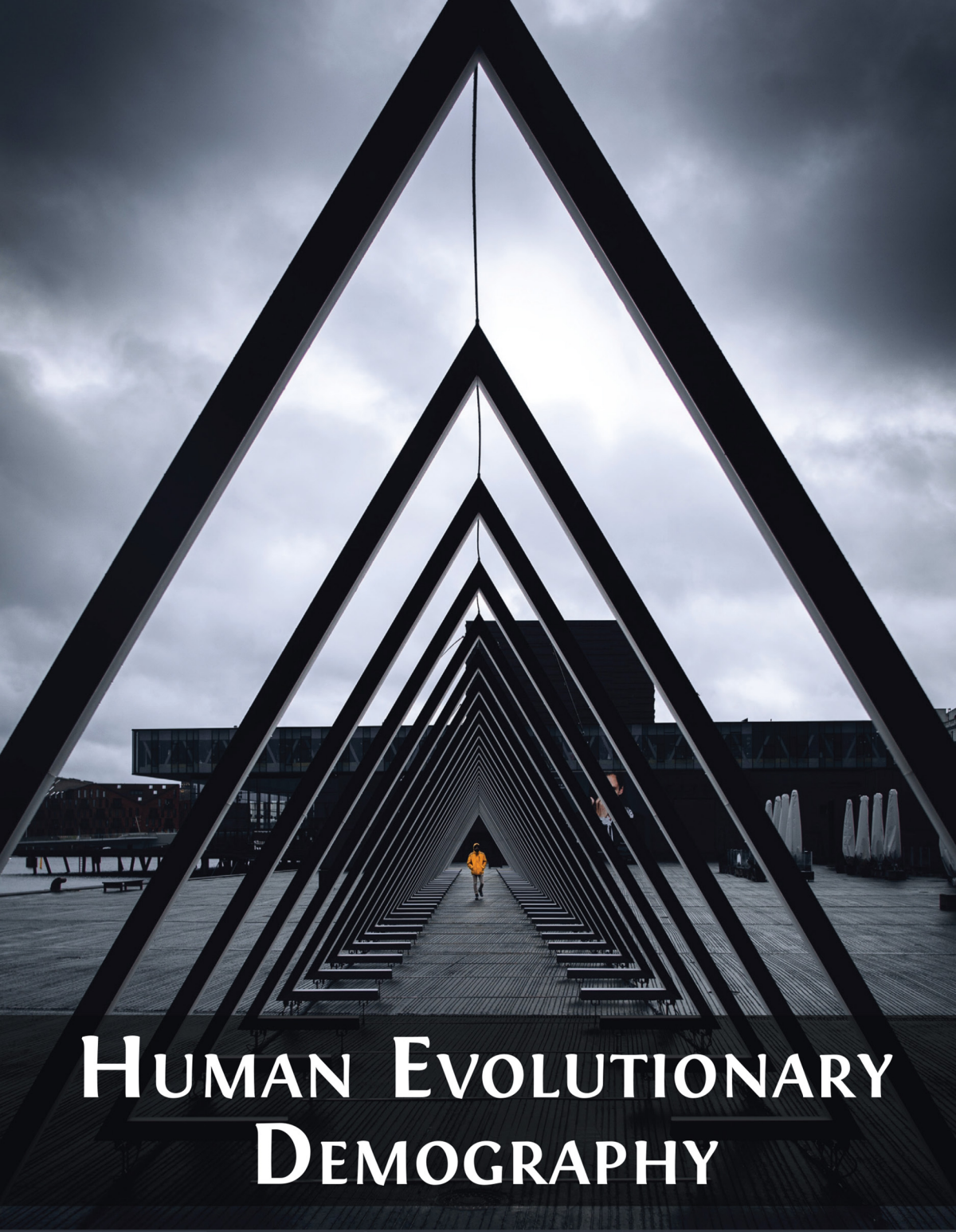

# Human Evolutionary Demography

Edited By

Oskar Burger, Ronald Lee and Rebecca Sear

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# 31. Trade-Offs between Mortality Components in Life History Evolution: The Case of Cancers

*S. Pavard and C. J. E. Metcalf*

Little is known about the relative importance of different causes of death in driving the evolution of senescence and longevity across species. Here we argue that cause-specific mortality may be shaped by physiological trade-offs between mortality components, challenging the theoretical view that physiologically independent processes should senesce at the same rate, or that interactions between causes of death will make selection blind to the effects of specific causes of death. We review the evidence that risk of cancers trades off with risks of mortality from other diseases, and investigate whether this might explain two of the most puzzling paradoxes in cancer evolution. First, among species, cancer prevalence is not a function of species' size and longevity, despite the fact that cancer incidence is known to be a function of the number of cell divisions (and therefore of size) by unit of time (and therefore of longevity). Second, within species, despite the fact that genomic instability is thought to be the proximal cause of both cancer incidence and senescence, mortality rates rise with age while cancer incidence decelerates and declines at old ages. Building on a relatively novel theory from cellular biology, we construct a preliminary model to reveal the degree to which accumulation of senescent cells with age could explain this latter paradox. Diverting damaged stem cells towards a senescent-state reduces their risk of becoming tumorous; however, conversely, the accumulation of senescent cells in tissues compromises their rejuvenation capacity and functioning, leading to organismal senescence. Accumulation of senescent cells with age may then be optimal because it reduces cancer mortality at the cost of faster senescence from other causes. Evolution will drive species towards a balance between these two sources of mortality.

## Introduction

For any organism, all fitness components cannot be maximized simultaneously. The result would be a so-called "Darwinian demon" (e.g. a species with both large survival and fertility, (Law, 1979)); which is improbable based on observations across species, and impossible based on logical considerations. Indeed, individuals are constrained by limited resources, which must be allocated to different functions of the organism at different times during the organism's life. The result is trade-offs across fitness components. Classic trade-offs in life history evolution include investment in current reproduction to the detriment of future survival or reproduction

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(the costs of reproduction, (Williams, 1966)), investment in fast growth during juvenile life to the detriment of adult fitness, or investment in the production of many offspring to the detriment of their survival (the quantity-quality trade-off, (Lack, 1947)). An alternative trade-off would be investment in a biological function linked to better surviving one cause of death, to the detriment of survival of another cause of death. Surprisingly, this is rarely considered.

Our aim here is to explore the question: do mortality components (potentially translating to specific causes of death) trade with each other? We start by briefly summarising the evidence for individual level trade-offs between mortality components, a requisite for allowing the evolution of varied strategies among species. We also critically review two major predictions that may have curtailed research into evolution associated with trade-offs between mortality components. We then narrow our focus to one of the most puzzling mortality patterns in evolutionary biology: **cancer mortality** defies prediction both within and between species. First, comparing between species, since genomic instability with age is thought to be an important proximal cause of senescence, and is known to be the key proximate driver of cancer, cancer mortality is expected to map closely to a species' actuarial senescence, and thus longevity. That this is not the case and is known as **Peto's paradox** (Nunney, 1999): cancer prevalence does not correlate with a species' size and longevity, suggesting that cancers are not "only" a by-product of senescence across species. Moving from comparison between species to comparisons within species, in humans, as in rats, incidence of cancer decelerates and even declines at older ages (reviewed below and in (Anisimov, et al. 2005)), decoupling cancer from senescence in these species. This lack of association of prevalence of cancer with longevity across species and senescence rates with cancer incidence by age within species suggests that the molecular and physiological mechanisms underlying cancer may be different or at least act differently on morbidity from those underlying other causes. Evolutionary theory is thus urgently needed to shed light on how cancer development at the level of organisms and species evolved together with lifespan and life-history (Casás-Selves and Degregori 2011). This is true even when species cancer prevalence is low in the wild (or large only due to recent human-driven changes, (Hochberg and Noble, 2017)) because, in most species, especially the large and the long lived, the puzzling question is how "the development and architecture of our tissues were evolutionarily constrained by the need to limit cancer" (Casás-Selves and Degregori 2011, DeGregori 2011).

Recent evidence for a negative correlation between cancer prevalence and that of other diseases further emphasizes the disconnection between cancer and other causes of mortality. Applying a competing risks model to data on underlying and secondary causes of death in the U.S. between 1968–2004, Yashin and colleagues (Yashin, et al. 2009) estimate a negative correlation between cancer and asthma (about –2.5%), Parkinson disease (ranging between −3% to −5%), Alzheimer's disease (ranging from −1 to −10%), diabetes (about −10%), cerebrovascular accidents (about −12%) and coronary heart disease (ranging from −25 to −15%). These intriguing negative patterns have been shown to also hold in the more finely resolved data from the Framingham Heart Study (Ukraintseva, et al. 2010). Importantly, negative correlations can emerge from mechanisms other than the physiological trade-offs required to drive evolutionary processes. However, molecular and cellular physiologists have several hypotheses of mechanisms that could drive these negative correlations (Ukraintseva, et al. 2010). Among them, the accumulation of cells in senescent-state in tissue may be the

physiological mechanism mediating negative correlations between mortality by cancers and from other causes, by impeding cell divisions and progress towards cancer. Despite its potential to illuminate patterns of cancer mortality both within and among species by capturing trade-offs between mortality components, this *senescent-cells theory of ageing*, has not formally been previously modelled.

In this chapter, after summarizing the general question of the potential for trade-offs between mortality components, and reasons for their relative neglect in life history evolution studies, we detail the core paradoxes around cancer mortality in the context of life history evolution. We then introduce a simple preliminary model of the optimization of the dynamics of non-senescent, tumorous and senescent cells built around the *senescent cells theory of ageing* and discuss implications for evolutionary outcomes related to cancer mortality. This model aims to be a "proof of principle" for two main concepts: first, trade-offs between mortality components may induce an increase of mortality by age that nevertheless reflects an optimal strategy emerging from balancing trade-offs between two different risks of death and; second, the *senescent cells theory of ageing* may be a mechanism that underpins such a trade-off. We conclude by discussing how this physiological framing of a trade-off between mortality components might resolve paradoxes relating to patterns of cancer prevalence among species, and patterns of cancer incidence across age within species. We place this discussion within the context of existing theory on aging, and point to methodological approaches that could open the way to further investigation of trade-offs between mortality components.

## Potential for Trade-offs Between Mortality Components into Life History Theory

To survive, an organism must invest considerable energy into maintenance, which encompasses many different physiological functions; from higher physiological functions (breathing, digesting, maintaining homeostasis, cardiac and neural activities, maintaining the immune system and performing immune responses, etc.) to molecular and cellular functions (controlling and repairing DNA, maintaining proteostasis and cellular metabolism, etc.). Although these functions are tightly interconnected physiologically, they nevertheless depend on specific genetic architectures that do not completely overlap. For instance, genes involved in immunity differ from those controlling cell replication and tumour suppression. Categorizing genes according to their functions (or phenotypes) is one of the most intense current research focuses of molecular biologists. Construction of vast databases reporting action of genes at a higher integrative level (e.g., **Poly**morphism **Phen**otyping v**2**) is underway. A crucial focus of this effort is to link these emergent functions or phenotypes to the vast epidemiological genetic literature on diseases resulting from polymorphisms at underlying genes. This effort has yielded increasing evidence for so called "antagonistic pleiotropic" effects of gene(s), meaning effects which are positive for one fitness component, but negative for another. In particular, evidence for genetic trade-offs between mortality components has emerged. The most famous example is polymorphisms in *APOE*-ε4, a gene involved in many neurodegenerative syndromes in adults but that allows higher levels of vitamin D absorption, and for instance protects children against diarrhoea (reviewed in (Oriá, et al. 2007)). There are therefore multiple lines of evidence supporting the existence of genetic level trade-offs between mortality components.

But do these potential trade-offs, detectable in the impacts of a single gene, translate into unavoidable physiological trade-offs, reflecting differential allocation of resources between physiological functions linked to survival, thus of importance for life history evolution? To our knowledge, this has never been formally evaluated, and the mapping between evidence for antagonistic pleiotropy and physiological trade-offs is likely to be complex. Nevertheless, striking gradients across species in investment in survival-related functions suggest that physiological, resource allocation-based trade-offs are likely. For example, investment in immune system function, a key line of defence against pathogens, and thus important for individual survival, is highly variable across species (reviewed in (Schmid-Hempel 2003)). Digestive organs consume a significant fraction of metabolic energy (20–25% in vertebrates, reviewed in (Karasov and Douglas 2013)), but this varies considerably among species according to the biochemistry of food intake. Intriguingly, the surface of the intestine is also the major contact zone between the immune system and food-borne and microbial antigens, making interactions and trade-offs between digestive and immune systems crucial in ecophysiology (Meitern, et al. 2016). Similarly, the brain is an extremely energy consuming organ which demands high levels of maintenance. Yet brain size varies substantially across species and correlates positively with basal metabolic rate in mammals (Isler and van Schaik 2006). Given these striking life history gradients across species, one might therefore wonder why trade-offs between underlying mortality components (and associated physiological functions) have been little incorporated into evolutionary demography and life-history theory. Two theoretical predictions may have been responsible for curtailing research in this direction.

First, in George Christopher Williams' seminal article on the evolution of senescence, it is predicted that: "senescence should always be a generalized deterioration, and never due largely to changes in a single system" (Williams 1957). The idea, reframed by John Maynard-Smith (Smith 1962), is that all physiologically independent processes should senesce at the same rate as "natural selection will always be in greatest opposition to the decline of the most senescence-prone system" (Williams 1957). We illustrate this principle in Figure 1 showing three Gompertz-shaped distributions of deaths by age and by cause. The observed density of deaths from $c_1$ (red polygon) is much larger than densities of deaths from $c_2$ and $c_3$ (green and blue polygons) because few individuals survive until ages where $c_2$ and $c_3$ are most likely. This shows that selection pressure on susceptibility alleles to a specific cause of death is affected by the age-specific risk of other causes of death to which the population is exposed. For example, removing $c_1$ from the population will drastically increase the strength of negative selection on $c_2$. More generally, gradients of selection occur not only across age, but also emerge as a result of other causes of death. For example, assume that the spectrum of susceptibility alleles to $c_2$ is at a mutation-selection balance, and selection is just above the threshold at which it can overcome genetic drift. As a result, negative selection is weak but will eventually purge deleterious mutations associated with $c_2$. All else being equal, susceptibility alleles to $c_1$ will be more intensely negatively selected. Purifying selection will thus decrease the number and the frequency of $c_1$ alleles, eventually decreasing the frequency of deaths from $c_1$. By contrast, susceptibility mutations to $c_3$ are neutral and mutations will accumulate, eventually increasing the frequency of death from $c_3$. Overtime, therefore, natural selection will tend to homogenise the rate at which cause-specific mortality increases with age.

The validly of this hypothesis has been extensively discussed, and empirical evidence for challenges to it reviewed (Gaillard and Lemaître 2017). Several studies show that demographic, phenotypic and functional traits do not senesce synchronously (e.g., in Soay sheep in (Hayward, et al. 2015) or in reptiles in (Massot, et al. 2011)). However, this lack of synchronicity in rates of senescence among different functions is, as yet, largely unexplained. As shown in figure 2.B (solid line) trade-offs between mortality components may provide part of the answer.

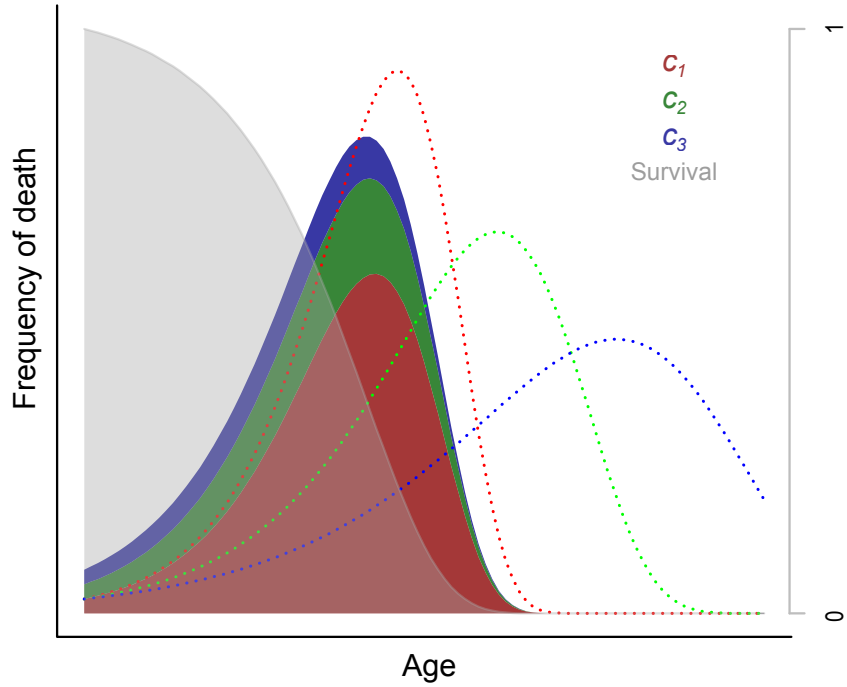


Fig. 1 Stacked distributions of deaths $f_c(t) = S_1(t)S_2(t)S_3(t)h_c(t)$ across age $t$ for three causes of death $c_1$, $c_2$ and $c_3$ (red, green and blue polygons, respectively); the corresponding overall survival over age $S(t) = S_1(t)S_2(t)S_3(t)$ (grey polygon and right axis); as well as the distribution of death from each cause $f_c(t) = S_c(t)h_c(t)$ in the case where individuals die from only this cause (red, green, and blue dotted lines). In this example, cause-specific mortality hazards are Gompertz-shaped (such that $h(t) = ae^{b_c t}$, , with $a = 0.001$, $b_1 = 0.1$, $b_2 = 0.07$ and $b_3 = 0.05$).

The second theoretical feature that may have reduced research into the question of trade-offs between causes of death is the lack of independence among causes of death: multiplicative effects are likely to be ubiquitous. For example, inflammation underlies multiple causes of death, from heart disease to cancer (Coussens and Werb 2002, Willerson and Ridker 2004). This major concept in epidemiology also raises inferential difficulties in characterizing causes of death. Many causes likely contribute to each death, particularly in older individuals, and disentangling their contribution is consequentially statistically challenging, especially as each mortality event occurs only once. To disentangle these complex causal pathways, epidemiologists distinguish between proximal and distal factors leading to death. This has led researchers to envision senescence as the accelerated accumulation of a health deficit whose ultimate outcome, death, whatever its cause, cannot be seen as the result of the deterioration of a sole physiological function (Kulminski, et al. 2007, Yashin, et al. 2007). As a consequence,

selection on allocation strategies between mortality components at an evolutionary scale might be obscured by covariation between causes of death at the individual scale.

However, to our knowledge, this has not been formally framed, and we explore this in Figure 2. Extending the model presented in Fig. 1, we assume this time that the third cause of death is the result of an interaction between mortality components respectively responsible for causes of death 1 and 2. This model captures the fact that, over the course of an individual's life, factors that increase the risk of cause of death $c_1$ may also have the effect of increasing $c_2$ and *vice versa*. Figure 2A show the distribution by age and causes in the scenario where 25% of deaths result from these interactions. Assuming that cause-specific senescence rates result from an allocation strategy in the maintenance of the respective physiological components, we illustrate in figure 2B that an allocation strategy optimizing life-expectancy can still be identified in the case where causes of death ($c_1$ and $c_2$) covary, such that the cause of death is indistinguishable in 25% of cases. This scenario flattens the optimal allocation balance between the two biological functions relative to the case where both are fully independent (Figure 2B, solid line), but an intermediate optimum can still be identified (Figure 2B, dashed line).

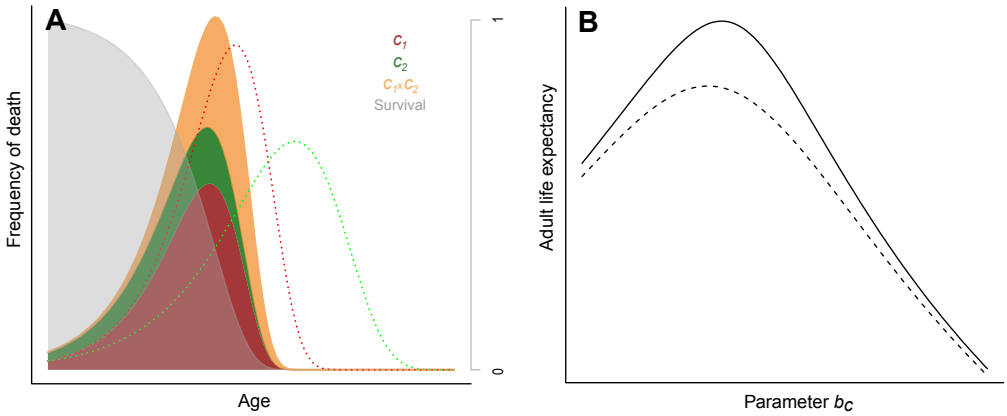


Fig. 2 As for figure 1, but in the case where causes of death are not independent. Cause $c_3$ is now the product of the interaction $c_1 \times c_2$ between $c_1$ and $c_2$ such that $h_{1\times 2}(t) = za^2e^{(b1+b2)t}$ (where $z$ is the coefficient of this interaction, $b_1$ is a parameter shaping the hazard associated with cause $c_1$, and likewise for $b_2$). Panel (**A**) shows the distribution of deaths in this case (taking $z = 35$ such that $c_1 \times c_2$ accounts for more than 25% of observed deaths). Panel (**B**) further assume a stationary population of a species whose fertility rates are constant over age, such that remaining life expectancy $e_\alpha$ at age $\alpha$ is an adequate measure of adult fitness. We assume a linear negative relationship between $b_1$ and $b_2$ that captures a trade-off between causes of death. The remaining life expectancy $e_\alpha$ is then depicted for a range of parameters ($b_1$, $b_2$) in the case where $z = 0$ (no interaction between causes of death, solid line) and in the case where z = 35, dashed line).

## Cancers and Physiological Ageing

Ageing is multifactorial. In their seminal review (Lopez-Otin, et al. 2013), Carlos López-Otín and colleagues described nine mechanisms leading to functional deterioration with age. Core aspects of deterioration have been usefully categorized as primary causes of intracellular damage (genomic instability, telomere attrition, epigenetic alteration and loss of proteostasis),

cellular dysfunction (deregulated nutrient sensing, mitochondrial dysfunction, and cellular senescence) and altered tissue dynamics (stem cells exhaustion, altered intercellular communication). To incorporate these proximal functional deteriorations into an evolutionary demographic framework for understanding ageing requires understanding to what extent each is linked to mortality in general, and to specific causes of death in particular.

Cancers may be the pathology for which this link is the most straightforward. All cancers appear to be genetic diseases at the cellular level. The current dominant theory of a cell carcinogenesis (but see below) is a multistage process requiring the accumulation of (epi) mutations in a mitotic cell lineage (often called "hits"), ranging up to large chromosomal abnormalities and aneuploidy. The outcome is liberation of neoplastic cells from homeostatic mechanisms of cell division, potentially resulting in development of cancer. This multistage theory of carcinogenesis was first proposed in the fifties by Peter Armitage and Richard Doll (Armitage and Doll 1954) and mathematically formalized in its most frequently used expression by Richard Peto (Peto 1977). However, the underlying multistage genetic processes required to generate the series of 6 to 8 "hallmarks" of cellular physiology that transform a normal cell to a neoplastic cell have only recently been characterized (reviewed in Hanahan and Weinberg 2011). The number of "hits" required for carcinogenesis varies from two (Knudson 1971) to eight (Vogelstein, et al. 2013) as a complex — and yet unknown — interactions between species, tissues and cancer types (Nunney and Muir 2015). Quantifying the rate of accumulation of somatic mutations with age (due to increased mutation rate and decreased repair efficiency) and amongst species; for example using transgenic LacZ animals (reviewed in Moskalev, et al. 2013) is therefore fundamental to characterizing the links between proximal somatic mutation accumulation to distal cancer morbidity.

Importantly, despite the detailed mechanisms proposed to explain carcinogenesis, the functional relationship between mutation accumulation in stem cells lineages and cancer risk remains poorly described. It has been shown recently that lifetime risk of cancer correlates with total number of cell divisions in tissues (Tomasetti, et al. 2017, Tomasetti and Vogelstein 2015), but the kinetics of damage accumulation with age, and how this shapes cancer incidence is still little known and intensively debated. As recently pointed out, about 50% of stem cell somatic mutations occur during ontogenesis; and this mutation accumulation does not translate into increases in cancer at that life stage. By contrast, cell divisions slow down during adult life, yet this does translate into an exponential increase in cancer incidence (Rozhok and DeGregori 2016). The Doll-Armitage multistage model is therefore not sufficient to explain cancer incidence by age and alternative evolutionary-based hypotheses have been proposed (DeGregori 2017).

Telomere inhibited-attrition is also linked to risk of cancer. In normal cells, telomerase inhibition and telomere shortening limits the number of cell divisions, a phenomenon denoted as "the Hayflick limit" (Hayflick and Moorhead 1961), corresponding for example to under 50–70 divisions in fibroblasts. Once this limit is reached, cells enter a so-called "senescent" state and stop replicating. In most human cancers, telomerase activation past this limit impedes telomere attrition and confers cell immortality (Donate and Blasco 2011, Shay and Bacchetti 1997). The role of epi-mutations in carcinogenesis is also increasingly studied. Recently, a strong correlation between chronological and epigenetic age has been identified, accounting for tissues and cells type (Horvath 2013). Epi-mutations — mutations leading to abnormal

repression or activation of genes — have been proved to be a frequent proximate mutational event leading to carcinogenesis (Banno, et al. 2012).

Risk of cancers is also linked to cellular dynamics. Carcinogenesis can indeed be framed as the result of a dynamical interplay between predation by the immune system, and competition between cancer and normal cell lineages in a changing fitness landscape (Rozhok and DeGregori 2016), with a pinch of stochastic drift (Crespi and Summers 2005, Pepper, et al. 2009, Shpak and Lu 2016). This "ecological theater of carcinogenesis" (Crespi and Summers 2005) also changes through age, in ways expected to make cancer occurrence more likely. For example, hematopoietic stem cell exhaustion resulting from other ageing processes (such as increased genetic instability due to accumulation of oxidative damage (Ito, et al. 2004)) leads to a decline of the production of adaptive immune cells with age (a process called immunoscenescence) and therefore reduces the organisms ability to keep cancerous cell lineages in check (reviewed in Henry, et al. 2011).

Overall, and although alternative theories are emerging (DeGregori 2017), (epi)genetic instability leading to mutation accumulation in stem cell lineages is still considered the primary factor required for cancer development at the cellular level; and prevention of telomere attrition the most common way for cancer cells to escape replication homeostasis. Accumulation of mutations with age should therefore correlate with increased cancer incidence. Importantly, these drivers are the very same as those invoked for senescence at the individual level. However, this link is paradoxical at two levels: between and within species.

## Prevalence of Cancers Across Species and Peto's Paradox

Cancers are ubiquitous in multicellular organisms and occur each time that a cheating cell escapes the bounds defining cooperation among cells by escaping inhibition of proliferation and cellular death (Aktipis, et al. 2015). Data on the prevalence of cancers across the tree of life are scarce and the ecological, physiological and phylogenetic determinants of a species cancer prevalence are mostly unknown (see below). However, preliminary results (based on limited data) tend to confirm one of the most puzzling paradoxes of evolutionary biology (Abegglen, et al. 2015): the fact that cancer prevalence is not a function of organism size or longevity.

The fact that this is paradoxical was first pointed out by Sir Richard Peto (Peto 1977): in a multistage carcinogenesis process, accumulation of damage within cells' lineages should be a function of the number of cell divisions, itself a function of the number of cells and lifespan. However, while mice are 1000 times smaller and about 30 times shorter lived than humans, cancer incidence is about the same (Rangarajan and Weinberg 2003). This led Peto to ask whether our stem cells are "a billion or a trillion times more "cancer-proof" than murine stem cells?" and "Why don't we all die of multiple carcinomas at an early age?" (Peto 1977, pp. 1413–14). Nunney (1999) first denoted this "Peto's paradox"; and explored the issue via a population genetic model where cancer incidence depends on the number of "hits" required for a given cell to turn into cancer. This model demonstrated that highly proliferating tissues require additional controls of carcinogenesis as organism size increases to prevent cancer prevalence from wiping out the entire species (Nunney and Muir 2015).

The degree to which Peto's paradox holds across taxa remains however largely unresolved. To date the most extensive comparative study of cancer incidence with body mass and lifespan included only 31 mammal species; and cancer incidence estimates for a subset of these species were based on only 10 necropsies (Abegglen, et al. 2015). Both richer data, but also more complete

statistical analyses are required to answer this question. The latter is necessary because, first, while multistage carcinogenesis theory predicts that longevity should be positively correlated with cancer prevalence; cancer morbidity is obviously negatively correlated to longevity and comparative studies should account for this. Second, longevity emerges from both a species' magnitude of intrinsic mortality per unit of time (e.g. the *a* parameter of a Gompertz-shaped mortality, or the intercept of the log mortality function) but also the rate at which mortality rises with age (e.g., the *b* parameter of a Gompertz-shaped mortality, or the slope of the log mortality function). Each, both or neither might be associated with cancer incidence and thus inform the generality of Peto's paradox. Overall, age-specific data are urgently needed in comparative oncology to assess the role played by cancer in ageing.

Furthermore, cancer prevalence does vary between species beyond the effect of size. A recent review of cancer prevalence and etiology in wild and captive animal populations (Madsen, et al. 2017) revealed that prevalence in wild vertebrates ranges from 0.2% to more than 50%. Two striking conclusions emerged from this review. First, in some species, cancers are one of the most prevalent current causes of death in nature, making them an important fitness components, and therefore, of crucial ecological and evolutionary significance (McAloose and Newton 2009, Vittecoq, et al. 2013) (although one should note that the extent to which the documented cancer risks emerge from recent environmental conditions is still unclear (Hochberg and Noble 2017)). Second, cancer prevalence depends less on species' size and life expectancy and more on phylogeny (e.g., reptiles seem more sensitive to cancer than mammals) or ecology (e.g., small carnivores exhibit larger average prevalence of cancer than large herbivores). Further, despite some such broad patterns, most of the time, species specific cancer prevalence defies prediction (e.g. one of the larger prevalences of cancer, about 50%, is observed in a large herbivorous mammal, the Cape mountain zebra, but this results from a particular case of equine skin cancer (Marais and Page 2011)). In domestic dogs, large dogs have larger rates of cancers than small dogs (Fleming, et al. 2011). This is likely due to artificial selection on size, which has also resulted in the fact that life expectancy of large dogs is lower than that of small dogs (Kraus, et al. 2013) and which makes dogs an outlier relative to the usual pattern linking size to lifespan across species, and therefore preventing generalization. Other species, such as the naked mole rat, exhibit as yet unexplained low cancer incidence (Buffenstein 2008, Taylor, et al. 2017). More generally, rodents are promising model species for research on cancer suppression mechanism and its links to ageing (Gorbunova, et al. 2014).

Despite these heterogeneities, arguably, the broad sweep of available evidence continues to align with Peto's paradox. Many explanations have been proposed to resolve Peto's paradox (reviewed in (Caulin and Maley 2011)). Among others, a lower mutation rate could be efficient in limiting carcinogenesis — for example, a threefold decrease in the mutation rate in humans compared to mice would be sufficient to lead to similar cancer incidence (Caulin, et al. 2015). However, mutation rates have not yet been proved to differ between mice and humans. Alternatively, differences in the efficiency of "gatekeeper" tumour suppressor genes — genes enforcing checkpoints to suppress neoplastic transformation — could make the number of "hits" required for carcinogenesis differ among species. It has been mathematically shown several times that increasing the number of "hits" required for neoplastic transformation is a particularly efficient approach to preventing cancers in large species (Caulin, et al. 2015, Nunney and Muir 2015), but, to date, there is no empirical evidence to support this. For example, the number of replicates of tumour suppression genes of the *TP* family might be expected to

correlate with species' size, as this would make tumour suppression more efficient. However, this does not seem to be the case overall, although, suggestively, a large number copies of *TP53* is found in elephant species (Caulin, et al. 2015). Cells' dynamics (mainly influenced by cells' anatomical compartmentalization, and cells' effective size, both of which affect the stochastic disappearance of cancer cell lineages), immune and apoptotic efficiencies, regulation of the number of potential divisions through telomere length are all good hypotheses that should be investigated with respect to the link between size, cancers, and phylogeny. The metabolic hypothesis is also receiving increasing support (Caulin and Maley 2011, Dang 2015): because the by-products of metabolism (such as reactive oxygen species) correlate with metabolic rate, and because basal metabolic rate scales with mass, cells may be less exposed to metabolic damages as an animal's size increases. Finally, an aspect that may have received too little attention to date is the role of cell division rate. Caulin et al. (2015) demonstrate that a decrease from 1 division every four days to 1 division every 8–13 days would be enough to account for similar cancer incidence between species differing in size by a factor 1000.

Overall, these various lines of evidence suggest that there is striking gap in life history theory around understanding the role of cancers, particularly in the context of Peto's (as yet unresolved) paradox, and associated elucidation of the drivers of cross-species patterns. As physiological trade-offs are the clay from which life-history is moulded, a key step will be to identify which other life-history components are affected by physiology investments that reduce cancer incidence.

## The Paradox of Deceleration and Decline of Cancer Incidence with Age

Close examination of existing research on the topic of cancer incidence reveals another striking paradox that has so far been neglected in studies of life history evolution. As summarized above, cancer is the cause the death that is the most easily tied to the most proximal functional mechanisms of senescence, in particular, the accumulation of damage in somatic cells lineages with age due to genomic instability. Cellular dysfunctions also increase with age and are linked to increased cancer incidence. Together, these patterns suggest that increases in cancer incidence should significantly contribute to, and closely match in shape, the increase of mortality with age. Surprisingly and paradoxically, this is not the case. The proportion of deaths due to cancer decreases after age 50–60 years old, mostly to the gain of diseases of the circulatory and respiratory systems (see figure 3A and 3B). As a result, cancers become the cause of death the least involved in senescence past these ages. A decline in cancer mortality rates has even been demonstrated for very old ages (Smith 1996). The general pattern for most cancers in humans is that incidence first increases with age, then decelerates and even declines at old ages (see figure 3C). This has been known since the sixties (e.g. in (Cook, et al. 1969)) and has since been demonstrated for a large diversity of cancers and populations, for example in 2005 France (Bélot, et al. 2008) or in 2012 Korea (see Fig. 3A in (Jung, et al. 2015)). Deceleration is even visible for a given population of a given age, at a given site, but for different histopathologic subtypes of breast cancers (Anderson, et al. 2006). This proves true even when prevalence of cancers differs due to environmental conditions, or between the sexes. For example, prevalence of oesophageal cancer is much larger in rural than in urban China, and in males than in females (Chen, et al. 2014). However, a deceleration of incidence of cancer past 70 years old, or its decline past age 80 is always observable. It must be stressed that deceleration of cancer

incidence alone is paradoxical; but the decline in the incidence in the oldest old makes it even more puzzling. Yet, recent reviews of the literature unambiguously confirm this decline in the oldest old (Harding, et al. 2008, Nolen, et al. 2017, Pavlidis, et al. 2012); making cancer one of the least prevalent causes of death in centenarians. For example, cancers account for 24.5% of the deaths at 80–84 years old in 2001–2010 England and drop down to 4.4% in people surviving 100 years old. Finally, humans are not exceptional in this respect. Similar decelerations and declines of cancer incidence with age has also been demonstrated in rats (e.g., (Pompei, et al. 2001) and reviewed in (Anisimov, et al. 2005)) and in domestic dogs (Fleming, et al. 2011).

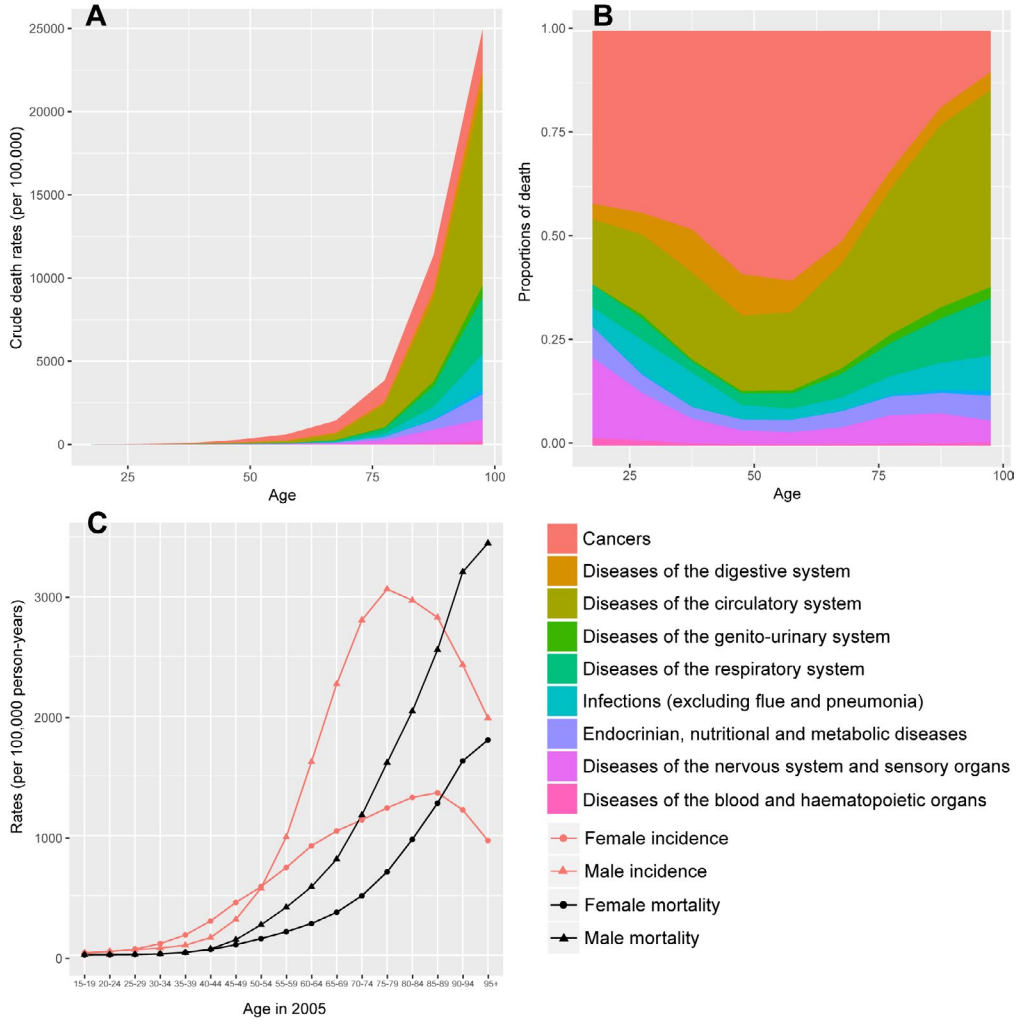


Fig. 3 Stacked crude death rates (**A**) and proportions of death (**B**) per causes in France in 2005. Data were gathered by the Centre d'épidémiologie sur les causes médicales de décès de l'Institut national de la santé et de la recherche médical (Inserm-CépiDc). Data, data documentation, and methods for death rates calculation can be found here http://www.cepidc.inserm.fr/. Panel (**C**) shows sex-specific incidence and mortality by cancers by age in 2005 France. Figure is reproduced from Bélot et al. (2008); where exceptionally detailed data on cancer incidence per site can also be found.

Several explanations for deceleration and decline in cancer incidence with age are discussed in (Anisimov, et al. 2005, Arbeev, et al. 2005, Hanson, et al. 2015). Detection bias (i.e. resulting from the fact that diagnosing cancers is more difficult in the oldest, frailest individuals, because many procedures are too invasive) or cohort-period bias (i.e. resulting from the fact that oldest cohort may have been less exposed to a cancer-prone environment) can only partially explain the results in humans, and are unlikely in other species. Two major hypotheses remain. Both were first proposed in studies carried out by A.I. Yashin. The first hypothesis is an application to cancer mortality of "the impact of heterogeneity in individual frailty on the dynamics of mortality" developed by (Vaupel, et al. 1979). The selective disappearance with age (also called differential selection) of individuals genetically or environmentally more susceptible to cancer will mean that the proportion of individuals less prone to cancer will increase with age. Change in population structure in oldest age-classes may lead to an apparent decline of the aggregated incidence rates (Vaupel and Yashin 1986). However, evidence from laboratory animals that display this decline despite low levels of genetic and environmental heterogeneity (Anisimov, et al. 2005) suggest that this heterogeneity is unlikely to be the sole cause of this pattern. Even in humans, aspects of the age profile of mortality suggest that heterogeneity in cancer susceptibility is unlikely to be the only factor underlying this pattern. In a frailty model, the inflection of the hazard should be maximal when selective disappearance is the highest. In most cases of cancer, this inflection occurs at the oldest ages (after age 75–85) while cancer incidence starts rising quickly much sooner, at ages around 40–50 (e.g., (Jung, et al. 2015)), suggesting that inflection in incidence should occur sooner than observed in most cases (although further investigation is necessary). But this may also be because magnitude and typology (individual, familial or social; (epi)genetic or environmental; inherited or acquired) of heterogeneity in cancer susceptibility is unknown for most cases of cancers. At the end of the day, the role played by heterogeneity (among other causes) in shaping cancer incidence has been largely understudied (Hanson, et al. 2015).

A good example of this is breast cancer, perhaps the type of cancer for which genetic determinants are the best known. In this case, it is estimated that "only" 5–10% of women with breast cancer have a familial history, making selective disappearance of women at higher risk of cancer due to genetic susceptibility or shared familial cancerogenous environment likely insufficient to explain decline of incidence at old age (Balmain, et al. 2003, Melchor and Benítez 2013). For example, in 2000–2005 USA, breast cancer incidence starts declining after age 75 years old. This decline is unlikely to be due to the selective disappearance of individuals carrying mutations on the two major susceptibility gene to breast and ovarian cancers, *BRCA1* and *BRCA2*, because recent evidence show that they account only for about 20–25% of the familial risk and because 39–65% and 11–39% of carriers would have already developed either a breast or ovarian cancer by this age. However the age-specific incidence of numerous susceptibility genes of low, moderate and high penetrance, and accounting for about 25% of the familial risk, have yet to be investigated (Melchor and Benítez 2013). About 50% of familial risk is as yet unknown, and is likely to result from polygenic risk factors, gene-environment interactions or shared familial cancerogenous environment. Finally, both the age at which the deceleration starts and the age at which the decline in incidence occurs varies widely between populations (e.g., between Japan and US (Tsuchida, et al. 2015) or between Asian populations (Youlden, et al. 2014)). The range of differences is far too large to result from differences in frequencies

of genetic susceptibility between populations, emphasizing the role played by other types of heterogeneity (beyond the familial or genetic to social or environmental) — in shaping breast cancer incidence by age.

A second set of hypotheses relates to the fact that somatic ageing may slow down incidence of cancer with age (Ukraintseva and Yashin 2001, Ukraintseva and Yashin 2003). As introduced above, cancer incidence may be linked to metabolic rates, and cell proliferation rates. Although humans have been recently proved to have a larger basal (or resting) metabolic rate (BMR) than great apes (Pontzer, et al. 2014), this latter declines with age in adults ((Mitchell 1962); reviewed in (Manini 2010)), and this might thus shape declines in cancer incidence. However, the existence of such a decline across species is debated (reviewed, and argued for, in (O'Connor, et al. 2002)) preventing generalizations as to this cause of declines in cancer incidence with age across species. Moreover, it is expected that such a decline in metabolic and cell proliferation rates would reduce genomic instability and therefore should decelerate both cancer incidence and senescence; failing therefore to solve the paradox of the deceleration/decline of cancer incidence with age. A related set of hypotheses specifically involve trade-offs between cancers and other causes of death (reviewed in (Ukraintseva, et al. 2010)). A novel one (not discussed by Yashin and colleagues, and so far rarely considered in the literature) is rooted in the role of the accumulation of cells in senescent-state in tissues with age. We discuss this in detail in the next section.

Overall, whether decline in cancer incidence is related to selective disappearance at the population level, or molecular or physiological mechanisms occurring at the individual level, is a question of fundamental importance for life-history theory. Increases in mortality with age have been shown to be erratic in many species (Jones, et al. 2014). Whether this pattern occurs because of population levels bias in the estimation of vital rates aggregated at the population level (for example resulting in mortality plateaus), or the product of physiological mechanisms occurring at the individual level is the subject of intense debate. Resolving this debate is likely to require leveraging existing knowledge of physiological mechanisms underpinning causes of mortality. As a result, focusing on cancers may provide crucial progress towards solving this question.

## Avoiding Death by Senescence: The Senescent-cells Theory of Ageing as a Unifying Theory?

In renewing tissues, mitotic cells (i.e. pluripotent stem cells or unipotent progenitor cells) divide to produce a specialized cell that assures tissue function, and a mitotic cell that maintains the tissue's rejuvenating capabilities. The mitotic cells' division is paramount to maintaining tissues' integrity as they age. Tissue stem cells avoid mutations, and excessively rapid telomere shortening, by dividing very infrequently (once every 40 weeks for hematopoietic stem cells according to (Catlin, et al. 2011)). Still, dividing cells are more at risk of accumulating DNA mutations (Moskalev, et al. 2013), and are thus at risk of turning neoplastic. This is why the number of cell divisions is limited, a fact first discovered by (Hayflick and Moorhead 1961) who showed that in vitro cultivated fibroblasts eventually stop replication even when space and nutrients are abundantly provided. Known as the Hayflick limit, this is due to the fact that cells enter a life-cycle state known as cellular senescence: "a stable arrest of the cell coupled to stereotyped phenotypic changes" (Lopez-Otin, et al. 2013). These phenotypic changes

(reviewed in (Campisi and d'Adda di Fagagna 2007, Kuilman, et al. 2010)) include a permanent growth arrest, mainly in G1 phase, linked to altered gene expression, and the secretion of pro-inflammatory molecules. Importantly, they also include resistance to apoptosis, meaning that senescent cells ultimately die by necrosis and are eliminated by phagocytosis.

Causes of cellular senescence are reviewed in (Campisi and d'Adda di Fagagna 2007, Collado, et al. 2007, Kuilman, et al. 2010, Lopez-Otin, et al. 2013). Most of them are associated with mechanisms preventing the replication of cells that have accumulated intracellular damage. As such, these mechanisms obviously play a crucial role in preventing cancers. First, telomeres shorten at each division. When telomeres become critically short, the *p53* tumour suppressor protein pathway activates either cellular senescence or apoptosis (although the drivers directing a given cell towards one or the other fate are, as yet, unknown). This limits the number of normal cell divisions, and contributes to replicative senescence (Kuilman, et al. 2010). It may also lead to premature senescence of cells that have initiated neoplasic transformations: as discussed above, in most cases of cancers, cells have mutated to higher activation of telomerase, and associated telomere length maintenance. Severe DNA damage (unrepaired DNA damage and chromosomal damage) can also activate p53 pathways towards senescence or apoptosis. Molecular biologists have also identified many pathways (e.g., Ras/Raf/MEK) that detect problems in the expression of specific genes which may induce cancers (called oncogenes). These pathways then activate the production of two major proteins $p16^{\text{INKa}}$ and $p19^{\text{AFR}}$ (in mice, or $p14^{\text{AFR}}$ in humans) which induce cellular senescence.

While cellular senescence plays a key role in preventing development of cancers, importantly, it may also have deleterious effects: accumulation of senescent cells in tissues may alter their renewal and function. There is ample evidence that cells in a senescent state do accumulate in tissues as individuals age (e.g., (Dimri, et al. 1995) in humans or (Herbig, et al. 2006) in baboons, reviewed in (Jeyapalan and Sedivy 2008)); although the kinetics of this accumulation over age remains unknown. Moreover, evidence that this accumulation is a cause rather than a consequence of ageing has long been largely circumstantial. Recently, the development of a technique allowing selective killing of senescent cells in tissues in transgenic mice (Baker, et al. 2011) allowed the issue to be resolved. Removal of senescent cells delayed onset of age-related disorders (Baker, et al. 2011, Ogrodnik, et al. 2017) and even increased lifespan (Baker, et al. 2016, Ogrodnik, et al. 2017). Unexpectedly, this procedure also delayed carcinogenesis, the opposite of what would have been expected under the "senescent cells theory of aging". Possible explanations for this discrepancy include delayed carcinogenesis as a consequence of the complicated experimental procedure on transgenic mice lineages used in these studies; or potentially non-linear patterns of damage accumulation in stem cells lineages as organisms age, under differential replication rates and relative importance of apoptosis and senescent-state transitions, making the age at which treatment is applied drive potentially different outcomes. A final explanation might link this outcome to induction of hyperplasia (often an initial stage of cancer) associated with the pro-inflammatory phenotype of senescent cells demonstrated in some cases of experimentally induced cellular senescence (Campisi 2013), as for instance in the case of genotoxic chemotherapies (Demaria, et al. 2017).

Overall, recent studies tend to confirm a hypothesis expressed by many molecular and cellular biologists: molecular pathways that suppress carcinogenesis (such as the p53–ARF pathway) are also involved in apoptosis, and cell entry into a senescent-state (Alderton 2007). As such,

cellular senescence or telomere shortening are "strategies that protect us from cancer" but also "might hasten our rate of ageing" (Finkel, et al. 2007). Accumulation of senescent cells in tissues with age could be an adaptive mechanism to prevent cancers, at the cost of a decline of tissue function and rejuvenation capacity with age. This maps onto the definition of a physiological trade-off in life-history theory, but, strikingly, it is framed as a trade-off between two mortality components: mortality by cancer, and mortality by other causes of death underpinning actuarial senescence. Following this logic through using an evolutionary biology perspective suggests that senescence could be optimal because it allows reduced cancer mortality at early ages, at the cost of increased mortality associated with deterioration of physiological function at older ages. It has curiously not yet (to our knowledge) been confronted with evolutionary theory of trade-offs and ageing; and even less been mathematically modelled.

## A Preliminary Model of Cellular Dynamics with Age

Applying a mathematical model to investigate the implications of this trade-off is a key step: an integrated theory encompassing different forms of mortality may have the power to solve both Peto's paradox and the paradox of the deceleration/decline of cancer incidence with age. First, if accumulation of senescent cells with age is optimal, it may lead to non-continuous increases of mortality by cancer and senescence with age (investigated below), thus resolving the incidence by age paradox. Second, since an accumulation of senescent cells with age is, at least partially, a function of the number of replicating cells in a given organism, this sets it in line with all hypotheses proposed to solve Peto's paradox. If senescent cells optimally accumulate at different paces within tissues between species of different sizes and longevities, large and long-lived species may exhibit increased aging rates that would consequently decrease prevalence of cancers.

To investigate whether the accumulation of senescent cells with age could be optimal, and might lead to deceleration and decline of incidence of cancer with age, we develop in Box 1 a simple preliminary model of the dynamics of senescent and tumorous cells with age, and their effects on cause-specific mortality (see Box 1 for the definition of tumorous cells used here).This model incorporates three core attributes describing cellular dynamics, including, first, an increased risk that a cell becomes oncogenic as the organism's age increases (captured by the expression $\alpha_{x_i}$ which increases linearly from 0 to 1 over $\Phi$ time-steps, implying that age is "biological", corresponding to the unspecified amount of chronological time required for a proportion $\alpha_x$ of cells to turn neoplastic); second, a constant probability that tumorous cells enter a senescent state (reflected by the parameter $\sigma$); and third, a probability that a tumorous cell turns neoplastic as a function of the proportion of senescent cells in a focal tissue (modulated by a parameter $r_{CS}$). Two parameters are further used to translate the cellular makeup of an individual into morbidity: $r_{OS}$ and $r_{OT}$ respectively modulate the organism's morbidity as a function of the proportion of senescent and tumorous cells (both sources of morbidity are assumed to be increasing concave up functions of their respective fractions).

**Box 1** — A demographic model for senescent and tumorous cells dynamics and their consequent effects on organism morbidity.

We consider a model organism dying only from two causes: cancer or mortality resulting from the accumulation of senescent cells in the organism. We denote $S_x$ the proportion of senescent cells at exact age $x$ , and $T_x$ the proportion of tumorous cells of exact age $x$ amongst non-senescent cells. Tumorous cells are defined as cells which have accumulated damage, and are at risk of turning neoplastic, and thus leading to cancer, but have not done so yet. Senescent cells do not further replicate, do not participate in tissue functioning and eventually die from necrosis (not formally modelled here). Tumorous cells are cells that have accumulated enough unrepaired deleterious mutations (or "hits"), yet have not been eliminated by apoptosis, putting them at risk of carcinogenesis if they do not enter into a senescent-stage. In one time-step, the proportion of new tumorous cells $\delta_x$ is defined by:

$$\delta_x = (1 - S_x - T_x)[\alpha_x + (1 - \alpha_x)(S_x)^{rCS}], \tag{0.1}$$

where $\alpha_x$ is the increasing proportion of cells becoming tumorous with age in a tissue (modelling a potentially increased genomic instability with age $x$) where there are no senescent cells. This might reflect either an increase of genomic instability with age, a decrease in apoptosis efficiency with age, or their interaction — i.e. apoptosis rates increase with age and the resulting gaps might allow replication of damaged neighbouring cells, allowing them to become oncogenic. The term $(1 - \alpha_x)s(x)^{rCS}$ captures the fact that tumorous cells might be more likely to be generated in tissues whose cell functioning is compromised by the accumulation of senescent cells; $r_{CS}$ captures cells' ability to withstand the impact of the proportion of senescent cells. The proportions $S_x$ and $T_x$ are respectively then given by:

$$S_{x+1} = S_x + (T_x + \delta_x)\sigma, \tag{0.2}$$

where $\sigma$ is the proportion of tumorous cells entering into senescence, and:

$$T_{x+1} = (T_x + \delta_x)(1 - \sigma). \tag{0.3}$$

In each time-step, the probability of surviving mortality via senescence and mortality via cancer are defined from and such that:

$$P^s_x = 1 - (S_x)^{rOS}, \tag{0.4}$$

where $r_{OS}$ is the organism resistance to accumulation of senescent cells for its survival, and:

$$P^c_x = 1 - ((T_x + \delta_x)(1 - \sigma))^{rOT}, \tag{0.5}$$

where $r_{OT}$ is the organism resistance to tumorous cells.

With this framework in hand, we numerically identified the optimal value $\sigma^*$ that maximizes the organism's life expectancy for a set of parameters ($\Phi$, $r_{CS}$, $r_{OS}$, $r_{OT}$) . It must be stressed that optimality is used here in its loose sense as a proof of principle that, somehow, natural selection may have an influence on the evolution of the trait (Orzack and Sober 1994) — here entrance in a senescent-state — which may in turn have shaped incidence of cancer by age and senescence.

Optimal $\sigma^*$ is found for a large range of parameter as soon as $r_{OS} < r_{OT}$. Parameter $r_{CS}$ has little effect on the optimum but controls the pace of the decline in cancer incidence at old age. One example that maps closely onto the empirical patterns of mortality we describe above is illustrated in Figure 4. The optimal strategy is to accumulate senescent cells at a low rate with $\sigma^* \in [0, 0.1]$. As a result, cancer incidence increases rapidly with age then decelerates and declines; thus leading to one potential resolution to the paradox of incidence of cancer with age.

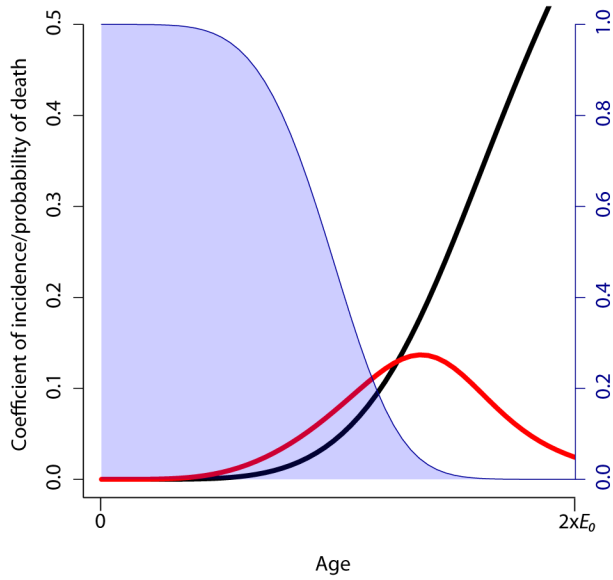


Fig. 4 Incidence of cancer (red) and probability of death resulting from the accumulation of senescent cells (black) for an optimal accumulation of senescent cells by time-step of $\sigma^* = 0.05$ for parameters $\Phi = 500$, $r_{CS} = 2.5$, $r_{OS} = 2$, $r_{OT} = 2.6$. In this case $E_0(\sigma^*) = 27$.

In the example illustrated here (Figure 4), the optimal strategy consists of diverting 5% of damaged cells per time step towards the senescent-state. This optimal strategy allows the accumulation of damaged cells early in life, leading to an early and rapid increase in cancer incidence (red line). In parallel, senescent cells accumulate at a slower pace, such that mortality by other causes rises more slowly than cancers (black line). Eventually, however, when ~40% of stem cells are in the senescent-state, cell proliferation becomes sufficiently reduced as to considerably decrease the number of new damaged cells per time-step; leading to a decline in cancer incidence, thereby preventing cancers from wiping out the entire cohort in a few time steps. Beyond this point in time, the increase of new senescent cells per time-step obviously also slows down. And yet, as the addition of even a small proportion of senescent cells considerably compromises tissue functioning, mortality by other causes of death continues to rise (black line). The optimal $\sigma^*$ results therefore from a balance between mortality due to cancer early in life and mortality by other causes later in life.

## Discussion

We have taken the first step towards characterizing the implications for life history evolution of *the senescent-cell theory of ageing*, proposed by molecular and cellular biologists. Senescent-cells (i.e. stem cells that have ceased to replicate) accumulate in tissues with age, and, according to the theory, this has two implications for individual mortality. First, diverting damaged stem cells towards a senescent-state prevents their replication, and thus prevents accumulation of more mutations, and the risk of that these cells become neoplastic, ultimately resulting in a reduction

in the risk of cancer. However, the accumulation of senescent cells in tissues compromises their rejuvenation capacity and functioning, and this leads to organismal senescence (Alderton 2007). Following this logic through, we suggest that senescence could be (at least in part) selected for because accumulation of senescent cells allows reduced cancer mortality at early ages, at the cost of increased mortality-associated deterioration of physiological function at older ages. Our preliminary model optimizes organism life expectancy as a function of the dynamics of non-senescent, tumorous and senescent cells within tissues over age, and their respective relationships with mortality from cancer and other causes. We show that accumulation of senescent cells with age can be under the influence of natural selection leading to a peculiar pattern of cancer age-incidence: an increase in early life followed by a deceleration and decline at old ages.

This novel result might resolve what we refer to as the "the incidence by age paradox" (see above). The paradox is that despite the fact that genomic instability is thought to be the proximal cause of both cancer incidence and senescence, and accumulation of mutations with age leads to an exponential rise of mortality by many causes, cancers oddly show reduced incidence at old ages (at least in humans and rats). Our model shows that this pattern may emerge as a result of the senescent cell theory of ageing. We also argue (although we did not formally model this) that accumulation of senescent cells with age might also resolve Peto's paradox, e.g., the fact that cancer prevalence is not a function of species' size and longevity. If senescent cells accumulate at different paces within tissues between species of different sizes and longevities, large and long-lived species may exhibit increased aging rates and consequently postponed incidence of cancers.

This preliminary model provides a "proof of principle" that trade-offs between mortality components can interestingly shape mortality patterns over age, and provides a first step in investigating these phenomena. But there are many key directions for further investigation, including (i) explicitly incorporating models of apoptosis and carcinogenesis (as in (Nunney 1993, Nunney and Muir 2015)); (ii) exploring the effect of size and metabolism across the tree of life for developing predictions about the potential of the senescent cells theory to resolve Peto's paradox (as in (Dang 2015)); (iii) incorporating more life-history parameters, including fertility and extrinsic mortality into the demographic model framed here. Moreover, the kinetics of senescent cells accumulation with age in tissues, and how it relates to cancer incidence by age, is not known. We hope that further modelling of tissues dynamics will help generate testable predictions on these functional relationships.

Is the senescent cells theory really a new theory of aging? In this field of work, there is a tendency to elevate a new finding related to senescence to the rank of an evolutionary theory. To us, rather than a new theory of ageing, and although this should be further discussed, this may be a core mechanism that fits within the broader umbrella of the Disposable Soma Theory (DST) (Kirkwood 1977, Kirkwood and Holliday 1979). The DST explains senescence by the accumulation of damage at different physiological levels due to the fact that some resources have to be invested in other functions, mainly to reproduction, then repair and maintenance. For the DST, senescence is the outcome of an evolved optimal allocation strategy under the constraints of physiological trade-offs. We see the senescent cells theory as a special case of DST where the allocation strategy concerns trade-offs between two mortality components, and determines the level at which organisms invest in tissue rejuvenation and slower actuarial senescence, at the

cost of an increased risk of cancer (of course, controlling for an organism's size, metabolism, phylogeny, mutation rates, efficiency in DNA repair and alternative immunological and anatomical mechanisms preventing cancer). Many authors have tried to reconcile DST with the Antagonistic Pleiotropy theory of aging (Williams 1957) *via* the existence of genes determining the allocation strategies between investing in early versus late fitness components (Kirkwood and Rose 1991, Partridge, et al. 1991). The senescent cells theory may very well be one of the rare examples for which evidence could be obtained: genes controlling the entrance of a cell into a senescent-state control the amount of cell division and will therefore control the amount of energy invested in rejuvenating tissue, thus defining the core processes underpinning cell dynamics over the course of an organism's life span. Selection on such genes will ultimately result in a balancing of the trajectories of the two types of mortality.

Considering empirical evidence for this and other theories on trade-offs between mortality components, we note the challenges in using aggregated population level data: in our model both cancer mortality and mortality by other causes will increase over most of the organism's life, making trade-offs more difficult to observe than, for instance, if the decline of one cause were correlated to the increase of the other. The only solution to addressing this challenge is to derive strong theoretical expectations regarding the age-specific shape of cause-specific mortality in a model where trade-offs of the kind we describe here are formally implemented. Furthermore, because individuals die only once, trade-offs are also not observable at the individual level if one has only information on cause of death. To investigate such trade-offs using individual data will require (i) grouping individuals according to factors likely to shape cause-specific mortality outcomes (for instance according to their genotypes or the experimental setting), or (ii) measuring biomarkers known to be good predictors of individuals' future cause-specific mortality, or (iii) empirically manipulating, over the course of an individual's life, the functions underpinning trade-offs between mortality components (for example, via the technique that allowed selective killing of senescent cells (Baker, et al. 2011)). Finally, comparison between species requires simultaneously comparing differential investment in physiological functions and relating these to differential pattern of cause-specific mortality.

In conclusion, trade-offs between mortality components are likely to be an important driver of life history evolution and yet have been strangely neglected by the field to date; possibly for both theoretical but also logistical reasons that we outline above. In particular, given the challenges to empirical investigation, we feel that such trade-offs cannot be investigated by evolutionary demographers acting alone, but detailed epidemiological and demographic data on causes of death must be allied with a nuanced understanding of the molecular, cellular, physiologic drivers at the individual and species level, likely requiring a profoundly interdisciplinary approach.

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