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# Is There a Link Between Psychological Stress and Adverse Life Events with Increased Risk of Developing Cancer?

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**Abstract.** Does psychological stress and other social stresses in humans affect cancer risk? This was a big question that was hovering for many decades among people and scientists contemplating the causes of cancer. There is a widespread public belief that psychological stress leads to disease, including cancer. Medical studies and clinical evidence were observing that stressful events in humans can alter the levels of hormones in the body and adversely affect the immune system. But there were many difficulties to support clear evidence that these changes could lead to mechanisms of initiation and progression of cancer and increased risk to develop neoplastic tumours. Studies in the 1980 and 1990s suggested that psychological stress and stress variables (death of children, relatives, divorce, separation, health worries, etc) can cause cancer, particularly breast cancer. But the evidence for this has not been substantiated by recent studies with high numbers of participants. Women diagnosed with breast cancer frequently attribute their cancer to previous periods of psychological stress, and adverse life events prior to diagnosis, but scientific evidence is inconclusive. While some studies have found a link between breast cancer and psychological stress, they have often only looked at a small number of participants or asked women to recall if they were stressed before they developed the disease. Scientists observed that psychosocial stress in humans leading to physiological stress response, increased secretion of hypothalamic and pituitary stress hormones. These stress biomarkers can trigger and maintain chronic inflammation, which has been shown to have various roles in cancer initiation and progression. Another dimension of stressful life events is increased unhealthy habits, like tobacco smoke, alcohol consumption, excessive food intake, obesity and lack of exercise. All these changes in life style are associated risk factors for chronic inflammation, carcinogenic mechanisms and increased cancer risk. Also, healthcare professionals hold the view that stress has a role in the development of the disease, but these views might be from recall bias (patients possibly over-reporting past exposures to stress). But in the most recent epidemiological study with the participation of high numbers of cancer patients, the results have found that stress does not increase the risk of cancer. Researchers combining the results from many different studies (meta-analyses, including over 100,000 people, 2013) found no link between stress and bowel, lung, breast or prostate cancers. This review is a systematic compilation of research papers, scientific reports, epidemiological and meta-analysis studies on the possible association of psychological stress with chronic diseases, inflammation and cancer.

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## 1. Introduction : Can Psychological Stress Cause Cancer?

Health professionals from practical observations know that stress in small doses can be positive in humans because it makes humans more alert and aware of problems in adverse social and health situations. But it is evident that long periods of stress can contribute to high blood pressure and mental health problems such as anxiety and depression. Also, it has been observed that stressful situations can encourage less healthy choices (smoking, overeating and heavy drinking, lack of exercise, obesity, reduce hygiene, etc). All these activities are very important risk factors to inflammatory processes and can lead to cancer. In this respect, medical professionals indicated long time ago that stress could indirectly increase cancer risk to humans.[1,2]

Epidemiological studies showed that psychological stress can cause a number of physical health problems, but evidence that stress can cause cancer is weak. Some studies in the past decade have indicated a link between various psychological factors and an increased risk of developing cancer, but others have not. In the other hand, links between psychological stress and cancer could arise in several ways. For example, people under stress may develop certain behaviours, such as smoking, overeating, or drinking alcohol, which increase a person's risk for cancer. Or someone who has a relative with cancer may have a higher risk for cancer because of a shared inherited risk factor, not because of the stress induced by the family member's diagnosis.[3,4]

The major causes of cancer have been established by numerous studies and statistical global data in the last decades. Cancer organizations, such as the Cancer Research UK, the World Health Organization (WHO), the National Cancer Institute, have used these statistics to present a comprehensive list on the causes of cancer in their information internet platforms. Research (epidemiological, clinical, meta-analysis) showed that a high proportion of cancer deaths are due to lifestyle: smoking, unhealthy diets (low fruit and vegetables, animal fat, lack of vitamins), alcohol and obesity. Diet, physical inactivity and obesity are related to approximately 30–35% of cancer deaths. Tobacco

smoking is responsible for more than 30% of cancer deaths because is associated with many forms of cancer and is particularly responsible for 80% of lung cancer. Worldwide approximately 18% of cancer deaths are related to infectious diseases. Up to 10% of invasive cancers are related to radiation exposure, including both ionizing radiation and non-ionizing UV radiation. The vast majority of cancers are non-hereditary ("sporadic cancers"). Hereditary cancers are primarily caused by an inherited genetic defect. Less than 0.3% of the population are carriers of a genetic mutation which has a large effect on cancer risk and these cause less than 3–10% of all cancer. Some hormones play a role in the development of cancer by promoting cell proliferation. Carcinogenic chemicals (asbestos, PAHs, heavy metals, benzene, vinyl chloride, tar, etc) can cause cancer after prolonged exposure in the working environment (~5%). Air pollution also causes up to 3-5% cancer deaths in people living in highly polluted urban areas.[5-7]

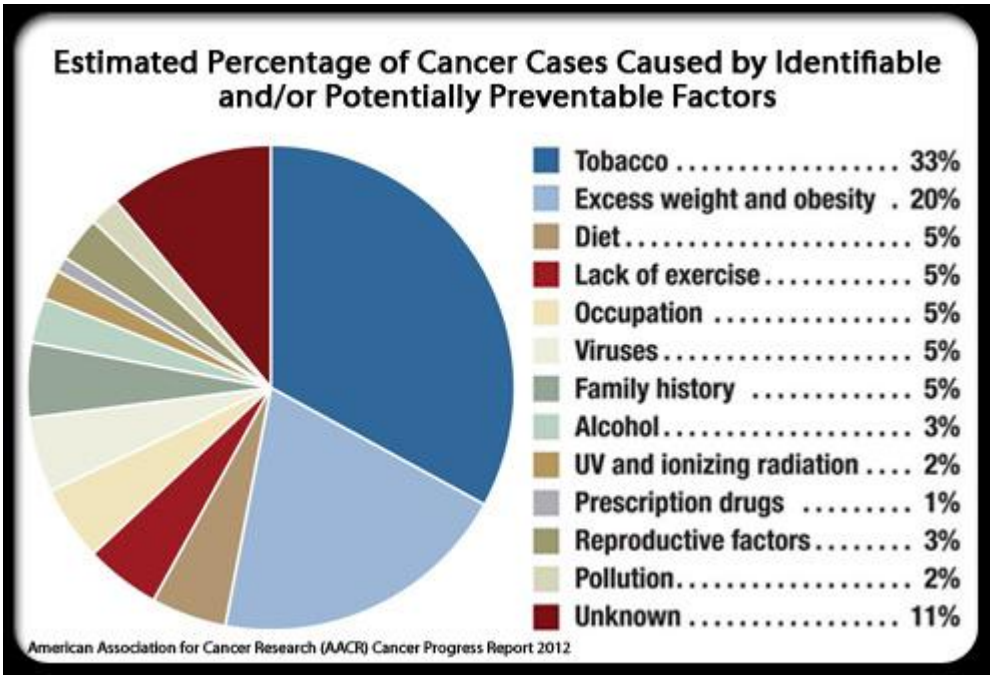



**Figure 1**. The causes of cancer. American Association for Cancer Research. 2012. Diet, tobacco, sunlight & radiation, infections, occupational exposures, reproductive factors. Psychological stress is not among causes of cancer, although unknown factors are estimated at 11%

Medical experts support the link between cancer and psychological stress, based on the assumption that stress decreases the body's ability to fight to kill cancer cells. But, the National Cancer Institute (USA) emphasized the scientific facts that: "…although studies have shown that stress factors alter the way the

immune system functions, they have not provided scientific evidence of a direct cause-and-effect relationship between these immune system changes and the development of cancer". Similarly, the American Cancer Society stated : "…There are many factors to look at in the relationship between stress and cancer. It's known that stress affects the immune system, but so do many other things. Despite many studies, a link between psychological stress and cancer has not been proven. Looking at the studies that have been done, it seems they sometimes come to opposite conclusions".[8]

The widespread public belief that psychological stress can influence initiation of cancer in humans was very strong among psychologists in the 1990s. A group of well known scientists (including HJ Eysenck, Dpt of Psychology, Institute of Psychiatry, London) were strong supporters of the theory that psychological factors can influence risk to cancer through the working of the immune system. According to the theory there was not any doubt that psychological determinants constitute an important risk factor for cancer, and interact synergistically with other risk factors (smoking, genetic influences, etc).[9,10]

In 2000, they published a study (which started in 1973) supporting the link of mammary cancer and psychological risk. The study included 8,059 healthy women (mean age 58 yrs) with the aim of establishing the presence or absence of a variety of physical and psychological risk factors for mammary cancer. Mortality was established 15 yrs later in 1988. Both physical and psychological risk factor predictors were highly significant. They found that physical risk factors (diet, smoking, etc) were more predictive than psychological ones, but both interacted synergistically to predict mortality (this was a suggestive comment with very little experimental evidence). They admitted that psychological stress factors had little effect, while physical factors did. However, they concluded that psychological stress factors seemed to potentiate the effect of physical factors, particularly in the middle range. The causal relevance of psychological factors was established in a special intervention study, using autonomy training as a method of prophylactic therapy.[11]

Despite widespread public belief that psychological stress leads to disease, scientists from the biomedical community in western countries remain skeptical of this conclusion. A paper discussed the plausibility of the belief that stress

contributes to a variety of disease processes and summarized the role of stress in 4 major diseases: clinical depression, cardiovascular disease (CVD), human immunodeficiency virus (HIV)/AIDS, and cancer.[12] Strong experimental evidence showed that chronic and acute psychological stress is directly implicated in cardiovascular diseases (CVD), through the modulation of immune, endocrine and metabolic pathways. Scientists put more attention to the bidirectional interaction between psychological stress in relation to CVD. Experimental research into the biological pathways involved in stress-induced cardiovascular complications show important roles for metabolic and immunologic maladaptation, resulting in increased disease development and progression. A recent overview presented the most important research papers on human and experimental animal data linking chronic and acute stress to CVD risk and progression of atherosclerosis.[13]

Various arguments among the scientific community appeared in the scientific publications in the 1980s. Especially, about the controversial assumptions for the mechanisms of psychological stress might alter the immune function in a manner that influences the development of malignant tissues. A paper by Andersen et al (*J Natl Cancer Inst*, 1988) demonstrated an association between psychologic stress and cellular immune function in cancer patients. The association was based on the premise that stress may alter the function of the immune system in a manner that influences the development or growth of malignant tissue. This premise was considered by other scientists quite controversial and in the editorial of the same journal explained their underlying assumptions. “There is evidence for a number of mechanisms through which psychologic stress might alter immune function. These include direct innervation of lymphatic tissue by the central nervous system and stress-elicited release of hormones from the brain that bind to and alter the functions of immunologically active cells. The mechanisms also include behavioural changes that often occur in response to stress: an increase in smoking, an increase in drinking alcohol, a loss of sleep, a reduction in exercise, a degradation of the diet, and a decrease in adherence to medical regimens”. “…Andersen have linked psychologic experience to immunity in patients whose immune systems are already compromised by disease. The question remains whether the immune changes associated with stress have implications for cancer progression and metastasis. If

they do, it also remains to be seen whether stress-reduction interventions can ameliorate cancer progression through immune enhancement. The article by Andersen et al. provided an important piece of this fascinating puzzle, but the solution is still a ways off." [14,15]

The aim of this review is to present and analyse recent research papers and scientific reports dealing with the link between psychological stress and other social stress variables (including clinical depression) and risk for the development of various diseases, including cancer. Scientists promoted recently a biologically plausible, multilevel theory that describes neural, physiologic, molecular, and genomic mechanisms that link experiences of social-environmental stress with internal biological processes that drive depression pathogenesis. Although results indicate biological mechanisms, inflammation, adverse effects on the immune system and other changes, large prospective studies and meta-analysis did not find consistent associations with various types of cancer. For example, in the most recent epidemiological study breast cancer incidence was analysed with respect to stress variables collected at enrolment in a prospective cohort study of 106,000 women in the United Kingdom, with 1,783 incident breast cancer cases. This large prospective study did not show consistent evidence for an association of breast cancer risk with perceived stress levels or adverse life events in the preceding 5 years, or loss of parents during childhood and adolescence.[16]

## 2. Multilevel Theory for Psychological and Social Stresses as Risk Factors for Diseases

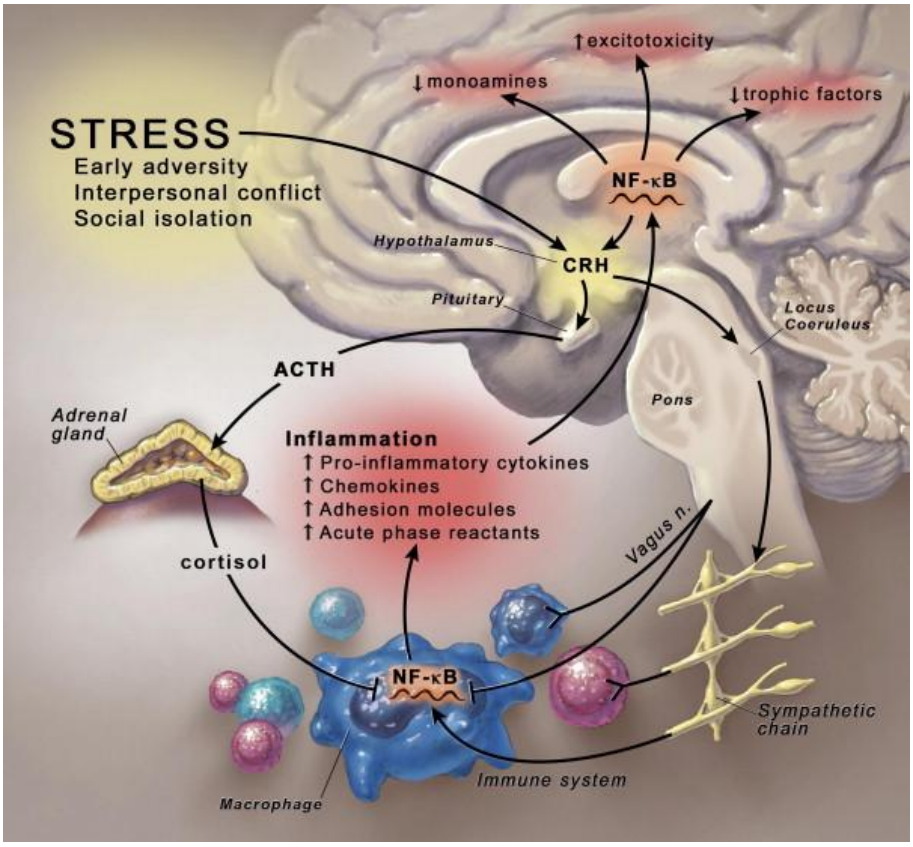
Major life stressors, especially those involving psychological stress, various social stress variables and social rejection, are among the strongest proximal risk factors for depression and the development of chronic diseases. In the last decade scientists proposed a biologically plausible, multilevel theory that describes neural, physiologic, molecular, and genomic mechanisms that link experiences of social-environmental stress with internal biological processes that drive depression pathogenesis. The central theme to this *social signal transduction theory of depression* was the hypothesis that experiences of psychological stress and social stress variables (divorce, deaths, etc) have adverse health effects that up-regulate components of the immune system

involved in inflammation. Researchers suggested that key mediators of this response, called *pro-inflammatory cytokines*, can in turn elicit profound changes in behaviour, psychological stress and initiation of depressive symptoms. This biological response leads to an increasingly pro-inflammatory phenotype and is connected with several somatic conditions including asthma, rheumatoid arthritis, chronic pain, metabolic syndrome, cardiovascular disease, obesity, and neurodegeneration.[17]

A research team in 2012 published a paper (Prof. Sheldon Cohen, Carnegie Mellon University) which observed that chronic psychological stress is associated with the body losing its ability to regulate the inflammatory response and as a result can promote the development and progression of various diseases. The leading researcher explained the results: "….Inflammation is partly regulated by the hormone cortisol and when cortisol is not allowed to serve this function, inflammation can get out of control". Prolonged psychological stress alters the effectiveness of cortisol to regulate the inflammatory response because it decreases tissue sensitivity to the hormone. The study contacted intensive stress interviews with 276 healthy adults who were exposed to a virus that causes the common cold and monitored in quarantine for five days for signs of infection and illness. The research team found that experiencing a prolonged stressful event was associated with the inability of immune cells to respond to hormonal signals that normally regulate inflammation. In the second part of the study, 79 healthy participants were assessed for their ability to regulate the inflammatory response and then exposed to a cold virus and monitored for the production of pro-inflammatory cytokines. It was found that those who were less able to regulate the inflammatory response as assessed before being exposed to the virus produced more of these inflammation-inducing chemical messengers when they were infected. These data provided support for a model suggesting that prolonged stressors result in glucocorticoid receptor resistance, which, in turn, interferes with appropriate regulation of inflammation.[18]

Recent laboratory-based experiments with healthy female participants implicated psychological stress with increased markers of inflammatory activity. In this respect scientists suggested that inflammation may be a key biological mediator linking stress and adverse health effects. Healthy 31 female participants

were exposed to a brief episode of stress while they underwent an fMRI scan (functional Magnetic Resonance Imaging, is a neuro-imaging procedure that measures brain activity by detecting changes associated with blood flow). Blood samples were taken before and after the stressor, and plasma was assayed for markers of inflammatory activity. Exposure to the stressor was associated with increases in levels of inflammation. Analyses linking the neural and inflammatory data revealed that heightened neural activity in the amygdala (almond shaped mass of nuclei located deep within the temporal lobes of the brain) in response to the stressor was associated with greater increases in inflammation. These data, according to the scientists, show that greater amygdala activity in response to a stressor, as well as tighter coupling between the amygdala and the dorsomedial prefrontal cortex (DMPFC), are associated with greater increases in inflammatory activity. Results from this study begin to identify neural mechanisms that might link stress with increased risk for inflammation-related disorders. [19]




[ http://drsircus.com/medicine/vagus-nerve-inflammation-heart-rate-variability/ ]

**Figure 1.** Diagram of the mechanisms triggered by stress. Recent advances in immunology reveal a significant pathogenic role for inflammation in the development and progression of these chronic diseases. Inflammation accelerates

deposition of atherosclerotic plaques leading to myocardial and cerebral infarction, mediates insulin resistance and stimulates tumour growth.

Stress-induced immune dysregulation results in significant health consequences for immune related disorders including viral infections, chronic autoimmune disease, and tumor growth and metastasis. A 2013 review presented the sympathetic, neuroendocrine and immunologic mechanisms by which psychosocial stress can impact on cancer biology. In the last decade human and animal studies have shown the sympathetic and neuroendocrine responses to psychosocial stress significantly impacts cancer, in part, through regulation of inflammatory mediators. Psychosocial stressors stimulate neuroendocrine, sympathetic, and immune responses that result in the activation of the hypothalamic–pituitary–adrenal (HPA)-axis, sympathetic nervous system (SNS), and the subsequent regulation of inflammatory responses by immune cells. Social disruption (SDR) stress, a murine model of psychosocial stress and repeated social defeat, provides a novel and powerful tool to probe the mechanisms leading to stress-induced alterations in inflammation, tumour growth, progression, and metastasis.[20]

Stress, especially short-term, can be good for humans as many clinical studies observed. Although the concept of stress has earned a bad reputation, it is important to recognize that the adaptive purpose of a physiological stress response is to promote survival in humans under difficult conditions. While long-term stress is generally harmful, short-term stress can be protective as it prepares the biological organism to deal with challenges. Scientists after reviewing many studies have proposed that short-term stress is one of the nature's fundamental but under-appreciated survival mechanisms that could be clinically harnessed to enhance immunoprotection. Short-term stress advances mechanisms of immuno-enhancement which include changes in dendritic cell, neutrophil, macrophage, and lymphocyte trafficking, maturation, and function as well as local and systemic production of cytokines. In contrast, long-term stress suppresses or dysregulates innate and adaptive immune responses by altering the Type 1–Type 2 cytokine balance, inducing low-grade chronic inflammation, and suppressing numbers, trafficking, and function of immunoprotective cells. Chronic stress may also

increase susceptibility to some types of cancer by suppressing Type 1 cytokines and protective T cells and increasing regulatory/suppressor T cell function. [21]

## 3. The Role of Inflammation in Chronic Diseases

Over the past decade a series of health research discoveries observed that inflammation plays an important role in many disease conditions that cause substantial morbidity and contribute to early mortality. For most scientists, it has become widely accepted that inflammation is a driving force behind chronic disease, including cancer, diabetes, obesity, Alzheimer's disease and atherosclerosis. Statistical data for deaths in 2012 showed that inflammation is involved in at least 8 of the top 10 leading causes of death in the United States. The basic problem for scientists is understanding of how inflammation promotes poor health, and how and when we can intervene to reduce inflammation-related disease risk, should thus be a top scientific and public priority.[22]

Many scientists associate chronic psychological stress, including several psychological conditions, anxiety, depression, schizophrenia and post-traumatic stress, with the human body losing its ability to regulate the inflammatory response.[12] Researchers have begun investigating how interactions between immune and related regulatory systems predict health outcomes.[23]

An excellent example is provided by a recent research project that examined how neuroendocrine and inflammatory factors in serum and from cerebrospinal fluid (CSF) interrelate and predict clinical outcomes in the context of traumatic brain injury (TBI). The results showed that high cortisol levels over the six-day post-TBI period conferred a 3.5-fold increased odds of poorer clinical functioning six months later. Also, the effects of TBI-induced increases in CSF inflammatory activity were mediated by patients' post-TBI cortisol trajectories, The third finding showed associations between CSF cytokine-cortisol dynamics and subsequent clinical functioning differed for patients in the high-versus low-cortisol trajectory group. The results suggested that unfavorable outcome after TBI may result from dysfunctional neuroendocrine–immune communication wherein an adequate immune response is not mounted or, alternatively, neuroinflammation is

prolonged. These results present a novel biomarker-based index from which to discriminate outcome and emphasize the need for evaluating tailored treatments targeting inflammation early after injury.[24]

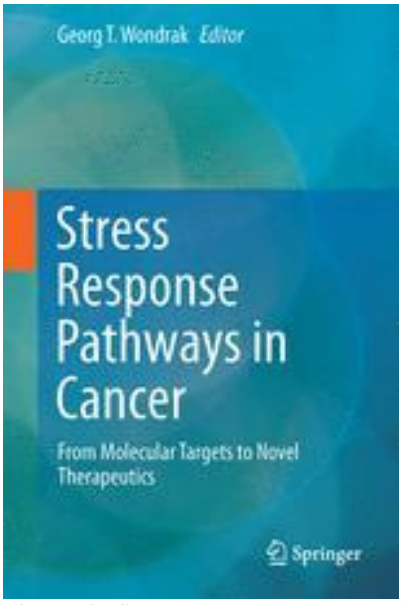

**Figure 3**. Mahin Khatami (Ed). *Inflammation, Chronic Diseases and Cancer. Cell and Molecular Biology, Immunology and Clinical Bases*. , ISBN 978-953-51-0102-4, 442 pages, Publisher: InTech, Rijeka, Croatia, 2012. ISBN 978-953-51-0102-4. Time special issue on inflammation as 'The Secret Killer" (19.10.2015).

Most of the chronic diseases (cancer, CVD, Alzheimer disease, Parkinson disease, arthritis, diabetes and obesity) are the result of life style factors, poor nutrition, tobacco use, lack of physical activity, alcohol consumption and infections. All these risk factors have been shown by scientific observations to up-regulate inflammation in humans. Therefore, downregulation of inflammation-associated risk factors could prevent or delay these age-associated diseases. A recent review presented extensive medical evidence on how chronic inflammation leads to age-associated chronic disease.[25]

A large body of evidence has emerged over the past years to show the critical role played by inflammation in the pathogenesis of several diseases including some cardiovascular, neoplastic, and neurodegenerative diseases, previously not considered inflammation-related. Some researchers focused their research on the influence of strong anti-inflammatory action of -3 polyunsaturated

fatty acids (PUFAs). The results of these studies showed the possible mechanisms underlying the beneficial effects of -3 PUFAs, especially the molecular pathways involved in inflammatory process, including the production of inflammatory cytokines and lipid mediators active in the resolving phase of inflammation. A recent review summarized the current knowledge regarding the modulating effects of -3 PUFAs on the production of inflammatory cytokines and pro-resolving or protective lipid mediators in the context of inflammatory, metabolic, neurodegenerative, and neoplastic diseases.[26]

Similar anti-inflammation studies have been contacted with the vitamin E family of tocopherols and four tocotrienols. These compounds have unique antioxidant and anti-inflammatory properties that are superior in prevention and therapy against chronic diseases. Studies showed that vitamin E forms scavenge reactive nitrogen species (RNS), inhibit cyclooxygenase- and 5-lipoxygenase-catalyzed eicosanoids, and suppress proinflammatory signaling such as NF-κB and STAT3/6. Animal and human studies showed that tocotrienols are useful against inflammation-associated diseases in clinical intervention studies.[27]




Wondrak GT (Ed). Stress Response Pathways in Cancer. From Molecular Targets to Novel Therapeutics. Springer Science +Business Media, Dordrecht, 2015.


Aggarwal BB, Sung B, Gupta SC (Eds). Inflammation and Cancer. Advances in Experimental Medicine and Biology. No. 816. Springer, Basel, 2014.

**Figure 4**. Stress, inflammation and cancer have been investigated by numerous studies and many scientific publications in the last decade focused on the subject.

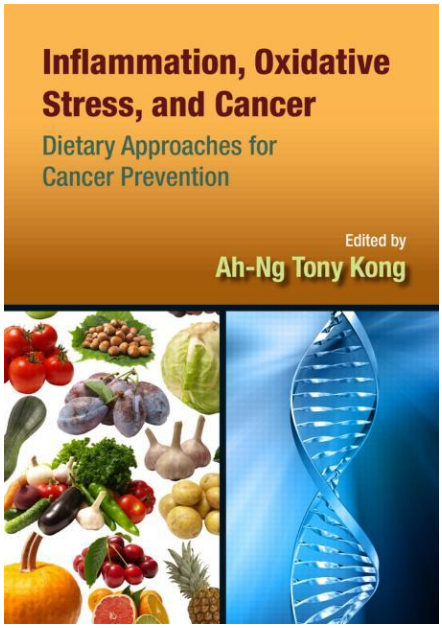
Scientists are in the beginning to unravel the complexities of the inflammatory mechanisms that are integral to the initiation and progression of cancer. From large observational studies, to in-depth mechanistic *in vivo* modeling studies every aspect of inflammatory dysregulation has been examined in the last decade. Better understanding of the cellular and molecular processes mediating cancer associated inflammation and the vital role it plays in cancer progression have begun to be exploited for therapeutic benefit.[28]

## 4. Oxidative Stress, Inflammation, Cancer

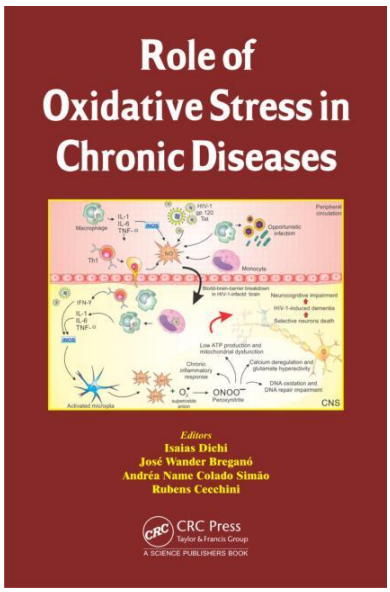
A great number of studies have observed in the last decades that reactive oxygen species or reactive nitrogen species (ROS, RNS) in the human body and oxidative stress especially in the respiratory system increase the production of mediators of pulmonary inflammation and initiate or promote mechanisms of carcinogenesis. The most vulnerable part of the human body to oxidative stress and inflammatory damage is the respiratory system. The lungs are exposed daily to oxidants generated either endogenously or exogenously (air pollutants, cigarette smoke, *etc.*).[29]

Cells in aerobic organisms are protected against oxidative damage by enzymatic and non-enzymatic antioxidant systems. Recent epidemiologic investigations have shown associations between increased incidence of respiratory diseases and lung cancer from exposure to low levels of various forms of respirable fibers and particulate matter (PM), at occupational or urban air polluting environments. Lung cancer increases substantially for tobacco smokers due to the synergistic effects in the generation of ROS, leading to oxidative stress and inflammation with high DNA damage potential. Physical and chemical characteristics of particles (size, transition metal content, stable free radicals, *etc.*) play an important role in oxidative stress. In turn, oxidative stress initiates the synthesis of mediators of pulmonary inflammation in lung epithelial cells and initiation of carcinogenic mechanisms. Inhalable quartz, metal powders, mineral asbestos fibers, ozone, soot from gasoline and diesel engines, tobacco smoke and PM from ambient air pollution ($PM_{10}$ and $PM_{2.5}$) are involved in various oxidative stress mechanisms. Pulmonary cancer initiation and promotion has been

linked to a series of biochemical pathways of oxidative stress, DNA oxidative damage, macrophage stimulation, telomere shortening, modulation of gene expression and activation of transcription factors with important role in carcinogenesis. The most important studies on inflammation were presented with their results in a review.[29]




Kong A-N T. *Inflammation, Oxidative Stress, and Cancer*. CRC Press, Boca Raton, FL, 2013.




Dichi I, Wregano JW, Simao ANC, Cecchini R. *Role of Oxidative Stress in Chronic* Diseases. CRC Press, Boca Raton, FL, 2014.

**Figure 5.** Oxidative stress and factors that initiate oxidative mechanisms in biological organisms are associated with chronic diseases and cancer.

Scientific advances in the last decade have contributed much to the dissection of the complex molecular and cellular pathways involved in the connection between cancer and inflammation. The evidence for this connection in humans is based on the association between infection or chronic inflammation and cancer. The decreased incidence of tumours in individuals who have used nonsteroidal anti-inflammatory drugs is supportive of a role for inflammation in cancer susceptibility. Obesity is a contributing factor and various studies have observed incidence of tumours in overweight patients. Adipose tissue has a critical role in inflammation and energy metabolism increasing the risk for cancer. Energy metabolism, obesity, and genetic instability are regulated in part by the relationship of the organism with commensal bacteria (normal microflora, indigenous microbiota) that affect inflammation with both local and systemic

effects. Different aspects of inflammation appear to regulate all phases of malignant disease, including susceptibility, initiation, progression, dissemination, morbidity, and mortality.[30]

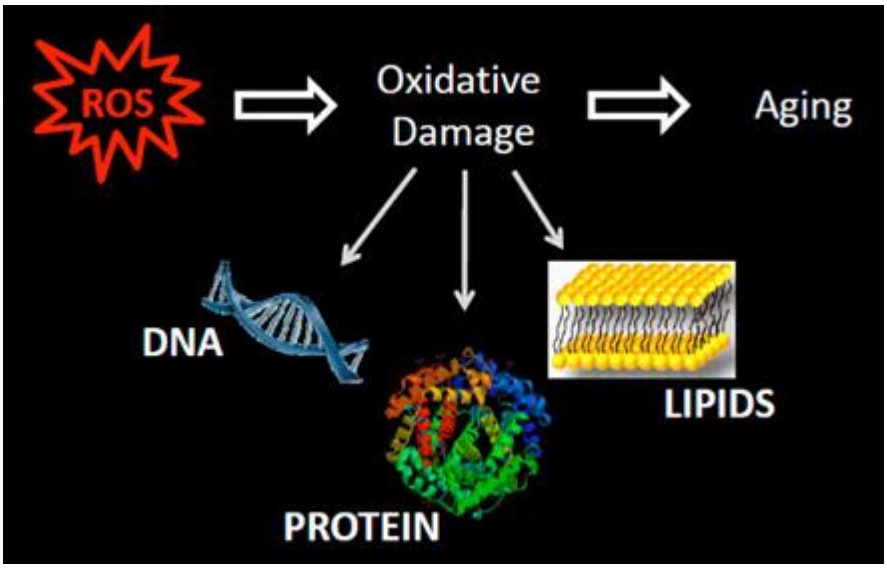



**Figure 6**. Excess generation of reactive oxygen species (ROS) escaping antioxidant defenses result in. oxidative stress. Oxidative damage to proteins-enzymes, lipids and cellular DNA are causes of neurodegenerative diseases and ageing.

Many studies in the last years observed an important role of lipid peroxidation (caused by ROS) and oxysterols in the development of neurodegenerative diseases and inflammation-related cancer. Recent research identified and characterized carbonylated proteins revealing oxidative damage to heat shock proteins in neurodegenerative disease models and inflammation-related cancer, suggesting dysfunction in their antioxidative properties. In neurodegenerative diseases, DNA damage may not only play a role in the induction of apoptosis, but also may inhibit cellular division via telomere shortening. Immunohistochemical analyses showed co-localization of oxidative/nitrative (caused by oxygen/nitrogen free radicals) of DNA lesions and stemness markers in the cells of inflammation-related cancers. A recent review collected and presented studies for the role of oxidative stress and its significant roles in neurodegenerative diseases and cancer.[31]

It is well known that in normal cells there are low-level concentrations of ROS and RNS under physiological conditions regulated by a series of enzymatic and non-enzymatic mechanisms. These free radical compounds are short-lived

and highly reactive. Their biochemical role is very important in numerous intracellular mechanisms and are required for signal transduction before their elimination. Excessive production of ROS and RNS by exposure to various factors (e.g. smoking, air pollution) is associated with oxidative stress and inflammation. Also there is an additional factor. Studies showed that cancer cells, which exhibit an accelerated metabolism, demand high ROS concentrations to maintain their high proliferation rate. Different ways of developing ROS resistance include the execution of alternative pathways, which can avoid large amounts of ROS accumulation without compromising the energy demand required by cancer cells. Examples of these processes include the guidance of the glycolytic pathway into the pentose phosphate pathway and/or the generation of lactate instead of employing aerobic respiration in the mitochondria.[32]

## 5. Large Prospective Studies on the Association of Stress and Cancer.

For many decades the psychological stress has been claimed by medical professionals to contribute to the onset of cancer and to increase mortality from a number of non-malignant diseases. But large epidemiological prospective studies in the last decade did not support the association. Epidemiologists in Denmark investigated the effect of a genuine psychological stressor, i.e. cancer in a child, on the incidence of cancer and mortality from non-malignant diseases of 11,231 parents in a Danish nationwide population-based study. The children were identified from records in the Danish Cancer Registry for the period 1943-85; their parents were identified from population registers. Overall, 1,665 parental malignancies were diagnosed from the date the cancer of the child was reported until 1992, compared with 1,702 expected from national incidence rates, yielding standardized incidence ratios of 1.0 (95% confidence interval, 0.9-1.0) for all parents. No statistically significant deviation of the relative risk from unity was seen for any period of follow-up after the stressful event, and no excess risk was seen for any particular type of cancer. Moreover, a total of 2,137 parental deaths were observed over the period 1974-92, compared with 2,333 expected from national mortality rates, giving an overall standardized mortality ratio of 0.9 (range

0.9-1.0). These results indicate that there is no excess mortality from causes associated with allergic illness, autoimmune conditions, chronic illness or changes in behaviour. The final conclusion of the researchers was: "…Our data provide no support for the hypothesis of an association between psychological stress and the incidence of cancer or mortality from non-malignant diseases. We conclude that the human organism is highly adaptable, even to extreme psychological stress".[33]

The scientific literature is full of epidemiological studies in the last 20 years with the association of psychological stress and stressful life events and increased risk of cancer. In 2003 an investigation was published on the relationship between stressful life events and risk of breast cancer among 10,808 women from the Finnish Twin Cohort by self-administered questionnaire in 1981. The researchers used the Finnish Cancer Registry, 180 incident cases of breast cancer were identified (1982-1996, which is a small number of cases). The multivariable adjusted hazard ratio (HR) for breast cancer per one-event increase in the total number of life events was 1.07 (only a small increase of 7% of risk). But then the study was extended to only major stressful events and risk estimate rose to 1.35 (95% CI: 1.09, 1.67). Also, researchers subdivided the stressful cases, when total life events, divorce/separation were taken into account the HR increased to 2.26. For death of a husband HR increased to 2.00, and for death of a close relative or friend HR was 1.36. These stressful events were all associated with increased risk of breast cancer. But we must note questionannaires were contacted 17 years before and the total recorded number of cases of cancer were very small. [34]

Another case-control study from Poland (2012) examined the relationship between severe life events and breast cancer risk based on examination of 858 Polish invasive breast cancer cases and 1,085 controls matched by age and place of residence. Data on life events, sociodemographic characteristic, reproductive factors (confounders which unobserved exposures associated with risk), family history of breast cancer, current weight and height, and lifestyle habits were collected between 2003-2007 using a self-administered questionnaire. Odds ratios with 95% confidence intervals were estimated as the measure of the relationship between stressful life event and breast cancer risk using unconditional logistic regression analyses. The results showed that women with four to six individual major life events had 5.33 times higher risk for breast cancer (this is a very high

increase of risk not found by other studies), compared with those in the lowest quartile. Several life events (death of a close family member, personal injury or illness, imprisonment/trouble with the law, retirement) were significantly associated with breast cancer risk. The study include women prisoners.[35]

Another recent study (2013) used 12 European cohort studies in a meta-analysis with a statistical process that combined the results of multiple scientific studies. It investigated whether work related stress, measured and defined as job strain, is associated with the overall risk of cancer and the risk of colorectal, lung, breast, or prostate cancers. The study pooled prospective individual participant data from 12 studies including 116, 056 men and women aged 17-70 who were free from cancer at study baseline and were followed-up for a median of 12 years. Work stress was measured and defined as job strain, which was self reported at baseline. Incident cancers (all n=5,765, colorectal cancer n=522, lung cancer n=374, breast cancer n=1,010, prostate cancer n=865) were ascertained from cancer, hospital admission, and death registers. Data were analysed in each study with Cox regression and the study specific estimates pooled in meta-analyses. Models were adjusted for age, sex, socioeconomic position, body mass index (BMI), smoking, and alcohol intake. Results showed that a harmonised measure of work stress, high job strain, was not associated with overall risk of cancer (hazard ratio 0.97, 95% confidence interval 0.90 to 1.04) in the multivariable adjusted analyses. Similarly, no association was observed between job strain and the risk of colorectal (1.16), lung (1.17), breast (0.97), or prostate (0.86), cancers. There was no clear evidence for an association between the categories of job strain and the risk of cancer.[36]

Breast cancer was in the past decades one of the most important type of cancer that was associated by various researches and cancer patients with psychological stress. In the past there were many studies with questionnaires asking women diagnosed with breast cancer if they attributed their cancer to psychological stress. A large number of these breast cancer women frequently mentioned a period of stressful events prior to the diagnosis. In 2016 British scientists investigated whether experienced frequency of stress and adverse life events affected subsequent breast cancer risk. The research project analysed breast cancer incidence with respect to stress variables collected at enrolment in a

prospective cohort study of 106,000 women in the United Kingdom, with 1,783 incident breast cancer cases. Relative risks (RR) were obtained as hazard ratios using Cox proportional hazards models. Results showed that there was no association of breast cancer risk overall with experienced frequency of stress. Risk was reduced for death of a close relative during the 5 years preceding study entry (RR = 0.87, 95 % confidence interval: 0.78–0.97), but not for death of a spouse/partner or close friend, personal illness/injury, or divorce/separation. In the other hand the study found that there was a positive association of divorce with oestrogen-receptor-negative (RR = 1.54, 95 % CI: 1.01–2.34), but not with oestrogen-receptor-positive breast cancer. Risk was raised in women who were under age 20 at the death of their mother (RR = 1.31, 95 % CI: 1.02–1.67), but not of their father, and the effect was attenuated after excluding mothers with breast or ovarian cancer (RR = 1.17, 95 % CI: 0.85–1.61). The final conclusion was that a large prospective study did not show consistent evidence for an association of breast cancer risk with perceived stress levels or adverse life events in the preceding 5 years, or loss of parents during childhood and adolescence.[37]

A large epidemiological study investigated cases of early-life exposure to stress that have been associated with subsequent psychiatric and cardiovascular morbidity and its potential role in cancer development later in life. Researchers of this study hypothesized that severe emotional stress, such as the loss of a parent through death during childhood, may increase the risk of cancer in early life. The statistical data of this study were based on the Swedish Multi-Generation Register, by identifying a cohort of 4,219,691 individuals who had both parents identifiable in the same register (followed from birth to the age of 40 years, in the period 1961-2006). Through information retrieved from the Swedish Causes of Death and Cancer Registers, researchers ascertained death among the parents and cancer diagnosis among the cohort individuals. They used Poisson regression to calculate the relative risks (RRs) and 95 % confidence intervals (CIs). The results showed that parental death was not associated with total cancer risk. However, parental death during childhood was associated with a higher risk of human papillomavirus (HPV) infection-related cancers (RR 1.4) and loss during early adulthood (>18 years) entailed a higher risk of cancers of the stomach (RR 1.8), lung (RR 1.7), rectum (RR 1.4) and

breast cancer (RR 1.1). The higher risk for breast cancer was only 10%. The results established significant association for pancreatic cancer for both loss during childhood (RR 2.6) and afterward (RR 2.8). Researchers concluded that severe psychological stress in early life may be associated with premature development of certain malignancies, particularly cancers related to smoking and HPV infection.[38]

Another recent Danish study investigated (published in 2015) the association between stress and cancer incidence. The study examined the association between posttraumatic stress disorder (PTSD) and various cancers. The nation-wide cohort study included all Danish-born residents of Denmark from 1995 to 2011. The exposure was PTSD diagnoses (*n* = 4,131). The main outcomes were cancer diagnoses including: (1) all malignant neoplasms; (2) hematologic malignancies; (3) immune-related cancers; (4) smoking- and alcohol-related cancers; (5) cancers at all other sites. Standardized incidence ratios (SIR) were calculated. Null associations were found between PTSD and nearly all cancer diagnoses examined, both overall [SIR for all cancers = 1.0, 95 % confidence interval (CI) = 0.88, 1.2] and in analyses stratified by gender, age, substance abuse history and time since PTSD diagnosis. This study was the most comprehensive examination to date of PTSD as a predictor of many cancer types. The conclusion of the scientists was: "… data show no evidence of an association between PTSD and cancer in this nationwide cohort".[39]

A current meta-analysis (published 2013) was designed to assess the relationship between striking life events and primary breast cancer incidence in women. The method use in this study was a systematic computerized searching of the PubMed, Science Direct, Embase, and BMJ databases which identified a total of 307 papers (1995-2012). Only 7 studies case–control or cohort studies were selected because of their quality and the association between striking life events and primary breast cancer incidence in women was measured. The seven studies used in the final meta-analysis included 99,807 women**.** A meta-analysis showed that the pooled OR (odds ratios) for striking life events and breast cancer was 1.51 (95% CI 1.15 - 1.97, *P* = 0.003), indicating that women with striking life events were at 1.5-fold greater risk of developing breast cancer. The pooled OR for severe striking life events and breast cancer was 2.07 (95% CI 1.06 - 4.03),

indicating that women with severe striking life events were at 2-fold greater risk of developing breast cancer. [40]

A systematic review (2014) analyzed the beliefs among cancer patients for causal attributions, especially for the case of breast cancer among women previously diagnosed with breast cancer. These attributions were compared with risk factors identified by published scientific evidence in order to determine the level of agreement between cancer survivors' attributions and expert opinion. A comprehensive search for articles (1982-2012) found 5,135 potentially relevant articles, of which only 22 studies met the inclusion criteria. The results indicated a consistent belief among survivors that their own breast cancer could be attributed to family history, environmental factors, stress, fate, or chance. Lifestyle factors were less frequently identified, despite expert health information highlighting the importance of these factors in controlling and modifying cancer risk. According to researchers the review demonstrated that misperceptions about the contribution of modifiable lifestyle factors to the risk of breast cancer have remained largely unchanged over the past 30 years. The findings indicated that beliefs about the causes of breast cancer among affected women are not always consistent with the judgement of experts who regularly identified causal factors supported by expert consensus such as age, physical inactivity, breast density, alcohol consumption, and reproductive history. [41]

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