The role of psychological stress in cancer initiation: clinical relevance and potential molecular mechanisms

Marta Falcinelli [1], Premal H. Thaker[2], Susan K. Lutgendorf [3], Suzanne D. Conzen[4], Renée L. Flaherty[5], and Melanie S. Flint[1]*

[1]School of Pharmacy and Bimolecular sciences, University of Brighton, Centre for Stress and Age-related Diseases, Moulsecoomb, Brighton, BN2, 4GJ, UK. [2]Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Washington University School of Medicine, St Louis, Missouri. [3]Department of Psychological and Brain Sciences, University of Iowa, Iowa City, Iowa. [4]Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, Texas, USA. [5]Division of Breast Cancer Research, The Breast Cancer Now Toby Robins Research Centre, The Institute of Cancer Research, London, SW3 6JB, UK.

*Corresponding author. M.flint@brighton.ac.uk. School of Pharmacy and Bimolecular sciences, University of Brighton, Centre for Stress and Age-related Diseases, Moulsecoomb, Brighton, BN24GJ, UK. Tel: 01273643986. Running Title: stress in cancer initiation

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Abstract

The hypothesis that the physiological response to psychological stress influences the initiation of cancer is highly controversial. The link between initiating stressors, the psychological stress response, and disease is plausible considering that the stress response is associated with defined physiological outcomes and molecular mechanisms. In light of this, we review the clinical relevance of psychological stress on the risk of cancer, and we propose potential molecular pathways that may link the stress response to early stages of malignant cell transformation.

Introduction

Exposure to psychological stressors is highly relevant amid the current COVID-19 pandemic. Increased levels of stress and anxiety have been reported globally due to social isolation, lockdowns, and job losses(1,2). Exposure to psychological stressors produces a physiological response involving the activation of the hypothalamic-pituitary axis (HPA) and the sympathetic nervous system (SNS)(3). Mediators of this stress response are cortisol, which activates downstream glucocorticoid receptor (GR) signalling pathways, and catecholamines (adrenaline and noradrenaline), that stimulate the adrenergic pathway through the β-adrenoceptors(3–5) (Fig.1A). Stress is defined as acute or chronic depending on the length of exposure to the stressor and the response. Acute stress is short-term and activates the "fight or flight" response, increasing alertness and readiness for physical activity, whilst inhibiting functions such as feeding or reproduction(6). While the body readily adapts to acute stress, prolonged exposure to stress due to chronic stressors can cause an inappropriate basal activity or hyper-responsiveness to stressors that may lead to long-term damage to tissues such as the hippocampus and prefrontal cortex in the brain(7–9). Chronic stressors can include situations such as caregiving, bereavement, socioeconomic burden, societal micro-aggressions, and social isolation. These stressors generally result in an increased and continued release of stress hormones that may favour tumour initiation(10). However, the individual response to stressors can vary, affecting levels of stress hormones(11). For example, an individual's perception of a stressor and appraisal of their ability to cope influences the downstream biological response(11).

Chronic psychological stress clearly influences the pathogenesis of some cardiac and dermatological diseases (12–15); therefore, it is not unreasonable to postulate that a vigorous stress response can promote cancer initiation by influencing stress-related biochemical pathways. It is widely accepted that bacterial, viral infections, autoimmune diseases, and environmental exposures can induce inflammation leading to increased cancer risk(16). Inflammation can increase mutation rates as activated inflammatory cells producing reactive oxygen species (ROS) and reactive nitrogen species (RNS) that are capable of inducing DNA damage and genomic instability(17). Additionally, psychological stress can promote negative health behaviours such as smoking, alcohol consumption, and sleep disruption that can increase the risk of developing diseases such as heart disease and cancer(18).

So far, there is a paucity of data identifying the molecular mechanisms through which stress might affect cancer initiation. Malignant tumour growth results from multiple cell type-specific processes and the contribution of psychological stress through stress hormone signalling may vary according to cancer subtype. However, in this opinion article, we discuss unifying processes underlying the influence of psychological stress on cancer initiation by analysing the classic physiological stress response involving the release of glucocorticoids and catecholamines. We present a critical analysis of the literature describing clinical aspects of the psychological stress response in cancer development, and review how stress hormone signalling can affect common pathways involved in carcinogenesis with a focus on DNA damage and repair, epigenetic and immune mechanisms.

Clinical Perspectives

The concept that psychological stress might contribute to tumour initiation was considered during the second century. The “seed and soil” hypothesis proposed by Paget specifically relates to cancer metastasis(19); however, it is feasible that repetitive stress enables a permissive environment for primary cancer initiation. Clinicians have observed that severe life disruptions often occur before the onset of cancer (20–23). However, the idea of stress as a factor contributing to cancer risk has been controversial with early evidence linking stress and cancer initiation resulting in inconsistent findings.

Here, we first discuss evidence showing a positive association between stress and cancer risk/incidence (Table 1a). One of the most compelling studies was conducted in a cohort of 10,808 Finnish women aged ≥24 with a 15-year follow-up. A retrospective questionnaire detailing a range of life experiences was administered with an assessment of psychological stress including stress of daily activities, life, and satisfaction. Women with an accumulation of adverse life events (death of a spouse, relative or close friend) 5 years before a cancer diagnosis showed the strongest association with an increased risk of breast cancer(24). Evidence from a prospective study of 1,462 Swedish women (middle aged) reporting any type of stress up to 24 years previously showed that breast cancer incidence was increased 2-fold compared to women reporting no stress(25). This effect was not reduced when adjusted for family history of breast cancer or variables related to socioeconomic status. A prospective case-control study of 514 Australian women (average age 61) biopsied after routine mammographic screening examined the role of self-reported stressful life events and coping and breast cancer incidence(26). A significant association was observed between highly stressful life events and lack of social support and breast cancer incidence. Another case-control study conducted in 858 invasive breast cancer patients and matched controls in Poland(27) found that women who had breast cancer scored highest for previous stressful life events (from 0-21 years following diagnosis), after adjustment for potential risk factors, with the death of relative or spouses increasing breast cancer risk significantly. Similarly, in a prospective study of 115 Finnish women, breast cancer patients were found to have a significantly higher level of perceived stress in the 10 years prior to diagnosis than women with benign breast disease, suggesting a convincing link between stress and breast cancer incidence(28). To determine the effect of low-level chronic stress as opposed to acute high impact stress such as death, job strain stress was examined in 36,332 Swedish women working full-time or part-time. In women working full-time there was a weak correlation between low job control, high job demands and breast cancer risk, suggesting that even chronic low level daily stressors may be associated with elevated breast cancer risk(29). An Israeli cohort of bereaved parents showed increased incidence of lymphatic, hematopoietic and skin cancers(30). Interestingly, childhood physical abuse was associated with 47% higher odds of being diagnosed with a subsequent cancer(31). A recent study suggests that workplace

stress exposure is associated with an increase of prostate cancer in men >65(32). In addition, persistent depression in older adults was shown to be associated with an 88% increase in cancer risk, which is important considering that chronic stress is also associated with the development of depression(33). Other studies highlight a positive correlation of stress and post-traumatic stress disorder in prostate, ovarian and breast cancer(34–36).

In contrast, several studies show no association between stress and cancer incidence. A cohort investigation of 106,000 UK women did not show consistent evidence for an association of breast cancer risk with perceived stress levels (e.g. adverse life events or significant stress such as loss of parents) with a 5 year follow up(37). Two separate prospective studies involving 11,467 healthy UK and 10,519 Finnish women found no evidence of an association between social stress over a 10-year period and breast cancer incidence(38) or between daily stress and breast cancer risk(39). There was no correlation even with adjustment for confounding factors such as smoking status or BMI. Evidence from nationwide cohort defined by the Fertility Register also showed no association between death of a child and breast cancer risk(40). Similarly, there was no association with caregiving stress and cancer incidence(41). In the Women's Health Initiative, 84,334 post-menopausal American women were examined for cancer incidence in relation to stressful life events (e.g., death of a family member) and social support(42). After adjusting for confounding variables there was no association between stressful life events or social support and breast cancer incidence. However, the follow-up time was only ~7 years. A 15 year prospective study in 2,739 women in Australasia also showed no association between acute and chronic stressors and breast cancer risk(43). Finally, a prospective study in 6,689 participants in Denmark showed that higher levels of perceived stress correlated to a lower risk of breast cancer(44). This was attributed to the fact that stress may impair oestrogen synthesis.

Meta-analyses on this topic have generally shown small effect sizes (Table 1b). For example, a meta-analysis of 27 breast cancer studies showed a modest association between death of spouse and breast cancer risk, although there was no overall association between stressful life events and breast cancer risk(45). However, a larger meta-analysis of 165 longitudinal studies showed that psychosocial factors and

stressful life experiences were associated with higher cancer incidence, poorer cancer survival, and higher mortality(46). Two other meta analyses on breast cancer also report positive associations with breast cancer incidence(47,48). In contrast, other studies in breast cancer yielded opposite results. An epidemiological study of the link between stress and breast cancer examined 29 studies of adverse life events and breast cancer risk. No link was found between breast cancer and bereavement, or any other adverse life event(49). A meta-analysis from 12 studies on work stress (50), on 116,056 participants was studied to ascertain if high job strain correlates to an increased risk of breast cancer, and there was no association even after adjustment for various risk factors e.g. BMI and smoking. However, interestingly, there is evidence that night shift work may affect breast cancer occurrence(51).

The irregularity in findings of case control/ population and meta-analysis studies reflects the complexity of tumour initiation studies. Study design and control for confounding variables such as socioeconomic status, smoking, drinking alcohol, BMI etc. are not always recorded. Furthermore, the type and timing of stress exposure, and follow-up times all vary between studies, making direct comparisons challenging. Prospective studies can be influenced by recall bias as patients may interpret stressful events differently following a diagnosis. However, there are considerably more population and meta-analyses studies showing a positive association between high stress and breast cancer incidence.

Stress and common carcinogenesis pathways

The process of tumour initiation involves multiple events whereby cells acquire malignant characteristics. These hallmarks of cancer include increased proliferation, evasion of cell death, deregulating cellular energetics, induction of angiogenesis, and evasion/editing of the immune system(52,53). In the following sections, we discuss pathways that are activated in response to psychological stress, and which are also involved in tumour initiation (Summarised in Fig 1b).

A more prominent role of psychological stress has been demonstrated in the initiation of cancers with a viral aetiology (e.g. cervical carcinoma, lymphoma, and hepatocarcinoma)(11). Early work suggested that oncogenic transformation of primary cells with a combination of HPV-16 DNA and the activated form of the

human H-ras oncogene occurred only in the presence of the glucocorticoid, dexamethasone(54). Indeed, human papillomavirus type 16 glucocorticoid response elements have been proven functional for cell transformation, transient expression, and DNA-protein interactions(55). Steroid hormones are thought to increase the expression of the E6 and E7 HPV 16 oncogenes, which bind to and degrade *p53* leading to tumour initiation(55). Cortisol can also regulate the HPV-E6-p53-miR-145 pathway(56). Interestingly, hepatocarcinoma is closely linked to chronic viral hepatitis infection which is affected by chronic stress. In mice, chronic restraint stress promoted hepatocarcinoma growth through β-adrenergic signalling. This was mediated by the CXCR2-CXCL2/CXCL3 axis and recruitment of myeloid cells, which are thought to be immune suppressive(57).

One of the main characteristics that normal cells acquire during malignant transformation is inappropriate proliferation. Although the role of psychological stress on proliferation has been studied in cancer progression, less is known about the mechanisms affecting cancer initiation(58–60). A role in mediating tumourigenesis in B-RAF mutated cells is exerted by the long glucocorticoid-induced leucine zipper (L-GILZ). Blockade of BRAF activity in thyroid cell line (8505C) carrying BRAFV600E mutation led to the inhibition of proliferation, an effect mediated by the upregulation of L-GILZ expression(61,62). This suggests that BRAF mutations can promote proliferation by downregulating L-GILZ expression and contribute to tumour initiation. Glucocorticoids also play a role in the escape from the oncogene-induced senescence (OIS), a quiescence mechanism. *BRAFV600E* expression in non-cancerous cells triggers two opposing responses. Neural stem cells expressing *BRAFV600E* showed signs of transformation by growing in an anchorage-independent manner, a hallmark of cell transformation, and forming colonies in soft agar(63). However, proliferation was blocked by entering OIS(63,64). Cells in OIS can remain quiescent for long periods of time before progressing to malignancy(64). These two opposite responses activated by *B-Raf* signalling create a balance between a pro-oncogenic signal and a senescent proliferative arrest. The switch towards tumour initiation might be sustained by other important tumourigenic stimuli. *BRAFV600E*-induced senescence was also bypassed by the addition of glucocorticoids, albeit at pharmacological doses, in human fibroblasts allowing for cancer transformation. Furthermore, growth arrest was mediated by *BRAFV600E* via the

activation of the early growth response protein (EGR1) which stimulates the expression of tumour suppressor genes such as the cyclin-dependent kinase 4 inhibitor B (*CDKN2B*) and cyclin-dependent kinase inhibitor 1 (*CDKN1A*). Treatment with clobetasol, a synthetic corticosteroid, decreased *EGR1*, *CDKN2B*, and *CDKN1a* levels consistent with allowing evasion from senescence and promoting cancer initiation(65).

It is noteworthy that there is a role of the outgrowth of nerves (axonogenesis) and SNS signalling in cancer initiation(66). Novel work in a pancreatic cancer mouse model showed active bidirectional communication between the pancreas and sensory neurons (which interact with parasympathetic neurons) prior to the establishment of tumours. Ablation of sensory nerves in mouse models of pancreatic adenocarcinoma slowed cancer initiation(67). Although it can be argued that these mice are genetically engineered to develop cancer it still highlights the importance of the nervous system in supporting inflammation associated with oncogenic Kras-induced neoplasia(67). Catecholamines can also mediate tumour proliferation and alter gene expression pathways associated with carcinogenesis. Ovarian and fallopian tube surface epithelial immortalized cells show a differential gene expression when treated with noradrenaline compared to controls(68). These genes include salt-Inducible kinases 1-3 (*SIKs*) each having different functions in cancer and are candidates for initiation(69). SIK1 works as a p53 regulator promoting anoikis and protecting from cancer initiation. SIK1 suppression in mammary epithelial cells enhances cell transformation by expressing cancer related mutations (such as *PIK3-H1047R*) and promoting anchorage-independent growth(70). Noradrenaline upregulates *SIK1*(68), highlighting a possible protective effect of the stress hormone. However, long-term effects of noradrenaline on SIK1 remain unknown. SIK2 and SIK3 may also contribute to tumour development due to their roles in cell cycle regulation(69). The role of SIK2 in cancer initiation has emerged because it is a key factor in hepatic steatosis which increases the chance of developing hepatocarcinoma(71,72).

Another interesting protein is the anti-apoptotic Dual Specificity Phosphatase 1 (DUSP1), which is upregulated by stress hormones(68). *DUSP1* encodes a Serine/Threonine specific protein phosphatase (MPK-1) involved in the MAP kinase dephosphorylation, and highly expressed in many epithelial tumours

including breast cancer(73–78). Interestingly, *DUSP1/MPK-1* expression is lower in hepatocarcinoma and head and neck cancer compared to normal tissues(79). Noradrenaline upregulates *DUSP-1* in normal ovarian and fallopian tube epithelial cells and is overexpressed in ovarian cancer cells(68). Noradrenaline-induced *DUSP1* protects ovarian cancer cells from apoptosis and impairs chemotherapy-induced cell death(80). *DUSP1* is also upregulated by GR activation in ovarian tissues(81,82) suggesting that both glucocorticoids and catecholamines may decrease chemotherapy-induced apoptosis in human epithelial cancers through the activation of anti-apoptotic signalling. Mechanisms underlying *DUSP1/MKP-1* expression in cancers are complex as they are regulated by environmental factors such as oxidative stress, DNA damage, and hypoxia(79) (Fig.1C). In summary, the observation that stress hormones can regulate molecular mediators of tumour formation such as *SIKs* and anti-apoptotic genes such as *DUSP-1* suggests that these genes may contribute to tumour initiation.

Stress mediators on DNA damage and repair

Damage to DNA is understood to be one of the major events in cancer initiation. In response to DNA damage, pathways are activated to identify and repair the damage. Stress hormones have the propensity to induce DNA damage and modulate the transcription of DNA damage related genes(83) (Fig.1D). This was demonstrated in 3T3 fibroblasts exposed to cortisol, adrenaline, and noradrenaline which induced significant DNA damage and inhibited DNA repair through modulation of DNA damage sensors and cell cycle progression genes(83). However, there is conflicting evidence of noradrenaline on DNA damage. In a non-tumourigenic ovarian epithelial cell line (IOSE-29), noradrenaline significantly reduced constitutive levels of DNA breaks and attenuated DNA damage induced by treatment with bleomycin. This effect was mediated by the anti-oxidant properties of noradrenaline which prevented Reactive Oxygen species (ROS)-induced DNA damage(84). In contrast, using the β-adrenergic agonist, isoproterenol, adrenergic signalling led to accumulation of DNA damage(85). Chronic stimulation of β2-adrenoceptor with isoproterenol, adrenaline, or noradrenaline in mice or in cultured U2OS cells, led to decreased levels of p53 and accumulation of DNA damage. Isoproterenol activated the murine double minute 2 (MDM2) via beta-arrestin-mediated PI3K/AKT MDM2 phosphorylation and promoted p53 degradation(86). The accumulation

of DNA damage was a result of a decreased repair. There is emerging data showing that stress hormones can reduce p53 function through the activation of MDM2(86). Similarly, a study in mice showed that restraint stress, via release of glucocorticoids results in decreased p53 and tumourigenesis in heterozygous p53+/− irradiated mice(87). This evidence highlights the possibility that a pharmacological blockade of these pathways should be further investigated in tumour initiation can represent a therapeutic option in managing the negative effects of chronic stress(88). Other studies have shown that stress hormones can induce DNA damage through the production of ROS and reactive nitrogen species (RNS) capable of interacting with DNA, causing base changes and strand breaks(89). We can conclude that stress hormones can elicit damaging effects on DNA and impact the repair processes, known contributors to tumour initiation.

Given the highly mutagenic landscape of cancer cells, subtle and transient increases in DNA damage because of psychological stress are hard to observe in tumour samples. It is therefore prudent to highlight the limitations of DNA damage studies which have been confined to cancer cell lines, which allow controlled exposure and quantification of any stress hormone-induced damage. Whilst there is limited evidence of the direct effect of stress hormones on DNA damage in patient tumours, Gidron *et al*. summarise literature relating to psychological factors and DNA damage in a range of animal models and human studies(90,91). Meta-analysis of rodent studies (up to the year 2006), indicates that psychological stressors such as sensory stress can elevate the oxidative DNA damage marker 8-hydroxy-2' -deoxyguanosine (8-OHdG). Furthermore, several studies have linked psychological perturbations such as perceived stress, depression and anxiety to elevated levels of 8-OHdG(92–94). Excreted 8-OHdG has been shown to be a reliable biomarker of risk in colon and breast cancer risk indicating an association between stress hormones, oxidative DNA damage and cancer(95–97).

Dysregulation of DNA damage response and repair pathways are key in cancer initiation, as the ability to maintain genomic integrity is compromised in favour of proliferation. In certain types of tumours, DNA repair capacity and tumourigenesis are closely linked because of mutations in breast cancer type 1 and 2 susceptibility (*BRCA1 and BRCA2)* genes, encoding for proteins involved in DNA repair. Mutations in *BRCA*

genes increase the risk of breast, ovarian, and to a lesser extent other types of cancer such as prostate, pancreatic, and melanoma(98). As already discussed, cortisol can induce DNA damage and alter DNA repair mechanisms in cancer cells through the production of ROS/RNS, known contributors to carcinogenesis(99,100). Indeed, *BRCA* deficient cells are more sensitive to the effects of oxidative stressors and in *BRCA1* deficient breast epithelial cells, a number of ROS inducing compounds promoted an increase in DNA damage(101,102). This suggests that stress-mediated DNA damage through the production of ROS/RNS together with an impaired DNA repair mechanism exerted by mutated *BRCA1* can contribute to an accumulation of genomic alterations that are crucial for tumour initiation. Although the effects of stress can contribute to carcinogenesis, the concurrent impairment of other molecular mechanisms implies that stress may not necessarily be the cause but may be a contributing factor to tumour initiation. These considerations also suggest that stress signalling and BRCA1 function might have reciprocal interactions.

There is compelling evidence of the effects of glucocorticoids on BRCA1 expression and vice versa. Hydrocortisone and dexamethasone can downregulate expression of the *BRCA1* gene in a non-malignant mouse mammary cell line(103). Further investigation of the mechanism revealed that glucocorticoids specifically repress *BRCA1* promoter activity. Hydrocortisone decreased *BRCA1* luciferase gene reporter expression in non-malignant mammary cell lines, but not in malignant lines. Furthermore, long-term repression of the *BRCA1* promoter was only achieved in the continuous presence of hydrocortisone(103). This suggests that stress hormones may contribute to breast cancer initiation via reducing *BRCA1* expression in normal breast epithelium, allowing DNA damage to occur without effective repair.

Manipulation of unliganded GR expression was observed to upregulate activity on the *BRCA1* promoter(104). Binding of glucocorticoids negated this positive effect, reducing promoter activity. Whilst this study supports the hypothesis that an increased risk of breast cancer could be associated with psychological stress, it's possible that basal levels of GR may be linked to *BRCA1* expression. Indeed, the unliganded GR may act as a cooperative transcription factor for BRCA1. Expression of GR varies across tissues, as well as in certain subtypes of breast cancer, with increased expression of GR associated with shorter relapse-free survival in the aggressive ER-negative subtype(105). The liganded-GR dampens

oestrogen receptor mediated breast cancer cell proliferation, and decreases ER occupancy at proliferative gene enhancer sites, as well as inhibiting recruitment of crucial protein complexes to the ER-bound enhancer(106,107). However in ER-negative breast cancer, GR-regulated genes involved in proliferation and cell survival were associated with poor prognosis and relapse(108). Further studies reveal that the GR and ER can work in a complex and taken together these results suggest ER status may be an important factor in the GR transcriptional activity among breast cancer subtypes(109). Furthermore, whilst high basal expression of the GR may promote BRCA1 activity, a sustained increase in its ligand - as seen during prolonged periods of psychological stress - could feasibly suppress *BRCA1* expression more so than in GR-low tissues, leading to an increased risk. Interestingly, methylation of the GR promoter resulting in downregulation of GR expression was more frequently observed in breast tumours, compared to normal tissue samples(110). In a follow up study, knockdown of the GR in mammary epithelial cells by transfection with GR directed short-hairpin RNA (shRNA) generating a stable shGR line also demonstrated positive regulation of *BRCA1* by GR(111). Microarray analysis of the shGR line also identified several pro-apoptotic genes regulated by the unliganded GR in a similar manner to *BRCA1*(111). This may suggest an anti-tumourigenic role for the unliganded GR in non-cancerous cells, although in breast cancer this depends on the ER status, and that the release of glucocorticoids from psychological stress could abolish this and promote tumour initiation.

The crosstalk between the GR and BRCA1 in mammary epithelial cells (Fig.1D) points towards potential implications for patients with breast cancers driven by hereditary BRCA1-mutations that are prone to ER-independent breast cancers. Chronic elevation of cortisol because of continued stressors such as cancer diagnosis and treatment, which have been reported as major stress-inducing factors for women with breast cancer, can lead to increased stimulation of the GR. In turn this could place additional burden on DNA repair mechanisms in BRCA1-deficient cells, leading to an accumulation of DNA damage. Combined with the increase in oxidative DNA damage also triggered by stress hormones, this has the potential for an additional risk for women with BRCA1 mutations.

Stress hormones and epigenetics

Dysregulated epigenetic mechanisms as a non-genomic risk in cancer initiation have received increased attention. GR activation causes epigenetic modifications via methylation in cytosine-guanine dinucleotides of the DNA; changes in histone methylation and acetylation and regulation of microRNAs (miRNAs), such as miR-708 in breast cancer(112). Recent work in neurons has demonstrated that stress exposure and glucocorticoids alter N^6-methyladenosine and N^6,2'-O-dimethyladenosine mRNA methylation that regulates transcript processing and translation(113). Glucocorticoids can also increase the expression of enzymes involved in active demethylation, e.g. the Tet family of 5-methylcytosine dioxygenases, and decrease the expression and activity of the maintenance DNA methyltransferases DNMT1 and DNMT2 and *de novo* methyltransferase DNMT3(114). GR activation can promote dynamic chromatin remodelling that may alter accessibility of GR-binding sites to the transcriptional machinery(113–115).

There is increasing evidence that glucocorticoids induce long lasting epigenetic modifications in many tissues and these modifications are tissue-type specific. For example, an interesting study in mice showed that cortisol exposure decreases DNA methylation of the GR chaperone *FKBP5* in the hippocampus and hypothalamus and also causes CPG demethylation of *FKBP5*(116). Others have shown that stress and ageing synergistically decrease DNA methylation in *FKBP5* CpGs in immune cells prompting NF-kB mediated inflammation(117). Epigenetic upregulation of the GR chaperone *FKPP5* may therefore induce inflammation and cancer risk. It is important to note that glucocorticoid-induced changes in DNA methylation last many weeks even following removal of glucocorticoids. Stress exposure has been shown to induce lasting epigenetic modifications through DNA methylation, histone modification etc. throughout the lifespan(115,118–120). The epigenome is sensitive to stressors across all periods of mammalian life, but it may be particularly susceptible during periods of rapid epigenetic remodelling or deficient functioning of epigenetic maintenance systems, such as in early development or older age, which may be important with regards to tumour initiation(115).

There is evidence linking stress exposure in early development to an increased cancer risk via epigenetic mechanisms. A study in Israel on 152,622 Holocaust survivors who were followed for over 45 years showed

that Holocaust survivors have a small but consistent increase in the risk of developing cancer. Intergenerational effects of maternal Holocaust exposure on FKBP5 methylation have also been reported(121). A large British birth cohort study also showed that cancer risk may be influenced by exposure to psychosocial adversity in childhood. Women who experienced two or more adverse events doubled their risk of having a cancer before 50 compared to women who had had no childhood adversities(122). Stress exposure during childhood can lead to long term epigenetic modifications e.g. persistent demethylation of CPGs located near the glucocorticoid response elements of the *FKBP5* gene(123). A model whereby exposure to life stress via glucocorticoid signaling may alter the epigenetic landscape across the lifespan impacting genomic regulation and function has been proposed(124). These are important aspects of the transgenerational stress response and potential non-genomic effects of the activated neuroendocrine system on cancer susceptibility.

Stress, cell mediated immunity and inflammation.

We have discussed how stress can contribute to tumour initiation by acting on specific carcinogenic pathways. However, a dysregulation of immune and inflammatory processes can also contribute to carcinogenesis(125). In principle, tumour initiation can be controlled by innate and adaptive immune cells; additionally, these cells express β2-adrenoceptors and GR indicating that they can be regulated by stress. Stress hormones can directly modulate multiple aspects of the immune response including cell-mediated immunity, humoral immunity, lymphocyte proliferation, macrophage response and polarization, NK cell function and immune cell trafficking(125,126). Stress can suppress immune surveillance mechanisms, enhance inflammation, and upregulate immunosuppressive signals(127–129), thus impairing an individual's ability to recognise and destroy transformed cells. A human study demonstrated that laboratory stressors increase levels of circulating and stimulated cytokines(130). It is possible that these responses contribute to associations between exposure to life challenges and vulnerability to diseases such as cancer. The role of stress on immune cell trafficking, suppression and inflammation is key to tumour initiation. Immune cells constantly traffic between the blood and various lymphoid and non-lymphoid organs and studies in rodents suggest that behavioural stress induces a significant redistribution of T cells in the body(131). Similarly, SNS

innervation of the spleen and lymph nodes also modulates the progression of peripheral immune responses by dampening lymphocyte trafficking to tissue. Activation of lymphocyte β2-adrenoceptor enhances the responsiveness of chemokine receptors (CCR7 and CXCR4) that promote lymph node retention of lymphocytes, and consequently inhibits their lymph node emergence(132).

Stress hormone signalling can upregulate immunosuppressive signals. A mouse study showed that chronic stress increased the susceptibility of UV-induced melanoma through shifting the balance of protective immune cells towards suppressive (T regulatory cells) immunity(133). Interestingly, studies in rats showed that social isolation increased the risk of spontaneous mammary tumours(134). A vast body of literature highlights the anti-inflammatory properties of glucocorticoids and how they can affect immune signalling pathways and inhibit inflammatory mediators(135). The SNS also regulates inflammation and immunity(136). Catecholamines influence inflammation by increasing the recruitment of hematopoietic stem and progenitor cells (HSPCs) to the spleen supporting long-lasting splenic myelopoiesis(137). Furthermore, β-adrenergic up-regulation of myelopoiesis is one molecular mechanism by which chronic stress may result in a pro-inflammatory shift(138). A recent study showed that stress hormones, via β2-adrenoceptor can cause the release of pro-inflammatory S100A8/A9 complexes by neutrophils. This led to the release of oxidized lipids directly activating proliferation of dormant tumour cells through an upregulation of the fibroblast growth factor pathway(139). Fibroblasts can also secrete lipids leading to activation of mitogenic pathways. Indeed, fatty acids secreted into the microenvironment can impact infiltrating immune cell function and phenotype(140). With their role in suppressing host immunity, promotion of inflammation and release of DNA damaging ROS and oxidized lipids, it is likely that stress hormones can promote a favourable niche sustaining malignant cell transformation.

Conclusions

The research outlined in this review supports the notion that persistent and chronic stress exposure might contribute to tumour initiation in specific cancers. This research is still in its early stages compared to research on stress and tumour progression, and evaluation of the physiological stress response and cancer

initiation mechanisms is greatly needed. A more detailed examination of biomolecular mechanisms that underlie physiological stress responsiveness and how stress-hormones contribute to tumour-initiating pathways in susceptible patients is warranted. In light of the COVID-19 pandemic, with increased reports of chronic stress, social isolation, and reluctance to visit the General Practitioner, the aforementioned studies should encourage clinicians and cancer biologists alike to consider psychological stress as a synergistic risk factor to inherited genetic and environmental factors that increase cancer risk. These findings also raise the importance of addressing resilience in response to psychological stress e.g., in high-risk patients such as those with germline mutations in DNA repair mechanisms and other cancer susceptibility pathways.

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Table 1

Cancer Type	# Subjects	Stress measures	Positive association	Refs
Case control/population studies				
Breast	10,808	Questionnaire: modified standardised life event inventory	Divorce/separation, death of a husband/close relative or friend were associated with increased risk of breast cancer.	(24)
Breast	1,462	Questionnaire: stress	Self-reported stress was associated with a significant increase in breast cancer incidence.	(25)
Breast	514	Questionnaire: Brown and Harris Life Event and Difficulties Schedule & psychosocial variables	Highly stressful events and no emotional support significantly increased breast cancer risk.	(26)
Breast	858	Questionnaire: socioeconomic status and stressful life events	Death of relative or spouses significantly increased breast cancer risk.	(27)
Breast	115	Questionnaire: Beck Depression and Spielberger Trait Inventory and interview	Stressful life events significantly increased breast cancer risk.	(28)
Breast	36,332	Questionnaire: assess job demands, control and social support	Weak correlation between low job control, high job demands and breast cancer risk.	(29)
Many	6,284	Bereavement question	Bereavement correlated with an increased incidence of cancer.	(30)
All	13,092	Survey questions: childhood &adult Socioeconomic status	Childhood physical abuse was associated with increased risk of cancer.	(31)
Prostate	1,933	Questionnaire: perceived Stress	Prolonged workplace stress was associated with an increase in risk of cancer.	(32)
Many	4,825	Questionnaire: Center for Epidemiologic Studies-Depression scale	Six years of depression was associated with an increased risk of cancer.	(33)
Breast	867	Questionnaire: Life Events Scale Holmes and Rahe scale	Cumulative adverse life events perceived as stressful were associated with increased risk of breast cancer.	(34)
Ovarian	54,710	Modified version of the Brief Trauma Interview	PTSD symptoms were associated with increased risk of ovarian cancer.	(35)
Breast & Prostate	991 women & 5,743 men	Questionnaire	A weak association between stress and risk of prostate risk but not breast cancer.	(36)
Cancer Type	**N number**	**Stress measures**	**Negative association**	**Refs**
Breast	106,000	Questionnaire: perceived frequency of stress, experience of adverse life events and bereavement	A positive association of divorce with ER-negative but not ER-positive breast cancer. No consistent evidence for an association of breast cancer risk with perceived stress levels or adverse life events, or loss of parents during childhood and adolescence.	(37)
Breast	11,467	Questionnaire: Health and Life Experiences and assessment of social & psychosocial circumstances	No evidence of social adversity correlating with cancer incidence.	(38)
Breast	10,519	Questionnaire: Stress of Daily Activities	No association between daily stress and breast cancer risk.	(39)
Breast	167,368	Nationwide cohort (Fertility Register)	No increase in breast cancer risk after the death of a child.	(40)
Breast	69,886	Questionnaire: informal caregiving	No association between higher levels of caregiving and breast cancer incidence.	(41)
Breast	84,334	Questionnaire: stressful life events, social support	No independent association between stressful life events and breast cancer risk.	(42)
Breast	2,739	Questionnaire: acute and chronic stress	No association between acute or chronic stress and breast cancer risk.	(43)
Breast	6,689	Questionnaire: perceived stress	High perceived stress resulted in a lower risk of breast cancer.	(44)
Meta Analyses/Reviews				
Breast	27 studies	Questionnaire and interview	A modest association between death of spouse and breast cancer risk but no overall association between stressful life events and breast cancer risk.	(45)
Lung	165 studies	Questionnaire	Stress-related psychosocial factors are associated with higher cancer incidence in initially healthy populations.	(46)
Breast	N = 471	Observational studies and review	A positive association of perceived stress, together with potentially risky lifestyle behaviours with breast cancer.	(47)
Breast	N = 530	Questionnaire: striking life events	A positive association between striking life events and primary breast cancer incidence.	(48)
Breast	27 studies	Questionnaire	A modest association between death of spouse and breast cancer risk and no association bereavement, or other adverse life event.	(49)
Many	12 studies	Questionnaire: Job Content and Demand	No association between stress and breast cancer risk.	(50)
Many	review	Self -reported work stress	Inconclusive data but nightshift work may affect incidence.	(51)

Fig 1a. Stress stimulus produces a physiological response which involves the central nervous system (CNS) and the periphery. The stress response includes the activation of two endocrine systems: the hypothalamic-pituitary axis (HPA) and the sympathetic nervous system (SNS). The final mediators of the stress response are cortisol and catecholamines (adrenaline and noradrenaline) secreted by the adrenal cortex and medulla respectively. SNS signalling also occurs via nerves. **Fig 1b. Stress regulation of tumour initiation.** Reported stress effects on the hallmarks of cancer proposed by Hanahan and Weinberg(52,53). **Fig 1c. Proposed mechanisms of glucocorticoids and catecholamines on tumour initiation.** The adrenergic pathway mediates the effect of catecholamines by binding the β2-adrenoceptor and activating into adenylyl cyclase which converts ATP in cAMP. cAMP activates two major effectors, protein kinase A (PKA) and the exchange factor directly regulated by cAMP (EPAC) respectively leading to the activation of CREB and AP-1, transcription factors that modulate gene expression. Cortisol activates the stress pathway mediated by glucocorticoid receptors (GRs). The binding of glucocorticoids to GRs results in the translocation of the complex from the cytoplasm to the nucleus where it modulates gene expression. Stress-regulated processes include important molecular mechanisms such as proliferation, cell cycle regulation, DNA damage and repair that might contribute to cancer initiation. Arrows indicate up/down regulation. **Fig 1d. Stress effects on DNA damage response** Glucocorticoids bind to the GR, induce ROS/RNS and activate the DNA Damage Response (DDR). Two key signal transducing kinases are ataxia telangiectasia mutated (ATM) and ataxia telangiectasia and Rad3-related (ATR) which are primarily involved in the responses to DSB's or stalled replication, respectively. ATM and ATR activation leads to phosphorylation of effector kinases, facilitating cell cycle arrest via cyclin-dependent kinase inhibition, DNA damage repair and apoptosis, through phosphorylation of substrates like p53 and BRCA1. Stress hormones also affect DNA repair by disrupting the signalling pathways mediated by RAD51 and BRCA1, contributing to DNA damage accumulation. The unliganded GR can directly interact and positively regulate activity on the *BRCA1* promoter. Binding of glucocorticoids negates this positive effect, reducing promoter activity.