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Cancer and stress: what's matter? from epidemiology: the psychologist and oncologist point of view

Nerina Denaro[1,2*], Letteria Tomasello[3] and Elvio Grazioso Russi[4]

*Correspondence: nerinadenaro@hotmail.com

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[1]Oncology Department, ASO Santa Croce and Carle Cuneo, Italy.
[2]Human Pathology Department, Messina University, Italy.
[3]Neuroscience Department, Messina University, Italy.
[4]Radiation Oncology Department, ASO Santa Croce and Carle Cuneo, Italy.

Abstract

Collective evidence points to a prominent role of stress in cancer growth and metastasis. Despite these results an etio-pathogenetic role has not been widely accepted. Reasons of controversies are the co-existence in stressed patients of high risk habits, the sample size, the heterogeneity and the retrospective origins of these studies. Experimental data and clinical observations argue about the possibility of an interaction between psychosocial events and tumours. However the number of involved variables and the long period of observation prevent with current technologies the definition of causal versus chaotic sequences of this hypothetical relationship. Psychotherapy may help to face up to stressful events, but its role e remains uncertain. Stress works through sympathetic nervous system and hypothalamic–pituitary–adrenal axis activation, along with related hormones, that have functionally and biologically significant impacts on the tumor microenvironment. This paper collects evidences through the hypothesis of correlation between stress, psychological factors and cancer focusing both on psychology and on molecular biology. Knowledge on stress induced neuroendocrine dynamics in the tumor microenvironment might allow the development of integrated pharmacological and bio-behavioral strategies to create more successful cancer therapies.

Keywords: Stress-induced disease, cancer, life events, immune system

Introduction

The correlation between cancer and stressful life has recently been investigated.

A seemingly significant association exists between shifts and stressful jobs, trauma, grief on the one hand and incidence of malignancy on the other hand.

Cancer and stress disease are both characterized by a huge complexity, heterogeneity and multi-factorial pathogenesis. It is well accepted that cancer growth involves the micro-environment, a space where tumour cells receive nutrients from the host tissue, produce angiogenetic factors and form new vessels. Additionally the whole process is in a subtle equilibrium involving immune system through a myriad of pathways: cytokines, growth factors, receptors, hormones and adhesion molecules. Initially tumour is in a symbiosis/parasitosis status in the host organism that tolerates it, then growth factors and microenvironments changes led to invasiveness with "tumour escape".

Stress was defined by Selye et al., [1] as "a general adaptation syndrome in which a complex mechanism of activation of neuro-endocrine system works to prepare the body to attack or escape behaviour". If the stimulus remains the organism continues to adapt (resistance phase) until the exhaustion (third stage). This adaptive syndrome is generally independent of the type of stress in the animal.

In humans the main source of stress is given by the meaning of the stimulus. Humans acutely elaborate stressful events triggering an immune-neuro-endocrine "metabolic storm": our body responds to the stress in two ways: positively activating an effective response with attenuation, disappearance of stress and return of biological mediators (eustress); negatively with ineffectively response to unavoidable stress, cognitive also, for which the biological parameters do not return to normal values and can lead to numerous diseases such as depression, anxiety, gastritis, ulcer, hypertension, colitis, cardiomyopathy. Stress induced diseases mostly depend on increasing of

catecholamine, cortisol, neurotransmitters, hormones and impairing of immune system.

All these mediators also impact on metastatic spread, immune system, mechanisms of DNA repair [2-5].

However stressed individuals are also more likely than stress-free individuals to smoke tobacco, consume excessive amounts of alcohol, and be obese, all these behaviors are risk factors for cancer and are associated with chronic inflammation. A role for inflammation in tumorigenesis is now generally accepted: an inflammatory microenvironment is an essential component of all tumors, including some in which a direct causal relationship with inflammation is not yet proven [6].

Up to 20% of cancers are linked to chronic infections, 30% of them can be attributed to tobacco smoking and inhaled pollutants (such as silica and asbestos), and 35% of them to dietary factors (20% of cancer burden is linked to obesity) [7].

Epidemiological and clinical studies over the past 30 years have provided strong evidence for links between chronic stress, depression, social isolation and cancer progression. By contrast, there is only limited evidence for the role of these behavioral factors in cancer initiation. Recent cellular and molecular studies have identified specific stress-induced signaling pathways that impact on cancer growth and metastasis [8].

Despite the amount of literature on this topic, spanning several decades and scattering between the fields of epidemiology, physiology, and molecular biology: it is not possible to give a clear answer about the connection between stress and cancer. The second part of this article reviews evidence regarding effects of psychotherapy on overall cancer survival time. Special emphasis is given to research on adverse effects of depression on cancer survival, analyzing the impact of psychosocial support on physiological pathways to prolong survival.

In brief the aim of this paper is to provide a review on the hypothesis of correlation between stress, psychological factors and cancer focusing on molecular biology. We revised the literature on stress induced cancer, bio-molecular markers, immuno-depression and psychotherapy to point out useful knowledge on this topic for oncologists, physicians and psychosocial providers.

Figure 1 points out mechanism of stress-cancer correlation, based on our literature review.

Review
Methodology
A comprehensive literature review was finalized in May 2014. Medline was used for research. Each author added a personal contribution supplementing electronic search results with, expert consensus meeting notes and reference lists from selected articles. The literature search was limited to articles in English and human patients. The following Medical Subject Headings terms and keywords were used in the search: "stress or stress-induced" AND "cancer or neoplasm or neoplasia" AND/OR "life events", AND/OR " depression". We analysed and discussed the literature, taking into account the previously reported reviews on this matter. Literature revision, made separately by two oncologists and a psychologist, was provided to analyse the topic from two different points of view.

Data on stress induced disease: from history to nowadays
The attempt to identify the psychological factors that influence carcinogenesis has ancient roots: firstly Galen (II cent BC) who argued that melancholic women have a higher probability of developing breast cancer, due to an imbalance of black bile [9]. In the XVI century, Ambroise Paré, a Renaissance surgeon, shares the etiological hypothesis of "imbalance melancholy" [10].

Gendron (1701), after discussing the different causes of cancer disease, admitted that "sometimes it follows a sudden interruption of the course of events caused by a "fright or an intense suffering". The English surgeon, Guy, in 1759 wrote "breast cancer seems more common in depressed, phlegmatic and melancholic women". Burrows (1783), writing about the effects of emotion on the body's physiology, states: "the painful passions of the mind in the long run weaken the blood circulation and predispose to cancer". Even Lobstein (1846), says that "the moral emotions bring a deficit in innervation, and that causes cancer". James Paget (1870) considers a "significant mental depression" as a contributing cause, while Tomas Watson (1871) claims to "have observed the sequence stress-cancer so often and not to be able to doubt". Herbert Snow, very famous surgeon for the "invention" of elective lymph node dissection in melanoma, (1893) argues repeatedly that "mental depression is a precursor to cancer". He was the first author to describe on 250 patients the association stress events-cancer, in the Snow Cancer Hospital; among these patients in 156 he detects "acute stress in the run-up", such as the loss of a close relative, in 32 reported "the hardness of the work", in 43 "stories of hardship that would allow to suspect a mechanical injury" while only 19 had no causal relationship [9,10].

During the XIX-XX century, according to the conception of the Enlightenment and Renaissance, the studies on relationship between oncological disease and mental state have been laid aside and only in the last 20-30 years the interest on this topic has re-emerged. Recently psychology has begun to study the role of psyche in cancer etio-pathogenesis focusing in particular on patient's feelings and reactions.

For Bahnson (1981), stress may act on patients through three mechanisms (a) a direct action of the central nervous system (CNS) tissue (bridge nervous) (b) an induction of endocrine disruption by the nervous structures (bridge endocrine) (c) a depression of the Immune System mediated via endocrine would not be able to control the production of neo-plastic cells.

Funch and Marshall (1988) in a long-term survival analysis (20 years), on 208 women, indicate that the presence of stressful events in the 5-years prior to diagnosis was associated with
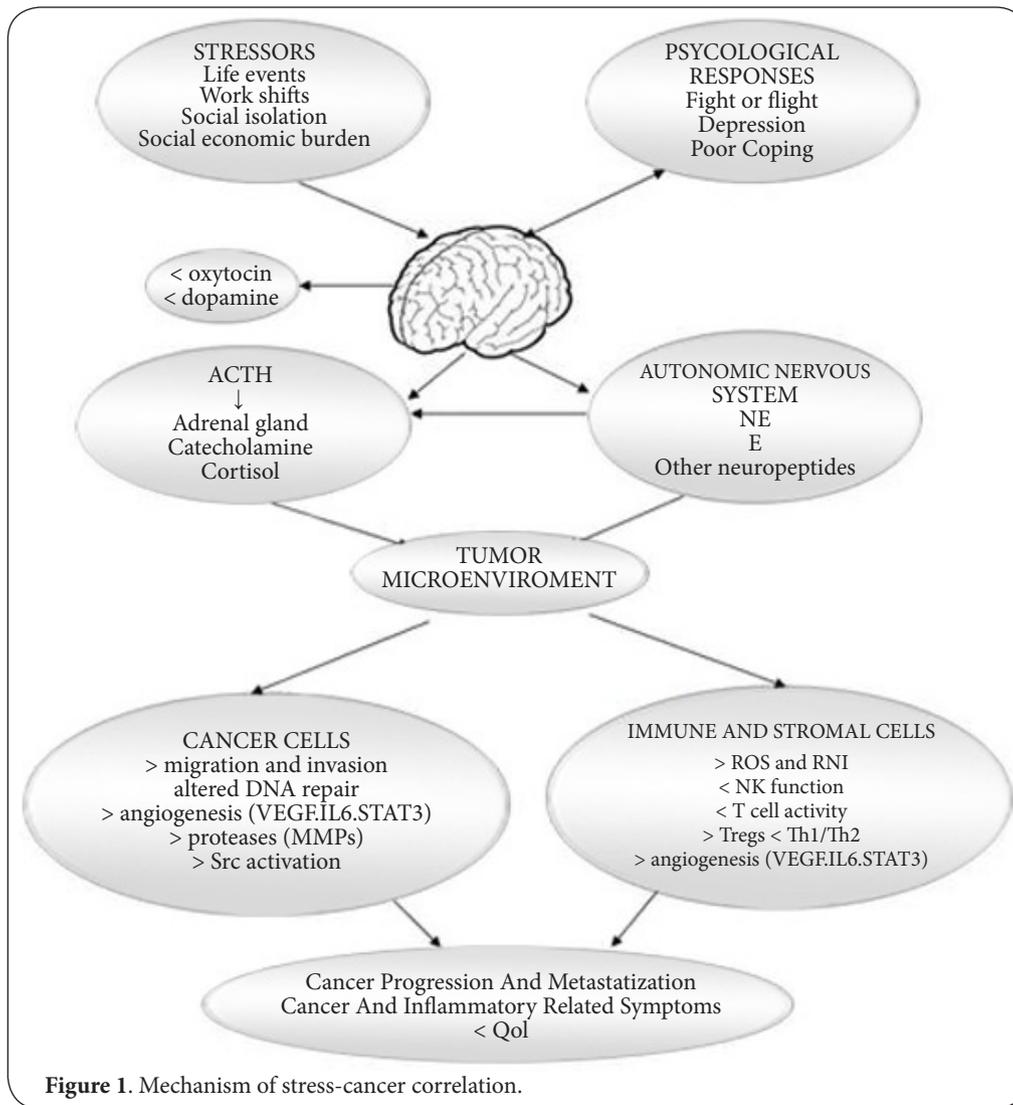
Figure 1. Mechanism of stress-cancer correlation.

shorter survival. These data were also confirmed by Ramirez, et al., (1989), who demonstrated that there was a relationship between stressful events and serious resumption of the disease [11].

Recently Lutgendorf et al., evaluating the association among chronic stress, negative affect, social adversity during and after cancer treatment reported bio-behavioral alterations (increased sympathetic nervous system signaling, hypothalamic pituitary adrenal axis deregulation, inflammation and decreased cellular immunity) [12].

Ultimately, the experimental data and clinical observations argue about the possibility of an interaction between psychosocial events and tumours, although the variables involved are so numerous and distributed over a period of several years to make it impossible, with current technologies, define the causal sequences or chaotic of this hypothetical relationship. Additionally, in the last few decades, many researches were focused on stress response after cancer-diagnosis and during

treatment while no further recent data were added on stress induced disease. There is no doubt about the role of positive psychological support: although it is widely accepted that the psychological support for cancer patients (by family), is both the most helpful in managing distress and may also be the most harmful if mismanaged [13-15].

Most of studies on stress-induced cancerogenesis are pre-clinical, while clinical ones are predominantly retrospective or on a limited number of cases and led to uncertain results, as well as those prospective, on large series [16].

Data from literature are not yet consolidated, some studies did not confirm a direct correlation among stress and cancer. For example, a meta-analysis on the role of stressful life events and risk of breast cancer, evaluating 58,787 patients concludes that there is not an increase in risk [17].

Conversely there are numerous clinical studies, quantitative rather than qualitative, though often criticized from the methodological point of view, which show not only a temporal

overlap between stress and or depression and cancer, but a causal link, especially for the considerable extension in time (in scope of decades) of both diseases. Furthermore, patients with breast cancer and depression have shorter survival compared to non-depressed [18].

But scientists against an etiological correlation argue that the tumour itself can secrete substances (cytokines, growth factors, hormones, etc..) which in turn can act on the central nervous system and induce depressive symptoms.

The hormones produced during stress periods may increase the rate of growth of some particular types of cancer, such as ovarian cancer and nasopharyngeal carcinoma.

A correlation has been found among night shift work and risk of endometrial, breast and colon cancer. Night workers have lower levels of melatonin, which may predispose them to develop cancer. In several reports each one on more than 100000 persons, women who reported more than 20 years of rotating night shift work experienced an elevated relative risk of breast and endometrial cancer compared with women who did not report any rotating night shift work [18-20].

In contrast with these results a meta-analysis of pooled prospective individual participant data, from 12 European cohort studies, demonstrate that high job strain, was not associated with overall risk of cancer (hazard ratio H.R 0.97, 95% confidence interval C.I.0.90 to 1.04) in the multivariable adjusted analyses. Similarly, no association was observed between job strain and the risk of colorectal (H.R.1.16,C.I. 0.90 to 1.48), lung (H.R.1.17, C.I.0.88 to 1.54), breast (H.R.0.97, C.I.0.82 to 1.14), or prostate (H.R.0.86, C.I.0.68 to 1.09) cancers. There was no clear evidence for an association between the categories of job strain and the risk of cancer. The study includes 116 056 men and women, aged 17-70, who were free from cancer at baseline, and have a median of 12 years follow-up [21].

Chronicity of negative affect, as manifested by depressed mood or hopelessness, appears to have stronger relationships with outcomes than do stressful events, suggesting that sustained activation of negative affective pathways may provide the strongest links to cancer progression.

To date correlation with life events is weak. Significant data were reported by Dujts et al., in a meta-analysis on husband/ife deaths [22].

In the same year, a Finnish study of over 10,000 women revealed that divorce/separation and husband death increase the risk of breast cancer [23].

Recently a meta-analysis by the London University group of psychobiology, made of 165 controlled studies, concludes that the psychological stress social-is related to an increased incidence of cancer, a worse prognosis and increased mortality [24].

Additionally a difference exists among chronic stress and repeated short term stress. The latter enhances immune cell traffic to and function within the skin and sentinel lymph nodes [25].

In short correlation Stress/Cancer clinical data deserve further confirmation.

Table 1 summarizes some of the most relevant epidemiologic studies.

The role of psychotherapy

Psychotherapy may decrease stress in cancer patients, potentially reducing the stress-induced cancer progression [26].

There are several types of psychotherapy used in oncology; their different methods of intervention derive from their theoretical models. However psychotherapy goal is to transform the passive attitude and the sense of helplessness and depression experienced by most patients, helping them to propose new objectives and plans for the future. Each method leads to reduce anxiety and depression; improving the mental adjustment to cancer by inducing a positive fighting spirit. Changing of patients' expectations and feelings transformation, from hopelessness and helplessness into feelings of hope and anticipation of healing, are factors that can help clinicians to cure better patients [27-31].

Various types of psychological and psychotherapeutic interventions and social support appear to have a positive impact on both quality of life, tumour progression and overall survival [32,33], probably through influences on the neuro-endocrine-immune [34].

Over 300 trials of psychological interventions have been conducted in cancer patients over the past 50 years, and most have been conducted in women with Breast Cancer (BCa). Newell et al., revising this topic concluded that psychosocial interventions, teaching relaxation and stress management, help patients ventilate feelings. Psychotherapy improves coping strategies, improves quality of life (QoL) and help pain management, providing social support. However the sample size of these trials are generally small to reach a statistical power and efficacy varied as a function of intervention content and format (group vs. individual delivery) [35].

More recent studies with larger samples have generally supported positive effects for psychosocial interventions on QoL indicators in cancer patients [36].

The effects of psychosocial interventions on bio-behavioral processes in populations other than BCa patients have only rarely been studied. One hallmark study, showed that a 6-week group-based psychosocial intervention focused on coping skills and interpersonal support was associated with improved mood, increased NKCC (Na-K-Cl cotransporter), and greater survival and disease-free interval in patients with malignant melanoma followed up to 10 years [37]. More recently, immunological effects of psychosocial interventions have been reported in prostate cancer and gynecological cancer patients. One study showed a 2-session stress management intervention (deep breathing, guided imagery and adaptive coping skills) offered to men prior to surgery for prostate cancer related to decreases in mood disturbance and increases in NKCC one week pre- to 48 h post-surgery [38].

Table 1. Some of the most relevant epidemiologic studies.

Study	pts	Cancer/Design	Stress	Control for confounding	Results
Kuper et al., 2007 [61]	36,332	Breast/Prospective cohort	Work	Done	Association found for low job control and high job demands (HR=1.3 (1.0 to 1.7) for both), and job strain (HR=1.4 (1.1 to 1.9))
Kruk et al., 2004 [62]	822	Case-control	Life events-work	Not done	Association found for major life events, stress of daily activity, and depression (OR=3.70; 95% CI, 2.61–5.26). No association found for stress at work (OR=1.16; 95% CI, 0.82–1.64).
Schernhammer et al., 2006 [18]	37,562	Breast/Prospective cohort	Work	Done	No association found for women in passive (RR=0.90 (0.76 to 1.06)), active (RR=0.83 (0.69 to 0.99)) or high-strain jobs (RR=0.87 (0.73 to 1.04))
Duijts et al., 2003 [22]	7666	Breast/meta-analyses	Life events	Done	The results of this meta-analysis do not support an overall association between stressful life events and breast cancer risk. Only a modest association could be identified between death of spouse and breast cancer risk. An increase in summary odds ratios, for the association between various categories of stressful life events and breast cancer risk, seems to run parallel with an accumulation in severity of these stressful life events.
Chen CC et al., 1995 [63]	41	Breast/Case reports	Life events	NR	Suggest an aetiological correlation
Michael et al., 2009 [64]	84,334	Breast/Prospective cohort	Life events	Done	Association found for one life event (HR=1.12 (1.0 to1.25)), no dose-response
Lillberg and Colleagues et al., 2003 [23]	10,808	Breast/Prospective cohort	Life events	Done	Associations found for major life events (HR=1.35 (1.09 to 1.67)), divorce/separation (HR=2.26 (1.25 to 4.07)), death of a husband (HR=2.00 (1.03 to 3.88)), or death of a close relative or friend (HR = 1.36 (1.00 to 1.86))

Abbreviations Life events:stressful life events, death of spouse, death of relative or friend, personal health difficulties, nonpersonal health difficulties, change in marital status, change in financial status and change in environmental status. NR: Not reported

Kuchler et al., demonstrated that a psychosocial intervention initiated prior to surgery was associated with improved 10-year survival in patients treated for gastrointestinal cancer [39].

Finally, an integrative medicine approach–Healing Touch–was associated with a greater preservation of NKCC in women with cervical cancer as they went through chemoradiation

treatments as compared to controls [12]. But there is also evidence that palliative care intervention may decrease pain and depression on the one hand and increase survival in metastatic lung cancer patients [40].

All of this work deserves replication in larger samples and longer follow-ups to determine whether these interesting bio-behavioral effects during treatment predict longer-term clinical outcomes.

Table 2 reports results of psychotherapy on cancer patients.

Data on bio-molecular marker and immunodepression
The stress response results by activating the autonomic nervous system and the hypothalamic pituitary adrenal axis. These processes led to tumor micro-environment changes.

The effects of catecholamine are mediated through adrenergic receptors (ADRs), which are the most extensively studied classes of G-protein-coupled receptors.

In the G-protein switching mechanism of control, ADRs can bind the stimulatory G-protein,(Gs), or the inhibitory G-protein, (Gi).

Table2. Influence of psychotherapy on cancer survival.

Study	Cancer	n	Psychological outcome
Spiegel et al., 1989 [65]	Breast	86	Lessdistress, pain
Richardson et al., 1990 [66]	Lymphoma leukemia	94	Better treatment adherence
Linn et al., 1982 [67]	Lung gastrointestinal	120	Less depression, more self-esteem, life satisfaction
Kissane et al., 2007 [68]	Metastatic breast	227	Prevented new depression less hopeless trauma
Andersen et al., 2010 [69]	Primary breast cancer	62	Improvedcoping
Temel et al., 2010 [40]	NSCLC	107	ImprovedQoL
Fawzy et al., 1993 [32]	Melanoma	66	Less distress better coping
Kuchler et al., 1999 [71]	Gastrointestinal cancers	271	Better stress management
Yang HC et al., 2008 [70]	Breast cancer	227	patients in the Intervention arm were found to have a reduced risk of breast cancer recurrence (hazards ratio [HR] of 0.55; P 5.034) and death from breast cancer (HR of 0.44; P 5.016) com-pared with patients in the Assessment only arm. Follow-up analyses also demonstrated that Intervention patients had a reduced risk of death from all causes (HR of 0.51; P 5.028).

Abbreviations: QoL: Quality of life; HR: Hazard ratio

Binding of Gs mediates activation of the cAMP-dependent posphokinases (PKA) system and results in downstream activation of several pathways, resulting in growth and migration of cells, while binding of Gi controls multiple signaling cascades, among them the mitogen activated protein kinase pathway, which is frequently over-activated in cancers [41].

Different type of ADR (8 types are known) stimulation leads to the activation of numerous cascades (such as for ADR alpha inhibition of adenylyl cyclase and the activation of phospholipase C).

Additionally ADRs effect in different cells vary in different cells [42].

In cancer cells β-adrenergic receptors (ADRBs) mediate many effects of catecholamine on target cells [41]. Increase in Neuro-hormones and catecholamine promotes tumor growth and angiogenesis in many murine models such as a mouse model of ovarian carcinoma [43].

Glucocorticoids (GCs) are a class of steroid hormones present in almost every vertebrate animal cell. GCs are part of the feedback mechanism that modulates immune activity and inflammatory responses. Pharmacologic doses of GCs are frequently used to treat conditions that are caused by an overactive immune system. GCs also interfere with various abnormal mechanisms in cancer cells, so they are used in high doses to treat certain malignancies [44]. Despite their anti-inflammatory action, recently their role in combination with chemotherapies has been discredited as several reports hint a role in inducing cancer progression by reduce immune system responses [45].

Therefore GCs have a bimodal effect on tumor cells. For example, at lower doses, dexamethasone (a synthetic GC) can stimulate tumor growth, but at higher doses it inhibits tumor growth [46].

Physiologically the GC Receptor (GCR) is located in the cytosol and it is activated by ligand binding. After binding, the newly

formed receptor–ligand complex translocate itself into the nucleus, where it binds to GC response elements in the promoter region of the target genes, resulting in the regulation of gene expression . This process is commonly referred as transactivation. An opposite mechanism also mediated by GCs is called trans-repression. The activated hormone receptor interacts with specific transcription factors (such as AP1 and NF-κB) and prevents the transcription of targeted genes. GCs are able to prevent the transcription of pro-inflammatory genes, including interleukins *IL-1B*, *IL-4*, *IL-6* and *IL-8*, chemokines, cytokines and *TNFA* genes. Through interaction with its GCR, GCs are also able to up-regulate the expression of anti-inflammatory proteins and down-regulate the expression of pro-inflammatory proteins.

IL-6 is a prominent angiogenic factor produced by tumor cells that disrupts this equilibrium.

In cervical cells GCs induce tumor necrosis factor receptor (GITR) leading to cancer invasiveness [47].

In addition, cortisol may act in a synergistic fashion with catecholamine. For example, cortisol has been shown to potentiate the isoproterenol-induced increase in cAMP accumulation in lung cancer cells [48].

Noraepinefrine (NE) has been shown to up-regulate VEGF in adipose tissue through the ADRB–cAMP–PKA pathway [49] Similar findings have been noted in ovarian cancer cell lines and these effects were abolished by a β-blocker, propranolol, and mimicked by isoproterenol [43]. Preclinical studies have shown that the increased levels of NE stimulates tumour secretion of two compounds-the metalloproteinase (MMP)-2 and MMP-9-which, acting on the microenviroment, cause to cancer cells extravasation and metastatization. Furthermore, NE increase stimulates the secretion of the vascular endothelial growth factor (VEGF), inducing angiogenesis within the tumour mass [50].

The NE-driven increases in VEGF synthesis, have been demonstrated in several human multiple myeloma cell lines (e.g., NCI-H929, MM-M1 and FLAM-76) and act via ADRB1 and ADRB2 [51].

Various psychosocial factors have been associated with VEGF in clinical cancer settings. Furthermore, social support has been linked to lower levels of *IL-6*, another pro-angiogenic factor, both in peripheral blood and in ascites from patients with advanced ovarian cancer [52].

This signaling pathway also implicated Src activation in mediating the increased *IL-6* mRNA synthesis through enhanced *IL-6* promoter activity . Since Src activation also induces other pro-angiogenic molecules such as VEGF and IL-8, NE and E (epinephrine) may be responsible for regulating the synthesis of these pro-angiogenic molecules.

Furthermore induced chemokine and cytokine expression also differ if the stress is a chronic or acute (short-term) [51].

For example acutely stressed mice showed higher levels of cutaneous T cell attracting chemokine (CTACK/CCL27, Rantes, IL 12 and IFN γ). These chemokine are involved in recruiting T cells and monocytes to sites of immune activation [25].

Immunodepression has been reported in several cases prior of cancer recurrences [53].

The importance of immunodepression is double: diagnosis and treatment anticipations.

From the one hand patients with eventual disease recurrence demonstrated reliable bio-behavioral alterations more than a year prior to their clinical diagnosis; from the other hand recognizing immune-depression can help to cure and prevent the metastatic disease strengthening the immune system and intervening earlier than is currently possible.

T helper (Th) cells are crucial for the development of an immune response by activating antigen-specific effector cells and recruiting cells of the innate immune system, such as macrophages and mast cells. There are two predominant Th-cell subtypes: Th1 and Th2. While Th1 cells directly kill tumor cells via release of cytokines that activate death receptors on the tumor cell surface, Th2 cells favor a predominantly humoral response. Th2 immunity may be enhanced by stress hormones (catecholamine and GCs) increasing a shift from predominantly Th1 to Th2 cells. This shift is thought to better enable tumor cells to evade immune surveillance [54]. The helper 17 cells play an active role in inflammatory and autoimmune diseases [55]; however, recent studies suggest a potential impact of Th17 on tumors. Kryczek and colleagues have shown that the levels of Th17 cells were significantly increased in peripheral blood, ascites fluid and tumor tissues in human ovarian, renal and pancreatic carcinomas [56]. Similarly, the proportion of Th17 cells in peripheral blood of gastric cancer patients was significantly higher than in healthy donors (6.7 ± 3.7 vs $1.8\pm1.1\%$; $p<0.01$). Moreover, patients with advanced disease had an even higher percentage of Th17 cells than patients with lower-stage disease or healthy controls. It is known that CD4+, CD25+, FoxP3+ and other additional regulatory T cells (Tregs) are elevated in cancers [57]. Tregs play a crucial role in tumor immune pathogenesis and tumor immune therapeutic efficacy [56]. Recent human cancer trials suggest that depleting Tregs may be clinically beneficial [57].

Among advanced breast cancer patients, depression has been related to a reduction in cellular immune response to a variety of specific antigens [58].

Another study showed that telephone-delivered psychosocial counseling intervention is associated with improved QoL and a shift toward a more favorable lymphocyte T helper (Th1/h2) cytokine ratio in women with cervical cancer [59].

Distress among ovarian cancer patients at the time of surgery has been associated with poorer NK-cell activity in tumor-infiltrating lymphocytes (TILs) and lower T-cell production of Th1 versus Th2 cytokines in peripheral blood and TILs, whereas social support was related to greater NK-cell activity in both peripheral blood and TILs [60]. Additionally activated inflammatory cells serve as sources of reactive oxygen species (ROS) and reactive nitrogen intermediates (RNI) that are capable of inducing DNA damage and genomic instability [50].

Taken together, these findings point out psychosocial modulation of immune factors relevant to cancer detection and control. It has been suggested that an inflammatory microenvironment can increase mutation rates, in addition to enhancing the proliferation of mutated cells.

Table 3 reports some of the most relevant molecular findings.

Conclusions

A large number of epidemiological studies have supported the relation between stress/stressful life events and risk of cancer, but the variables involved are so numerous that it is difficult with current technologies to define the causal or chaotic sequences of this hypothetical relationship. In

Table 3. Molecular findings.

Study	Models	Stress	Time	Stress type	Results
Dhabhar F et al., 2010 [25]	SKH1 mice	UVB exposure	3 time per week	Short term stress	Greater CTAK/CCL27,RANTES,IL12;IFNγ, higher skin infiltrating T cell, lower tumor incidence
Shuaasha et al., 2012 [72]	F344 rats and long-evans rats	Wet exposure	10 hrs of wet-cage exposure two weeks of daily alternating stress paradigms	Acute chronic	our findings indicate a generic and robust stress-induced reduction in plasma IL-12 levels, and suggest epinephrine, corticosterone, and prostaglandin-E(2), as potential mediators that should be scrutinized in vivo in the context of natural physiological stress responses.
Saul et al., 2005 [73]	SKH1 mice	UVB exposure	Daily 21 days	Chronic	Increasing susceptibility to lung cancer
Benish et al., 2008 [74]	F344 rats	Surgery (laparotomy)	1 day	Short term	Increase tumor cells lungs' retention
Scwartz et al., 2008 [75]	F344 rats	Surgery±8days exposure to IL-12 (1 microg/rat/day)	1 day	Short term	anti-tumor effects of IL-12 based on increased numbers of strategically located NK cells, and advocates a prophylactic approach against the potential metastasis-promoting effects of surgery.
Lamkin DM et al., 2012 [76]	SCID mice	Restraint stress	2h per 14 days	Chronic	Progression Acceleration of ALL tumor load via β adrenergic signaling pathway

Abbreviations: CTAK: Cutaneous T cell attracting chemokine; ALL: Acute lymphoblastic leukemia; microgr: Micro grammo

addition the event will be spread over a period of several years. However growing interest in this phenomenon has been reported in the recent years. For example it is known that "the big killers" (lung breast and colon cancer) are more common among people who had experienced stressful life events prior to the onset of their disease (compared to controls). Despite these data , the association between life events and cancer development is still highly controversial. The evidence available to date demonstrates the ability of many different psychosocial interventions to improve responses to the stress and adversity of the cancer experience in order to improve psychological adaptation.

Reduction in negative affect and social disruption and improvements in positive affect improve quality of life. Coping strategies have been linked to an improved physiological profile during and after treatment, which may increase the odds for disease-free survival in some cancers.

However the role of psychotherapy deserve further investigation to establish the reliable effects of these interventions on clinical outcomes (recurrence and survival) in more cancer populations Emerging biotechnologies (immune-biology, microenvironment analyses, bioinformatics and microarray) could clarify the juncture of neuro-immune communications underlying inflammatory/stress-induced micro-environment and tumor promoting cell signaling.

Different stress response led to enhance or reduce cellular immunity and resistance to cancer. The fight or flight stress response is one of nature's under-appreciated defense mechanism that activates multiple psycho-physiological systems to promote survival.

The knowledge of biological mechanisms about the "fight or flight stress response and its adjuvant-like immune-enhancing effects" may provide a novel mechanism to promote or increase immune system-mediated tumor detection/elimination. The goals of innovative approach should be to facilitate the biological mechanism of endogenous immune-enhancement. A close collaboration between oncologists and psychologists is desirable to deal promptly and effectively with stress-induced cancer and stress during neoplastic diseases.

List of abbreviations
NE: Norepinephrine
E: Epinephrine
ACTH: Adrenocorticotropic hormone
NK: Natural killer
Th: T helper
Tregs: Regulatory T cells
MMPs: Metallo-proteinases
Src pathway: Rous sarcoma virus pathway
ROS: Reactive oxygen species
RNI: Reactive nitrogen intermediates

QoL: Quality of life

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Authors' contributions	ND	LT	EGR
Research concept and design	✓	✓	--
Collection and/or assembly of data	✓	✓	--
Data analysis and interpretation	✓	--	--
Writing the article	✓	✓	--
Critical revision of the article	✓	--	--
Final approval of article	✓	✓	✓
Statistical analysis	✓	--	✓

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