

OPINION

How ageing processes influence cancer

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Abstract | The ageing of populations worldwide is leading to an unprecedented increase in cancer cases and fatalities. Understanding the links between cancer and ageing is therefore more important than ever. How the interplay of ageing-associated changes affects cancer initiation and progression is complex, however, and some ageing processes probably foster cancer development whereas others hinder it, possibly in a tissue-specific manner. In the emerging age of cancer, how can our growing understanding of the biology of ageing inform cancer biology?

Ageing is the biggest risk factor for cancer; the majority of tumours (in developed countries) are diagnosed in aged patients^{1,2}, and this is projected to be the global scenario by 2050 (REF. 3). The connection between cancer and ageing has been well-documented in numerous epidemiological studies⁴. After sexual maturity, cancer incidence increases exponentially with age (FIG. 1a). Given the ageing of the population in modern societies, it is not surprising that the burden of cancer is now the highest in human history and will continue to increase for the foreseeable future^{5,6}. However, the relationship between the biology of cancer and that of ageing is far from clear. According to the widely accepted multistep model of cancer in which various sequential mutations are required for a cell to become malignant, exposure time to a known or unknown carcinogen (or carcinogens) is a risk factor for cancer, and some authors have long argued that by itself this explains the increased risk of cancer with age^{1,7}. However, recent evidence from a variety of ageing studies demonstrates that there is at least some overlap between ageing and cancer processes: epidemiological data show that familial factors are associated with both low cancer occurrence and longevity⁸. Furthermore, various genetic and dietary manipulations that slow ageing in rodents also reduce cancer incidence^{9,10} and vice versa¹¹, and host tissue susceptibility to cancer changes with age⁹.

Although the age-related increase in cancer risk is well-established, the age-related patterns of cancer are far from straightforward^{4,12}; for example, cancer incidence levels off at advanced ages (FIG. 1a,b). Additionally, cancer morbidity and mortality have been reported to decline in the oldest age group, including in centenarians¹³. Even though the exact reasons for this are unknown, the decline in overall cancer-associated mortality may be caused by an age-related decrease in the heterogeneity of the population, as seems to occur during ageing¹⁴, whereby subpopulations that are prone to higher mortality die at younger ages, leaving individuals that are less susceptible to cancer in older age groups. The rate of age-related increase in cancer incidence also varies between cancer types with, for example, prostate cancer incidence accelerating much faster than brain cancer (FIG. 1b). Some cancers have early-life incidence peaks, such as osteosarcoma and acute lymphoblastic leukaemia^{4,9}, and the incidence of testicular cancer peaks at approximately age 30 years and then sharply declines (FIG. 1c). The incidence of other tumour types, such as cervical cancer, also levels off at middle age (FIG. 1d). Exposure to risk factors early in life, such as infectious diseases, could have a role in early-life peaks in cancer incidence, yet as the probability of cells becoming malignant is expected to increase with age, some inversely age-associated cancers, such as testicular cancers, seem to have no established explanation.

Apart from accumulating mutations, normal ageing causes many changes that may increase susceptibility to cancer initiation and/or create a tissue microenvironment that is more propitious for the growth of malignant cells, thus favouring cancer progression and metastases⁹. Ageing processes, including cell senescence and alterations to endocrine and immune systems, are possible explanations, although contentious, that are discussed herein. The broad aim of this article is to paint a picture of what we know and which crucial questions remain unanswered concerning the biological links between cancer and ageing.

Alterations to ageing affect cancer

Ageing is a complex process that entails multiple phenotypes: physiological and molecular changes that contribute to the degeneration and functional decline with age of practically all organs and body systems, increased susceptibility to various diseases and exponentially increasing mortality with age¹⁵. In spite of its complexity, one of the most exciting discoveries in biogerontology is the surprising plasticity of ageing^{10,16}. According to [GenAge: the Ageing Gene Database](#), hundreds of genes have been shown to modulate longevity in model organisms, including approximately 100 in mice¹⁷. Most genetic and dietary manipulations that affect ageing in rodents also have an impact on cancer incidence and/or progression⁹, suggesting overlapping mechanisms (FIG. 2). For example, mice with extra copies of *Trp53* (which encodes p53) and cyclin-dependent kinase inhibitor 2A (*Cdkn2a*; which encodes INK4A and ARF) exhibit strong cancer resistance, in addition to slightly increased longevity and lower levels of ageing-associated oxidative damage¹⁸.

Life-extending genetic alterations. In rodents, typically mice, single gene manipulations have been shown to increase lifespan by up to 50%¹⁷ and to retard various physiological and molecular aspects of ageing phenotypes. The fact that ageing as a whole, including multiple age-related changes and diseases, can be manipulated in rodents by single genes shows that ageing is not merely a collection of pathological processes running in parallel but rather that there are processes capable

of synchronizing and driving the progression of ageing in mammals¹⁵. As such, most of these genetic manipulations in mice also retard cancer incidence and development⁹. Notably, mutant mice with disrupted growth hormone (GH; also known as somatotropin) and insulin-like growth factor I (IGF1) signalling are long-lived and tend to have a smaller body size, decreased cancer incidence and often longer cancer latency compared with wild-type mice⁹. For example, one study found that a population of growth hormone receptor (*Ghr*)-knockout mice were less frequently tumour-bearing than wild-type controls (68% versus >90%, respectively), they also developed fewer different tumours, less frequently died of neoplastic diseases (42% compared with 83% in wild-type littermates) and had less-severe neoplastic lesions, although this was only significant for pulmonary adenocarcinoma¹⁹. A similar study in Ames dwarf mice, which are GH-deficient owing to an underdeveloped pituitary gland, found no differences in tumour incidence between Ames dwarf mice and wild-type

controls²⁰. However, fatal neoplastic disease occurred later in life in Ames dwarf mice, and the severity of lung adenocarcinoma was lower compared with wild-type littermates, thus suggesting a delayed progression of fatal neoplastic disease in Ames dwarf mice²⁰. This cancer-protective effect may not be surprising given that lower GH-IGF1 signalling results in less cell proliferation *in vivo*²¹. Interestingly, reducing the stimulus for cell proliferation can not only reduce cancer incidence but can also extend lifespan in mice²², and therefore mouse models of ageing may be useful for cancer studies.

Humans with *GHR* mutations, which result in GHR deficiency (also known as Laron syndrome) and low serum levels of IGF1 and IGF2, are also protected against cancer: among 30 individuals studied, no cancer deaths were observed compared with ~20% of deaths in relatives with no GHR deficiency²³. Contrary to *Ghr*-knockout mice, which are long-lived²⁴, GHR deficiency in humans does not seem to extend lifespan, possibly because it is associated

with an increased risk of heart diseases and with non-age-related causes of death²³. Epidemiological studies also suggest that short, small people tend to have a slightly lower cancer incidence, which could again reflect the association between reduced cell proliferation and cancer incidence²⁵.

Accelerated ageing and cancer. Numerous genetic manipulations in mice, and a few human diseases, have been classified as putative cases of accelerated ageing. Human progeroid syndromes include Werner syndrome, Hutchinson–Gilford syndrome and Cockayne syndrome. Patients with these syndromes exhibit signs and features of ageing at a relatively young age, including premature death, although none of these diseases is a perfect phenocopy of ageing²⁶. Of these three classical human progeroid syndromes, predisposition to cancer is only strongly observed in patients with Werner syndrome²⁶, although these patients develop different tumour types, in particular a higher ratio of sarcomas to carcinomas, when compared with the normal population²⁷. Many progeroid syndromes in mice and humans originate from mutations that disrupt DNA repair and/or DNA damage responses, resulting in an increased incidence of tumours that usually occur at a decreased latency⁹. Various authors have recently reviewed this topic and its relevance to cancer and ageing^{9,26,28,29}. The fact that disruption of DNA repair and/or DNA damage responses results in signs of premature ageing and often cancer predisposition gives weight to the idea that DNA changes with age are an important factor for cancer and ageing. Even though premature ageing is often associated with cancer susceptibility in mice and humans, exceptions exist, such as in Cockayne syndrome in which patients do not exhibit cancer predisposition^{26,28,29}. Likewise, not all mouse models of disrupted DNA repair systems result in accelerated ageing. One emerging picture is that disruption of specific DNA repair pathways is associated with ageing, cancer or both^{26,28,30}. In particular, it has been argued that disruption of pathways that result in the accumulation of DNA damage and mutations, such as global genome nucleotide excision repair (NER), predisposes to cancer, whereas disruption of DNA repair pathways resulting in loss of proliferative capacity or overall cell loss, such as transcription-coupled NER, often drives ageing²⁸.

Caloric restriction and the effects of diet on cancer and ageing. In addition to genetic manipulations of ageing, dietary manipulations also have a substantial impact on

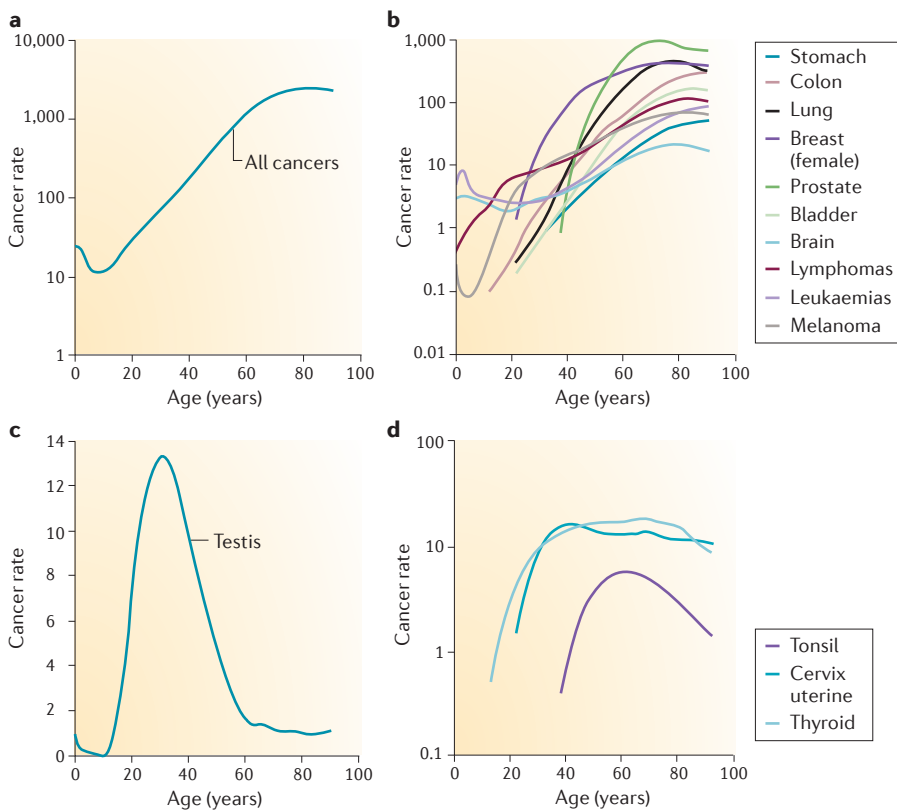


Figure 1 | The incidence of cancer diagnosis as a function of age. Cancer rate (per 100,000 people, in a logarithmic scale) from the entire United States population (1999–2009) by age for: all cancers (a); selected sites in which cancer incidence increases exponentially with age after maturity (b); testicular cancer (c); and selected sites in which cancer incidence peaks relatively early in life (d). Unless otherwise stated and unless for gender-specific cancers, data from males and females were combined. Data are from the United States Cancer Statistics, Wide-ranging Online Data for Epidemiological Research (WONDER) database¹³³.

cancer and ageing in animal models. The most widely studied life-extending intervention is calorific restriction (CR), which consists of restricting calorie intake without inducing malnutrition. CR extends lifespan in most species, and has been shown to significantly increase lifespan (by up to 50%) in mice and rats, although not in all strains¹⁰. Numerous studies in rodents have shown a marked reduction in cancer incidence from CR³¹, even in naturally occurring long-lived strains³² and when CR is started in 1-year-old, middle-aged mice^{33,34}. One study found that when CR in mice was initiated late in life (19-month-old animals), overall cancer incidence was not affected but the growth of tumours was reduced³⁵.

Two studies in rhesus monkeys, which did not encompass the whole lifespan as some animals are still alive, reported a decreased incidence of neoplasia in animals under CR^{36,37}. When CR was initiated late in life, neoplasia incidence was not reduced³⁷, in line with the studies of mice³⁵, although it is unknown whether CR can delay tumour growth in monkeys. The two studies in monkeys contradict each other in terms of mortality: one study at the Wisconsin National Primate Research Center (WNPRC) showed a marked decrease in mortality owing to CR³⁶, which was not observed in another study conducted at the US National Institute on Aging (NIA)³⁷. Conflicting results between studies could be due to differences in the controls' diets, as the controls in the NIA study were fed a healthier diet. For example, in the NIA study, food intake of control animals was slightly restricted to prevent obesity³⁷. Cancer, diabetes and cardiovascular disease were the most prevalent age-related diseases observed in controls in both studies, yet a decreased incidence of cardiovascular disease in monkeys under CR was only observed in the WNPRC study^{36,37}.

Obesity and excess adipose tissue have been associated with a shorter lifespan and with various age-associated diseases in humans, including cancer^{1,38–40}. Some of the health benefits of CR, including anticancer effects, could therefore be due to reduced fatness. Intriguingly, however, mouse strains with the least fat reduction under CR tend to exhibit life-extension and vice versa⁴¹; whether these effects of CR correlate with cancer incidence is not known, and it may be that excessive fat reduction is unhealthy in mice, yet these results question the role of fat reduction in CR effects.

Although the molecular mechanisms underlying CR remain the subject of debate, some evidence points towards a role for the

GH–IGF1 pathway (FIG. 2), the activity of which is decreased in rodents undergoing CR and in long-lived strains^{10,24,31,42}. High IGF1 levels have been associated with tumour progression⁴³. In a p53-deficient mouse model of bladder cancer, the restoration of IGF1 levels in mice undergoing CR prevented the slowing of tumour progression⁴⁴. Not surprisingly, animals undergoing CR are smaller, and the lack of mitogenic stimuli may help to explain the observed protection from cancer. Other potential molecular mechanisms of CR include: the mTOR pathway, which extends lifespan in animal models and might have a role in CR; the energy sensor AMP-activated protein kinase (AMPK), which has been associated with longevity and CR in invertebrates; and sirtuins, for example SIRT1, which has been hypothesized to be a key player in CR^{10,39}. However, the role of SIRT1 in mammalian ageing and CR remains controversial, with mixed results from rodents^{10,45}. The overexpression of SIRT1 in mice does not extend lifespan but seems to protect against some types of cancer⁴⁶, so a role for SIRT1 in the anticancer effects of CR cannot be excluded, as further discussed below. The PI3K pathway, and various players associated with it including AKT, PTEN and mTOR (FIG. 2), have long been associated with ageing in model systems¹⁶ and may be part of the signalling cascade involved in CR¹⁰. Given its role in the regulation of the cell cycle, the PI3K pathway is an attractive target for anticancer therapies⁴⁷ and might mediate the anticancer effects of CR.

Shared cancer and ageing mechanisms

The probability of tumour formation may increase with age simply because exposure time increases, yet ageing-associated phenotypes also seem to have a role in the increased incidence of cancer. However, a major open question is: are ageing-associated processes and changes making host tissues more or less susceptible to tumour initiation, progression and metastasis? Some of the processes that are thought to be most important are discussed below.

DNA damage responses. It is undeniable that DNA damage, mutations and genome instability increase with age^{26,28,48}. Recent large-scale studies have begun to quantify this increase in humans: one study using blood and buccal samples found a low frequency (0.23%) of detectable clonal mosaicism until age 50, which then gradually increased with age up to 1.9% in individuals aged 75–79 years⁴⁹; another study found similar results⁵⁰. However, human studies have been

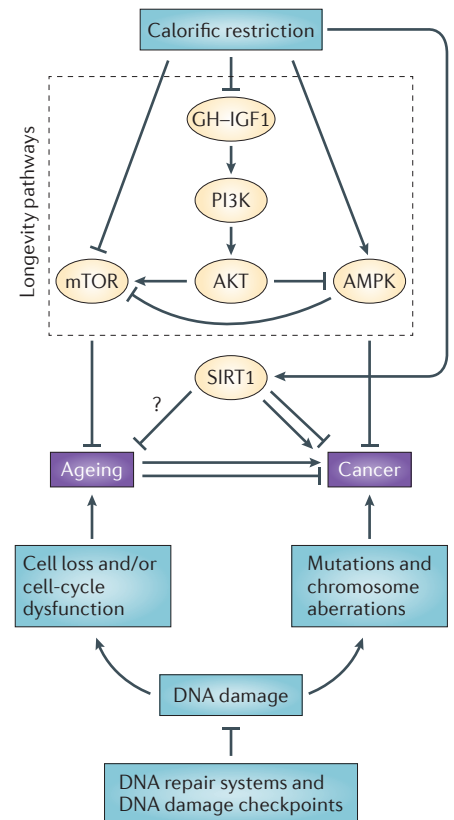


Figure 2 | Major longevity pathways with overlapping effects on ageing and cancer. The growth hormone (GH)–insulin-like growth factor I (IGF1) pathway and its signalling cascade, which involves PI3K and AKT, can modulate longevity and cancer in model systems. Calorific restriction inhibits GH–IGF1 signalling and can also inhibit mTOR and activate AMP-activated protein kinase (AMPK) and sirtuin 1 (SIRT1). Interactions between components of these pathways, and with SIRT1, remain incompletely understood. The role of SIRT1 in modulating mammalian ageing has not been demonstrated, and it seems to have a dual role in cancer. DNA repair systems and DNA damage checkpoints prevent the DNA damage accumulation that contributes to cancer and ageing, although possibly through different cellular mechanisms.

restricted to a small number of tissues, and much more detailed studies have been conducted in mice^{9,12,26,48}. Using transgenic mice with *lacZ* or *lacI* to measure the mutation frequency, various studies have found that the accumulation of mutations can occur from early in life, but they also found large differences in the rates of mutation accumulation between tissues^{48,51–53}. Although the accumulation of mutations with age in mice is highest in the small intestine, and can be observed in the liver, heart and most organs, it was not observed in the testis and brain^{48,51–53}. However, a more recent study found that

point mutations accumulate in subparts of the brain, namely the hippocampus and hypothalamus⁵⁴. Of note, the accumulation of mutations seems to be organ-specific and not clearly related to organ proliferative capacity⁴⁸. Clearly, as more cells accumulate more mutations with age, the probability of developing cancer increases. A role of epigenetic changes has also been hypothesized because both global hypomethylation and promoter hypermethylation have been reported in both ageing and cancer⁵⁵. For example, hypermethylation of the RAS association domain family 1 (*RASSF1*) promoter is associated with cancer and is also observed to increase with age and with adiposity⁵⁶.

Evidence is emerging that DNA repair pathways become less efficient with age, although the mechanisms involved are unknown^{26,57}. There also seems to be age-related changes in susceptibility to carcinogens¹². Studies by Anisimov and others^{9,12} in over 20 different tissues reveal conflicting findings; exposure to carcinogens in aged mice resulted in increased cancer development compared with younger controls in some tissues but not in others. For example, 15-month-old female rats exposed to *N*-nitroso-*N*-methylurea (NMU) had a higher frequency of tumours of the corpus and cervix uteri and a lower frequency of mammary and intestinal adenocarcinomas and tumours of the ovary and kidney than 3-month-old animals exposed to NMU⁵⁸. These mixed results might be explained by age-associated differences in susceptibility to carcinogens owing to changes in the activity of enzymes that are necessary for carcinogen activation or changes in proliferative activity that occur with ageing in a tissue-specific manner.

If the idea is correct that DNA damage accumulation is a major driver of ageing-associated phenotypes, then DNA damage would represent an overlapping mechanism between tumorigenesis and ageing (FIG. 2), even though, as aforementioned, different types of DNA repair and DNA lesions may be more relevant to each process. The various progeroid syndromes that result from mutations that disrupt DNA repair pathways give strength to the idea that DNA damage is not simply associated with ageing but may have a causal role. One recent study found that overexpression in mice of BUB1B, which is a mitotic checkpoint protein that controls chromosome segregation and maintains genetic stability, protects against cancer and extends healthy lifespan¹¹, although further work is necessary to prove that reducing DNA damage retards ageing²⁶.

Telomeres, replicative senescence and tissue homeostasis. Telomeres (which are repetitive sequences at the ends of chromosomes) shorten with cell division in normal human somatic cells and limit replicative potential *in vitro*⁵⁹. Because they can limit cell proliferation, telomeres have long been hypothesized to be a causal factor in ageing. Short telomeres activate DNA damage response pathways that cause cells to undergo irreversible growth arrest (cell senescence). Cellular stress, such as DNA damage, can also trigger senescence in a process termed stress-induced premature senescence^{60,61}. It is widely accepted that telomere shortening evolved as a tumour-suppressive mechanism, and disruption of players in the pathways that lead to replicative senescence are associated with cancer^{59,61,62}. Moreover, the observation that large, long-lived species tend to have short telomeres and low levels of telomerase (which is the enzyme that maintains telomere length) suggests that short telomeres and telomerase suppression are necessary for the evolution of large body sizes and longevity, presumably by suppressing cancer⁶³.

“ replicative senescence may render old tissues more fertile grounds for cancer development ”

A more controversial issue is the role of telomere shortening and replicative senescence in whole-organism ageing (reviewed in REFS 59–61). Several studies, including in humans, have observed telomere shortening *in vivo* during ageing⁵⁹. Likewise, senescent cells have been reported to accumulate with age in many mammalian tissues, and have also been observed in some pathological conditions such as atherosclerosis⁶⁴ and benign prostatic hyperplasia⁶⁵, although whether such senescent cells contribute pathologically is unknown, as they may merely reflect damage to tissues^{60,61}. One study found that the number of senescent fibroblasts increases exponentially with age in the skin of baboons, with senescent cells comprising >15% of cells in very old animals compared with ~2% in young animals⁶⁶. The incidence of senescent cells has also been found to increase in aged mouse tissues, such as in the liver⁶⁷, although it is possible that cell senescence in mice is induced through telomere-independent mechanisms because mice have relatively long telomeres⁶⁸. Likewise, markers of replicative senescence, such as the expression of the tumour suppressor INK4A — in which

genetic variants have been associated with other age-related diseases such as heart failure and type 2 diabetes⁵⁹ — have been found in the tissues of old mice^{69,70}. One hypothesis is that senescent cells impair tissue renewal and homeostasis, decrease organ function and thus contribute to ageing, although this hypothesis remains contentious.

Even if the issue of whether replicative senescence is a cause of ageing-associated phenotypes remains open, evidence suggests that senescent cells accumulate in some tissues with age and that these cells might contribute to cancer development. Telomere shortening and the resulting telomere dysfunction has been suggested to contribute to cancer susceptibility by increasing the risk of chromosomal aberrations caused by breakage–fusion–bridge cycles⁷¹. Furthermore, mice with short telomeres have a higher incidence of cancer⁷², including in p53-deficient mice⁷³, possibly because of increased genetic instability caused by loss of telomere function.

In spite of its role as a tumour-suppressive mechanism, replicative senescence may render old tissues more fertile grounds for cancer development. Campisi and colleagues⁷⁴ have shown that senescent cells can secrete pro-inflammatory cytokines, extracellular matrix components and other factors that disrupt the tissue microenvironment and promote tumorigenesis. Specifically, senescent human fibroblasts in culture stimulate the proliferation of premalignant and malignant epithelial cells, but not of normal cells⁷⁴. Interestingly, immunocompromised mice injected with premalignant or malignant epithelial cells together with senescent cells form more and larger tumours than with epithelial cells alone or with presenescent control cells^{74–76}. Using a *Cdkn2a*^{INK4A}-luciferase reporter mouse model, one recent study found an exponential increase in INK4A expression with age, and the induction of INK4A was observed in the benign stromal cells of the nascent neoplasm. However, total-body INK4A expression did not predict overall mortality or the development of spontaneous malignancy⁷⁷, which does not support a causal role for senescent cells in ageing or in tumorigenesis.

One recent study in mice reported that the clearance of senescent cells expressing INK4A delays ageing-associated phenotypes, such as lordokyphosis, sarcopenia and cataracts⁷⁸. However, it is important to note that the clearance of senescent cells in the transgenic progeroid mice used in this study did not extend lifespan. Therefore, although this study provides evidence that senescent cells may cause age-associated phenotypes in

this model, whether senescent cells contribute to normal ageing-associated phenotypes remains unknown. However, transgenic mice in which senescent cells can be inducibly ablated may allow researchers to evaluate whether the presence of senescent cells in aged tissues facilitates cancer development. Such models may also help to unravel the functions of senescent cells because it remains largely unknown why these exist in the first place — why not just trigger cell death?

Endocrine changes with age. Systemic changes during ageing may contribute to cancer susceptibility. For example, endocrine changes with ageing may decrease cancer risk: sex hormones, such as oestrogens and androgens, are known to contribute to some types of cancer⁷⁹, and their levels typically decline with age, thus potentially offering some protection from cancer⁶. Moreover, GH and IGF1 levels decline with age^{80,81}. As detailed above, low GH-IGF1 signalling has been associated with decreased cancer incidence, and thus one hypothesis is that these endocrine changes contribute to hinder cancer development in old age.

The ageing immune system. It is well-established that the immune system becomes compromised during ageing (known as immunosenescence), with inflammation increasing with age^{82,83}; in fact, mononuclear cells of healthy elderly people exhibit increased cytokine production⁸⁴. Ershler and colleagues^{85,86} have argued that immunosenescence will decrease host susceptibility to cancer because of the role of the immune system in driving tumour growth. By contrast, immunosurveillance also becomes compromised with age, and this may contribute to the increased cancer development in old age⁸⁷. However, the evidence for either scenario is far from conclusive, and the impact of immunosurveillance on fighting cancer is unclear. For example, although immunocompromised patients have a higher cancer incidence, it is not clear whether this is due to reduced immunosurveillance or a higher incidence of tumours caused by infectious agents¹.

It is now recognized that inflammation has a role in cancer aetiology, and various studies have found that inflammation can have tumour-promoting effects (reviewed in REFS 88,89). Inflammation is an established hallmark of ageing: the circulating levels of inflammatory cytokines, such as interleukin-6 (IL-6) and tumour necrosis factor (TNF), are increased at older ages^{83,90}, and inflammatory gene expression signatures are observed across aged mammalian tissues⁹¹.

For example, higher levels of IL-6 and TNF have been associated with the prevalence of colorectal adenomas⁹². It is also interesting to note that higher levels of inflammatory cytokines are associated with fat mass and obesity^{90,93}, which might contribute to the increased cancer incidence among obese individuals, and body fat as a percentage of body weight increases with age⁹⁴. It is therefore tempting to speculate that the increased inflammatory environment of ageing tissues may favour cancer development.

Vascular ageing and angiogenesis. Because tumour vascularization is essential for the growth of solid tumours, vascular ageing has been proposed to contribute to a decline in the angiogenic potential of aged tissues, which hinders the progression of solid tumours in old age⁸⁶. Some evidence from mice supports this view: it has been reported that the slower growth of some tumour cells in older mice when compared with that in younger animals may be related to a reduced capacity to vascularize tumours^{95,96}, which may be further augmented by short telomeres⁹⁷. Slower tumour growth and reduced tumour vascularity were also observed in mice with genetically induced atherosclerosis (apolipoprotein E (*ApoE*)^{-/-} mice) than in young or non-atherosclerotic mice, suggesting that vascular ageing and disease can affect tumour progression⁹⁶.

Are old tissues fertile ground for cancer?

Given that mutations accumulate with age, aged tissues will tend to have a higher number of cells in an advanced stage of carcinogenesis, and this is a major factor in the observed increased cancer incidence with age^{9,12}. Indeed, when *Trp53* is deleted in mice of different ages, a shorter latency of tumour development results when the gene is ablated in older animals, which may be explained by wild-type p53 keeping in check a growing number of oncogenically activated cells with age⁹⁸. A more controversial issue is whether ageing-associated changes contribute to create a more fertile ground for cancer development rather than cancer occurring simply because the probability of tumour initiation increases with time. By contrast, if normal processes that are often hijacked by tumours degenerate with age then this may confer cancer protection. This pivotal issue of whether ageing processes create a more or less fertile ground for cancer has not been studied in a systematic manner, and the studies conducted to date provide contradictory evidence.

In the classic study of Peto *et al.*⁹⁹ the authors found that exposing mice to carcinogens resulted in the induction of cancer

that was independent of the age of the animals. Peto *et al.* interpreted these results as evidence that cancer development is independent of ageing⁹⁹, although the oldest mice used were only ~1 year of age, and thus they may not have been sufficiently old for any differences to be observed. As discussed above, more recent results have been mixed, and there seem to be carcinogen-specific and tissue-specific effects of ageing.

Other studies have used xenografts to study tumour growth in animals of different ages. Again, systematic studies are lacking and results are contradictory, yet substantial effects of ageing have been observed¹⁰⁰. These effects vary between tumour types; for example, one prostate cancer cell line grows as quickly in old mice as in young mice¹⁰¹. Ershler *et al.*¹⁰² found that B16 mouse melanoma cells grow considerably faster and form more tumour colonies in younger mice, whereas another study found reduced proliferation and increased apoptosis of rat liver tumour cells in young rats relative to old rats¹⁰³.

In humans, the commonly held belief that cancer is less aggressive in older patients has not been demonstrated for most types of cancer (FIG. 3); several tumour types are more aggressive in old age^{6,86,100}. For example, the prognosis of acute myeloid leukaemia¹⁰⁴ and of ovarian cancer¹⁰⁵ is worse in the elderly. By contrast, the prognosis for breast cancer is worst for young women and best for middle-aged (45–49 years old) women¹⁰⁶. However, the poorer prognosis in elderly individuals (FIG. 3) may also be related to confounding factors, such as less aggressive treatment. Another caveat of human clinical

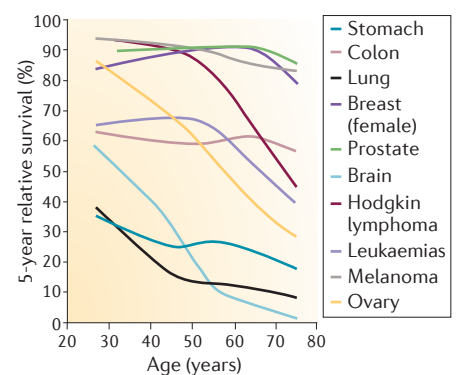


Figure 3 | Cancer survival as a function of age. Five-year relative survival with age for selected sites. Data are for patients in England, UK, diagnosed 2006–2010 and followed-up until 2011. Unless otherwise stated and unless for gender-specific cancers, data from males and females were combined. Data are from the UK Office for National Statistics.

data is that tumours often have different genetic backgrounds between young and old patients with cancer, and it is therefore not possible to compare tumours that develop in individuals with similar genetic backgrounds at different ages.

Overall, several studies in rodents have shown substantial effects of ageing on the tumour host. However, these studies were conducted using different strains and experimental conditions and unsurprisingly failed to render a clear picture. Some ageing processes seem to act synergistically to promote cancer initiation and growth (such as the accumulation of senescent cells and increased inflammation), whereas others seem to antagonize cancer initiation and growth (such as vascular ageing and a decline in GH levels) (FIG. 4). It is also important to emphasize that the effects of ageing on cancer vary markedly across tumour types and tissues. For example, differences in antigenicity between tumours are likely to be important for determining whether particular tumours may benefit from, or be hindered by, an ageing immune system^{6,85,100}. Clearly, the effects of ageing on the tumour host merit a more systematic inquiry.

Applications in the cancer clinic

One of the most exciting prospects in the field is translating findings from the biology of ageing into the clinic^{10,31}. Despite its benefits in model organisms, CR is a challenging diet to undergo, and clinical trials are extremely difficult given the length of

time required to assess the effects on ageing. Nonetheless, one study found that anorexic women have a lower incidence of breast cancer; like CR, anorexia leads to reduced levels of IGF1 and oestrogens, suggesting that CR may protect against cancer in humans¹⁰⁷. Fasting in mice reduces IGF1 levels and protects normal cells, but not cancer cells, from the cytotoxic effects of high-dose chemotherapy¹⁰⁸. The efficacy of fasting before chemotherapy is currently being explored¹⁰⁹.

Small molecules with life-extending properties in model organisms, such as rapamycin and resveratrol, are being tested as treatments against cancer¹⁰. Although both rapamycin and resveratrol have been studied for their anticancer properties before the discovery of any longevity effects, the finding that resveratrol extends longevity no doubt has put this compound in the spotlight. However, some controversy surrounds resveratrol. Briefly, resveratrol has been shown to extend lifespan only in obese animals, and its putative main target, SIRT1, is equally contentious^{10,45}. Studies have shown that SIRT1 may protect mice from colon cancer¹¹⁰ and breast cancer¹¹¹, and SIRT1 activators are undergoing clinical trials for anticancer therapy¹⁰. However, high levels of SIRT1 have been observed in some tumours, and SIRT1 inhibition also shows promise in anticancer therapies¹¹², for example in leukaemias in which SIRT1 has been found to be overexpressed¹¹³. As such, depending on the context, SIRT1 may have oncogenic or tumour-suppressive properties¹¹⁴.

Rapamycin and the mTOR pathway are another link between ageing and cancer. mTOR inhibition, through treatment with rapamycin or genetic manipulation, has been associated with increased longevity in animal models¹⁰, including in normal¹¹⁵ and in *Trp53*^{-/-} mice¹¹⁶. Another drug that might mimic, at least partly, the beneficial effects of CR is metformin, which is used to treat patients with type 2 diabetes¹⁰. Metformin activates AMPK via the tumour suppressor liver kinase B1 (LKB1; also known as STK11), and it can inhibit cell growth in an AMPK-dependent manner¹¹⁷, although in some cell lines mTOR inhibition by metformin has been shown to be AMPK-independent¹¹⁸. Epidemiological studies in patients with type 2 diabetes suggest that metformin may decrease cancer risk¹¹⁹, and metformin is now being explored as a cancer treatment in clinical trials (for example, NCT01101438). Other drugs that are associated with life-extension in mice — such as aspirin, which slightly extends the lifespan of male mice¹²⁰ — are also being explored as cancer treatments^{121–123}.

Overall, studies of ageing can help to focus attention on drug targets for cancer therapies and on the development of anti-cancer lifestyles, diets and drugs. Mice, even naturally occurring long-lived strains³², die primarily of cancer⁹. As such, the vast majority of life-extending interventions in mice, including drugs, have an impact on cancer. Thus, these interventions may be useful to study further in terms of potential human applications, either to enhance traditional treatments such as chemotherapy or for prevention in cancer-prone patients.

Concluding remarks

The interplay between cancer and ageing is complex and far from straightforward. The accumulation of mutations with age^{49,50} is still widely held as the major driver of the age-related increase in cancer incidence^{1,7,9,12}. However, a picture is emerging of how several age-associated changes might foster cancer development in old age, whereas other changes may hinder it (FIG. 4). It is important to note that there is no evolutionary selection for ageing, just as there is no selection for age-related increases in cancer incidence, because individuals are affected after reproductive maturity. Therefore, ageing and cancer have no evolutionary purpose, which contributes to their complexity and entropy, and it is thus not surprising that ageing processes may aid or hinder cancer depending on the tissue and tumour type. Because of this intrinsic complexity of ageing and cancer, I am convinced that we need to move

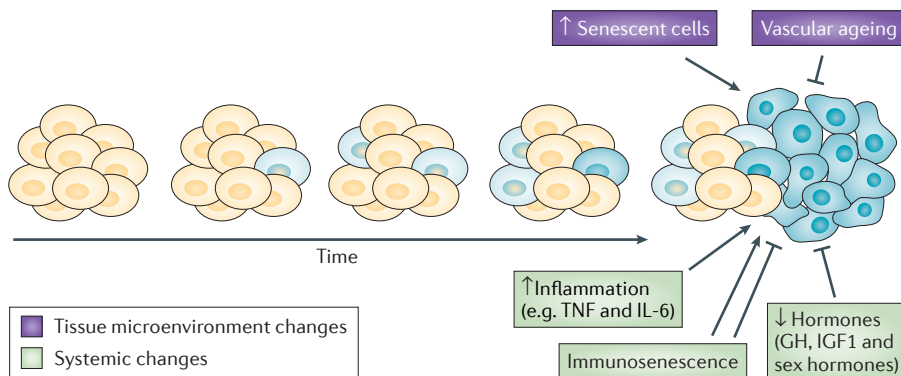


Figure 4 | The interplay between ageing processes and cancer. It is well-established that the accumulation of DNA changes (darker cells represent cells with DNA mutations) is the primary process that is responsible for the age-associated increase in cancer incidence. Various other ageing-associated processes also seem to contribute to, or suppress, cancer initiation and growth. These can be divided into age-related changes affecting the tissue microenvironment and systemic changes. Changes to the tissue microenvironment include vascular ageing, which may hinder cancer progression, and the accumulation of senescent cells, which may favour it. Systemic changes include decreasing circulating levels of various hormones, which possibly hinders cancer development, as well as immunosenescence (the role of which in cancer is controversial) and inflammation (which probably favours cancer development). The interplay between these factors, as well as their tissue-specific impact, remains unknown. GH, growth hormone; IGF1, insulin-like growth factor I; IL-6, interleukin-6; TNF, tumour necrosis factor.

Box 1 | Models of cancer resistance

Cancer research is largely based on animal models, particularly mice and rats, that develop cancer at a much higher rate than humans do. However, an unexplored paradigm is the use of cancer-resistant organisms to identify genes, mechanisms and processes that protect against (rather than cause) cancer^{124,125}. One such organism is the naked mole-rat (*Heterocephalus glaber*), the longest-living rodent that is capable of living for over 30 years¹²⁴. To date, in over 1,000 animals examined, neoplasia has not been observed¹²⁶, and thus *H. glaber* must have evolved mechanisms that confer exceptional cancer protection. Cellular studies have begun to reveal possible tumour-suppressive mechanisms in *H. glaber*¹²⁷, such as INK4A-mediated hypersensitivity to contact inhibition compared with mouse cells¹²⁸, and *H. glaber* cells exhibit resistance to experimental tumorigenesis induced by the expression of the combination of the oncogenes *Hras*^{G12V} and SV40 large T antigen¹²⁹. Another genus of mole-rats, *Spalax*, are also cancer-resistant and relatively long-lived (maximum longevity of more than 20 years); a mechanism of necrotic cell death in *Spalax* has been recently shown to be initiated to limit proliferation¹³⁰. Lastly, as observed by Peto *et al.*⁹⁹, if the chance of each cell becoming malignant is the same, then large, long-lived species such as whales would have an impossibly high probability of developing cancer¹²⁵. For example, the bowhead whale (*Balaena mysticetus*) is the second largest animal on earth and has been estimated to live for >200 years¹³¹. Therefore, species such as whales, even though they can develop cancer, must have evolved robust antitumour mechanisms compared with humans. Perhaps long-lived and cancer-resistant species undergo a more complex, multistep pathway to tumorigenesis, and more mutations are necessary to produce a lethal cancer. Because all of these species are mammals, most genes will have human homologues, and genome comparisons may help to elucidate mechanisms that are involved in the evolution of longevity and cancer protection¹³². Discovering the 'tricks' that are used in different species to suppress cancer development could lead to a better understanding of cancer mechanisms and may lead to cancer prevention in humans¹²⁵.

beyond reductionist approaches and to integrate processes at the molecular, cellular and physiological levels to understand the links between ageing and cancer.

Importantly, a number of questions remain unanswered: why does the incidence of some tumours (for example, testicular cancer) peak early in life? Can we identify genes that protect against cancer from studies in long-lived individuals or long-lived species (BOX 1)? Which tissues does ageing render more and less fertile for tumour formation and why? How do age-related endocrine changes influence cancer development? How does immune-system dysfunction contribute to cancer susceptibility, and does increased inflammation with age contribute to cancer development? Can we translate findings from the biology of ageing (for example, CR) to fight cancer?

Understanding the biological underpinnings of the relationship between cancer and ageing could have broad implications. Strikingly, young rodents are the most widely used animal model of cancer, yet most tumours affect aged people. A systematic, in-depth understanding of the role of ageing processes in cancer is imperative. Taking into account ageing-associated processes may be crucial to develop preventive strategies and effective therapies against cancer. Moreover, substantial age-associated differences in incidence and progression are observed between cancer sites that probably reflect different processes and risk factors that are specific

to each tissue and tumour type. Unravelling which factors and ageing-associated processes are more important for oncogenic development in different tissues could allow more personalized cancer treatments.

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Competing interests statement

The author declares no competing financial interests.

DATABASES

ClinicalTrials.gov: <http://www.clinicaltrials.gov/NCT01101438>

National Cancer Institute Drug Dictionary: <http://www.cancer.gov/drugdictionary>
aspirin | metformin | rapamycin | resveratrol

FURTHER INFORMATION

João Pedro de Magalhães's homepage:

<http://pcwww.liv.ac.uk/~aging>

GenAge: the Ageing Gene Database:

<http://genomics.senescence.info/genes>

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OPINION

Plasticity of tumour and immune cells: a source of heterogeneity and a cause for therapy resistance?

Michael Hölzel, Anton Bovieer and Thomas Tüting

Abstract | Immunotherapies, signal transduction inhibitors and chemotherapies can successfully achieve remissions in advanced stage cancer patients, but durable responses are rare. Using malignant melanoma as a paradigm, we propose that therapy-induced injury to tumour tissue and the resultant inflammation can activate protective and regenerative responses that represent a shared resistance mechanism to different treatments. Inflammation-driven phenotypic plasticity alters the antigenic landscape of tumour cells, rewires oncogenic signalling networks, protects against cell death and reprogrammes immune cell functions. We propose that the successful combination of cancer treatments to tackle resistance requires an interdisciplinary understanding of these resistance mechanisms, supported by mathematical models.

Normal tissues show a highly structured organization, with specialized cell types residing in well-defined niches to fulfil their physiological functions. For example, the skin consists of the epidermis and the dermis, with numerous blood vessels, nerves, hair roots and several types of glands. Epidermal keratinocytes arise from precursors in stem cell compartments, differentiate, and form the lipid-rich outermost corneal layer as a barrier to the environment and for the prevention of water loss. Pigment-producing melanocytes, which are interspersed in the basal epidermis and the hair follicles, provide protection against ultraviolet (UV) irradiation (FIG. 1a). Skin cancer can result when incorrectly repaired UV-induced DNA damage disturbs growth signalling pathways and cell cycle control mechanisms in epidermal keratinocytes or melanocytes (FIG. 1b). In cancerous tissues, the rules of normal tissue organization are replaced by a new metastable order of aberrant cell proliferation, differentiation and death¹. Genetically and phenotypically heterogeneous malignant cells engage in novel associations and interdependencies with abnormal fibroblasts, endothelial cells and immune cells in the tumour microenvironment that sustain tumour growth despite fluctuations in nutrient and oxygen supply. Finally, cancer cell invasion and the development of metastases compromise the integrity and survival of the organism as a whole. Indeed, in patients with widely

metastatic disease, such as that arising in patients with melanoma, a cure with surgery is no longer possible. The use of systemic treatment approaches to eradicate tumour cells in such patients² is likely to disrupt any metastable order that has been established during the long process of tumour evolution (FIG. 1c). The initiation of an injury response results in the recruitment of inflammatory immune cells that normally restores tissue organization under physiological conditions. Unfortunately, in most patients with metastatic disease, tumour regressions and remissions are brief (FIG. 1d). Ultimately, resistance to therapy arises that results in relapse and the death of the patient (FIG. 1e).

Patients with unresectable solid melanoma metastases have been treated with the DNA-damaging agent dacarbazine as the standard of care for many years² (FIG. 2a). In the past decade, advances in tumour biology and immunology have led to the development of new rationally designed treatment approaches that impair oncogenic signal transduction pathways — for example, with inhibitors of the BRAF kinase^{3–6} (FIG. 2b) — or that strengthen tumour-specific cytotoxic T cell responses — for example, with antibodies that target cytotoxic T lymphocyte protein 4 (CTLA4)^{7,8} or programmed cell death protein 1 (PD1)^{9,10} (FIG. 2c). When applied as monotherapies, these new treatment strategies could induce responses and remissions, but melanomas frequently relapse. Clinical trials are already under