Stress and cancer: mechanisms, significance and future directions

Anabel Eckerling, Itay Ricon-Becker, Liat Sorski, Elad Sandbank and Shamgar Ben-Eliyahu ✉

Abstract | The notion that stress and cancer are interlinked has dominated lay discourse for decades. More recent animal studies indicate that stress can substantially facilitate cancer progression through modulating most hallmarks of cancer, and molecular and systemic mechanisms mediating these effects have been elucidated. However, available clinical evidence for such deleterious effects is inconsistent, as epidemiological and stress-reducing clinical interventions have yielded mixed effects on cancer mortality. In this Review, we describe and discuss specific mediating mechanisms identified by preclinical research, and parallel clinical findings. We explain the discrepancy between preclinical and clinical outcomes, through pointing to experimental strengths leveraged by animal studies and through discussing methodological and conceptual obstacles that prevent clinical studies from reflecting the impacts of stress. We suggest approaches to circumvent such obstacles, based on targeting critical phases of cancer progression that are more likely to be stress-sensitive; pharmacologically limiting adrenergic–inflammatory responses triggered by medical procedures; and focusing on more vulnerable populations, employing personalized pharmacological and psychosocial approaches. Recent clinical trials support our hypothesis that psychological and/or pharmacological inhibition of excess adrenergic and/or inflammatory stress signalling, especially alongside cancer treatments, could save lives.

For decades, stress has been suggested to affect cancer incidence and cancer progression[1,2]. However, both epidemiological studies and clinical trials have yielded mixed results, or indicated small or clinically insignificant effects of stress on cancer progression. Consequently, current medical routines do not include measures to prevent stress responses as a means to improve cancer survival. Within the medical community, this may reflect a disbelief that stress is a significant biological factor underlying cancer aetiology and progression.

By contrast, in recent years, animal studies have provided solid evidence that stress can facilitate growth and metastasis of many types of cancer. Most importantly, numerous endocrine, cellular and molecular mechanisms underlying these effects have been identified. For example, animal models have shown that stress factors can promote most established hallmarks of cancer[2], and that stress responses can facilitate cancer growth and metastasis via directly affecting molecular characteristics of the malignant tissue[3–5], its microenvironment[6], antitumour immune activity[4,7–9] and other indirect modulators of cancer progression[10,11]. In patients with cancer, stress has been shown to activate many of these processes[8,10–13], supporting the clinical significance of these findings.

We suggest that the discrepancy between preclinical studies and clinical or epidemiological studies stems from two sources. First, preclinical studies can synchronize stress or stress-reducing interventions with critical periods along cancer progression that are highly susceptible to the impacts of stress. Second, conceptual and methodological difficulties in conducting clinical studies may obscure the impact of stress on cancer progression.

In this Review, we describe and discuss stress and stress responses at the organism level and in the context of cancer. We further explain mechanisms via which stress can facilitate cancer initiation, impair cancer treatments and promote cancer growth and metastasis, based on animal studies and on parallel human correlative or causative studies. We also review epidemiological studies and clinical trials in patients with cancer, and discuss why we believe many of these studies are predisposed to show minor or no effects, and then suggest approaches that we hypothesize will provide more conclusive evidence on whether stress significantly affects long-term cancer outcomes in humans.

Sagol School of Neuroscience and School of Psychological Sciences, Tel Aviv University, Tel Aviv, Israel.

✉*e-mail:* *shamgar@tauex.tau.ac.il*

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Sympathetic nervous system
(SNS). Part of the autonomic nervous system that is involuntarily activated by stressors (for example, a dangerous or stressful situation) and orchestrates the 'fight or flight' response through adrenergic innervation of the adrenal medulla and of various organs (for example, the heart) through systemic and local release of adrenaline and noradrenaline, respectively.

Hypothalamic–pituitary–adrenal (HPA) axis
A neuroendocrine system with negative feedback that increases systemic glucocorticoid (for example, cortisol) levels in various circumstances, including stressful conditions. Hypothalamic corticotropin-releasing hormone (CRH) elevates systemic release of adrenocorticotropic hormone (ACTH) from the anterior pituitary, which triggers the release of glucocorticoids from the adrenal cortex, which also trigger negative feedback through the pituitary and hypothalamic levels.

Damage-associated molecular patterns
Endogenous host-derived molecules that are released by damaged and dying cells. They are recognized by pattern recognition receptors on numerous cells, which lead to migration and activation of various immune cells and consequent innate and adaptive immune responses.

Stress and stress responses

Hans Selye in 1956 (REF.[14]) described stress as a response of the body to the demands made upon it in an attempt to return to homeostasis. Meeting the demands of life, spanning from day to day tasks to major threats such as the diagnosis and treatment of cancer, requires mobilization of metabolic energy to sustain necessary physiological adaptive responses. This is achieved by activation of the sympathetic nervous system (SNS) and the hypothalamic–pituitary–adrenal (HPA) axis, leading to local and systemic secretion of adrenergic factors from sympathetic nerve endings and the adrenal medulla (mostly noradrenaline (also known as norepinephrine) and adrenaline (also known as epinephrine), respectively), the release of glucocorticoids (such as cortisol) from the adrenal cortex, and the secretion of opioids, oxytocin and other stress mediators (FIG. 1).

The stress responses described above are initiated by the central nervous system (CNS) following processing of various stimuli, including physiological inner-body responses to various conditions, such as tissue damage (including during surgery and under anaesthesia), or being subjected to low temperature; external stimuli, such as being attacked by an assailant with a weapon or being informed of having cancer; or ongoing CNS activities, resulting from being anxious or ruminating about financial insecurity, social isolation, interpersonal relationships or having cancer (FIG. 1). Notably, both depression and social isolation involve activation and/or dysregulation of the HPA axis, and are characterized by a pro-inflammatory state[15,16], which triggers similar pathways to stress responses (discussed below). Last, stress and depression promote each other[17], and most animal models of depression are based on stress exposure[18].

Stress can be both beneficial and deleterious (BOX 1). The effects of stress on the capacity of an organism to cope with challenges typically follow an inverted U shape[19] — when the intensity, duration or nature of the stressor is moderate, stress facilitates adaptive natural changes, but when stress exceeds the resources of the individual to cope, and becomes 'toxic stress', the risk for disease increases[20]. McEwen and Stellar defined allostasis as the naturally occurring continuous adaptations towards different homeostatic states[21]. When allostasis becomes strenuous, and the allostatic load increases to the point of overload, patients are at greater risk[21].

Notably, the intensity and duration of stress responses to internal or external stimuli markedly differ between individuals, and depend on physiological factors, including genetic and developmental variations[19], and physical fitness (BOX 2); individual psychosocial characteristics, including perceived social support[22], perceived ability to cope[23] and other personal traits; and the characteristics of the stressful life events previously experienced[24–26], including childhood adversity[27]. It follows that stressors such as cancer diagnosis, treatment and survivorship are likely to be differentially experienced by patients, provoking different stress responses. Thus, stress-management therapies, behavioural or pharmacological, should be individually tailored. Additionally, understanding specific physiological mechanisms mediating deleterious (or beneficial) effects of stress responses may point to effective downstream pharmacological therapeutic approaches, which may also surpass individual differences at higher psychological/cognitive levels.

Critical periods in cancer progression

Normal cells transform into malignant cells through acquisition of unique characteristics with evolutionary advantages, known as the 'hallmarks' of cancer[28,29]. These characteristics include resistance to apoptotic signals, independence from external growth signals, the capacity to attract vascularization, evasion of immune destruction and the acquisition of invasive properties into distant organs with a permissive microenvironment to form metastases. Importantly, along this transformation, pre-malignant or malignant foci may be eliminated, may become dormant or slowly progressing[30], or may advance to a clinical manifestation.

Theoretically, some phases may be more critical along this multimodal non-linear process. Examples include activation of the 'angiogenic switch' that enables increased growth or escape from dormancy[31]; initial interactions with immune cells following neovascularization and/or release of damage-associated molecular patterns[32]; the passage of circulating tumour cells through pulmonary or hepatic capillaries, where highly active marginating natural killer cells recognize and eliminate such aberrant cells[33–35]; survival of circulating tumour cells in the circulation and extravasation into new organs[36]; and the capacity of a micrometastasis to grow independently of the primary tumour[37].

Stress may have greater impact during such potential critical phases. Moreover, whether stress will exacerbate or mitigate malignant processes may depend on the phase of malignant progression, specific tumour characteristics and the spectrum of stress responses. Also, immune system–tumour interactions may either impair or promote tumour growth[38], and stress hormones can regulate both processes[7,9]. Thus, interactions between stress and cancer are expected to be non-linear, and the impact of stress could depend on the phase of cancer progression.

Hypothetically, an acute or chronic stress episode that is synchronized with a critical phase may bear a greater impact on cancer progression than non-synchronized episodes. Studies in animal models, more than clinical or epidemiological studies, can focus on a critical phase, employing specific tumour types, and/or stress paradigms, and thus maximize our ability to observe the potential impact of stress. For example, stressing animals shortly before and after intravenous tumour cell inoculation maximizes the deleterious impact of stress on the capacity of marginating pulmonary natural killer cells to prevent experimental lung metastasis[33,39,40]. In breast cancer mouse models, chronic stressors did not affect growth of primary tumours but did promote their dissemination and metastatic growth[41,42]. Last, subjecting mice to chronic social isolation before mammary tumour inoculation exerted no effects on primary tumour growth, whereas if initiated when tumours were palpable, primary tumour growth was increased[43].

In the clinical setting, some critical phases cannot be recognized but others, especially those related to cancer

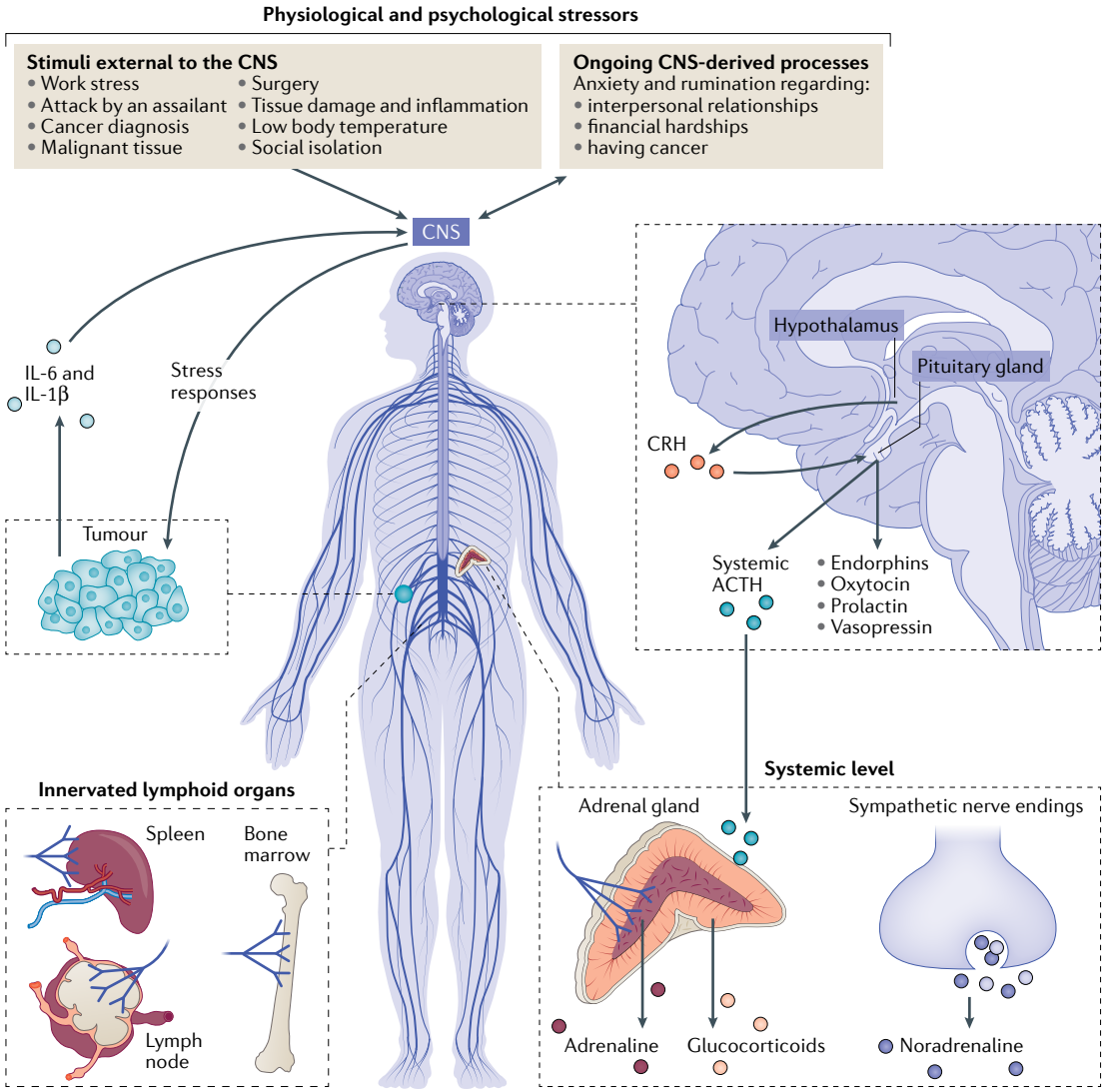

Fig. 1 | **Stress responses and reciprocal stress–cancer interactions.** Physiological and psychological stressors including stimuli external to the central nervous system (CNS), such as being informed of having cancer, undergoing surgery or the presence of malignant tissue and its related inflammation, and ongoing CNS-derived processes (for example, anxiety and rumination about cancer) are perceived and processed by the CNS and trigger stress responses. Consequently, the pituitary gland releases endorphins, oxytocin, prolactin, vasopressin, adrenocorticotropic hormone (ACTH) and other stress mediators, and activation of the hypothalamic–pituitary–adrenal (HPA) axis through hypothalamic corticotropin-releasing hormone (CRH) and systemic ACTH release leads to secretion of glucocorticoids (for example, cortisol) from the adrenal cortex. Simultaneously, the CNS activates the sympathetic nervous system (SNS), leading to secretion of adrenergic factors from the adrenal medulla (mostly adrenaline) and sympathetic nerve endings (mainly noradrenaline). The latter also innervate lymphoid organs (for example, spleen and lymph nodes), bone marrow and various organs. These stress factors promote most hallmarks of cancer through impacting the malignant tissue, its microenvironment, immunity, lymphatic flow and distant potential pre-metastatic niches (FIG. 2). Malignant tissue can facilitate stress responses through local and systemic inflammation (for example, through interleukin-6 (IL-6) and IL-1β) that affects the CNS, dysregulates HPA axis activity[220,221] and promotes depression, sleep disturbances and cancer-related fatigue. Overall, CNS-initiated stress responses may lead to exacerbated tumour growth and spread, and to peripheral stress–inflammatory–cytokine responses, which feed back to the CNS, altering cognition and mood, and facilitating stress responses, creating a vicious cycle.

treatment, are known to impact cancer progression (BOX 3), and can perhaps be exploited to mitigate the effects of stress on cancer progression.

Mechanisms of stress impacts on cancer

As briefly reviewed below, a vast body of literature indicates that stress can promote most hallmarks of cancer[2], and mechanisms mediating these effects by specific stress hormones, their receptor systems and intracellular molecular mechanisms have been identified (reviewed in REFS[3,4,6,44]). We herein discuss and refer to tumour initiation as transformation from non-malignant to malignant tissue, in contrast to tumour progression that follows this transformation, although most hallmarks of cancer can affect both initiation and progression of the disease. We present causative findings from

Box 1 | **Acute and chronic stress**

Acute stress is defined as lasting minutes to hours, whereas chronic stress can last days, weeks, months or longer[271]. A short-term transient stress response can be adaptive, as part of the 'fight or flight' response, where sympathetic nervous system (SNS) and hypothalamic–pituitary–adrenal (HPA) axis activation increases the heart rate, blood pressure and glucose availability. Such stress responses can also promote the release of pro-inflammatory cytokines (for example, interleukin-6 (IL-6) and IL-1β) and trafficking of leukocytes to the skin following stress cessation[272,273], potentially to allow skin pathogen resistance in the case of injury[271]. By contrast, long-lasting or repeated stress exposures can lead to HPA axis dysregulation, glucocorticoid resistance and/or insensitivity to HPA axis negative feedback[274]. These may lead to chronic inflammation secondary to disrupted HPA axis-induced inhibition of pro-inflammatory responses[274]. Nevertheless, chronic elevated levels of glucocorticoids contribute to immunosuppression[275]. Moreover, animal studies have demonstrated that both acute and chronic stress paradigms can suppress immunity[40,273] and promote certain anti-inflammatory responses, such as decreased plasma IL-12 levels[276].

Notably, the distinction between acute and chronic stress is often ambiguous. Chronic stress paradigms in animals are often based on repeated[41] or alternating[85] acute stressors, rather than continuous stressors. Furthermore, there is no unified definition of acute or chronic stress[62,85,92,135], with 3–5 consecutive days of repeated acute stressors defined both as acute[92] and as chronic[85] stressors. Also, continuous chronic social isolation was found to increase reactivity to acute restraint stress[67,137], demonstrating mutual interdependence between acute and chronic stress. In humans, acute events can generate a chronic threat perception and/or chronic stress responses[277], especially given pre-event anticipation and post-event ruminations[27]. In the context of cancer treatment, the overlapping nature of acute and chronic medical and psychological stressors, and the psychological consequences of these events, may mask the distinction between acute and chronic stress and their impact on cancer progression. Moreover, some naturally adaptive responses to acute stress, such as redistribution of leukocytes to the skin at the expense of internal organs, may increase the risk for internal organ metastasis, as indicated by animal studies employing acute stressors[40,133]. Thus, the intricacies of acute and chronic stress responses in the context of cancer progression and treatment suggest caution in making any generalizations.

Catecholamines
A family of molecules that are characterized by a catechol and an amine group in their chemical structure, and function as neurotransmitters and hormones within the body. These include dopamine, noradrenaline and adrenaline, all of which are synthesized from the amino acid tyrosine.

Restraint stress
An experimental stress paradigm, where the animal is placed in a confined space (a tube-shaped apparatus perforated for air exchange) that prevents free movement but does not press or induce pain to the animal. Such restraint can last minutes to hours and can be repeated daily for several weeks as a chronic stress paradigm.

Sympathetic denervation
Refers to experimental methods for ablation of sympathetic nerves (also called sympathectomy), by either surgical cut of sympathetic nerve fibres or chemical ablation (for example, using 6-hydroxydopamine).

animal studies, which often are followed by parallel clinical findings, complementing each other in terms of methodological robustness and clinical relevance.

Cancer initiation

DNA damage. Specific stress factors have been shown to cause DNA damage and jeopardize DNA repair, potentially facilitating malignant transformation. Specifically, in a mouse fibroblast cell line, serum derived from stressed mice, or adrenaline, noradrenaline and cortisol (each factor alone as well as synergistically when combined), increased DNA damage and/or reduced DNA repair following UV irradiation[45]. In murine and human non-cancer cell lines, β-adrenergic receptor (β-AR)-mediated generation of reactive oxygen species and β-arrestin–MDM2-dependent p53 degradation increased DNA damage and inhibited DNA repair[46]. Corresponding in vivo studies confirmed that chronic stress induces these two β-AR-mediated processes[47], and that glucocorticoid-mediated response can also cause MDM2-dependent p53 downregulation and increase resistance to apoptosis following ionization irradiation[48]. In humans, several studies indicated that psychological stress is associated or causatively linked to increased DNA damage[49], and several human cancer cell lines exhibited accelerated DNA damage in vitro following β-adrenergic and glucocorticoid signalling[50–52], in part through activation of the ATR–p21 pathway[52]. Nevertheless, it should be noted that DNA damage alone is insufficient to cause tumour initiation, as mutations need to be maintained and accumulated across repeated cell divisions, and should lead to acquisition of resistance to apoptosis and to increased proliferation, among other characteristics.

Oncogenic viruses. Thirteen to 15% of human cancer incidence is attributed to carcinogenic infections[53,54], and stress can also increase the risk for cancer initiation by promoting the prevalence and outbreak of oncogenic viruses. Following in vitro infection of various human cell lines, major oncogenic human viruses were shown to be reactivated by either glucocorticoids or catecholamines, including human papillomaviruses (HPVs), Epstein–Barr virus, Kaposi sarcoma-associated herpesvirus and hepatitis B and C viruses[55]. Additionally, stress hormones were shown to stimulate oncogene expression in human cells infected with oncogenic viruses, as well as to suppress expression of type I interferons (IFNα and IFNβ) in leukocytes, impairing antiviral immunity[55–57]. In humans, academic examination stress in cadets, and/or activation of the SNS or HPA axis, was associated with reactivation of latent oncogenic viruses[58,59]; higher levels of perceived stress were associated with impaired HPV-specific T cell responses in women with cervical dysplasia[60]; and loss of a child predicted increased risk for HPV-associated cancers in a cohort of more than four million parents in Sweden[61].

Tumorigenesis. Several in vivo animal studies assessed the effects of stress on actual tumorigenesis, rather than on interim indices, such as DNA damage or reactivation of oncogenic viruses. Repeated restraint stress[48,62], social isolation[63] and cold ambient temperature[64] promoted carcinogen-induced tumorigenesis. In transgenic models of spontaneous cancer, repeated restraint stress increased pancreatic tumorigenesis through β_2-AR signalling[65], whereas sympathetic denervation decreased tumorigenesis in a prostate cancer model[66]. However, in such models that are based on accelerated induction of cancer, it is hard to distinguish between effects of stress on tumour initiation and its effect on tumour progression, as the time course of stress largely overlaps with both initiation and progression periods[48,65,67,68]. Thus, stress can potentially exacerbate the effects of carcinogenic exposure, yet it is unclear whether stress is a significant factor in tumour initiation in the absence of known exposure to carcinogens.

Cancer progression

Direct effects on tumour cells. Stress hormones, secreted systemically or released locally in the tumour microenvironment from sympathetic nerve endings, immune cells[69,70] or tumour cells[71–73], can directly affect tumour cells, promoting their malignant characteristics. Specifically, noradrenaline and adrenaline were shown in vitro to promote tumour cell proliferation[74–76], survival (anti-apoptosis)[74,75,77], migration[74,78,79], invasion[74,78–81], epithelial–mesenchymal transition (EMT)[42,78,82,83] and production of prostaglandins[76,79] and matrix metalloproteinases (MMPs)[76,80,81] (FIG. 2). Accordingly, behavioural or physiological stressors (for example, social

Prostaglandin receptors
A class of cell surface G-protein-coupled receptors that bind different prostaglandins and are expressed on various cell types, including immune cells; for example, prostaglandin E_2 binds to the prostaglandin E_2 receptor 1–4 subtypes.

T helper 1 cell
(T_H1 cell). A $CD4^+$ T cell that participates in the pro-inflammatory type 1 or cellular immune response against intracellular pathogens and malignant cells. Naive T cells are differentiated into the type 1 phenotype following exposure to interleukin-12 (IL-12), and are known for the secretion of interferon-γ (IFNγ), which is also involved in the effector functions of cytotoxic T cells.

confrontation, restraint and surgery) in animal models were shown to increase tumour growth and metastasis through activation of tumour β-AR, as indicated by their specific pharmacological[41,74,80,84–86] or molecular[87,88] blockade, or by genetic knockout[84].

Recent studies have indicated the contribution of tumour innervation to tumour progression[89]. Tumours can secrete neuronal growth factors, increasing sympathetic tumour innervation. This creates a feedforward loop that promotes cancer progression under stress-induced sympathetic activation, as a result of higher tumoural noradrenaline levels[65]. Correspondingly, numerous human cancers were found to express β-AR[65,74,75,78,79,81,83,90], and their higher expression[74,75,78,79,83] or higher tumour noradrenaline[91] and/or plasma adrenaline[82] levels were correlated with larger tumour size, advanced stage, lymph node metastasis and/or reduced survival in several cancer types. Interestingly, low social support in patients with ovarian cancer predicted higher tumour levels of noradrenaline[91].

Behavioural stress can also promote tumour growth through glucocorticoid secretion[48,92], and synthetic glucocorticoid receptor (GR) agonists (for example, dexamethasone) promoted metastasis and reduced survival in xenograft and syngeneic breast cancer models[93]. In patients with breast cancer, higher tumour expression levels of GR and GR-regulated kinases predicted poorer survival[93,94].

Box 2 | **Physical exercise, stress and cancer**

Physical exercise exerts a challenge to whole-body homeostasis, promoting extensive adaptations of cells, tissues and organs[278]. Moderate physical exercise is known to improve cardiometabolic indices, to increase cognitive performance and to improve numerous health conditions and support their treatment, including cancer[279]. Physical exercise increases the levels of stress hormones (for example, adrenaline, endorphins and cortisol) for the duration of the exercise, blunts hormone responses to stress[280,281] and modulates inflammatory status and cytokine levels during exercise (for example, increased interleukin-6 (IL-6), IL-10 and IL1Rα, but not TNF and IL-1β)[282]. In the context of cancer, physical exercise was shown to have beneficial impact on quality of life, fatigue, anxiety, depressive symptomatology and psychological distress[283–287]. The effect of exercise on inflammation is complex. In the general population, physical exercise is generally associated with reduced inflammation[282], whereas in patients with cancer this association is more limited[288]. Importantly, prospective correlational studies indicated that physically active patients have significantly lower mortality rates than non-active patients[289,290]. Interestingly, whereas stress responses exert numerous pro-tumorigenic effects (as reviewed herein), physical exercise-induced stress factors exhibit antitumorigenic properties[291]. For example, in preclinical studies, exercise-conditioned serum, derived from healthy humans and patients with cancer, had growth-inhibitory effects on breast cancer cell lines in vitro and in vivo[292]. Moreover, mice subjected to voluntary physical exercise had attenuated tumour growth and enhanced antitumour activity via β-adrenergic signalling[292–294]. Hypothesized explanations for the apparent contradictory beneficial and deleterious effects of β-adrenergic signalling include the rapid and transient increase and decrease of adrenergic responses to exercise; inhibited stress responses following physical exercise; and the rapid exercise-related mobilization of cytotoxic immunocytes (for example, $CD8^+$ T cells, natural killer cells)[295] to the circulation, as opposed to stressors and their aftermath that induce immunosuppression. Additionally, physical exercise was shown to exert the production of dihydroxyphenylalanine (DOPA) and dopamine (as part of the catecholamine response)[296] that were reported to antagonize tumour progression[10], whereas these responses are generally not induced by stressors. Overall, these results warrant further studying of the mechanisms by which physical exercise improves psychological indices, physical adaptation to stress and malignant conditions, and devising suitable exercise regimens for patients with cancer to potentially improve short-term and long-term outcomes.

Angiogenesis and lymphangiogenesis. In vitro findings indicated that noradrenaline and adrenaline increase tumour cells' expression and secretion of several angiogenic factors, including vascular endothelial growth factor (VEGF), interleukin-6 (IL-6) and IL-8 (REFS[81,95–97]), and that noradrenaline-mediated angiogenesis is reinforced following direct contact between tumour cells and endothelial cells[98]. In stressed nude mice orthotopically implanted with human ovarian carcinoma cells, β_2-AR–cyclic AMP (cAMP)–protein kinase A (PKA) signalling increased tumour expression of VEGF, and tumour vascularization and growth[87]. Similar findings were confirmed in pancreatic cancer[99], colorectal cancer (CRC)[100] and breast cancer[41,101] models. Stress-induced β-AR signalling also inhibited the anti-angiogenic factor thrombospondin 1 (TSP1) in prostate cancer xenografts through epigenetic modulation[102]. In patients with ovarian carcinoma, lower social well-being and elevated distress or depressive symptoms correlated with higher plasma and tumour VEGF levels[103,104], and higher ascites and plasma IL-6 levels[105,106].

Tumour lymphatic vessel density and lymphangiogenic growth factors are associated with metastases and with reduced survival in patients with cancer[107]. Chronic restraint stress in mice, through β-AR signalling, increased expression of the lymphangiogenic factor VEGFC in tumour and stromal cells, and increased expression of cyclooxygenase 2 (COX2; also known as PTGS2) in tumour-associated macrophages (TAMs). These changes led to elevated lymphatic vessel density and increased metastasis[108]. In patients with cancer, acute blockade of SNS activity reduced lymph flow in patients with cervical carcinoma[108], and breast tumours in socially isolated women exhibited increased density of lymphatic vessels[109].

Immunomodulation and inflammation. Stress has been shown to promote both inflammation and immune evasion[8]. Most immune cells express β-ARs[110], prostaglandin receptors[111] and GRs[44], and the effects of stress on their activity and distribution have been extensively studied in animal models and in patients with cancer[7–9,110].

In murine models, natural killer cell activity against tumour cells was suppressed by stress-induced β-adrenergic signalling or β-adrenergic agonists[33,40,112,113], and a stress-induced increase in lung metastases was shown to be mediated by suppression of natural killer cells[114]. In patients with ovarian cancer, lower social support and higher distress correlated with lower natural killer cytotoxicity[115]. Stress was also shown to induce a shift from T helper 1 cell (T_H1 cell)-type to T helper 2 cell (T_H2 cell)-type cytokine production, to increase tumour growth in mouse models of CRC[116] and squamous cell carcinoma[62], as well as to increase tumour growth through β-AR-mediated suppression of $CD8^+$ T cells in mammary and melanoma mouse models[84]. Correspondingly, in patients with ovarian carcinoma, depressed and anxious mood correlated with a reduced T_H1 cell/T_H2 cell-type cytokine ratio[117]. Additionally, in mouse models, a stress-induced β-adrenergic response promoted tumour growth by upregulation of suppressive

Box 3 | **Critical time frames during cancer treatment**

Along the course of cancer treatment, there are recognized critical phases where susceptibility to the impacts of stress may be heightened. These include the surgical removal of the primary tumour, and neoadjuvant and adjuvant therapies. Specifically, during the short perioperative period (days before and after surgery), surgical excision of the malignant mass may increase shedding of tumour cells to the circulation[297,298], terminate primary tumour-related secretion of anti-angiogenic factors[299,300] and induce the release of growth factors[301,302]. These processes cumulatively or synergistically increase the risk of metastatic disease[198,199]. Moreover, stress and inflammatory responses are elevated as a result of psychological distress, tissue damage, hypothermia, blood transfusions, pain and specific analgesic/anaesthetic approaches[198,199]. These neuroendocrine responses, especially catecholamine and prostaglandin signalling, suppress antitumour immunity[9,303], and directly facilitate progression of residual disease, as elaborated in the main text. Most importantly, as the short perioperative period holds a delicate balance between pro-metastatic and anti-metastatic processes, stress responses during this time can tilt the balance towards the pro-metastatic direction, creating a 'snowball effect' that impacts long-term cancer outcomes[186]. Indeed, several clinical perioperative events (for example, anastomosis leak and/or secondary surgery) or specific medical routines (for example, use of the sedative dexmedetomidine) were associated with worse long-term cancer outcomes[304], and animal studies provided causative evidence that such events can increase the deleterious impacts of stress on cancer metastasis[305]. Additionally, a recent study in rodents reported that the effects of pre-surgical behavioural stress exacerbate the deleterious effects of surgery on lung metastasis[133].

The peri-adjuvant time frame also constitutes a critical period of cancer progression. Adjuvant therapies and their side effects are accompanied by psychological distress[306], induce inflammatory responses[307] and can promote tumorigenic and metastatic processes[308]. For example, the chemotherapies cisplatin and paclitaxel activate the pro-inflammatory nuclear factor-κB (NF-κB) pathway, inducing the expression of various pro-tumorigenic and pro-metastatic factors such as interleukin-6 (IL-6) and IL-8, and promoting angiogenesis and tumour cell proliferation, survival and epithelial–mesenchymal transition (EMT)[307]. Adjuvant therapies can lead to selection of drug-resistant tumour clones, and to host-derived responses that promote cancer recurrence[308]. Thus, as adjuvant therapies have both pro-tumour and antitumour effects, and as stress during cancer therapy can impair its efficacy (as discussed in the main text), stress may have greater impact during the peri-adjuvant time frame.

As the short perioperative and the peri-adjuvant time frames are characterized by excessive stress and inflammatory responses and by accelerated tumour progression, they could be exploited therapeutically for anti-metastatic approaches, and specifically interventions that reduce stress and inflammation.

immune cells such as myeloid-derived suppressor cells (MDSCs) and regulatory T cells[62,84,100,118], whereas in patients with breast cancer, higher levels of stress correlated with reduced numbers of circulating MDSCs[119].

With respect to inflammation, stress-induced β-adrenergic signalling in preclinical studies was shown to promote COX2 expression and prostaglandin secretion in both tumour cells and TAMs[41,79,108], to stimulate secretion of pro-inflammatory cytokines (for example, IL-6)[95,97] and to increase tumour recruitment of macrophages and their M2 polarization[41,90,120,121]. Correspondingly, in patients with cancer, social isolation correlated with upregulation of M2 polarization in breast tumours[109], higher levels of depression were associated with higher levels of prostaglandins in ovarian tumours[79], and tumour expression levels of genes encoding β_2-AR and prostaglandins predicted reduced survival[79].

Metastasis. Metastases are promoted by many of the aforementioned mechanisms, as well as by additional stress-induced processes. For example, in mice, stress-induced β-AR activation promoted migration of circulating tumour cells to the bones, through increased expression of receptor activator of nuclear factor-κB ligand (RANKL) by bone marrow stem cells (BMSCs)[122], or to the lungs by CC-chemokine ligand 2 (CCL2)–CC-chemokine receptor 2 (CCR2)-mediated attraction of macrophages[85], consequently forming pre-metastatic niches and increasing organ-specific metastasis. Additionally, stress increased tumour cell EMT[42,82,83], tumour and stromal cell secretion of MMPs[41,74,80,99] and tumour cell resistance to anoikis[77], promoting malignant cell detachment, invasiveness and survival in the circulation[123]. In patients with breast and ovarian cancer, perceived stress, depressive symptoms or social isolation predicted higher tumour expression of EMT-related genes[109,124], and higher MMP9 levels in tumour cells and/or TAMs[104]. Importantly, β-AR blockade reduced stress-induced metastasis in many murine models, of both experimental and spontaneous metastases[33,41,74,85,108,122,125]. Correspondingly, in patients with gastric and lung cancer, tumour β-AR expression levels correlated with lymph node metastasis[74,126], and incidental use of β-blockers was associated with decreased metastasis or recurrence in patients with breast and ovarian cancer[108,127,128] and with improved survival in melanoma and breast cancer[129,130], but not in lung and ovarian cancer[131,132]. These diverse outcomes are expected given differences between the indices studied (for example, metastasis versus survival), diverse cancer types and the uncontrolled settings of correlational studies, and call for randomized controlled trials (RCTs) to test the effects of β-blockers on long-term cancer outcomes.

Acute and chronic stressors. Although most animal studies report that stress, whether acute or chronic, promotes primary tumour growth and metastasis, a few studies report that stress can decrease primary tumour growth. For example, several paradigms of acute stress were reported to increase primary tumour growth and metastasis in rodents, including restraint stress[92], 16-h tilt–light stress[133], 30–60 min of intermittent swim stress[39,40,113], laparotomy[100,114,133] or 7 h of social confrontation stress[134], whereas other studies showed that acute restraint stress[135] and foot shock stress[136] can inhibit primary tumour growth. Heterogeneity of the acute stressors, tumour models, animal species and phase of tumour progression during stress exposure may underlie this apparent inconsistency (as discussed above). With respect to chronic stress, and examining a more standardized setting of chronic social isolation in breast cancer models, stress exposure increased[67,137], decreased[68,138] or had transient[43] effects on primary tumour growth. Although there are physiological differences between acute and chronic stress (BOX 1), comparison between acute and chronic restraint stress showed that whereas the stress duration had differential effects on spleen T lymphocytes, neither acute nor chronic stress affected the growth of primary mammary tumours but both increased blood vessel density in metastatic foci[101]. Additionally, chronic social isolation, but not chronic restraint, reduced survival of mammary tumour-bearing mice[101]. As elaborated in BOX 1, there is ambiguity regarding the definitions of acute and chronic stressors, and some adaptive characteristics of

T helper 2 cell
(T_H2 cell). A $CD4^+$ T cell that participates in type 2 or humoral immune response against extracellular pathogens (for example, helminths) and allergens. Naive T cells are differentiated into a type 2 phenotype following exposure to interleukin-4 (IL-4), and are known for the secretion of IL-4, IL-13 and IL-5, and promotion of the production of antibodies.

β-Blockers
A class of drugs with antagonistic activity towards β-adrenergic receptors (β-ARs). The drugs vary in specificity to the different β-ARs (β_1-AR, β_2-AR and β_3-AR) and are classified as selective or non-selective to a certain receptor subtype.

Tilt–light stress
An experimental stress paradigm in which the home cage of rodents is placed in a lit room in a 45° tilted position, starting before the onset of the animals' dark period, resulting in reduced available floor space and disruption of the dark–light cycle.

Swim stress
An experimental stress paradigm where a weight is attached to the tail of rodents (usually rats, up to 2.5% of total body weight), which are then placed in a room temperature water tank for few minutes, followed by a rest period. This swim–rest cycle is usually repeated several times.

acute stress responses in the natural setting may promote cancer progression. Importantly, no generalization can be drawn regarding stress chronicity and cancer progression, and other aspects of stress–cancer interactions may be more critical. Overall, the majority of animal studies report that stress promotes primary tumour progression, rather than inhibits it. The impact of stress on metastasis seems even more consistent, with the great majority of studies reporting increased pro-metastatic processes, and few reporting no impact.

In summary, the effects of stress, acute or chronic, on tumour progression and metastasis are robust; are mediated by β-adrenergic signalling; are mediated to a lesser degree by HPA axis signalling[114]; and occur through affecting tumour cells, and their microenvironment, including immune and stromal cells (FIG. 2; TABLE 1). Notably, β-AR signalling that promotes tumour progression corresponds with natural adrenergic effects on healthy/non-malignant tissue, including adrenergic effects on EMT[139,140], inflammation[141–143] and angiogenesis[144,145] (not in the context of cancer). Last, whereas rodent models and in vitro cell culture provide causal evidence for specific links between stress responses and tumour progression, findings from studies in patients are mostly correlative, with the exception of a few intervention studies reviewed below.

Epidemiological studies

Stress and cancer incidence

A comprehensive meta-analysis of 142 prospective studies published in 2008 (REF.[146]) (average sample size of 87,000 people per study) indicated that psychosocial stress predicts a 6% increase in cancer incidence (hazard ratio = 1.06; 95% CI 1.02–1.11, $P = 0.005$). Of note, depression was a major factor in this effect, rather than stressful life events. However, the meta-analysis identified a significant publication bias, suffered from marked heterogeneity in the outcomes of the included studies and was criticized for meta-analytic methodological flaws[147]. Moreover, 76% of the studies reported a

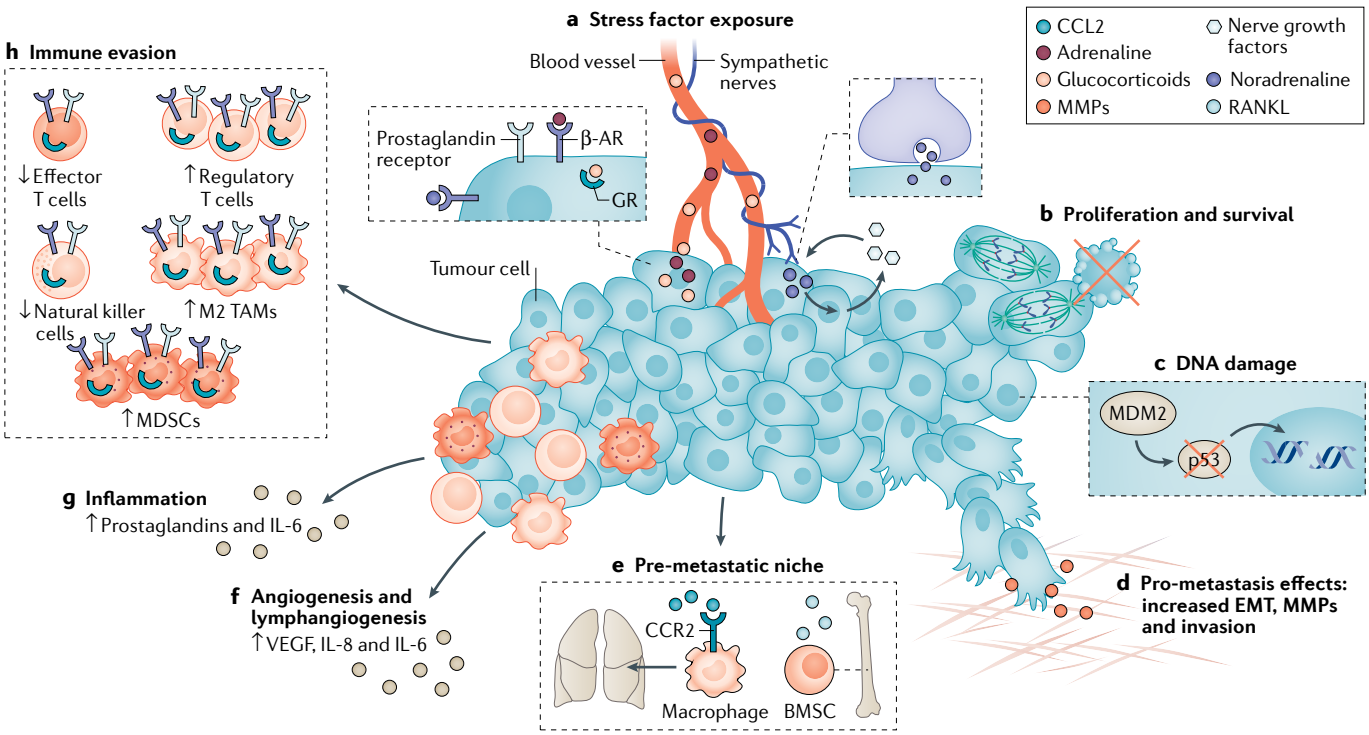

Fig. 2 | **Effects of stress on the tumour and its microenvironment.** Malignant tissue is exposed to systemic stress factors, including adrenaline, noradrenaline and glucocorticoids (for example, cortisol in humans), and to locally released noradrenaline through sympathetic tumour innervation (part **a**). Tumours can also release nerve growth factors that increase their sympathetic innervation and noradrenaline exposure, creating a feedforward loop. Through membrane-bound β-adrenergic receptors (β-ARs), which bind adrenaline and noradrenaline, and intracellular glucocorticoid receptors (GRs), all of which are expressed by tumour, immune and stromal cells, stress factors promote most hallmarks of cancer. Tumour cell proliferation and resistance to cell death are increased (part **b**). In addition, activation of β-ARs and GRs also induces activation of the E3-ubiquitin ligase MDM2 and consequent degradation of p53, which leads to impaired genome maintenance and accumulation of DNA damage (part **c**). Stress factors promote invasion and metastasis by inducing tumour epithelial–mesenchymal transition (EMT) and the release of matrix metalloproteinases (MMPs) (part **d**). Furthermore, activation of β-ARs promotes the formation of organ-specific pre-metastatic niches through processes such as CC-chemokine ligand 2 (CCL2)–CC-chemokine receptor 2 (CCR2)-mediated attraction of macrophages to the lung and receptor activator of nuclear factor-κB ligand (RANKL) secretion by bone marrow stem cells (BMSCs), which attract circulating tumour cells (part **e**). Stress factors promote the release of various pro-angiogenic (part **f**) and inflammatory (part **g**) factors, such as vascular endothelial growth factor (VEGF), interleukin-8 (IL-8), IL-6 and prostaglandins, from tumour and stromal cells, all of which promote tumour progression. Stress-induced immune suppression facilitates tumour immune evasion by upregulation of myeloid-derived suppressor cells (MDSCs), regulatory T cells and M2 tumour-associated macrophage (TAM) polarization, and through downregulation of effector T cell and natural killer cell activity (part **h**). Activation of prostaglandin receptors and activation of β-ARs each induces the same intracellular downstream processes (not shown), including the cyclic AMP (cAMP)–protein kinase A (PKA) pathway, suggesting that simultaneous blockade of β-adrenergic and prostanoid signalling might be important to improve cancer treatment.

Table 1 | **Biological effects of stress on cancer progression: preclinical studies and related observations in patients with cancer**

Cancer	Model	Stressor	Effect (location)	Mediator	Refs
Angiogenesis					
Melanoma, breast, ovarian	Human cells in vitro	Adrenaline or noradrenaline	↑ Angiogenesis; ↑ VEGF;↑ IL-6; ↑ IL-8	Tumour–endothelial cell contact (β_2-AR–Jagged 1–Notch); tumour cell β_1-AR and/or β_2-AR–cAMP–PKA signalling	81,95–98
Ovarian[a], pancreatic[a], colorectal[b], mammary[b], prostate[a]	Mice; human or mouse cells in vitro	Social isolation, chronic restraint, audio of screaming rats, laparotomy or orisoproterenol	↑ Tumour vascularization; ↑ tumour VEGF; ↑ tumour growth; ↓ TSP1	β_2-AR–cAMP–PKA signalling; ↑HIF1α; ↓CXCL4; macrophage recruitment; β-AR–CREB–HDAC2 pathway	41,87, 99–102
Ovarian	Patients with cancer[c]	Low social support[d] or helplessness	↑ Plasma VEGF; ↑ tumour VEGF	NA	103,104
Ovarian	Patients with cancer[c]	Low social attachment[d] or vegetative depression[d]	↑ IL-6 (plasma, ascites); ↑ nocturnal cortisol (saliva)	NA	105,106, 220
Lymphatic modulation					
Breast[a,b]	Mice	Chronic restraint	↑ Tumour VEGFC; ↑ tumour LVD; ↑ lymphatic dilation, flow; ↑ lymph node metastasis	β-AR; ↑ COX2; macrophage recruitment	108
Breast[c], cervical	Patients with cancer	Social isolation[d] or SNS activity	↑ Tumour LVD; ↑ lymphatic flow	NA	108,109
Inflammation and immunity					
Mammary[b], leukaemia[b]	Rats; blood samples from stressed rats studied ex vivo	Laparotomy, swim stress, wet cage, metaproterenol or adrenaline	↓ NKCC	β_1-AR and/or β_2-AR	33,40, 112–114
Colorectal[b], squamous cell carcinoma [b], mammary[b] or melanoma[b]	Mice; mouse cells in vitro	Chronic restraint, 22 °C housing temperature, audio of screaming mice or laparotomy	↓ T_H1 cell/T_H2 cell-type cytokine ratio (serum); ↓ effector $CD8^+$ and $CD4^+$ TILs; ↑ tumour growth; ↑ MDSCs (tumour, spleen); ↑ regulatory T cells (tumour, blood)	↓CXCL4; β-AR; β_2-AR–STAT3 signalling	62,84,100, 116,118
Ovarian or breast	Patients with cancer[c]	Low social support[d], high distress[d], depressed/ anxious mood[d] or psychological stress	↓ NKCC (tumour, blood); ↓ T_H1 cell/T_H2 cell-type cytokine ratio (blood, ascites, tumour); ↓ MDSCs (blood)	NA	115,117,119
Breast[a,b] or ovarian [a]	Mice; human or mouse cells in vitro	Chronic restraint or social isolation	↑ Macrophage recruitment; ↑ prostaglandin (tumour cells, TAMs); ↑ TAM M2 polarization	β-AR; β_2-AR/NF-κB–prostaglandin E_2 axis; β-AR–cAMP–PKA– MCP1 production	41,79,90, 108,120
Ovarian or breast	Patients with cancer[c]	Psychological stress, depression or social isolation[d]	↑ Plasma IL-1Rα; ↑ tumour prostaglandin; ↑ M2 polarization of TAMs	NA	79,109,119
Metastasis					
Breast[a,b], gastric[a] or pancreatic[a]	Mice; human or mouse cells in vitro	Chronic restraint, alternating stressors, or audio of screaming rats	↑ Pre-metastatic niche; ↑ EMT; ↑ MMPs (tumour, stroma)	β-AR–RANKL; β-AR–CCL2/CCR2 axis; miR-337-3p–STAT3	41,42,74, 80,82,85, 99,122
Breast[a,b] or gastric[a]	Mice or rats	Chronic restraint, laparotomy, alternating stressors, wet cage or swim stress	↑ Spontaneous and experimental metastasis	β_1-AR and/or β_2-AR	33,40,41, 74,85,108, 114,122,125
Ovarian or breast	Patients with cancer[c]	Perceived stress[d], social isolation[d] or depression[d]	↑ Tumour EMT genes; ↑ TAM MMP9	NA	104,109,124

All findings are causal, except those indicated as correlational findings in the 'Model' or 'Cancer' column. ↑, increase; ↓, decrease; β-AR, β-adrenergic receptor; cAMP, cyclic AMP; CCL2, CC-chemokine ligand 2; CCR2, CC-chemokine receptor 2; COX2, cyclooxygenase 2; EMT, epithelial–mesenchymal transition; HDAC2, histone deacetylase 2; IL-6, interleukin-6; LVD, lymphatic vessel density; MDSC, myeloid-derived suppressor cell; MMP, matrix metalloproteinase; NA, not applicable; NKCC, natural killer cell cytotoxicity; NF-κB, nuclear factor-κB; PKA, protein kinase A; RANKL, receptor activator of nuclear factor-κB ligand; SNS, sympathetic nervous system; TAM, tumour-associated macrophage; T_H1 cell, T helper 1 cell; T_H2 cell, T helper 2 cell; TIL, tumour-infiltrating lymphocyte; TSP1, thrombospondin 1; VEGF, vascular endothelial growth factor. [a]Xenograft. [b]Syngeneic. [c]Correlational findings. [d]Adjusted for disease stage.

null effect, whereas 18% indicated harmful effects and 6% indicated protective effects.

More recent studies linked various specific stressors, including a cold climate[148], bereavement[61], war[149] and depression[150], to higher incidence of various cancer types, yet other studies reported null effects[151–153]. Focusing on work stress as a risk factor, two meta-analyses yielded inconsistent conclusions: the first[154] reported null effects of prospective studies, whereas the second[155] reported elevated relative risk (of 1.24 and 1.36 in lung cancer

and CRC, respectively), but the latter also included case–control studies that are susceptible to retrospective recall and interpretation bias. Last, it is important to note that in humans, malignant transformation is a prolonged process and subclinical cancer dormancy is highly prevalent[30]. Thus, cancer incidence may be elevated not only by initiation of the disease but also by escape from dormancy or faster progression of cancer to clinical manifestation. Indeed, animal studies report that stress and stress factors can induce escape from dormancy in tumour cells[156–158].

Stress and cancer progression

Effects of stress on cancer progression are commonly studied by assessing survival rates in patients diagnosed with cancer. The overall hazard ratio indicated by 157 prospective studies included in the 2008 meta-analysis discussed above[146] was 1.03 (95% CI 1.02–1.04, $P<0.001$), with more than 73% of studies reporting null findings. This small effect should be interpreted with caution. First, stress (for example, life events) was commonly assessed irrespective of its timing relative to cancer detection, and the specific impact of stress while having cancer, including the critical perioperative period, was not assessed. Second, most patients with cancer experience some levels of cancer-related distress[159,160], which may suffice to generate a similar effect on cancer progression, irrespective of whether patients were categorized with low versus high stress levels. This could mask relations between stress levels and cancer progression in such circumstances, but nevertheless could enable marked beneficial effects of stress-reducing interventions. Third, although comprehensive, this meta-analysis is 13 years old, and has narrowed down analyses to either distinct cancer types or defined stressors. More recent meta-analyses have focused on more specific conditions, and have reported larger effect sizes. Specifically, depression in patients with breast cancer predicted 29% elevated risk for cancer-specific mortality[161], and low levels of perceived social support, a smaller social network, being unmarried or being depressed predicted a 12–25% elevated relative risk for cancer mortality in various cancer types[162,163].

Indeed, recent studies confirmed that the effects of stress on survival are stressor-specific and cancer-specific. For example, depression that followed cancer diagnosis predicted decreased survival in breast[161] and renal[164] cancers, but not in ovarian cancer[165]. Low social support and low social attachment predicted decreased survival in patients with ovarian cancer[165], breast cancer[166] or CRC[167], whereas work stress had no effect[152]. Importantly, previous life history of stress and adversities may interact with post-diagnosis stress[168,169], as early adverse experiences can shape maladaptive responses to stressors[27].

Overall, given the small and inconsistent effects reported by epidemiological studies, and the heterogeneous methodological approaches, populations studied and type of stressors, it remains uncertain whether stress can increase cancer incidence, and to what extent it facilitates cancer progression. Potentially, stress has a larger impact in certain conditions or populations. Clearly, epidemiological studies face significant obstacles. The subjective perception of stress in patients with cancer is influenced by the physical and mental burden of the disease, and therefore studies that retrospectively assess pre-diagnostic or post-diagnostic stress by subjective reports are biased[147]. On the other hand, objective exposure to adverse life events (for example, based on national registries of divorces or deaths) does not include the individual subjective experience. As described below, the use of stress-reducing interventions in RCTs can circumvent many of these obstacles.

Stress management in patients with cancer

The most methodologically sound approach to test in humans whether stress affects cancer progression would be RCTs, where the intervention is a verified stress-management approach and the outcomes include psychological indices, interim biomarkers and, most importantly, long-term cancer outcomes. Such RCTs are not practical for studying cancer incidence but are feasible for studying cancer progression and mortality. Such psychological and pharmacological RCTs have been conducted during the last four decades, as discussed below.

Psychological RCTs: long-term outcomes

Recent meta-analyses[170–173] have cumulatively identified 22 RCTs that employed psychosocial interventions as being methodologically stringent, using Cochrane or other criteria. Most interventions were initiated at least a month postoperatively (16/22 RCTs) and/or were conducted in patients with metastatic disease (12/22 RCTs); and most studies employed group interventions (14/22 RCTs), rather than individual (7/22 RCTs) approaches. Importantly, most interventions did yield improvement in psychological indices (TABLE 2), and a few improved physiological biomarkers (for example, natural killer cell activity)[174–176] (BOX 4). Based on these meta-analyses (each considering 11–15 trials)[170–173] and our own assessment of all 22 studies (TABLE 2), there is no clear evidence for improvements in long-term cancer outcomes[171,172], but the results are nevertheless informative. Specifically, there seems to be an agreement that some interventions can delay disease progression during the first post-intervention years, but less so or not at all beyond this initial period[171,172]. Psychosocial interventions may have temporary effects either because their impact on tumour biology is short-lasting or because patients' adherence to the psychological intervention reduces along the follow-up period. It is suggested that some patients, more than others, may benefit from psychological interventions, specifically patients who are older, unmarried and psychologically vulnerable or stressed[8,170], as well as patients in earlier disease stages (for example, early-stage melanoma)[177]. It should be noted that some of these studies have been criticized for having methodological flaws[178–180] (but also see the response to criticism)[181], including not having the statistical power to study cancer mortality, employing only 30–150 patients per group, which may lead to exaggerated effect sizes. Some interventions have been suggested to act through improving patients' treatment

Laparotomy
An experimental stress paradigm in which a midline abdominal incision is performed under anaesthesia, and often the small intestine is externalized and left hydrated in a soaked gauze pad for 30 min. The intestine is then internalized and the abdomen is sutured.

Social confrontation stress
An experimental stress paradigm where an intruder rodent (a non-cage-mate animal) is introduced into a home cage populated with several stable cage-mates. The intruder is usually attacked by the residents cage-mates and/or displays submissive behaviour.

Foot shock stress
An experimental stress paradigm that is executed in an apparatus containing an electrified grid floor, in which the animal is exposed to electric shocks of varying intensity and duration. The paradigm can be acute or chronic, and is also used for fear-conditioning.

Hazard ratio
The ratio of the probability of events in a treatment group to the probability of events in a control group.

Publication bias
The tendency to publish a study based on its results (positive rather than negative findings or significant rather than non-significant findings). Existence of this bias can be statistically assessed in meta-analyses by Egger's linear regression test.

Cochrane
A non-profit organization (maintaining no conflict of interests), which, among other activities, publishes methodologies and guidelines to produce high-quality systematic reviews and meta-analyses.

Table 2 | **Psychosocial stress-reducing interventions in RCTs and long-term cancer outcomes**

Study	Patient numbers	Intervention (setting; timing; duration (weeks)[a]; treatment type)	Psychological benefit	Survival effect	Survival effect size[b]
Early-stage breast cancer					
Burton et al. (1995)[187]	*n* = 200, 4 groups of 50 each[c]	Individual; preoperative; 1; one interview + 30-min psychotherapeutic intervention	Yes	No	First-year recurrence rates: T = 7–10%; C = 14%; simple contrast between control and intervention groups; NS
Kissane et al. (2004)[257]	*n* = 303, T = 154	Group; post surgery; 20; CBT-supportive therapy sessions + 3 relaxation sessions	Yes	No	Median survival time (months): T = 81.9, C = 85.5; multivariate Cox analysis, HR = 1.35, NS
Andersen et al. (2008)[258]	*n* = 227, T = 114	Group; post surgery; 16 weekly sessions + 8 monthly sessions; stress management	Yes	Yes	Mortality, 11-year follow-up: T = 24/114, C = 30/113; multivariate Cox analysis, HR = 0.44; *P* = 0.016 Median time to recurrence (months): T = 33.6, C = 26.4; multivariate Cox analysis, HR = 0.55, *P* = 0.034
Boesen et al. (2011)[259]	*n* = 210, T = 105	Group; post surgery; 8; comprehensive psychoeducation + supportive therapy	No	No	Mortality, 4-year follow-up: T = 6/105, C = 3/105; statistical analysis not preformed due to low event number
Stagl et al. (2015)[260]	*n* = 240, T = 120	Group; post surgery; 10; cognitive-based stress management	Yes	Yes[d]	Mortality, 8–15-year follow-up: T = 15/120, C = 15/120; multivariate Cox analysis using four covariates[d], HR = 0.21, *P* = 0.04
Metastatic breast cancer					
Spiegel et al. (1989)[182]	*n* = 86, T = 50	Group; post surgery; 52; supportive-expressive therapy + self-hypnosis	Yes	Yes	Mean survival time (months): T = 36.6, C = 18.9; log-rank test, *P* < 0.0001
Cunningham et al. (1998)[261]	*n* = 66, T = 30	Group; post surgery; 35; supportive + CBT	No	No	Median survival time (months): T = 28.8, C = 23.6; log-rank test, *P* = 0.35
Edelman et al. (1999)[262]	*n* = 124, T = 62	Group; post surgery; 8 weekly sessions + 3 sessions once a month; CBT	Yes[e]	No	Median survival time (months): T = 11.64, C = 12.84; log-rank test, NS
Goodwin et al. (2001)[184]	*n* = 225, T = 158	Group; replication study, similar[f] to Spiegel et al. (1989)[182]	Yes[g]	No	Median survival time (months): T = 17.9, C = 17.6; Cox univariate analysis, HR = 1.06, NS
Kissane et al. (2007)[263]	*n* = 227, T = 147	Group; similar to Spiegel et al. (1989)[182] + 3 relaxation classes	Yes	No	Median Survival time (months): T = 24, C = 18.3; univariate Cox analysis, HR = 0.92, NS
Spiegel et al. (2007)[183]	*n* = 125, T = 64	Group; replication study, same as Spiegel et al. (1989)[182]	Yes	No/yes[h]	Median survival time (months): exploratory subgroup findings (*n* = 25 ER-negative[h]); T = 29.8, C = 9.3; Multivariate Cox analysis, *P* = 0.002
Andersen et al. (2010)[264]	*n* = 62, T = 29 (a subgroup of patients from Andersen et al. (2008)[258])[i]	Group; same as Andersen et al. (2008)[258]	Yes	Yes	Mortality after recurrence: T = 19/29, C = 25/33; median survival after recurrence (months): T = 38.4, C = 20.4; multivariate Cox analysis, HR = 0.41, *P* = 0.014
Melanoma					
Fawzy and Fawzy (2003)[177]	*n* = 68, T = 34	Group; post surgery; 6; health education + stress management + coping skills + psychological support	Yes	No	Mortality, 5–6-year follow-up: T = 3/34, C = 10/34; log-rank test, *P* = 0.03 Mortality, 10-year follow-up: T = 9/34, C = 11/34; log-rank test, NS
Boesen et al. (2007)[185]	*n* = 262, T = 131	Group; replication study, similar to Fawzy and Fawzy (2003)[177]	Yes[j]	No	Mortality, 4–6-year follow-up: T = 8/128, C = 8/130; univariate Cox analysis, HR = 0.99, NS
Other cancer types					
Linn et al. (1982)[265] (several cancer types)	*n* = 120, T = 62	Individual; NR; NR; supportive therapy	Yes	No	Mean survival time (months), 1-year follow-up: T = 3.7, C = 4.37; life table method, χ^2 test, NS
Ilnyckyj et al. (1994)[266] (several cancer types)	*n* = 127, four groups:[k] T = 31, 30, 35, C = 31	Group; NR; 24; supportive discussion group sessions	No	No	Mean survival time (months), 10-year follow-up: T = 70.7, C = 82.4; log-rank test, NS

Table 2 (cont.) | **Psychosocial stress-reducing interventions in RCTs and long-term cancer outcomes**

Study	Patient numbers	Intervention (setting; timing; duration (weeks)[a]; treatment type)	Psychological benefit	Survival effect	Survival effect size[b]
Other cancer types (cont.)					
Ratcliffe et al. (1995)[267] (lymphoma)	*n* = 63, T = 36	Individual; post third cycle of chemotherapy; NR; relaxation training with or without hypnosis	Yes	Yes	Mortality, 5-year follow-up: T = 14/36, C = 13/27; multivariate Cox analysis, HR = 0.66, *P* = 0.06
Kuchler et al. (2007)[188] (gastrointestinal cancers)	*n* = 271, T = 136	Individual; pre surgery to discharge from hospital; 2–25 sessions; individually tailored psychological support	Yes	Yes	Survival, 2-year follow-up: T = 69/136, C = 45/135; log-rank test, *P* = 0.002; survival, 10-year follow-up: T = 29/136, C = 13/135; log-rank test, *P* = 0.006
Ross et al. (2009)[268] (colorectal cancer)	*n* = 249, T = 125	Individual; post surgery; 10 meetings over 24 months; home visits by a medical doctor or nurse providing emotional support or information	No	No	Mortality, 6.5–9.5-year follow-up: T = 75/125, C = 73/124; log-rank test, NS
Temel et al. (2010)[269] (metastatic non-small cell lung cancer)	*n* = 151, T = 77	NR; intervention group patients were assigned to early palliative care[l]	Yes	Yes[l]	Median survival time (months): T = 11.6, C = 8.9; log-rank test, *P* = 0.02
Guo et al. (2013)[270] (several cancer types)	*n* = 178, T = 89	Individual; during radiotherapy; 4–6; psychoeducation + CBT + supportive-expressive therapy	Yes	No	% survival, 2-year follow-up: T = 83.1%, C: = 84.3%; log-rank test, NS
Zhang et al. (2013)[189] (oesophageal cancer)	*n* = 60, T = 31	Individual; pre surgery; 3 weeks, sessions every other day; health education, psychological support, stress management, coping strategies and behaviour training	Yes	No	Survival, 4-year follow-up: T = 15/27, C = 18/28; log-rank test, NS

C, control group; CBT, cognitive behavioural therapy; ER, oestrogen receptor; NR, not reported; NS, not significant; RCT, randomized controlled trial; T, treatment group. [a]One weekly session, unless otherwise specified. [b]Log-rank test and univariate Cox analyses address differences between groups that are driven only by group assignment, whereas multivariate Cox analyses incorporate additional factors into the statistical model beyond group assignment. [c]The different groups were: preoperative interview; preoperative interview + 30-min preoperative psychotherapeutic intervention; preoperative interview + chat (attention); and routine hospital care control. [d]Equivalent number of deaths between groups; difference was statistically significant in a Cox multivariate analysis addressing age at diagnosis, disease stage, tumour size, HER2 status and hormonal treatment. [e]Improved psychological measures at the end of the intervention were not sustained at 3 and 6-month follow-up. [f]Relaxation techniques were taught instead of self-hypnosis. [g]In patients with high baseline of distress. [h]Cox proportional hazard analysis showed a significant interaction between ER status and treatment, indicating that ER-negative patients allocated to the intervention survived longer than control patients. [i]Participants in this study were patients who previously participated in Andersen et al. study[258]. [j]Psychological benefits were only evident shortly after the intervention, and enrolled patients exhibited low baseline levels of psychological distress. [k]The different groups were: group meetings professionally guided by a social worker for 6 months; group meetings professionally guided for 3 months + 3 months of unguided meetings; unguided group meetings; and control (no group meetings). [l]Earlier initiation of palliative care, also addressing individual psychosocial needs of the patients.

adherence, patients' health behaviour and quality of the medical treatment (for example, additional surveillance and care) following improved communication with medical personnel[180]. Thus far, no research group has replicated previously reported positive outcomes, although given the objective difficulties of intervention trials and lack of funding, only a few replications have been attempted[177,182–185]. Notably, each of the 22 studies used a different treatment protocol, initiated treatment at different times during cancer progression, provided treatment for a different duration and/or studied a different patient population and cancer type (TABLE 2). These heterogeneities may be the source of inconsistent outcomes, and different results of meta-analyses. At the single study level, 8 of the 22 interventions reported a significant survival advantage of a psychosocial intervention (TABLE 2). Beyond the legitimate debate of the validity of specific studies, eight successful demonstrations could indicate promising outcomes. However, as only eight such demonstrations have been reported, and the results of these eight interventions have not been replicated in published studies, combined with the likelihood of unpublished studies with null effects, this raises questions regarding the effectiveness of these psychosocial interventions in improving cancer survival.

However, we believe that these inconsistent outcomes are expected a priori, given the following considerations. First, as discussed above and in BOX 3, critical time periods, such as the immediate perioperative time frame in patients undergoing surgery, may bear a non-proportional high impact on the fate of metastatic disease, especially in patients harbouring only scattered tumour cells and micrometastases[186]. Psychological interventions have been commonly initiated weeks following surgery, which would miss this critical period (only 3/22 studies in TABLE 2 are perioperative)[187–189]. Such delayed interventions may impact metastases at a more advanced and therapeutically resistant stage, thus confronting a greater challenge in preventing metastatic disease, but still having the ability to delay a metastatic outbreak[171,172,174,177]. Second, many medical procedures, including surgery and chemotherapy, induce stress-related inflammatory responses of local physiological origin, including cellular responses of injured tissue (for example, increased levels of damage-associated molecular patterns and prostaglandins) (BOX 3). Psychosocial interventions alone are unlikely to significantly reduce such local responses, which may mask the potential beneficial effects of psychosocial interventions during medical procedures (BOX 4). Third, in many

Box 4 | **Behavioural stress management and its impact on short-term cancer-related indices**

Multiple psychological, behavioural and physiological interventions have been used to target different aspects of stress in patients with cancer, such as massage, acupuncture, yoga, tai chi, mindfulness and cognitive behavioural stress-reduction interventions (reviewed in REFS[8,10,12]). Such interventions were shown to reduce stress, anxiety and depression, and to improve quality of life[309,310] in patients with cancer (for example, in breast cancer[174] and melanoma[175]). Accordingly, current guidelines for optimal oncological care include screening and addressing psychosocial concerns[311].

Importantly, Antoni and Dhabhar[8] suggested that stress-management interventions can have physiological protective effects against tumour progression through improving protective immunity (for example, immunosurveillance), reducing chronic inflammatory processes and inhibiting immunosuppressive mechanisms (for example, regulatory T cell activity). Indeed, in breast cancer survivors, yoga and tai chi reduced pro-inflammatory processes[312,313], and mindfulness-based stress reduction increased the T helper 1 cell (T_H1)/T helper 2 cell (T_H2) ratio[314], decreased nuclear factor-κB (NF-κB) activity and increased anti-inflammatory signalling and gene expression of type 1 interferon[315]. Similar effects were noted by Antoni, studying the effects of a cognitive behavioural therapy (CBT)-based stress-management intervention in patients with breast cancer following surgery[316]. In addition to significant psychological benefits, the intervention enhanced protective immunity (that is, increased gene expression of type 1 interferon, and serum levels of interferon-γ (IFNγ) and interleukin-2 (IL-2)), and reduced inflammatory processes (for example, reduced expression of the genes encoding IL-1β, IL-6 and TNF, and increased prevalence of glucocorticoid receptor (GR) response elements)[176,317].

Missing from these studies are specific assessments of sympathetic activity and potential reduction of tumour-associated noradrenaline and/or systemic adrenaline levels in treated patients with cancer. Correlative studies in patients with cancer do suggest association of these indices with stressors such as social isolation[91].

Taken together, these changes may predict favourable prognosis for a broad range of patients with cancer, and were suggested by Antoni and Dhabhar[8] to explain the beneficial effects of stress-management interventions on long-term cancer survival[258,260,264]. Such interventions should be initiated as early as possible after cancer diagnosis, and potentially before cancer surgery[197], to improve their impact on both mental health and long-term cancer outcomes.

patients, psychosocial interventions cannot be expected to be effective, either given low stress levels at study entry or given individual characteristics of psychological needs or coping style, not addressed by prevalent standardized group therapies. Last, if one expects the effect size of psychological intervention to be similar to those of chemotherapy or hormonal therapy, hundreds of patients of the same cancer type would need to be included. We assert that, given appropriate funding, all of these obstacles can be overcome, as detailed below, enabling better assessment of the efficacy of stress management for improving cancer survival.

Pharmacological RCTs: cancer biomarkers

Recently, several biomarker RCTs have employed pharmacological interventions to antagonize stress responses in patients with cancer, all employing the non-selective β-blocker propranolol. Among other reasons, this drug was chosen based on its early promising outcomes in animal models of stress or surgery-induced cancer progression[41,74,85,108,125], the involvement of both β_1-AR and β_2-AR in various pro-malignant mechanisms[6,40,65,87] and its high safety profile relative to other adrenergic antagonists, especially regarding potential cardiovascular and tissue healing-related complications[190–192]. Among other positive prognostic outcomes in treated patients, propranolol downregulated the expression of mesenchymal genes, the EMT transcription factors Snail and Slug, and activity levels of the inflammatory transcription factors nuclear factor-κB (NF-κB) and AP-1 in primary breast tumours[193], facilitated a decrease in CA-125 serum levels in ovarian cancer[194] and decreased classical monocyte activation in haematopoietic cell transplant recipients[195]. Propranolol is also currently being tested in combination with immunotherapy in patients with melanoma[196].

It is important to note that adrenergic stress responses and inflammatory responses often intertwine, especially during cancer treatments, as perioperative stress, tissue damage and other medical procedures simultaneously induce both adrenergic and prostanoid responses[197–199] (BOX 3), because each response facilitates the other[197] and because β-adrenergic and prostaglandin receptors activate the same intracellular immunosuppressive and tumour-promoting mechanisms (for example, cAMP–PKA signalling)[197]. Therefore, it may be necessary to simultaneously block β-adrenergic and inflammatory responses to overcome the metastatic promoting effects of stress and/or medical procedures. Indeed, several preclinical studies indicated that simultaneous blockade of β-AR and COX2 activity (using propranolol and etodolac, respectively) was synergistically more effective than each approach alone in preventing immunosuppression and cancer metastasis[33,125,200,201].

These insights have been recently implemented clinically in the context of curative oncological surgeries, in two RCTs that have initiated combined propranolol and etodolac treatment 5 days before surgery, for a total of 11–20 days, in patients with breast cancer[190,202] or CRC[203]. In resected tumours from both RCTs, the treatment decreased EMT and the activity of several pro-metastatic and pro-inflammatory transcription factors (for example, those of the GATA, STAT, EGR and CREB families), and improved the profile of infiltrating leukocytes and tumour proliferation markers (for example, Ki-67)[190,202,203]. In patients with breast cancer, where repeated perioperative blood samples were also analysed, treatment improved systemic inflammatory and immunological markers, including IL-6, C-reactive protein (CRP) and natural killer cell CD11a expression, before and/or after surgery[190,202]. Although not powered to assess survival, the treatment improved 3-year disease-free survival (DFS) in patients with CRC who were protocol compliant[203], and our as yet unpublished data also show improved 5-year DFS.

Overall, these clinical findings indicate that β-adrenergic blockade, with or without COX2 inhibition, can significantly improve numerous biomarkers of cancer progression, and justify larger RCTs to test long-term cancer outcomes of pharmacological stress management, as currently being conducted (NCT03838029 (REF.[204]), NCT03919461 (REF.[205])).

Additional pharmacological approaches were also studied. Specifically, the use of anxiolytic and antidepressant drugs (for example, selective serotonin reuptake inhibitors and serotonin and noradrenaline reuptake inhibitors) in patients with cancer is prevalent and effective in reducing anxiety and depression[10,16]. Nevertheless, epidemiological studies assessing their impact on cancer

CpG class C
(CpG-C). A synthetic oligodeoxynucleotide (ODN) that functions as a Toll-like receptor 9 (TLR9) agonist and induces a physiological host-dependent activation of the immune system.

Glucopyranosyl lipid-A stable emulsion
(GLA-SE). A synthetic agonist of Toll-like receptor 4 (TLR4). For administration, GLA is dissolved in an oil–water stable emulsion that serves as an adjuvant delivery system.

survival yielded inconsistent results[206–208], and no effects on cancer survivorship were noted when causally assessed in an RCT that enrolled patients with advanced cancer of various types[209]. Additionally, the effects of anxiolytic and antidepressant drugs on cancer-related biomarkers is largely unknown, and their impact on such indices in controlled preclinical studies is contradictory[210–212]. Thus, more preclinical and clinical research is needed to assess the impact of such pharmacological approaches on cancer-related biomarkers and long-term outcomes.

Stress and cancer reciprocal relations

In the clinical setting, stress and cancer can promote each other. Patients with cancer often experience peaks of stress on initial diagnosis, on cancer treatment and on cancer recurrence[159,160,198,213,214]. Throughout cancer survivorship, anxiety decreases in some patients but persists in others[169], and patients with cancer show increased risk for anxiety and depressive disorders[214–216]. Consequently, stress responses and affective disorders may accelerate cancer progression through various mechanisms detailed above. Indeed, among patients with breast cancer, higher anxiety, stress, depressive symptoms or elevated diurnal cortisol levels were found to predict suppressed antitumour cell-mediated immunity[217–219]; and perceived stress, social isolation and depression predicted increased tumour cell EMT and levels of MMPs in patients with ovarian and breast cancer (controlling for disease parameters) (TABLE 1).

Simultaneously, the malignant tissue itself may heighten local and systemic stress responses, through tumour-induced increases in sympathetic tumour innervation and noradrenaline release[65], and through local and systemic inflammation that affects the CNS, dysregulates HPA axis activity[220,221] and facilitates depression, sleep disturbances and cancer-related fatigue[222–224]. Together with cancer-related cognitive impairments[225,226], these symptoms may induce or exacerbate stress responses[227], perpetuating a vicious cycle of stress and cancer (FIG. 1).

Importantly, the brain, tumours and the immune system all affect each other bidirectionally, either promoting or hindering tumour progression. For example, artificial activation of the brain reward system in mice was found to decrease a suppressive MDSC phenotype through reduced SNS signalling, resulting in attenuated tumour growth[228]. Crosstalk between stress and cancer is prominent within the perioperative period. In patients with breast, colorectal or ovarian cancer, plasma cortisol levels and/or stress inflammatory indices were elevated even before surgery, presumably due to psychological distress or tumour-derived inflammation[190,203,220], which may sensitize pain responses and worsen psychological stress[197]. Pharmacological blockade of stress and/or inflammatory responses before surgery reduces these indices, as well as tumour EMT and other pro-metastatic molecular indices in the malignant tissue[190,202,203].

Stress impairs cancer treatments

Stress was reported in both preclinical and clinical studies to impair adjuvant and neoadjuvant cancer treatments, including chemotherapy, radiotherapy and immunotherapy, through mediation of glucocorticoids and/or catecholamines. Specifically, in murine models, behavioural and/or surgical stress impaired the capacity of the (clinically studied)[229] immunostimulating agents, CpG class C (CpG-C) and glucopyranosyl lipid-A stable emulsion (GLA-SE), to reduce experimental metastases in mammary cancer and CRC models[133,230,231]; and in vitro, corticosterone suppressed IL-12 secretion from leukocytes following CpG-C or GLA-SE stimulation[133,232]. Social disruption stress or β-AR activation in melanoma and lymphoma mouse models compromised several immunotherapies through impairing $CD8^+$ T cell responses[233,234]; and restraint stress, catecholamines or glucocorticoids impaired the efficacy of chemotherapy in human breast and ovarian cancer cell lines, both in vitro and in xenograft models[52,235].

Additionally, treatment with cytotoxic therapy or sunitinib (an inhibitor of several tyrosine-kinase receptors exerting both anti-angiogenic and direct anti-tumour effects) was impaired by chronic restraint stress or administration of noradrenaline or adrenaline in CRC, prostate cancer and melanoma mouse models[236–238]. In mammary, pancreatic, melanoma, colon and lung cancer models, β-AR signalling, induced by ambient temperature stress, jeopardized cytotoxic therapies (cisplatin and nab-paclitaxel chemotherapies and TRAIL (TNF-related cytokine which induces apoptosis by binding to cell surface death receptors))[239], radiotherapy[240] and PD1-targeted immunotherapy[84]. Activation of β-AR also induced resistance to the HER2 targeted therapy trastuzumab in gastric and breast cancer mouse models[241,242]. Social disruption and acute restraint stress impaired chemotherapy and immunotherapy in lung cancer, CRC and fibrosarcoma mouse models, through glucocorticoid-induced expression of the immunosuppressive transcription factor TSC22D3 in dendritic cells, and consequent impairment of anti-tumour immunity[92]. Administration of the synthetic glucocorticoid dexamethasone induced chemotherapy and hormone-therapy resistance in prostate and breast cancer mouse models[93,243–245], as well as in vitro in breast cancer tumour samples and numerous human carcinoma cell lines[243,246]. Last, in mice, blockade of GR in combination with chemotherapy or hormone therapy potentiated in vivo therapeutic responses[244,245].

Corresponding clinical observations have been reported in patients. In breast cancer, tumour expression of β-AR negatively correlated with response to trastuzumab[242], and in patients with prostate cancer, increased GR expression in bone metastases following treatment with enzalutamide (anti-androgen receptor therapy) predicted poorer therapeutic response[244]. Retrospective observations indicated that incidental β-blocker usage with anti-angiogenic agents, immunotherapy, radiation and/or chemotherapy extended patient DFS and overall survival[247–250].

In sum, ample preclinical studies indicate that stress, noradrenaline, adrenaline and glucocorticoids can jeopardize adjuvant and neoadjuvant therapies, although clinical studies have not sufficiently addressed this important issue. Also concerning is the prevalent use of synthetic glucocorticoids (including dexamethasone) in

patients with cancer. These agents are routinely employed to reduce chemotherapy-induced emesis (nausea and vomiting)[251], to potentiate chemotherapy in lymphoid cancers[246,252] and to counteract inflammatory or autoimmune responses to immunotherapy[253]. Use of synthetic glucocorticoids in solid malignancies, which may or may not express GRs, could jeopardize adjuvant treatments and promote cancer progression. Indeed, in patients with non-small cell lung cancer, synthetic glucocorticoid use predicted decreased response to immune checkpoint inhibitors (including anti-PDL1 immunotherapy), and decreased DFS and overall survival[254–256].

Conclusions and perspectives

Although the evidence that stress promotes cancer initiation is inconsistent, there is robust evidence that stress can facilitate cancer progression through modulating most hallmarks of cancer. Molecular and systemic mechanisms mediating these effects have been identified in animal studies, and most have been recognized in patients with cancer. SNS-derived adrenergic stress responses, and adrenergic–inflammatory responses in the context of medical procedures, are key mediators of these deleterious effects of stress. The use of synthetic steroids, and stress-induced glucocorticoid release in some models, were also shown to promote cancer progression, and to reduce efficacy of adjuvant therapies. However, it should be noted that animal studies leverage their ability to synchronize stress exposure with specific phases of cancer growth and metastasis that are critically prone to stress. By contrast, epidemiological studies and most clinical trials assessing stress-reducing psychosocial interventions did not focus on stress-prone phases, some of which cannot be identified and addressed clinically. Thus, it is not a surprise that epidemiological and clinical intervention studies have shown small effect size or mixed outcomes. Importantly, psychological interventions have the potential to individually address patients' unique sources of stress responses, may exert enduring post-treatment effects without drug adverse effects and are feasible in patients with contraindications to drug therapy. Based on our current understanding of cancer biology, stress and the complex interactions between them along critical time frames in the continuum of cancer, we hypothesize that stress-management interventions can reduce cancer recurrence and mortality, especially in patients undergoing curative oncological surgery. To facilitate such beneficial effects, we suggest that stress-management interventions should be tested during critical periods affecting cancer progression, especially the short perioperative period and adjuvant treatments, and compared with other time periods; should be accompanied by pharmacological approaches to overcome stress and inflammatory responses that are unavoidably triggered by medical procedures; and should include individualized modules to accommodate patient-unique characteristics and needs, and focus on patients with higher manifestation of stress symptomology. Such studies should be powered similarly to testing a new drug therapy, and will likely require prioritization by non-profit funding organizations. Recent biomarker clinical trials, including pharmacological stress-reducing interventions, indicate the potential capacity of such approaches to reduce cancer mortality. Based on the current data, we believe that such approaches should be tested through large collaborative multicentre RCTs, assessing the impact of unified interventions on long-term cancer outcomes, with similar rigour to that employed when studying a new agent for cancer therapy.

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