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Cancer-related accelerated ageing and biobehavioural modifiers: a framework for research and clinical care

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Abstract

A growing body of evidence indicates that patients with cancer who receive cytotoxic treatments (such as chemotherapy or radiotherapy) have an increased risk of accelerated physical and cognitive ageing. Furthermore, accelerated biological ageing is a suspected driving force behind many of these observed effects. In this Review, we describe the mechanisms of biological ageing and how they apply to patients with cancer. We highlight the important role of specific behavioural factors, namely stress, sleep and lifestyle-related factors such as physical activity, weight management, diet and substance use, in the accelerated ageing of patients with cancer and cancer survivors. We also present a framework of how modifiable behaviours could operate to either increase the risk of accelerated ageing, provide protection, or promote resilience at both the biological level and in terms of patient-reported outcomes.

The physical and cognitive changes seen in a proportion of patients during and/or after receiving treatment for cancer have led to the hypothesis that certain malignancies and/or treatments might accelerate the ageing process[1-9]. Chemotherapy and radiotherapy are two examples of toxic exposures that could drive the increased risks of both physical and cognitive impairments (such as fatigue and memory complaints[10-14]), secondary morbidities and mortality[1,2,9]. Biological changes induced by cancer itself and by other treatment

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exposures (such as hormone therapy or immunotherapy) might also have a role[15,16]. Given the mounting evidence that cancer and cancer treatments might accelerate ageing in various ways, we consider what role behavioural factors could have in modifying these processes. We begin with a definition of ageing and a summary of the available evidence that cancer treatments accelerate this process, focusing on physical, cognitive and biological ageing. We then provide an overview of the evidence that biological ageing can be influenced by behaviour, with an emphasis on psychological stress and sleep disruptions, as well as a brief discussion of the roles of established protective health behaviours such as physical activity, weight management, healthy diet, moderate alcohol consumption and smoking cessation. Finally, we outline our model of biobehavioural modifiers of cancer and accelerated ageing and discuss possible avenues for future research and interventions.

Physical and cognitive ageing

Patterns of normative ageing vary across the population, with an increasing prevalence of physical and cognitive manifestations emerging as individuals reach a higher chronological age. Broadly, physical signs of ageing are characterized by common impairments that begin to interfere with day-to-day function, including increasing pain and fatigue, decreased mobility, declining strength, slowed gait speed and muscle loss[17,18]. Cognitive changes are also common in normative ageing, including poorer recall, short-term memory complaints, difficulties with maintaining concentration and working memory, slowed psychomotor speed, and impaired executive function[19]. These numerous manifestations of physical and cognitive ageing often co-occur and accumulate progressively with increasing chronological age, with the end stage of this process of deficit accumulation being described as a state of frailty[1,20,21]. Many of these same physical and cognitive effects are also commonly reported by both patients with cancer and cancer survivors as symptoms, including pain, fatigue and cognitive disturbances[8,22,23]. Importantly, these symptoms often occur at a higher frequency and/or at an earlier chronological age in those with ongoing or previous cancer compared to those without a cancer diagnosis, with substantial detrimental effects on quality of life[2,13-15,24-30]. In parallel with increased fatigue and declines in cognition, many patients with cancer and cancer survivors have declines in physical function after treatment as indicated by limitations in the ability to perform physical activities[31,32], decreased mobility and impaired muscle strength[3,6]. Adult recipients of bone marrow transplants have an increased risk of early development of metabolic and cardiovascular disease, physical performance deficits, and premature death[33,34]. Similar to adults, childhood-cancer survivors can have an earlier onset of comorbidities several decades after completion of treatment, such as heart disease, lung disease, renal dysfunction, diabetes and secondary cancers, at incidences usually seen only among much older adults[2,6,35,36]. In cancer survivors, these changes are increasingly being conceptualized as a progressive loss of function or deficit accumulation and frailty[37-39]. Such changes in physical and cognitive function have been observed with several different types of cancer treatment, including radiotherapy, chemotherapy, targeted therapy and immunotherapies such as immune-checkpoint inhibitors[40-45].

Biological ageing

Biological ageing is broadly defined as a gradual deterioration of tissue and cellular function as a direct result of damage accumulation over time. This damage and the failure of the related repair and/or clearance mechanisms are thought to be crucial drivers of ageing. Key hallmarks of biological ageing have been described, with general acceptance that this process begins with damage, commonly arising from inflammatory and/or oxidative metabolic sources, which affects several cellular structures, including DNA, lipids and proteins[46,47]. The consequences of such damage include genomic instability, telomere shortening, epigenetic alterations and a loss of proteostasis[46,47]. The functional effects of this damage include altered nutrient sensing and energy production, cellular replication arrest and senescence, and compromised mitochondrial performance[46,47]. Stem cells might replenish failing cells when supply permits, although depletion of or damage to stem cells from chemotherapy or radiation injury may lead to stem cell exhaustion[46,47]. As a cell accumulates damage, compromised performance can accelerate the phenotypic transition towards a state of senescence. This cellular senescence can be protective in that it prevents the replication of cells that harbour deleterious mutations that confer an increased cancer risk, yet the accumulation of these senescent cells is also thought to promote ageing[48].

Senescent cells can act as a major source of inflammatory mediators, termed the senescence-associated secretory phenotype (SASP), and are thought to be a major source of chronic, low-grade inflammation often described as ‘inflammaging’[49]. SASP profiles probably vary across different cell types but often include common inflammatory mediators, such as damage-associated molecular patterns (DAMPs), that are known to be released from damaged and/or necrotic cells and the upregulation of an inflammatory intracellular signalling cascade (notably the transcription factor NF-κB[50]), resulting in the secretion of pro-inflammatory cytokines such as IL-6, IL-8, TNF and intracellular adhesion molecule 1. This inflammatory cascade has been implicated in several ageing-related diseases, including cancer, cardiovascular diseases, dementia, arthritis, osteoporosis, sarcopenia and immune compromise[46,51-60]. Reductions in chronic inflammation and the partial recovery of physical functions have been observed upon removal of senescent cells, suggesting that senescent cells are a major cause of the physical decline observed with ageing[61-66]. However, the removal of senescent cells might also have a cost and this possibility needs to be investigated further. Indeed, several lines of research indicate that senescent cells have roles in tissue remodelling and regeneration as well as in the maintenance of blood — tissue barriers and that their removal might impair these important cellular processes[67-69]. In summary, the gradual accumulation of damage arising from energy consumption and various exposures drives biological ageing, cellular senescence, inflammation, and the failure of organs and/or physiological systems (such as the cardiovascular system).

Cancer treatments and ageing

Cancer treatments are a source of cellular damage that can contribute to accelerated biological ageing. Chemotherapy and radiotherapy can both act on key mechanisms that are known to influence the signalling pathways that regulate biological ageing (reviewed in detail elsewhere[9]). In brief, the effectiveness of radiotherapy is dependent on causing DNA

damage and the subsequent death of cancer cells during replication but might also involve the initiation of other downstream processes such as a localized inflammatory response that promotes the recruitment of immune cells to the tumour[70]. The non-malignant tissues surrounding a tumour are also likely to be altered by radiation exposure[70]. In preclinical models, whole-body irradiation leads to DNA damage[71] and senescent cell accumulation[66] as well as to secondary inflammation arising from the accumulation of senescent cells and tissue injury. Research involving animal models has also provided evidence that systemic chemotherapies (such as anthracyclines and taxanes) promote DNA damage, which induces systemic cellular senescence as indicated by the cellular expression of $p16^{INK4a}$ (REF.[65]). Mild exposure to DNA-damaging agents might promote stress resistance[72], whereas excessive exposure is likely to contribute to the accumulation of damaged cells. Targeted therapies, including hormone receptor antagonists and immune-checkpoint inhibitors, can also activate key ageing-related pathways such as those involved in DNA damage and repair, cellular senescence, and maintenance of telomere length[9].

Preliminary evidence from patients with cancer also suggests a role of cancer treatments in driving cellular senescence, with initial data suggesting greater levels of cellular ageing after exposure to cancer therapy, including increased expression of $p16^{INK4a}$ in T cells following chemotherapy in patients with breast cancer[73,74]. Similarly, we have observed increases in both epigenetic age and in cellular senescence immediately after chemotherapy and/or radiotherapy in patients with breast cancer[75]. We have also observed increased DNA damage and decreased telomerase activity in women with breast cancer 3–6 years after treatment with chemotherapy and/or radiotherapy, suggesting a lasting imprint on ageing biology[76]. Parallel findings have been observed in patients following autologous or allogeneic haematopoietic stem cell transplantation, with elevated cellular senescence observed after both 6 months and 2–9 years[5]. Similarly, data from patients with head and neck cancer demonstrate that treatment-related symptoms are correlated with greater epigenetic age and inferior overall survival outcomes[77]. Targeted therapies, including signal transduction inhibitors, immunotherapies and monoclonal antibodies[78], can also have lasting complications and toxicities[40-45]. Although beyond the scope of this Review, further investigation of how these approaches might influence biological and physical ageing is warranted; this will require long-term follow-up data.

Taken together, the available evidence supports a putative role of cancer treatments in accelerating biological ageing, with estimates ranging from 3 to 14 years of age acceleration depending on the characteristics of the patients that were studied and the types of treatment exposure[73-75]. However, important variations exist in the extent of vulnerability to accelerated ageing, particularly in clinical research. The research described above[73-77] reveals broad variations in the extent of biological ageing within cohorts, with some individuals having no notable alterations in biological age and others having more pronounced increases in ageing markers. These observations are consistent with symptom reports, in which a quarter to a third of patients will report persistent fatigue[79] and a third to half of all patients report declines in health and physical function after treatment[80], suggesting the manifestation of frailty among a subgroup of cancer survivors. Similar variability is evident for cognitive health, in that not all survivors report declines in perceived cognitive function[81-84] or have declines in performance on neurocognitive

function tests[81-84]. Host-specific factors associated with an increased risk of accelerated ageing need to be identified, especially targets that are potentially amenable to intervention.

Patient-specific factors

Patients receiving cancer treatments often present with pre-existing factors that can influence both their risk of cancer and responsiveness to cancer therapy. The life history of an individual before a cancer diagnosis might include external and internal environmental exposures, psychological stress and trauma, prior episodes of depression and anxiety disorders, and personal behaviours and habits that have the potential to affect cancer development as well as the patient's ability to tolerate certain treatments (for example, tobacco and/or alcohol use, obesity, exogenous hormone use and viral infections). A holistic assessment of all possible patient-specific factors is rarely conducted by clinical oncologists, for whom the focus is almost entirely on the tumour and its specific pathological and genomic features. The interplay between cancer treatment and patient factors should not be overlooked and probably accounts for a proportion of the tremendous variability in outcomes seen among certain subgroups of patients, even in well-controlled clinical trials.

We posit that patients with psychosocial and/or behavioural risk factors that either accelerate tissue damage and/or limit repair processes might be particularly vulnerable to the harmful effects of cancer treatments. A number of psychosocial and behavioural risk factors have been linked to accelerated biological ageing outside of the context of cancer, including early-life adversity, social determinants of health (such as access to housing, food, adequate income, health insurance), psychological stress, sleep disturbance and lifestyle-related factors (such as obesity, a sedentary lifestyle or tobacco use)[85-93]. Notably, several of the same behavioural risk factors are associated with both cognitive and physical symptoms in cancer survivors[79,94-96].

Our model proposes that these risk factors, some of which are pre-existing social, behavioural and psychological exposures as well as concurrent or newly developing behaviours, might act as accelerants of biological ageing from treatment, thereby increasing the risks of both physical and neurocognitive effects (FIG. 1). The model builds upon previous biobehavioural models focusing on inflammation as a contributor to cancer-related symptoms and morbidity outcomes[94,95] by incorporating consideration of the accumulation of senescent cells as a potentially major source of inflammation. Our Review focuses on modifiable behaviours that could be targeted for intervention, although key patient characteristics (such as early-life stress, a history of depression or anxiety, or prior substance use) might also predispose patients to adverse effects of treatment and should be considered. In particular, accumulating evidence suggests that stress, insufficient sleep and other lifestyle-related factors can all directly interact with biological ageing pathways, and we outline a research agenda designed to test the role of behavioural factors that lead to accelerated ageing and interventions that might protect against cancer-related accelerated biological ageing. This view offers the potential for intervention and improvement of treatment outcomes.

Psychosocial stress and biological ageing

Psychosocial stress can be defined as any environmental demands that tax or exceed the adaptive capacity of an organism[97,98]. Sources of psychosocial stress include interpersonal relationships, work-related pressures, social and cultural factors such as structural racism and discrimination, exposure to violence, poverty and/or economic hardship, encountering existential threats, and numerous other negative daily life experiences. In addition to daily stress exposure, a history of early-life adversity, including stress exposure in utero, increases the risk of accelerated biological ageing as well as creating a heightened sensitivity and responsiveness to subsequent stressors[99-104]. Stress leads to both psychological and physiological responses, including activation of the body's two key stress response systems, the sympathetic nervous system and the hypothalamic–pituitary–adrenal (HPA) axis, which have effects on several downstream processes mediated via the release of catecholamines and cortisol, respectively. These stress hormones might increase the risk of biological ageing through three main mechanisms: increased metabolic activity, cellular damage and activation of inflammation (FIG. 2). Catecholamine signalling results in increased release of stored energy (such as glucose and lipids) and in direct stimulation of cellular metabolic activity, which is known to produce reactive oxygen species, resulting in damage accumulation[105-108]. Glucocorticoids probably also have a role in the ageing process as regulators of metabolism[85,109] and by decreasing telomerase activity[110], thereby driving vulnerable cells towards senescence. Evidence also suggests that glucocorticoids impair DNA damage and repair pathways[106]. Damage within cells and in the nearby tissue microenvironment can initiate a cascade of inflammatory responses via the release of DAMPs, which are known to be elevated in ageing tissues and released from senescent cells[111-113].

Stress hormones are also known to directly influence the production of pro-inflammatory cytokines by immune cells. These neuroendocrine–immune communication networks involve a distinct inflammatory pathway that can be activated by noradrenaline via catecholamine receptors expressed on immune cells, resulting in the activation of several inflammation-promoting transcription factors (such as NF-κB, AP1 and CREB)[114]. This pathway is reciprocally regulated by glucocorticoids, which typically have anti-inflammatory effects, although resistance to these effects can develop after prolonged exposure as is thought to occur under chronic stress[114]. Indeed, several studies have demonstrated increased inflammation as well as alterations in glucocorticoid resistance following both acute and chronic stress in individuals without cancer[115-117]. This excess inflammatory activity can then have direct effects on tissues, resulting in damage accumulation and accelerated ageing.

Animal models have also provided insights into the links between stress and biological ageing. For example, the upregulation of genes associated with the DNA damage response has been demonstrated in mice exposed to restraint stress[118] and research demonstrates the ability of social defeat stress to shorten the lifespan of mice by increasing the numbers of senescent cells[119]. Parallel research in humans has begun to disentangle the role of stress in biological ageing, with a growing body of evidence implicating shortening of telomere length among individuals exposed to various chronic stress conditions[86,120,121]. Chronic

stress has also been associated with other markers of biological ageing; for example, parents with high levels of perceived psychological stress have increased expression of $p16^{INK4a}$ in peripheral blood cells[122] and data from several studies indicate associations of psychological adversity, including both early-life and adult trauma, with greater epigenetic age[123-129].

We propose that individuals experiencing substantial psychological stress during and after cancer treatments might be more vulnerable to prolonged toxicities owing to the accumulation of stress-related damage and impairment of important repair mechanisms. The role of stress in the context of cancer is a crucially salient psychosocial factor given that both a cancer diagnosis and undergoing treatment pose considerable challenges to both psychological and physical wellbeing. Patients commonly experience concerns about their prognosis, the possibility of premature death, the adverse effects of adjuvant therapies, impacts on work and family life, and disruption of social ties and activities[130]. For some individuals, these concerns are more severe and persistent, with the potential for negative effects on both mental and physical health[130]. These issues are often exacerbated in individuals from socially and economically disadvantaged backgrounds and might be even more consequential among such patients[131]. A number of structural and institutional factors might also have important roles in the accessibility, adherence to and quality of cancer treatments received, thus limiting the potentially life-saving benefits of effective treatments[132,133].

These multiple sources of stress and individual stress response patterns might directly influence biological responses to treatment and the function of recovery pathways, creating a biological environment that makes cells more vulnerable to damage accumulation and ageing. In addition, individuals diagnosed with cancer who have higher levels of childhood or lifetime stress exposure, economic or educational disadvantages, or prior episodes of depression or anxiety disorders might already be on a path towards accelerated ageing that further increases their risk of inflammation and poor outcomes after cancer therapy[79,103,121,134-137]. Indeed, a robust association exists between childhood adversity and inflammation and fatigue before, during and after treatment in women with breast cancer[136,138-141]. Similarly, greater levels of lifetime stress exposure, low socioeconomic status and a history of depression are all associated with cancer-related fatigue[79] and declines in cognitive function[8,142-144]. Further research is warranted to examine other relevant pathways that might be altered during psychological stress in patients with cancer and in cancer survivors, including alterations in nutrient sensing and mitochondrial dysfunction[108]. Regardless, stress and the subsequent activation of neuroendocrine signalling pathways might be important targets both for interventions designed to improve psychological wellbeing (by reducing the severity of symptoms such as depression and anxiety) and in buffering the effects of treatment on physical and cellular ageing.

Sleep and biological ageing

Sleep is a state of rest, during which the body enters a period of relaxation and brain function is altered, with reduced levels of alertness and consciousness. This state is reached typically during a circadian 24-hour cycle. In humans, precise sleep requirements vary

across individuals, although the optimal quantity of sleep for most adults is thought to be 7–8 hours of nocturnal sleep[145]. Sleep is thought to provide the body sufficient time to restore energy after daytime activity. This long-held concept in sleep science can be extended to include restoration at the biological level. In waking hours, the body is responding to repeated demands that require energy consumption, often with minimal time to rest and restore. Biologically speaking, these demands require metabolic activity that incurs damage and the accumulation of waste products that require repair and/or removal[146]. Theoretically, therefore, sleep provides the body with time to repair and restore the system to a healthy state. Inadequate sleep might lead to damage accumulation and a gradual deterioration in cellular function as seen in biological ageing.

This theory of the utility of sleep is grounded in evidence from the past few years that sleep deprivation and sleep fragmentation accelerate ageing. In rats, chronic sleep fragmentation promotes the accumulation of senescent cells[90] and sleep deprivation contributes to increased cellular stress and accumulation of unfolded protiens[147]. Paralleling these observations, the clearance of waste products, including amyloid plaques in the brain, is significantly enhanced during deep sleep[148,149], suggesting that restrictions to sleep might compromise brain clearance of waste and contribute to brain ageing. In an experimental model of sleep restriction to 4 hours at night in older adults (61–86 years of age), we observed increased expression of genes associated with the DNA damage response and with a SASP profile, as well as greater expression of $p16^{INK4a}$ following a night of partial sleep deprivation[89]. Cross-sectional data have also linked sleep disturbances and insufficient sleep to shorter telomere length[150-159] and older epigenetic age[88]. Similar to psychological stress, sleep influences inflammation[160], with experimental and cross-sectional evidence documenting that insufficient sleep increases cellular and systemic inflammatory activity[161].

Sleep difficulties are highly salient in the context of cancer and its treatments. Sleep quality is often compromised in patients with cancer, with estimates suggesting that 30–70% of patients have sleep disturbances prior to and/or during treatment for cancer[162] and that those with sleep disturbances have an elevated risk of depression, fatigue, cognitive problems and earlier death[163-167]. Many cancer survivors also report sustained sleeping difficulties after completion of treatment, with as many as half having persistent reductions in sleep quality[167-170]. We propose that sleep disturbances occurring during and after treatment might lead to accelerated biological ageing and reduce the extent of damaged tissue repair, thus impairing recovery. By contrast, good quality sleep might reduce the risk of treatment-related damage and accelerated biological ageing. Thus, sleep problems during and after cancer treatments might be a particularly important modifiable factor in patients receiving treatment for cancer who seek to avoid treatment-related accelerated ageing.

Health behaviours

In addition to reducing stress and improving sleep, interventions targeting several other modifiable behaviours (such as physical inactivity, unhealthy diet and substance use) could protect the body from accelerated ageing in the context of cancer treatments and patient recovery. These include increased physical activity (adjusted according to performance status), maintenance of a healthy body weight, adequate nutrient intake and limited

substance use. Extensive recommendations have been published outlining the importance of diet, physical activity, weight management and avoidance of substance use[171]. A large, established body of literature on these topics already exists; therefore, we focus here on highlighting the relevance of these behaviours in the context of accelerated ageing in patients with cancer.

Physical inactivity.—Physical inactivity is associated with an increased risk of the cognitive and physical declines seen with ageing. Accordingly, sedentary lifestyles are associated with accelerated biological ageing[92,172,173] and increased physical activity seems to be protective[93,174,175], although excessive and/or inappropriate exercise might be damaging[176]. The biological ageing pathways involved in this effect include inflammation, dysfunctional metabolism and poor energy utilization, greater cellular damage and accumulated waste, and more accumulation of senescent cells[93,177]. Therefore, engaging in regular physical activity is potentially an important behavioural modification that has shown improvements in strength and mental wellbeing[178,179] as well as initial evidence of reductions in cellular senescence[180]; likewise, it could substantially improve ageing outcomes in patients with cancer. Inactivity has also been linked with inferior cancer-related outcomes, including an increased risk of disease recurrence and earlier mortality[181-183], as well as increased behavioural symptoms among patients with cancer, including fatigue[95], poor cognitive function[184,185] and mood disturbances[186-188].

Obesity.—Several lines of research demonstrate that individuals who are obese also have signs of accelerated ageing, including shortened telomere length and a greater degree of epigenetic ageing[92,189-192]. Whether obesity accelerates biological ageing or accelerated ageing increases the propensity to accumulate adipose tissue is not fully defined. However, research in animal models suggests that the induction of obesity using high-fat diets promotes the accumulation of senescent cells[193], whereas the elimination of senescent cells in obese mice reversed the metabolic syndrome[64]. Reduced caloric intake has been shown to alter several metabolic parameters and slows biological ageing in preclinical models[194,195], although evidence supporting the efficacy of caloric restriction in humans is growing yet currently inconclusive[196,197]. Components of the Mediterranean diet, such as high levels of fibre, healthier fats and antioxidants, are thought to prevent cellular damage[198], thereby protecting from biological ageing. Further research, including human intervention trials, is needed to understand what dietary factors might lead to accelerated ageing. Thus, a combination of poor diet and obesity might be particularly detrimental to long-term health outcomes and lead to accelerated ageing.

Obesity is a risk factor for both inferior cancer outcomes and the development of secondary cancers[199,200] and has also been shown to increase the risk of physical manifestations of ageing such as fatigue[201]. Weight management is therefore a behavioural target that could protect patients with cancer from accelerated ageing. Further research examining this pathway is needed and some studies that primarily focus on physical activity are currently under way (for example, NCT01635413)[202]. For example, the identification of weight management interventions that are most effective in protecting against accelerated

ageing in patients with cancer might differ from those that are most effective in non-cancer populations.

Alcohol consumption and tobacco use.—Both of these exposures are associated with an increased risk of several cancers, primarily owing to genotoxic effects[203-207]. Excess blood alcohol levels lead to increased inflammation and tissue damage, including through the accumulation of metabolites (such as acetaldehyde) in the liver[208]. Evidence of accelerated ageing among heavy drinkers is mixed, with a number of studies linking high alcohol consumption with an older epigenetic age[209] and shortened telomere length[208,210], whereas such associations have not been observed in others[211]. Inhaling smoke from cigarettes and other related products can trigger damage in lung tissues, leading to inflammation and oxidative stress[206,207]. Indeed, a positive correlation exists between pack years of smoking and accelerated biological ageing as demonstrated by DNA methylation-based biomarkers of age[92,209,212,213] and shortened telomere length[211,214-216]. These behaviours are also potential accelerants of biological ageing in patients with cancer and should continue to be important targets of both public health and clinician-led interventions.

Interventions

Intriguing evidence from preclinical models raises the possibility that biological ageing and, therefore, the related physical manifestations of ageing can be remedied using interventions that target the removal of senescent cells. Indeed, clinical trials testing the efficacy of senolytic agents in reversing cancer treatment-related ageing are currently under way[217,218]. Importantly, as outlined earlier in this Review, behavioural factors can also influence biological ageing and interventions targeting these processes offer considerable promise. Here, we outline and highlight several relationships between these aspects that could be considered targets for intervention (FIG. 3).

Targeting stress

Stress reduction might help to slow or reverse ageing. The first option for reducing stress is removal of the stressor, which is sometimes feasible but often not. A second option would be to block the neuroendocrine mediators driving the intracellular changes, for example, through administration of β_2-adrenoceptor antagonists (β-blockers). Several clinical trials examining the efficacy of this approach, specifically for delaying disease progression and the recurrence of cancer, are currently under way, with promising preliminary results pointing to reductions in metastasis potential and risk of disease recurrence[219-223]. These trials might be well positioned to also investigate the effects of β-adrenergic blockade on patient-reported outcomes and on the hallmark features of biological ageing. A third option is to alter patients' psychological and physiological responses to the stressors using behavioural interventions that target the cognitive, behavioural and/or biological processes associated with the stress response, with the goal of reducing the frequency and intensity of this response pattern. Importantly, several effective behavioural interventions have been demonstrated to reduce stress both in patients with cancer and in cancer survivors, including cognitive behavioural therapies and mind–body approaches[224-226]. These interventions can also have effects on ageing-related biological processes in patients with cancer. For example,

cognitive behavioural stress management has been shown to reduce levels of anxiety and expression of pro-inflammatory genes in women with breast cancer[227]. Furthermore, intervention-related changes in inflammatory and antiviral gene expression predicted a lower risk of breast cancer recurrence in this study, although the sample size was small[228]. Mindfulness interventions have also been shown to reduce levels of stress and depression and to improve wellbeing in breast cancer survivors while also leading to reductions in inflammation-related gene expression[229,230]. Furthermore, regular meditation has been proposed to influence other aspects of biological ageing, including telomere length and the epigenetic clock[109,231]. Yoga interventions have also demonstrated beneficial effects on ageing-related symptoms (such as fatigue or cognitive complaints) as well as inflammatory processes in breast cancer survivors[232-234]. Thus, interventions designed to reduce levels of stress might be a method of promoting resilience to both biological and physical ageing.

Treating sleep disturbances

Sleep disturbances can be addressed using one of several established treatment modalities. The gold standard of cognitive behavioural therapy for insomnia (CBT-I) has been demonstrated to be effective in cancer survivors[235,236]. Several new methods of accessing this therapy have been developed, including online administration, with similar efficacy[237]. In addition, mind–body therapies, including tai chi[238], mindfulness training[229,239,240] and yoga[241], have been shown to ameliorate sleep disturbances both in patients with cancer and in cancer survivors. Initial results suggest that acupuncture might also provide benefit for cancer survivors with insomnia, although the overall effectiveness of this intervention was lower than with CBT-I[242]. Notably, many of the interventions targeting insomnia also resulted in improvements in other symptoms, including fatigue and cognitive function[83,235,236,241]. These interventions have been efficacious in reducing levels of inflammation among those with insomnia[243,244], thus further highlighting the benefits of addressing sleep disturbances in patients with cancer.

Pharmaceutical treatments for sleep disturbances, which are typically less effective than cognitive behavioural therapies, are often desired by patients seeking temporary relief from acute symptoms and/or during a vital window for optimal healing (such as after surgery, radiotherapy or chemotherapy). However, such treatments are associated with declining efficacy with long-term use and high secondary health costs (such as dependency and a risk of falls for older adults)[162,166,245]. Novel data are beginning to demonstrate the crucial role of deep sleep for maintaining brain health and might lead to the development of novel targeted strategies that assist in maintaining deep sleep, such as auditory closed loop stimulation[246], which might in turn offer long-term amelioration of biological ageing in patients with cancer and cancer survivors. The availability of multiple effective treatments for sleep disturbances and the high prevalence of sleep difficulties both in patients with cancer and in cancer survivors, many of whom have ongoing sleep problems and are not offered remedies[162,166], make sleep an important target for clinical cancer care[247,248].

Intervening in health behaviours

A large body of literature exists on the importance of intervening in negative health behaviours in the general population, with existing recommendations available for

increasing physical activity[249], reducing obesity[250] and substance use[251-253]. Interventions targeting these aspects have demonstrated beneficial effects in cancer survivors[254-257] and evidence from the past decade suggests that these interventions also directly modify biomarkers of ageing[172,175,177,258,259].

Increasing exercise.—Exercise can potentially have a number of health benefits, including reducing stress, improving sleep quality, boosting mood, improving muscle strength and tone, and enhancing cardiovascular and lung health[178,260]. Therefore, physical activity is an important target for cancer prevention and control[183,259] as well as for improving quality of life and ageing outcomes[184,186,256,257] and should not be overlooked. Physical activity interventions not only have behavioural and health benefits but can also have positive effects on ageing-related biomarkers[175,261], making this an excellent behavioural target for intervention. Maintaining an active lifestyle during and after cancer treatment can be challenging, although patients should be encouraged to maintain levels of activity in order to prevent and/or reduce the severity of fatigue and other adverse effects of cancer treatment and to avoid a loss of mobility[262]. Improving the level of physical activity is particularly important for patients with sedentary lifestyles, with several interventions having shown efficacy, including those with tailored goals for individual patients[263], and increased accessibility owing to the use of remote instruction and/or smart devices[264]. Older cancer survivors might be more amenable to interventions such as gardening, which has the potential to increase both mobility and promote the consumption of fruits and vegetables[265].

Targeting energy balance.—Improving metabolic function might have the added benefits of helping to heal treatment-related cellular damage and protecting against cancer-related accelerated ageing[266]. Indeed, interventions targeting weight management, a healthy diet and physical activity might be beneficial across the cancer care continuum[254]. Changes in the timing and/or frequency of caloric intake, such as caloric restriction and intermittent fasting, also seem to modify certain mechanisms of ageing[267-269], including pathways involved in tumour growth (such as PI3K–AKT–mTOR signalling)[270], which can now be inhibited with targeted therapies[270]. Thus, diets that are thought to be protective against cancer also seem to ameliorate certain aspects of ageing, although the effects might vary according to the age of the organism; therefore, further research is needed to understand whether the effects of dietary interventions also differ by age in humans[271,272]. Nonetheless, interventions that target obesity and energy balance might prove beneficial in preventing or slowing ageing after cancer treatments. Diet might also be crucial in maintaining a healthy gut microbiota and future research should consider the role that the microbiota might have in resistance and resilience during and after cancer treatments[176]. Further research is also needed to understand the relevance of specific diets on the effects of cancer treatments and to provide clear recommendations on the optimal energy balance and nutrient intake during both treatment and recovery.

Reducing alcohol consumption and tobacco use.—This remains a crucial target of intervention for cancer prevention and control that not only reduces the risk of primary cancer but could also potentially reduce the risk of poor treatment outcomes, secondary cancers and future morbidities[252,253]. The modification of these factors might also have

major implications for efforts to ameliorate accelerated ageing in patients with cancer and future research should consider the direct effects of changes in alcohol consumption and tobacco use on markers of biological ageing. Existing guidelines on the use of several intervention strategies are available[251,273-275] and other methods of reducing the severity of cravings or other withdrawal symptoms include cognitive behavioural therapy, pharmacological treatments and support groups, all of which have resulted in a certain level of success in the general population.

Pharmacological interventions.—A number of promising drugs that target biological ageing are currently in development and several have entered clinical trials (NCT04815902, NCT04063124, NCT04210986, NCT04733534, NCT02848131, NCT04770064 and NCT04313634). A few agents worth highlighting here include senolytic agents and anti-inflammatory drugs[62,197,276]. In brief, senolytic agents target and degrade senescent cells as a means of reducing a source of both inflammation and impaired tissue function. Animal models of senolytic agents suggest an improved overall healthy lifespan (referred to as healthspan) and lifespan, presenting an extremely promising approach to the treatment of accelerated biological ageing[217]. In addition to senolytic agents, anti-inflammatory agents that specifically target the regulatory pathways that promote the SASP might also provide benefit in terms of reducing both symptoms and ageing[53]. A detailed overview of the mechanisms of action of these agents is provided elsewhere[62,276].

Future research priorities

Given the growing evidence linking behavioural factors with ageing, future research priorities should include a focus on characterizing the crucial role of these behaviours as a potential target to alter treatment-related accelerated biological ageing in patients with cancer and cancer survivors. Behavioural interventions might be beneficial at several points of the cancer trajectory; therefore, timing is likely to be an important consideration for the design of such interventions. The optimal timing of these targeted interventions will vary depending on a number of factors that clinicians and researchers will need to consider, including pre-existing patient-specific factors, interactions with treatment regimens and the time point at which these behavioural factors are most relevant (FIG. 3).

For interventions delivered at the time of diagnosis, clinicians will need to consider patient-specific factors and behaviours that might have put the patient at risk of cancer (such as tobacco and/or alcohol use or obesity) and directly address them as part of the cancer treatment plan (for example, encouraging tobacco use cessation). Certain interventions (such as exercise) might also increase the efficacy of treatments (such as chemotherapy[277,278]) and improve survival outcomes[279]. Screening for past and/or current symptoms of depression can be crucial for the management of patients in this setting as diagnosis and treatment might trigger a new episode that could interfere with treatment adherence[279]. Stress levels and sleep in particular might be affected at the time of diagnosis owing to considerable existential anxiety regarding the upcoming treatments and their probable outcomes[280-284].

Owing to the known benefits of regular high-quality sleep, successful interventions for insomnia[282] could, theoretically, be particularly beneficial as a means of clearing waste

products (particularly in the brain)[285,286], repairing damage caused by therapy, and/or aiding the body in healing tissue injury[146]. However, no research to date has tested this hypothesis. Likewise, in patients with circadian disruptions caused by surgery, light therapy could be delivered immediately after surgery to support the recovery of circadian alignment[283,284]. Several studies have also demonstrated substantial changes in sleep patterns in patients receiving chemotherapy[287] and data demonstrate the feasibility and preliminary effectiveness of a brief CBT-I intervention administered during chemotherapy appointments[288]. Mindfulness, meditation-based interventions and other stress-reduction techniques have also shown benefit when delivered during treatment[227,280,281,289].

After treatment completion, focused interventions designed to reduce excess fat stores by restoring a healthy energy balance through increasing levels of physical activity could assist in the prevention of a second primary cancer[199]. Intermittent fasting might also prove to be an important method of preventing secondary tumours and/or the growth or cancer cells not cleared by initial treatment given that this strategy alters the extent of glucose and/or insulin signalling[270], which are key pathways involved in the promotion of ageing and/or tumour growth and, interestingly, are also inhibited by several novel targeted therapies (via suppression of PI3K–AKT–mTOR signalling)[270]. In addition, interventions targeting behavioural symptoms in cancer survivors (such as fatigue and insomnia) are crucial for preventing impairments in quality of life and further acceleration of ageing processes.

Future research priorities include the optimal timing of behavioural interventions, particularly in terms of their effectiveness in restoring treatment-related biological damage and providing protection from accelerated ageing, as well as considering the timing of delivery given the opportunity for a teachable moment and access to services. In particular, research tracking biobehavioural factors in relation to the physical and biological effects of cancer and the various available treatments is needed. Several important and commonly seen adverse ageing outcomes exist and might be amenable to behavioural intervention (FIG. 3). These modifiable outcomes include levels of biological ageing markers, physical functional measures, cognitive and mental health, new morbidities and secondary cancers, frailty, and early mortality. Cancer is primarily a disease of older individuals (those >65 years of age); therefore, addressing relevant behaviours primarily in this population will probably contribute to more immediate improved health and wellbeing. Moreover, adoption of these behaviours will probably also contribute to a reduction in disease burden or symptoms from other concomitant chronic diseases (such as diabetes and cardiovascular disease). By contrast, for children and young adults who have survived cancer, whose lifespan is considerably longer, focusing on biobehavioural interventions has the potential to influence accelerated ageing and is likely to yield considerable benefit in terms of reducing the risk of secondary primary cancers and other chronic health problems that might not emerge until 2–3 decades later[266]. For these individuals, the prevention pay-off might be substantial. By targeting these potential behavioural modifiers across the cancer continuum, the potential exists to substantially improve the healthy lifespan and longevity of cancer survivors of any age.

Conclusions

In summary, this Review has outlined the growing literature linking cancer and its treatments to accelerated physical, cognitive and biological ageing and extended this model to include several important behavioural modifiers that might ameliorate these patterns of ageing. Key behaviours that are known to affect ageing biology in individuals without cancer include perceived stress, sleep disturbances and insomnia, a sedentary lifestyle, adiposity, poor diet, and substance use. Herein, we propose that these factors might also act as modifiers in the context of cancer and lead to accelerated ageing. Intervening to reduce stress, improve sleep health, increase physical activity, manage weight, and/or reduce alcohol and tobacco use could all prove beneficial for the long-term healthspan and lifespan of patients and survivors by directly altering biological ageing patterns. We propose several directions for future research designed to carefully determine actionable targets for interventions.

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Key points

- Cancer and its treatments are thought to promote accelerated biological ageing, leading to adverse cognitive, behavioural and functional outcomes in cancer survivors.
- Modifiable host-specific factors are known to affect ageing biology in individuals without cancer, including psychosocial stress, poor sleep, physical inactivity, obesity, and tobacco and alcohol use.
- Behavioural interventions and/or modifications targeting these host factors might directly alter biological ageing processes in patients with cancer and cancer survivors, thereby improving both healthspan and lifespan.
- We propose that these host factors be considered in models of cancer-related age acceleration and that interventions designed to reduce stress, improve sleep health, increase physical activity, manage weight, and/or reduce alcohol and tobacco use be investigated as promising approaches to address accelerated ageing in this context.

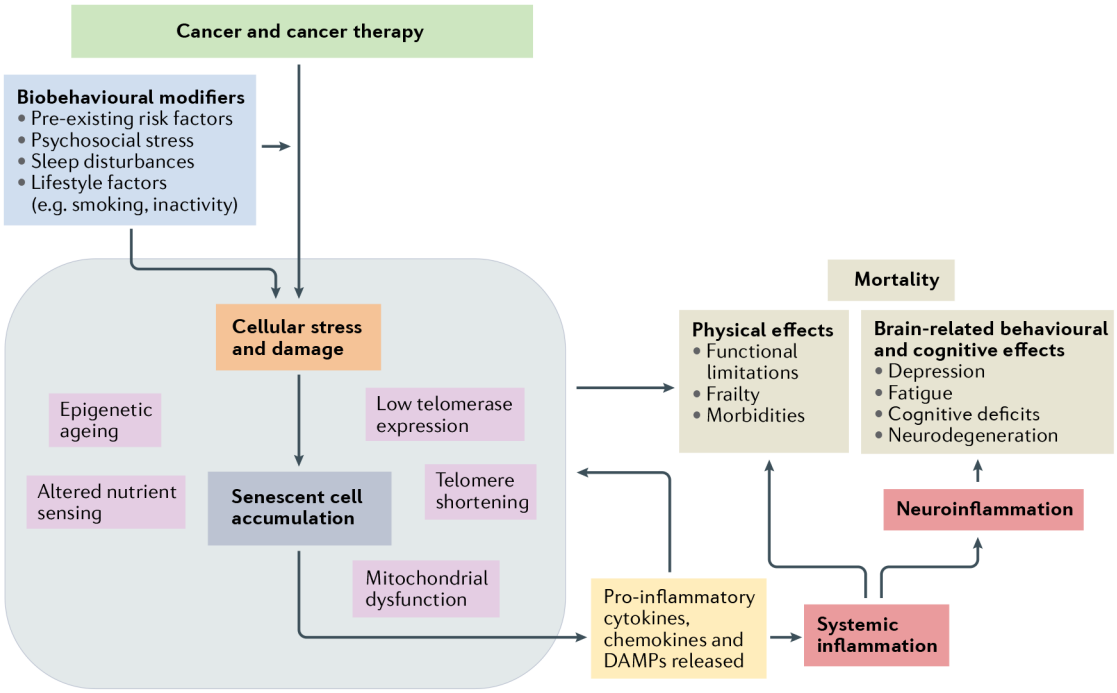

Fig. 1 |. Model of biobehavioural modifiers of cancer-related accelerated ageing.

In this model, several biobehavioural factors, including pre-existing risks and current psychological stress, sleep disturbances and lifestyle-related factors, along with exposure to cancer treatments, particularly chemotherapy and radiotherapy, result in cellular stress and damage[276]. This then leads to epigenetic ageing, telomere shortening and, if sufficient damage accumulation accrues, initiation of cellular senescence[46,49]. The senescent cells, which have an inflammation-biased secretome[48,277], increase the degradation of nearby tissues and promote the release of inflammatory cytokines, chemokines and damage-associated molecular patterns (DAMPs), which collectively induce the secondary recruitment of inflammatory cells[51,53,54,57] and lead to the further propagation of circulating inflammation and trafficking of immune cells into various tissue compartments. This gradual increase in inflammation impairs the function of several bodily systems, leading to alterations in both physical function and the ability to perform activities of daily living, such as slowing gait speed, declining muscle strength, increasing risks of frailty and an increased risk of comorbidities (such as cardiovascular disease, diabetes or osteoporosis). Inflammation can also signal across the blood–brain interface resulting in neuroinflammation, which can have both behavioural and cognitive consequences, including depression, fatigue and cognitive decline[92,278,279].

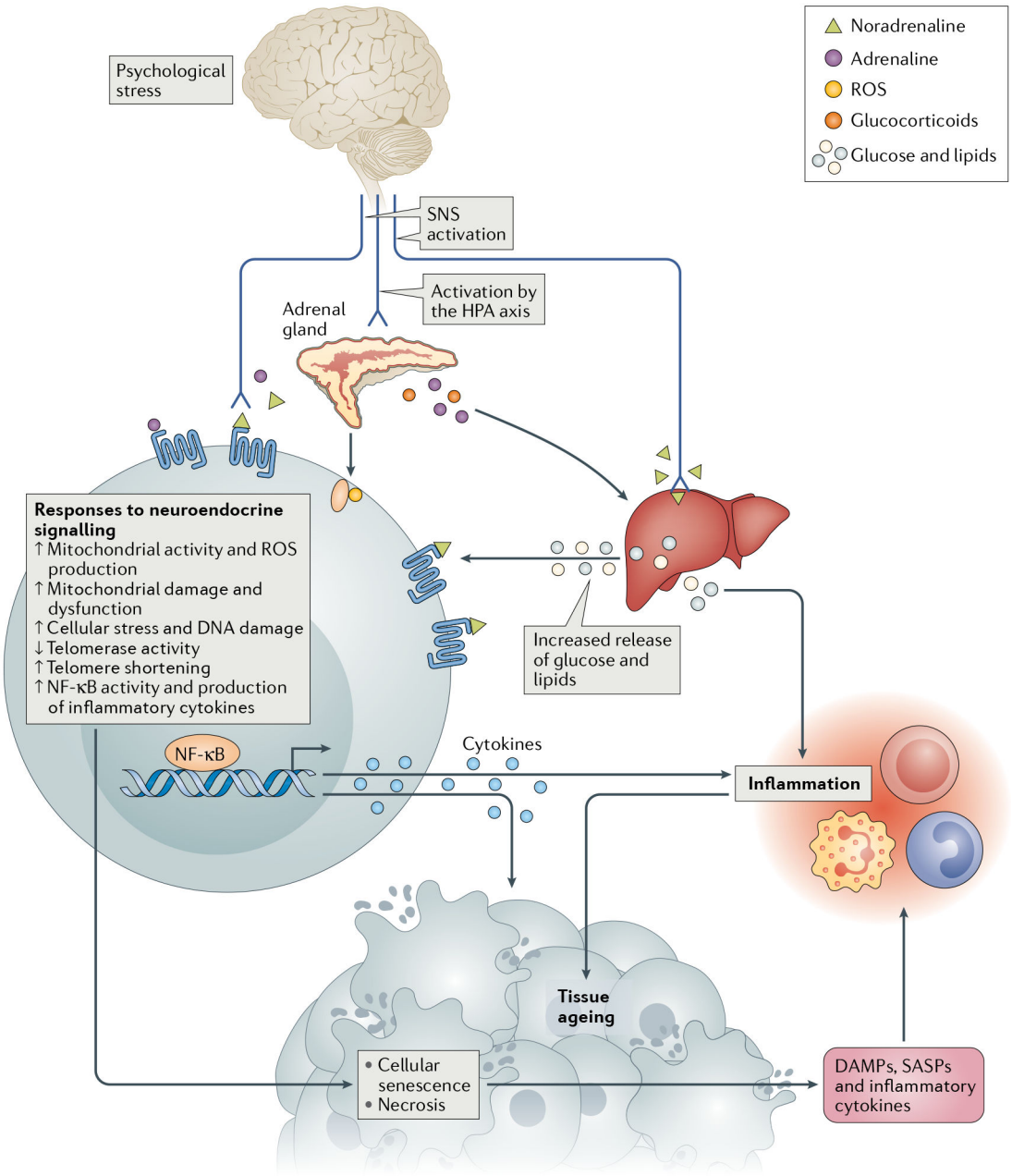

Fig. 2 |. Neuroendocrine-mediated pathways driving biological ageing following activation of the stress response.

The sympathetic nervous system (SNS) releases the catecholamines noradrenaline and adrenaline from nerve fibres and the adrenal gland, thus promoting the release of glucose and lipids from storage. These catecholamines also upregulate cellular metabolic activity, which produces reactive oxygen species (ROS), a source of tissue damage[105-108]. Damage to DNA and telomeres can lead to cellular senescence[48,290]. The hypothalamic–pituitary–adrenal (HPA) axis is activated during a stress response with release of glucocorticoids from the adrenal gland, thus further promoting metabolic activity[85,109], leading to increased levels of glucose and lipids as well as of oxidative stress and inflammation[291-293].

Activation of the HPA axis also promotes decreased telomerase activity[110] and impairs the function of DNA damage and repair pathways[106]. Damaged, necrotic and senescent cells release inflammatory signals, including damage-associated molecular patterns (DAMPs) and cytokines and chemokines that are characteristic of the senescence-associated secretory phenotype (SASP)[111-113].

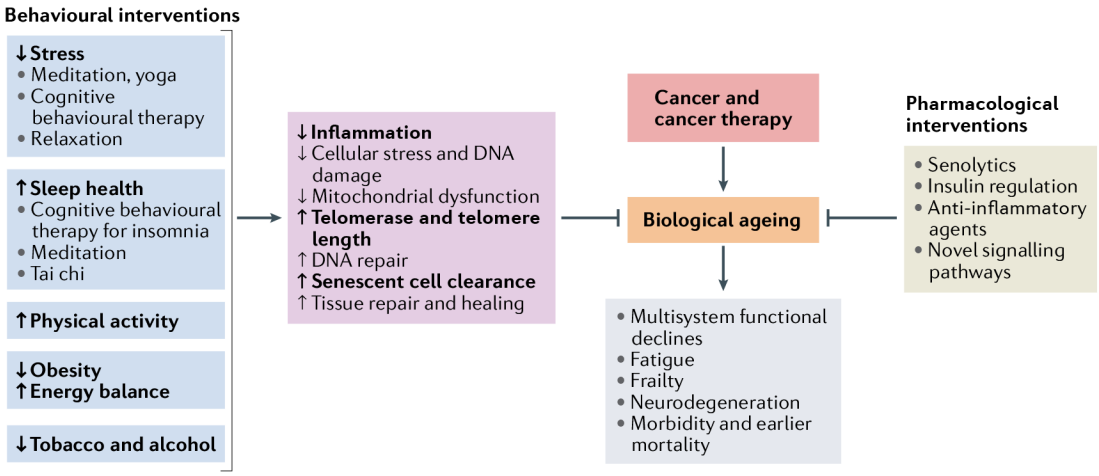

Fig. 3 |. Interventions proposed to inhibit the effects of cancer treatments on biological ageing and to modify long-term physical and cognitive health.

Patient-specific biobehavioral factors can influence biological ageing processes and are potential targets for interventions designed to slow or reverse the effects of cancer and its treatments on these outcomes. A variety of interventions targeting these host factors may act directly on biological ageing pathways such as inflammation, cellular stress, mitochondrial function, the telomere maintenance system, repair pathways and cellular senescence. As cancer and cancer therapies are thought to act as accelerators of biological ageing, these modifiable factors might also be potential targets for interventions designed to slow or reverse the effects of cancer and its treatments. Biobehavioural interventions targeting stress, sleep health, physical activity, obesity and substance use have been demonstrated to have beneficial effects on inflammation and some ageing biomarkers (highlighted with bold font), including empirical support for cognitive behavioural therapy, mind–body interventions, and exercise, dietary and substance use interventions. All of these interventions could then have implications for survivorship risk, including the risks of functional decline, fatigue, frailty, neurodegeneration, and early morbidities and mortality. Alternatively, pharmacological agents, such as senolytics or anti-inflammatory agents, might be able to directly reverse or modify the effects of biological ageing.