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IS THERE ANY EVIDENCE OF THE BELIEF THAT STRESS COULD INCREASE THE RISK OF FEMALE CANCERS?

L. DEL PUP

Gynecologic Oncology, National Cancer Institute, Aviano, PN, Italy

Abstract: *The question of whether psychosocial stress is a factor in female cancer etiology is frequently asked and challenging for the physician to answer. Stress-prone personality or unfavorable coping styles and negative emotional responses or poor quality of life are associated with higher cancer incidence, poorer survival and higher cancer mortality. Among female cancers the relation to stress is more extensively studied and a stronger link is found for breast cancer survival.*

An experimentally proven direct oncogenic mechanism is the stress-induced change in immune surveillance and/or in endocrine function that predisposes to female cancer. Stressful life experiences could indirectly promote high-risk behaviors such as smoking, poor diet, lack of exercise, obesity, excessive alcohol consumption, poor sleep or lower screening, early diagnosis or treatment adherence. Given the impossibility of avoiding stressors, promotion of better strategies of coping not only improves quality of life but it could theoretically help reducing cancer risk.

KEYWORDS: *Breast cancer, Gynecologic cancer, Stress, Cancerogenesis.*

INTRODUCTION

Stress is the internal reaction of the organism to its environment that is positive (eustress), as in conditions of acute danger, the body reacts with alert behavior to preserve integrity. Negative stress or "distress" occurs when the activation, intensity, and persistence of the stress results in physical and psychological disorders. Many gynecological diseases can be caused or contributed by stress, like menstrual dysfunctions, ovulatory infertility, and sexual dysfunctions[1]. Distress, as an effect of the diagnosis and treatment of cancers, could result in immune suppression and worsening of prognosis[2]. Whether psychosocial stress is a causal factor in female cancers is a frequently asked question. It is difficult for the physician to answer as literature is controversial; only some pathophysiological mechanisms are known, literature has many methodological limitations and the subject is difficult to study, as not only negative life events but mostly dysfunctional copying styles are the most important etiological factors.

MATERIALS AND METHODS

In order to find if there is any evidence of the belief that stress could cause female cancers, a review of the literature till December 15th 2017 was performed using the following Medline search strategies: ((("Stress, Psychological/COMPLICATIONS"[MH] OR ((DISTRESS[TI] OR (STRESS*[TI] AND (psychology OR emoti* OR PSYCHOLOG*[TI])) AND (RISK OR IMPACT[TI] OR COMPLICATIONS)))) AND (Genital Neoplasms, Female[MH] OR BREAST NEOPLASMS[MH] OR breast cancer[ti] OR ovarian cancer[ti] OR uterine cancer[ti] OR vulvar cancer[ti]) AND (female OR woman OR women OR girl*) AND (ITA[LA] OR ENG[LA] OR GER[LA] OR FRE[LA] OR SPA[LA])) NOT (NEOPLASMS/DIAGNOSIS[MH] OR NEOPLASMS/THERAPY[MH] OR NEOPLASMS/COMPLICATIONS[MH] OR cancer patient*[ti] OR CANCER SURVIVOR*[TI] OR CANCER DIAGNOSIS[TI] OR (diagnosed[tiab] AND cancer[tiab]) OR (THERAPY[TI] AND CANCER[TI]) OR Patient Acceptance of Health Care[MH] OR NEOPLASMS/PATHOLOGY[MH]).

Corresponding Author: Lino Del Pup, MD; e-mail: ldelpup@cro.it

RESULTS

A substantial body of research has investigated the association between stress related psychosocial factors and cancer. Brain, endocrine, and immune system, form a complex integrated circuit, communicating through multiple mediators that interact, such as neurotransmitters, neuropeptides, hormones, lymphoid tissue growth factors, cytokines and eicosanoids. Psychological factors, including stress and depression, alter these systems and could derange the endocrine and impair the immune function. This seems to be the main reason for an individual to develop cancer and many other female diseases[3]. Stress-prone personality or unfavorable coping styles and negative emotional responses or poor quality of life are associated with higher cancer incidence in initially healthy populations ($p = 0.005$), but more significantly poorer survival in patients with diagnosed cancer ($p < 0.001$), and higher cancer mortality ($p < 0.001$)[4]. For breast, lymphoid and hematopoietic cancers, stress-related psychosocial factors have effects on survival rather than incidence. Psychosocial stress is associated with both increased incidence and survival of lung cancer.

An experimentally proven direct oncogenic mechanism is the stress-induced change in immune surveillance and/or in endocrine function that predisposes to female cancer. Cortisol has protective effects on the organism by regulating immune function, promoting memory of dangerous events, increasing blood pressure and heart rate to meet the physical demands of a fight or flight response, and making fuel available for sustaining increased physical activity. Prolonged stress-response conditions similar to those stimulated by stressful life events, however, have been shown to predispose illnesses such as hypertension, atherosclerosis, osteoporosis, immune dysfunction, and cancer[5]. Stressful life experiences could also indirectly promote high-risk behaviors such as smoking, poor diet, lack of exercise, obesity, excessive alcohol consumption, poor sleep or lower screening, early diagnosis or treatment adherence. The main mechanism that could explain the putative role of stress in increasing the risk of female cancers is summarized in Table 1.

Possible direct oncogenic mechanisms of stress

Direct oncogenic pathways initially involve the central nervous system, where stress activates components of the limbic system, which includes the hypothalamus, hippocampus, amygdala, and other nearby areas. In response to neurosensory signals, the hypothalamus secretes corticotrophin-releasing factor (CRF) and arginine vasopressin (AVP), both of which activate the pituitary to produce hormones such as adrenocorticotropic hormone (ACTH). A cascade of information-processing pathways in the central nervous system (CNS) and periphery triggers fight-or-flight stress responses in the autonomic nervous system (ANS), or defeat/withdrawal responses that are produced by the hypothalamic-pituitary-adrenal axis (HPA). Circulating ACTH stimulates the production of glucocorticoids from the adrenal cortex.

The sympathetic nervous system originates from the brainstem, and the pre-ganglionic neurons terminate in the ganglia near the spinal column. From these ganglia, post-ganglionic fibers run to the effector organs. The main neurotransmitter of the pre-ganglionic sympathetic fibers is acetylcholine and the typical neurotransmitter released by the post-ganglionic neurons is noradrenaline. The adrenal medulla contains chromaffin cells, which release mainly adrenalin.

The aim is protective, but long lasting and/or intense stress impairs immune function and alters hormonal balance predisposing to the development of female cancer. Glucocorticoids control growth, metabolism and immune function, and have a pivotal role in regulating basal function and stress reactivity. Therefore, they are generally considered adaptive. However, under chronic stress, prolonged exposure to glucocorticoids and catecholamines is detrimental. The effects include the promotion of tumor-cell growth, migration and invasive capacity, and stimulation of angiogenesis by inducing production of pro-angiogenic cytokines modificating factors like CRF (corticotrophin-releasing factor), IL-6 (interleukin-6), MMP, (matrix metalloprotein-

TABLE 1. Possible mechanisms by which stress could increase female cancer risk.

Direct	*Indirect*
Reduced immune surveillance Altered endocrine function	Unhealthy lifestyle associated with stress: smoking, poor diet, lack of exercise, obesity, excessive alcohol consumption, loneliness and poor sleep. Busy life and reduced adherence or later access to cancer screening, early diagnosis or treatment.

ase) and VEGF (vascular endothelial growth factor). Stress hormones can also activate oncogenic viruses and alter several aspects of immune function, including antibody production, cytokine production profiles and cell trafficking. Collectively, these downstream effects create a permissive environment for tumor initiation, growth and progression.

Direct stress pathways of influence also include effects of catecholamines and glucocorticoids on tumor-cell expression of genes that control cell proliferation, invasion, angiogenesis, metastasis and immune evasion. Furthermore, neuroendocrine deregulation can influence the response to conventional therapies such as surgery, chemotherapy and immunotherapy[6].

Psychoneuroimmunology theories of cancer[7] consider the brain as an adaptive and dynamic synthesizer of experiential and perceptual processes that can participate in the complex regulation of signaling systems used by the diverse array of cells and structures to influence oncogenesis. The activation of the sympathetic nervous system and the hypothalamic-pituitary-adrenal axis influence molecular signaling pathways involved in DNA repair, angiogenesis, cell survival, inflammation, invasion, metastasis, and resistance to therapy. Tumor cells and stromal compartments within the cancer microenvironment can be sensitive to catecholamines (epinephrine, norepinephrine, dopamine) bind to α-adrenergic receptors (α-ARs) and β-adrenergic receptors (β-ARs), and to acetylcholine that binds to families of nicotinic (nAChRs) and muscarinic (mAChRs) receptors[8]. These hormones could modulate the activity of multiple components of the tumor microenvironment. Neuroendocrine receptor-mediated signaling can regulate leukocyte gene expression, molecular processes, and functional characteristics of cells within microenvironments influencing tumor cell growth, migration and invasive capacity, and stimulation of angiogenesis by inducing production of pro-angiogenic cytokines.

The influence is reciprocal and complex, as peripherally generated inflammatory and other innate immune mediators can signal back into the central nervous system, stimulate afferent nerves that produce local cytokines, change neuronal function, and cause sickness behaviors as an adaptive response to systemic pressures. Immune-to-brain communication cascades are thought to undergird cancer and treatment-related symptoms such as fatigue, depression, cognitive dysfunction, and sleep disturbance[9].

Stress-responsive neuroendocrine mediators can also influence malignant potential indirectly through activating oncogenic viruses and altering immune function, including antibody production, cell trafficking, and the production and release of proinflammatory cytokines[10].

Stress Indirect Effects

Stress might cause cancer indirectly promoting high cancer risk behaviors such as smoking, obesity, excessive alcohol consumption, poor diet, lack of exercise, poor sleep or lower treatment adherence. Stress and stress exposure are associated with the initiation and maintenance of smoking. Both smoke and more frequent food cravings are caused by stress and depressive symptoms. Cigarette smokers, especially those with higher nicotine dependence, may have greater difficulties in addressing food craving and changing eating habits, particularly in the context of depression and stress[11]. Increased levels of psychological distress induce use of both tobacco and electronic cigarettes[12]. However, as already mentioned by Chida et al[4], the effects of stress-related psychosocial factors on cancer incidence (HR 1.07, 95% CI 1.00-1.14, $p = 0.045$) and cancer survival (HR 1.90, 95% CI 1.28-2.83, $p = 0.002$) persisted even after fully controlling for these indirect factors

In the Wisconsin Longitudinal Study[13] using the 1957-2011 data from 3682 white non-hispanic women with 297 incident breast cancer cases, the effect of occupation in 1975 at age 36 on breast cancer incidence up to age 72 was studied. Higher-status occupations were linked to elevated breast cancer risks, which overcome the health advantage of higher social class: women in professional occupations had 72-122% and women in managerial occupations had 57-89% higher risk of a breast cancer diagnosis than housewives and women in lower-status occupations. The estrogen-related pathway (reproductive history, health behaviors, and life-course estrogen cycle) only partly explained the link that remained large and statistically significant. The association between managerial occupations and breast cancer incidence was instead better explained by job authority defined as control over others'work, which was related to higher breast cancer risk (HR = 1.57, 95% CI: 1.12, 2.18), especially with longer duration of holding the professional/managerial job. Maybe job authority by women in the 1970s involved stressful interpersonal experiences that may have promoted breast cancer development via prolonged dysregulation of the glucocorticoid system and exposure of the breast tissue to adverse effects of chronically elevated cortisol.

Stress and breast cancer

Various epidemiologic studies have indicated that psychological stress could increase in breast cancer risk. This is confirmed by recent literature and by meta-analysis[14-17], but the subject is still controversial.

Reduced protective brca function

BRCA1 is a tumor suppressor involved in the maintenance of genomic stability and prevention of cell transformation. *BRCA1* can be considered as a central rheostat of breast cancer risk, with its transcriptional regulation being controlled by a variety of factors, one of which is psychological stress. A significant event leading to the development of breast cancer is loss of BRCA1 function. Many studies showed that stress increases the binding of cortisol to the glucocorticoid receptor (GR) that interacts with BRCA1 promoter and activates BRCA1 expression. Hydrocortisone, binds the GR, eliminates the interaction and thus could increase the risk of breast cancer[18].

Reactivation of latent viruses

The second mechanism by which stress causes a deficiency of the GABP transcription factor involves the presence of certain latent viruses in the cell. GA-binding protein (GABP) exists as a heterodimer consisting of an *ETS* helix-loop-helix DNA-binding domain (DBD) subunit (GABPα) and a Notch-ankyrin repeat subunit (GABPβ), which contains the activation domain as well as a domain, required for the formation of tetrameric complexe. GABP has been implicated in the regulation of genes in response to cell growth, activation of respiration-related genes, as a downstream mediator of ErbB3 and ErbB4 signaling, in connecting mitochondrial metabolism and breast differentiation. The interaction of the α- and β-subunits with each other and with other transcription factors defines the ability of GABP to regulate the expression of its target genes. Many viruses consist of a core binding sequence as part of their enhancers, the N-box. When such a virus establishes a latent infection, the viral N-boxes bind the GABP·p300 transcription complex. Furthermore, since this complex is limiting, the viral N-boxes decrease the availability of the complex to cellular genes. As a result, the cellular genes that are stimulated by the GABP·p300 complex produce fewer proteins, and the genes that are suppressed by this complex produce more proteins. The abnormal levels of these cellular proteins induce disease; "microcompetition" describes the relationship between viral and cellular regulatory elements. It is interesting that many common viruses, which establish a latent infection, have a strong N-box in their promoters/enhancers: Epstein-Barr virus (EBV), Cytomegalovirus (CMV), Herpes Simplex Virus (HSV), Varicella Zoster Virus (VZV), Hepatitis B Virus (HBV), Hepatitis C Virus (HCV), and Human Papillomavirus (HPV). CMV has the strongest promoter/enhancer known[19].

Stress induced cortisol hyperactivation
Chronic strains of caring occupations are likely to be associated with systematically elevated cortisol that could contribute to breast cancer etiology[20].

Indirect effects

The importance of lifestyle and psychological stress on the development of early onset breast cancer has been analyzed in a comparative case-control study[21]. A total of 582 cases of young patients (≤40 years old) with breast cancer and 540 controls of young patients (≤40 years old) with benign breast disease were included in this study. The significant risk factors for breast cancer in young women included also disharmonious marital status (OR=1.16, 95% CI: 1.06-1.26), frequent depression (OR=1.32, 95% CI: 1.00-1.75), and negative emotional experiences (OR=1.15, 95% CI: 1.03-1.29). These chronic distresses are also associated with increased alcohol consumption, increased high-fat food consumption, decreased exercise and increased body mass index. Measurable effects are suppressed immune function and dysregulated cortisol both of which can support breast tumor progression. Stressed women tend to have a suboptimal screening even though they are at increased familiar cancer risk[22].

Stress and gynecologic cancers

Gynecologic cancers can be caused by a variety of factors: genetic syndromes, like BRCA and Lynch 2, oncogenic HPV, obesity and lack of exercise, reproductive and environmental factors and exposure to endocrine disruptors[23,24]; so, the contribution of each factor is difficult to study.

Literature specifically analyzing the putative net effect of stress on gynecologic cancers was not found in our review, but some oncogenic

mechanisms could be common with those already discussed. Cervical, vaginal, vulvar and anal cancer are related to oncogenic HPV. A direct evidence of the possible role of stress on these cancers could be reduced immune surveillance. An indirect link can be the oncogenic lifestyle like smoking, whose risk could be increased in stressed individuals. BRCA has a role in salpingeal - ovarian cancer as well, so the same effect of stress as in breast cancer could be supposed. We couldn't find data on the direct effect of stress on endometrial cancer, but a least an indirect effect mediated by stress effects on known risk factors of this cancer, like anovulation, infertility, body weight and sedentary, is very likely. Of note is the fact that frequent coffee consume significantly protects form endometrial cancer[25].

Methodological limitations of studies

Stress is intrinsically difficult to study, as it is a complex product of exposure to adversity, which cancer effects are influenced by cognitive appraisal, behavioral characteristics and coping style, personality, social support, and emotional responses highly subjectively variable among individuals. Maybe resilience and coping style are more important that stressful events per se, but much more difficult to study.

Acute and strong psychologically stressful events are relatively easy to be linked to short-term biological effects. Chronic stress variable in quantity and quality acting in an individual with subjective and evolving coping strategies is extremely difficult to be studied. Apparently, even light stress-related psychosocial factors have a slow but cumulative impact on cancer in long periods.

Cross-sectional and retrospective case-control studies are subject to recall bias caused by cancer diagnosis or memory distortion. Such studies cannot detect a longitudinal association between predictors and outcome variables: patients re-evaluate their lives and might selectively recall their experience before the disease diagnosis. If a patient believes that stress causes illness, then he or she may retrospectively reinterpret his or her earlier experience in order to make sense of the illness. Prospective studies that have assessed stress and related psychosocial factors before diagnosis cannot completely exclude a biological effect of cancer on psychological states, as the psycho-neuro-immune influence is reciprocal. Few studies have used meta-analytic techniques to quantify the extent to which psychosocial factors affect cancer. No randomized controlled studies in humans have been found. Variability between studies may also stem from the distinctive time windows of relevant exposure to stress examined. The latency period between stress exposure and cancer initiation is unknown: in case of breast cancer development is estimated to occur over 10 to 20 years or more. Breast cancer is frequent and well studied but the relation of stress with gynecologic cancer is poorly known.

CONCLUSIONS

The question of whether psychosocial stress is a factor in female cancer etiology is frequently asked and challenging for the physician to answer, as literature is still controversial due to the complex and highly subjective reaction to stressors. An experimentally proven and likely direct oncogenic mechanism is the stress-induced change in immune surveillance and/or in endocrine function that predispose to female cancer. Stressful life experiences could indirectly promote high-risk behaviors such as smoking, poor diet, lack of exercise, obesity, excessive alcohol consumption, poor sleep or lower screening or treatment adherence. Given the impossibility of avoiding stressors, the promotion of better strategies of coping with it not only improves the quality of life, but it could also be a further cancer preventive measure. Psychosocial interventions such as relaxation and cognitive behavioral techniques seem to modulate autonomic nervous system (ANS) and the hypothalamic-pituitary-adrenal (HPA) axis hormonal activity.

Stress management interventions that dampen chronic-stress-related physiological changes might facilitate immune surveillance. Group-based psychosocial interventions that combine relaxation with cognitive behavioral techniques, such as cognitive behavioral stress management (CBSM), have been shown to increase indicators of immune responses against potentially oncogenic viral infections, such as EBV. Such alterations are paralleled by decreased expression levels of cortisol in the serum, decreased in urinary cortisol and noradrenaline output, increased social support and enhanced relaxation skills[26].

Lonely people are highly stress-reactive, and produce more TNF-α, IL-6, and IL-1β production in response to an acute stressor. Social support may produce a better immune response, as it reduces the level of cortisol and restores the natural killer cell number and production of cytokines, whereas social isolation increases the risk of death associated with several chronic diseases[27-29]. Some pharmacological therapies could

potentially be used in the future, in conjunction with psychological and conventional cancer therapies, to maximize cancer treatment efficacy in stressed patients.

Beta-blockers have been shown to block many of the deleterious effects of stress; antidepressant medications might be promising, owing to a concomitant suppression of an inflammatory response associated with certain types of cancer[30]. Lithium inhibits prostaglandin E1, and tricyclic antidepressants antagonize thromboxanes and could help in the prevention and treatment of cancer[31]. These studies could help developing new preventive or therapeutic cancer strategies, although much more research should be done before validating pharmacologic prevention of stress induced female cancers.

Conflict of interests

The authors declared no conflict of interests.

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