

REVIEW ARTICLE

LIFE EVENT, STRESS AND ILLNESS

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The relationship between stress and illness is complex. The susceptibility to stress varies from person to person. Among the factors that influenced the susceptibility to stress are genetic vulnerability, coping style, type of personality and social support. Not all stress has negative effect. Studies have shown that short-term stress boosted the immune system, but chronic stress has a significant effect on the immune system that ultimately manifest an illness. It raises catecholamine and suppressor T cells levels, which suppress the immune system. This suppression, in turn raises the risk of viral infection. Stress also leads to the release of histamine, which can trigger severe broncho-constriction in asthmatics. Stress increases the risk for diabetes mellitus, especially in overweight individuals, since psychological stress alters insulin needs. Stress also alters the acid concentration in the stomach, which can lead to peptic ulcers, stress ulcers or ulcerative colitis. Chronic stress can also lead to plaque buildup in the arteries (atherosclerosis), especially if combined with a high-fat diet and sedentary living. The correlation between stressful life events and psychiatric illness is stronger than the correlation with medical or physical illness. The relationship of stress with psychiatric illness is strongest in neuroses, which is followed by depression and schizophrenia. There is no scientific evidence of a direct cause-and-effect relationship between the immune system changes and the development of cancer. However, recent studies found a link between stress, tumour development and suppression of natural killer (NK) cells, which is actively involved in preventing metastasis and destroying small metastases.

Key words : Stress, medical illness, psychiatric illness, cancer, immune system, personality

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Introduction

Stress is defined as a process in which environmental demands strain an organism's adaptive capacity resulting in both psychological demands as well as biological changes that could place at risk for illness (1). Things that cause us stress are called stressors. Stress affects everyone, young and old, rich and poor. Life is full of stress. Stress is an every fact of life that we must all deal with. It comes in all shapes and sizes; even our thoughts can cause us stress and make the human body more susceptible to illness. There are three theories or perspectives regarding stress; environmental stress, psychological (emotional) stress and biological

stress (1). The environmental stress perspective emphasizes assessment of environmental situations or experiences that are objectively related to substantial adaptive demands. The psychological stress perspective emphasizes people's subjective evaluations of their ability to cope with demands presented to them by certain situations and experiences. Finally, the biological stress perspective emphasizes the function of certain physiological systems in the body that are regulated by both psychologically and physically demanding conditions.

The relationship between stress and illness is complex. The susceptibility to stress varies from person to person. An event that causes an illness in

a person may not cause illness in other person. Events must interact with a wide variety of background factors to manifest as an illness. Among the factors that influenced the susceptibility to stress are genetic vulnerability, coping style, type of personality and social support. When we are confronted with a problem, we assess the seriousness of the problem and determine whether or not we have the resources necessary to cope with problem. If we believe that the problem is serious and do not have the resources necessary to cope with the problem, we will perceive ourselves as being under stress (2). It is our way of reacting to the situations that makes a difference in our susceptibility to illness and our overall well-being.

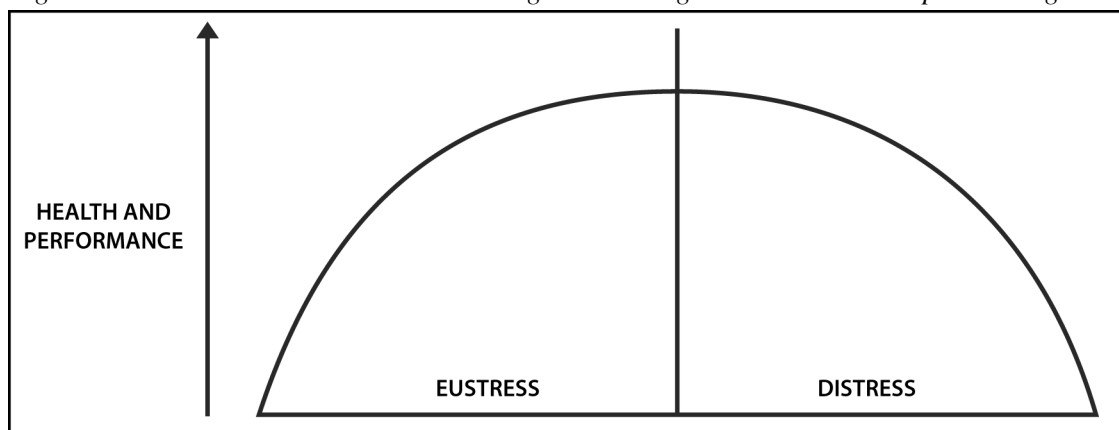
Not all stress has negative effect. When the body tolerates stress and uses it to overcome lethargy or enhance performance, the stress is positive, healthy and challenging. Hans Selye (3), one of the pioneers of the modern study of stress, termed this *eustress*. Stress is positive when it forces us to adapt and thus to increase the strength of our adaptation mechanisms, warns us that we are not coping well and that a lifestyle change is warranted if we are to maintain optimal health. This action-enhancing stress gives the athlete the competitive edge and the public speaker the enthusiasm to project optimally. Stress is negative when it exceeds our ability to cope, fatigues body systems and causes behavioral or physical problems. This harmful stress is called *distress*. Distress produces overreaction, confusion, poor concentration and performance anxiety and usually results in sub par performance. Figure 1 illustrates this concept.

There is a growing concern about the increasing cost and prevalence of stress-related disorders; especially in relation to work place. “Worked to death, drop death, work until you drop” are highlighted “work-related death” in the 21st

century. Countries renowned for their long working hours know this well enough; Japan and China each have a word for death by overwork – *karoshi* and *guolaosi* respectively. Both Japan and Korea recognize suicide as an official and compensatable work-related condition (4). The estimated prevalence of stress and stress-related conditions in the United Kingdom rose from 829 cases per 100,000 workers in 1990 to 1,700 per 100,000 in 2001/2002. In that year, 13.4 million lost working days were attributed to stress, anxiety or depression, with an estimate 265,000 new cases of stress. The latest HSE (Health and Safety Executive) analysis of self-reported illnesses rate revealed that stress, depression or anxiety affects 1.3% of the workforce (5). It is estimated that 80% to 90% of all industrial accidents are related to personal problem and employees’ inability to handle stress (6). The European Agency for Safety and Health at work reported that about 50% of job absenteeism is caused by stress (7).

The morbidity and mortality due to stress-related illness is alarming. Emotional stress is a major contributing factor to the six leading causes of death in the United States: cancer, coronary heart disease, accidental injuries, respiratory disorders, cirrhosis of the liver and suicide. According to statistics from Meridian Stress Management Consultancy in the U.K, almost 180,000 people in the U.K die each year from some form of stress-related illness (7). The Centre for Disease Control and Prevention of the United States estimates that stress account about 75% of all doctors visit (7). This involves an extremely wide span of physical complaints including, but not limited to headache, back pain, heart problems, upset stomach, stomach ulcer, sleep problems, tiredness and accidents. According to Occupational Health and Safety news and the National Council on compensation of insurance, up to 90% of all visits to primary care

Figure 1 : *Eustress is the action-enhancing stress that give athletes the competitive edge*



physicians are for stress-related complaints.

Stress and the immune system

Our immune system is another area which is susceptible to stress. Much of what we know about the relationship between the brain, the nervous system, and the immune response has come out of the field of *psychoneuroimmunology* (PNI). PNI was developed in 1964 by Dr. Robert Ader, the Director of the Division of Behavioral and Psychosocial Medicine at the University of Rochester. Psychoneuroimmunology is the study of the intricate interaction of consciousness (psycho), brain and central nervous system (neuro), and the body's defence against external infection and aberrant cell division (immunology) (8). More specifically it is devoted to understanding the interactions between the immune system, central nervous system and endocrine system. Although a relatively new medical discipline, the philosophical roots of the connection between physical health, the brain and emotions can be traced to Aristotle.

Immune responses are regulated by antigen, antibody, cytokines and hormones. Lymphocytes are most responsible for orchestrating the functions of the immune system. The immune system has about 1 trillion lymphocytes. Lymphocytes that grow and mature in the thymus are called *T cells*; other lymphocytes are called *B cells*. B cells secrete antibodies, chemicals that match specific invaders called antigens (humoral immunity). T cells do not secrete antibodies but act as messengers and killers, locating and destroying invading antigens (cellular immunity). Some T cells, called *helpers*, help activate the production of other T and B cells. Other T cells, called *suppressors*, stop the production of antigens, calling off the attack. The number of T and B cells must be balanced for them to perform effectively. When the ratio of T to B cells is out of balance, the immune response is compromised and does not work effectively. Other key chemicals that are produced by the immune systems are macrophages, monocytes and granulocytes. These chemicals envelop, destroy and digest invading microorganisms and other antigens. Known generally as *phagocytes*, they team up with more than 20 types of proteins that make up the immune system's complement system. This system is triggered by antibodies that lock onto antigens, which cause inflammatory reactions.

Cytokines are non-antibody messenger molecules from a variety of cells of the immune system. Cytokines stimulate cellular release of

specific compounds involved in the inflammatory response. They are made by many cell populations, but the predominant producers are helper T cells (Th) and macrophages. Th1 and Th2 cytokines inhibit one another's production and function: Th1 cells stimulate cellular immunity and suppress humoral immunity, while Th2 cytokines have opposite effect. Cytokines is a general name; other specific name includes lymphokines (cytokines produced by lymphocytes), chemokines (cytokines with chemotactic activities), interleukin (IL) (cytokines made by one leukocyte and acting on other leukocytes) and interferon (IFN) (cytokines release by virus-invaded cell that prompt surrounding cell to produce enzymes that interfere with viral replication).

Cytokines are produced *de novo* in response to an immune stimulus. They generally act over short distances and short time spans and at very low concentration. They act by binding to specific membrane receptors, which then signal the cell via second messenger, often tyrosine kinases, to alter its behaviour (gene expression). Responses to cytokines include increasing or decreasing expression of membrane proteins (including cytokines receptors), proliferation and secretion of effectors molecules. The largest group of cytokines stimulates immune cell proliferation and differentiation. Some common bacterial antigens activate complement and stimulate macrophages to express co-stimulatory molecules. Antigens stimulate adaptive immune responsiveness by activating lymphocytes, which in turn make antibody to activate complement and cytokines to increase antigen elimination and recruit additional leukocytes.

Several studies have shown that chronic stress exerts a general immunosuppressive effect that suppresses or withholds the body's ability to initiate a prompt, efficient immune reaction (9,10). This has been attributed to the abundance of corticosteroids produced during chronic stress, which produces an imbalance in corticosteroid levels and weakens immunocompetence. This weakening of immune function is thought to be associated with general strain on the various body parts associated with the production and maintenance of the immune system. For example, atrophy of the thymus or shrinking of the thymus results in its inability to produce T cells or the hormones needed to stimulate them. This can lead to an imbalance and inefficiency of the entire immune response. This is consistent with the finding that as we get older, we are prone to suffer

from infection, cancer, hypersensitivity and autoimmunity.

In a meta-analysis of 293 independent studies reported in peer-reviewed scientific journal between 1960 and 2001 with some 18,941 taking part, it is confirmed that stress alters immunity (11). Short-term stress actually boosts the immune system as it readies itself to meet and overcome a challenge such as an adaptive response preparing for injury or infection; but long-term or chronic stress causes too much wear and tear, and the system will break down especially if the individual has little control over events. The analyses (11) revealed that the most chronic stressors which change people's identities or social roles, are more beyond their control and seem endless—were associated with the most global expression of immunity; almost all measures of immune function dropped across the board. Duration of stress also plays a role. The longer the stress, the more the immune system shifted from potentially adaptive changes (such as those in fight-or-flight response) to potentially detrimental changes, at first in cellular immunity and then in broader immune function. They also found that the immune systems of people who are older or already sick are more prone to stress-related change.

The link between stress and illness

The critical factor associated with stress is its chronic effect over time. Chronic stressors include daily hassles, frustration of traffic jams, work overload, financial difficulties, marital arguments or family problems. There are, of course, many more things that can cause stress, but these are the stressors commonly encountered in daily life. The pent-up anger we hold inside ourselves toward any of these situations, or the guilt and resentment we hold toward others and ourselves, all produce the same effects on the hypothalamus. Instead of discharging this stress, however, we hold it inside where its effects become cumulative.

Research shows that almost every system in the body can be influenced by chronic stress. When chronic stress goes unreleased, it suppresses the body's immune system and ultimately manifests as illness. One can only wonder what would happen to the body if it remained in the fight-or-flight response. Fortunately, under normal circumstances, three minutes after a threatening situation is over and the real or imagined danger is removed, the fight-or-flight response subsides and the body relaxes and returns to its normal status. During this time heart rate, blood pressure, breathing, muscle tension,

digestion, metabolism and the immune system all return to normal. If stress persists after the initial fight-or-flight reaction, the body's reaction enters a second stage. During this stage, the activity of the sympathetic nervous system declines and adrenaline secretion is lessened, but corticosteroid secretion continues at above normal levels. Finally, if stress continues and the body is unable to cope, there is likely to be breakdown of bodily resources.

Medical illnesses

In asthma, both external and internal factors are involved; it is the internal factor that is most affected by acute effects of psychological stressors. Family therapy is widely incorporated in the management of asthmatic children. The improvement is attributed to minimizing the interaction with parents that produced frequent stressful situation. Additionally, asthmatics exposed to a harmless substance that they thought they were allergic would elicit a severe attack (12). A study by Gauci et al. (13) demonstrated significant positive correlations between a few of Minnesota Multiphasic Personality Inventory (MMPI) distressed-related scales and skin reactivity in response to allergens. Collectively, these data provide evidence for a clear association between stress, immune dysfunction and clinical activity of atopic and asthmatic disease. For further reference, Liu et al. (14) provided excellent evidence that stress can enhance allergic inflammatory response.

Gastrointestinal diseases such as peptic ulcer (PU) and ulcerative colitis (UC) are known to be greatly influenced by stress. PU occurs twice as often in air traffic controllers as in civilian copilots, and occurs more frequently among air traffic controllers at high-stress centers (Chicago O'Hare, La Guardia, JFK and Los Angeles International Airport) than low-stress centers (airports in less-populated cities in Virginia, Ohio, Texas and Michigan). Although stress is a risk factor in PU, more than 20 other factors are thought to be associated as well: blood type, sex, HLA antigen type, alcoholic cirrhosis, hypertension, chronic obstructive pulmonary disease, cigarette smoking, and even consumption of coffee, carbonated beverage or milk during college (12). Certain stressful life events have been associated with the onset or symptom exacerbation in other common chronic disorders of the digestive system such as functional gastrointestinal disorders (FGD), inflammatory bowel disease (IBD) and gastro-esophageal reflux disease (GERD). Early life stress in the form of abuse also plays a major role in

the susceptibility to develop FGD as well as IBD later in life (15).

Ulcers are caused by excessive stomach acid, and studies of patients with gastric fistulas have shown that anger and hostility increase stomach acidity, while depression and withdrawal decrease it. Other theory correlating the effects of stress on the development of ulcers linked to the mucous coating that lines the stomach. The theory states that, during chronic stress, noradrenaline secretion causes capillaries in the stomach lining to constrict. This in turn, results in shutting down of mucosal production, and the mucous protective barrier for the stomach wall is lost. Without the protective barrier, hydrochloric acid breaks down the tissue and can even reach blood vessels, resulting in a bleeding ulcer (16). However, it has recently been discovered that many cases of ulcers are caused by a bacterial called *Helicobacter pylori* (*H. pylori*) (17). Although the exact mechanism by which it causes ulcers is unknown, it is believed that *H. pylori* inflames the gastrointestinal lining, stimulates acid production or both.

Coronary Heart disease (CHD) has long been regarded as a classical psychosomatic illness in that its onset or course was influenced by a variety of psychosocial variables. Psychosocial aspects of CHD had been studied extensively and there is strong evidence that psychological stress is a significant risk factor for CHD and CHD mortality (18,19,20,21). Tennant (19) found a positive relationship between life stress and cardiac infarction and sudden death; while study by Rosengren et al. (20) reported that CHD mortality was increased two folds for men experiencing three or more antecedent life events. The INTERHEART study (21) revealed that people with myocardial infarction reported higher prevalence of four stress factors: stress at work and at home, financial stress and major life events in the past year.

Although the evidences supporting an association between type A behaviour (aggressive, competitive, work-oriented and urgent behaviour) and CHD were conflicting (22); some studies found that type A individuals generate more stressful life events and were more likely than others to interpret encountered life event in an emotionally adverse way (23, 24). If type A is a risk factor it may not operate by way of long-term physiological dysfunction (leading to atherogenesis), but by way of acute life events provoking severe strain on the heart. One of the components of Type A behaviour is hostility, which may be correlated with CHD risk. Some

studies (25, 26) noted that clinical CHD events

are predicted by hostility and this seems to independent of other risk factors. Hostility was also found to be related to atherosclerosis in some angiography studies (27,28). Other studies found suppression of anger was associated with CHD event (29) and atherosclerosis (27,28). In review of these findings, Tennant (30) concluded that the possibility emerges that hostility (or its suppression) may have some role in CHD, although the mechanism is unclear.

The three major risk factors commonly agreed to be associated with CHD are hypercholesterolemia, hypertension and cigarette smoking. In attempt to determine the causes of increased levels of serum cholesterol; Friedman et al. (31) conducted one of the early investigations of the relationship between stress and serum cholesterol. They found that stress is one of the causes of increased levels of serum cholesterol. Other researchers who studied the medical students facing the stress of exam (32), and military pilot at the beginning of their training and examination period (33) verified the findings. Since blood pressure and serum cholesterol increases during stress, the relationship between stress and hypertension has long been suspected; emotional stress is generally regarded as a major factor in the etiology of hypertension (34). One of the early evidence of this relationship came from the massive study of 1,600 hospital patients by Dunbar (35). He found that certain personality traits were characteristic of hypertensive patients; for example they were easily upset by criticism or imperfection, possessed pent-up anger and lack self-confidence. Recognizing this relationship, educational programs for hypertensive patients have included stress management.

It appears that some people are hereditarily susceptible to rheumatoid arthritis (RA). Approximately half of the sufferers of this condition have a blood protein called the rheumatoid factors (RF), which is rare in non-arthritic people. Since RA involves the body turning on itself (an autoimmune response), it was hypothesized that a self-destructive personality may manifest itself through this disease (16). Although the evidence to support this hypothesis is not conclusive, several investigators have found personality differences between RA sufferers and others. Those affected with this disease have been found to be perfectionists and are self-sacrificing, masochistic, and self-

conscious. Female patients were found to be nervous, moody and depressed, with a history of being rejected by their mothers and having strict fathers. It has been suggested that people with the RF who experience chronic stress become susceptible to RA (16). Their immunological system malfunctions and genetic predisposition to RA results in their developing of the condition.

Migraine headaches are the result of constriction and dilatation of the carotid arteries of one side of the head. The constriction phase, called the prodrome, is often associated with light or noise sensitivity, irritability and a flushing or pallor of the skin. When the dilatation of the arteries occurs, certain chemicals stimulate adjacent nerve endings, causing pain. Diet may precipitate migraine headaches for some people. However, predominant thought on the cause of migraine pertains to emotional stress and tension. Feeling of anxiety, nervousness, anger or repressed rages are associated with migraine. An attack may be aborted when the individual gives vent to underlying personality (8). A typical migraine sufferer is a perfectionist, ambitious, rigid, orderly, excessively competitive and unable to delegate responsibility.

There is also evidence that emotionally stressful experience is associated with endocrine disorder such as diabetes mellitus (36). Physical or psychological stressors can alter insulin needs; stressors may often be responsible for episodes of loss of control, especially in diabetic children. Type II diabetes is most often affected by stress, as it tends to occur in overweight adults and is a less severe form of diabetes (12). Additionally, children who had stressful life events stemming from actual or threatened losses within the family and occurring between the ages of 5 and 9 had a significantly higher risk of type I diabetes.

Acute stress can suppress the virus-specific antibody and T cell responses to hepatitis B vaccine (37). People who show poor responses to vaccines have higher rate of illness including influenza virus infection. There are several other studies which demonstrated a relationship between psychological stress and susceptibility to several cold viruses (38,39). This is not surprising, as stress does suppress the immune system; latent viruses then have an easier time resurging since the body cannot defend itself any more. Attempts to find an association between stress and disease progression in patients with acquired immunodeficiency syndrome (AIDS) have met with conflicting results (40). Analysis of the Multicentre AIDS Cohort Study failed to observe

an association between depression and the decline of CD4+ T lymphocytes, disease progression or death (41), but others have found significant association between immunological parameters reflective of HIV progression and psychosocial factors, particularly denial and distress (42), and concealment of homosexual identity (43).

Psychiatric illness

A large body of research in the past four decades has provided evidence that recent life events contribute to the onset of psychiatric illness (44). The association between stressful life events and psychiatric illness is stronger than the association with physical or medical illness. Vincent and Roscenstock (45) found that prior to hospitalization, patients with psychiatric disorders had suffered more stressful event than those with physical disorders. Meanwhile, Andrew and Tennant (46) failed to find the association between stress and physical illness. Although the exact relationship between stress and psychiatric illness is not clear, the final pathway is biochemical. As with medical illness, the appropriate model is one of multifactorial causations. Most life event research indicates a limit of 6 months to consider a stress having significant effect on illness. After that, the effect of stress diminishes with time.

Recent life events held to have a major etiological role in neuroses, a formative role in the onset of neurotic depression (mixed depressive illness) and a precipitating role in schizophrenic episodes (47). In other words, the association of stress with psychiatric illness is the strongest in neuroses, followed by depression and schizophrenia is the least. The correlation between neuroses and schizophrenia with stress is clearer. The weak association between stressful life events and onset of psychotic illness, particularly schizophrenia had been demonstrated in a few studies (48,49,50), in contrast with strong association between stress and neuroses (51,52, 53,54). However the degree of relationship between depressive illness and neuroses in relation to stress is rather controversial. Neither Paykel (55) nor Brown et al. (56) found the relationship between life event stress and illness is greater for neurotic depression than unipolar (endogenous) depression.

Bebbington et al. (57) found that there is an excess of life events preceding the onset of all types of psychoses, particularly in the first 3 months. In the study of recent onset of schizophrenia, schizophreniform disorder and hypomania, Chung et al. (49) found that threatening life events were

significantly related to the onset of schizophreniform psychosis but not schizophrenia. They also found that threatening events might precipitate hypomanic episodes. Other study (50) found that individuals with schizophrenia do not experience more stressful life events than normal controls, but they reported greater subjective stress. A study that investigated the relationship between recent life events and episodes of illness in schizophrenia found that, initial or early episodes of schizophrenia are more likely to be associated with recent life events than are later episodes (48).

On the other hand, bipolar disorders have received less study than unipolar. In bipolar disorder, the effect of life events is generally weaker than unipolar; however major life events may be important in first onset (58). Causative factors in bipolar disorders are multifactorial and complex, and genetic factor seems to influence life events exposure. Those with greater genetic loading, there were fewer stressful life events before the first episode and they had the earlier onset of the disease. A number of studies have shown that the onset of depression is often preceded by stressful life events (59,60). Stressful life events along with recent minor difficulties have also been identified as predictors of an episode of depression in a monozygotic female twin study. Kessler (61) who came with the same conclusion added that there is evidence that concomitant chronic stress enhances the effect of major life events on depression.

Cooper and Sylph (51) documented the role of life events in the causation of neurotic illness. They found that neurotic group reported 50% more stressful events than the control group. McKeon et al. (52) found that patients with obsessive-compulsive neuroses who have abnormal personality traits (obsessional, anxious and self-conscious) experienced significantly fewer life events than those without such traits. Zheng and Young (53) in comparing live event stress between neurotic patients and normal control found that neurotic patients had significantly higher level of stress and experienced more life event changes than the control group. Rajendran et al. (54) who compared the neurotic executives with healthy executives as a control group, found significant differences between normal and neurotic groups in terms of the frequency of the life events as well as the stress they experienced due to those life events.

Stress and cancer

The relationship between breast cancer and

stress has received particular attention. Some studies have indicated an increased incidence of early death, including cancer death among people who have experienced the recent loss of a spouse or loved one. A few studies of women with breast cancer have shown significantly high rate of disease among those women who experienced traumatic life events and loses within several years before their diagnosis. However, most cancers have been developing for many years and are diagnosed only after they have been growing in the body for a long time. Thus, this fact argues against an association between the death of a loved one and the triggering of cancer. There is no scientific evidence of a direct cause-and-effect relationship between these immune systems changes and the development of cancer. It has not been shown that stress-induced changes in the immune system directly cause cancer. However, more research is needed to find if there is a relationship between psychological stress and the transformation of normal cells into cancerous cells. One area that is currently being studied is whether psychological interventions can reduce stress in the cancer patients, improve immune function and possibly even prolonged the survival.

Studies in animals, mostly rats, revealed the link between stress and progression of cancerous tumors. Chronic and acute stress, including surgery and social disruptions, appear to promote tumor growth. It is easy to do such research in animal, but it is harder with humans. Furthermore, the interactions of many systems that affect cancer, from the immune system to the endocrine system, along with environment factors that are impossible to control for, make sorting out the role of stress extremely difficult. In addition, researchers cannot expose people to tumour cells as they do with animals. A recent study (62) found that there was a link between stress, tumour development and a type of white blood cells called natural killer (NK) cells. Of all the immune systems cells, NK cells have shown the strongest links to fighting certain forms of the disease, specifically preventing metastasis and destroying small metastases. Although the result of this study is not definitive, it indicates that stress acts by suppressing NK-cell activity. Other preliminary study showed the evidence of a weakened immune system in breast cancer patients who feel high level of stress compared to those experiencing less stress.

A new study shows stress and social supports are important influences in a man's risk for developing prostate cancer. Researchers (63) at State

University of New York at Stony Brook's medical school found men with high level of stress and a lack of satisfying relationships with friends and family had higher levels of Prostate-Specific Antigen (PSA) in their blood, a marker for an increased risk of developing prostate cancer. Based on the results, the risk of having an abnormal PSA was three times higher for men with high levels of stress. Likewise, men who had felt they had low levels of support from friends and family were twice as likely to have an abnormal PSA. The findings raise the possibility that a man's psychological state can have a direct impact on prostate disease.

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