Do psychosocial stressors contribute to cancer onset, progression or survival?

‚Controversial topic‘

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The latest discoveries and advances in molecular biology, neurology, endocrinology, immunology, oncology and psychology have shown how strong **the relationship** can be between **subjective experiences** and **biological processes**.

Human experience changes biology on a deep level

"A cell is a machine for turning experience into biology."
(Prof. Steve Cole, UCLA)

"Stress makes your body more hospitable to cancer."
(Prof. Lorenzo Cohen, Ph.D., MD Anderson Cancer Center in Houston)

The role of long-term stress in tumorigenesis remains controversial

It is controversially discussed whether stress-associated factors can cause the development or worsening of cancer

Why some studies have showed a link between various psychological factors and an increased risk of developing cancer, but others have not?

Why should be research results interpreted with caution?

- The **inconsistent results** of numerous studies can also be attributed to the **use of heterogeneous methods** in measures of psychological stress.
- Because of the **individuality, intensity and duration of the different stressors**, their cumulative effects and the extent of the **subjectively perceived stress** over many years, is a clear cause-effect relationship particularly difficult to determine.
- There is evidence of publication bias

State of research

Influence of psychosocial factors on cancer risk

The systematic review and meta-analysis of 11 cohort studies by Bahri et al, published in 2019, concluded that history of **stressful life events** slightly **increases the risk of breast cancer**.

Bahri (2019): The relation between stressful life events and breast cancer
Source: https://pubmed.ncbi.nlm.nih.gov/ 31004298/

The University of Helsinki prospective study found that **the loss of a close person** (divorce / separation / death of a husband, a close relative or friend) **can have a negative impact** on breast cancer risk. The findings **suggest a role for life events** in breast cancer etiology.

Lillberg (2003): Stressful life events and risk of breast cancer in 10,808 women
Source: https://pubmed.ncbi.nlm.nih.gov/ 12615606/

HARVARD RADIATION ONCOLOGY PROGRAM

The Aizers study, conducted on more than 700000 patients, highlights a potentially **significant impact that can have high social support** from close persons on cancer detection, treatment, and survival.

Aizer (Boston, 2013): Marital status and survival in patients with cancer
Source: https://pubmed.ncbi.nlm.nih.gov/ 24062405/

State of research

Influence of psychological factors on the course of diseases

A prospective study in 2012 showed that positive, **meaningful relationships** significantly increase the chances of survival for patients with ovarian cancer.

Lutgendorf (2012): Social influences on clinical outcomes of patients with ovarian cancer
Source: https://www.ncbi.nlm.nih.gov/pmc/articles/ PMC3410403/

A meta-analysis of 165 prospective studies concluded that **various stress-related psychosocial factors** (e.g. stress-prone personality, negative emotional responses, poor quality of life, unfavorable coping styles) can increase cancer incidence in initially healthy populations and reduce the probability of survival in cancer patients

Chida (2008): Do stress-related psychosocial factors contribute to cancer incidence and survival?
Source: https://pubmed.ncbi.nlm.nih.gov/18493231/

The meta-analysis of 31 randomized controlled trials by Clark et al. (published online in December 2020) showed that **early long-term psychological intervention** in primary and adjuvant settings (group therapy >6 months) can improve overall survival in breast cancer.

Clark (2020): The effects of physical activity, fast-mimicking diet and psychological interventions on cancer survival: A systematic review and meta-analysis of randomized controlled trials
Source: https://www.sciencedirect.com/science/article/pii/S096522992031921X

Psychoneuroendocrinoimmunology

How stress affects cancer risk?

- Stressful life experience

⬇

- Effect of stress

⬇

- Brain triggers a stress response

⬇

SAM — **HPA**

- Hormon release

⬇

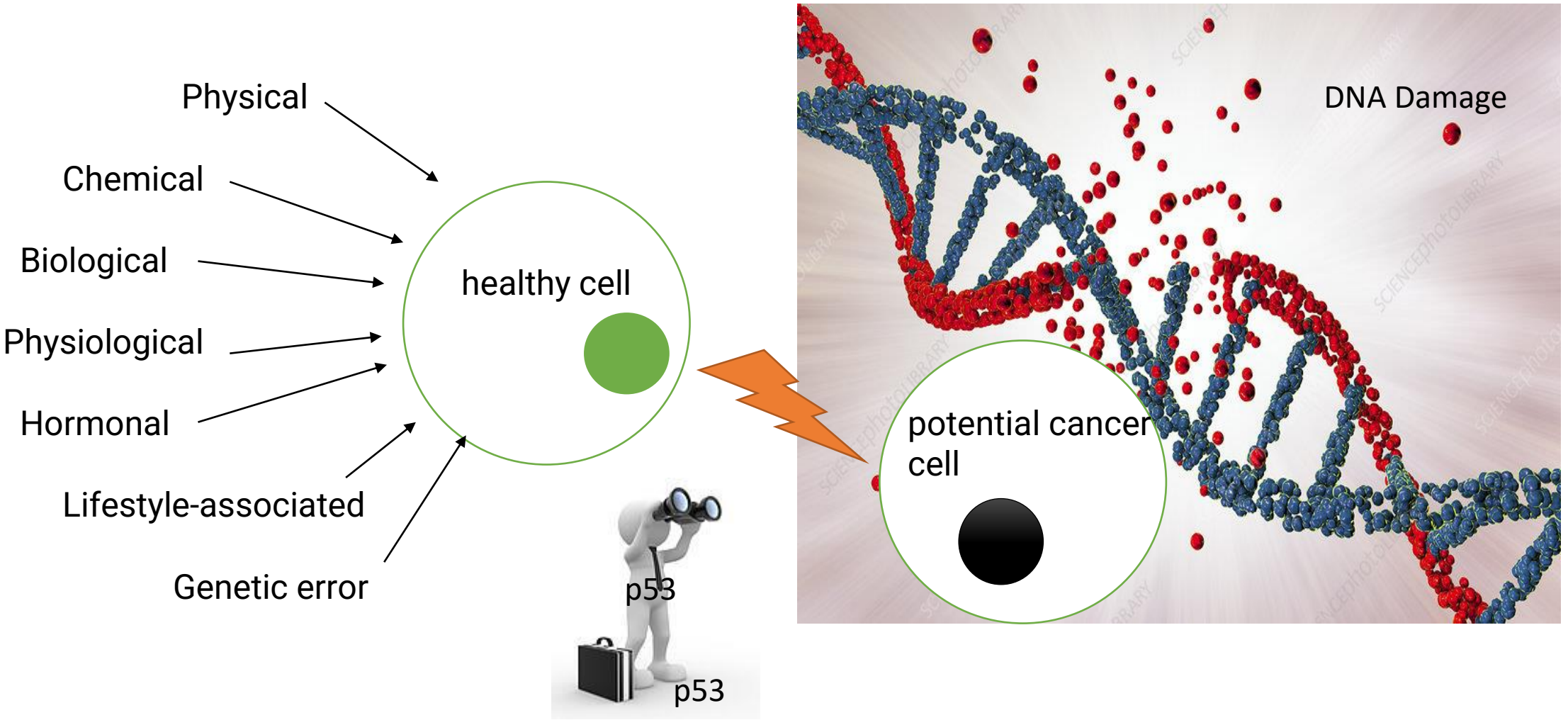
- Affecting the immune system

and influence of the tumour microenvironment

SAM=The sympathetic-adrenal medullary axis
HPA=The hypothalamic-pituitary-adrenal axis

Carcinogens and cancer risk

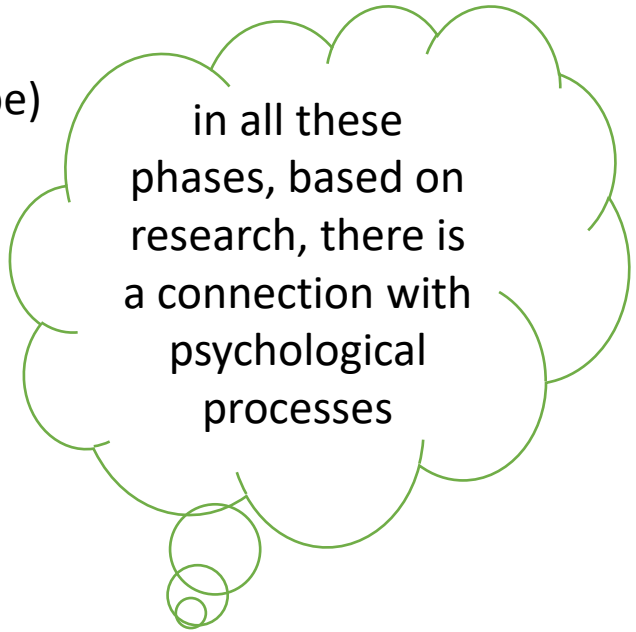
Why do cells mutate and turn into cancer?




Environmental Carcinogens
Bladder cancer, colorectal cancer, leukemia
(Chlorinated drinking water)
Leukemia, lymphoma & colorectal cancer
(Nitrates)
[drinking water]
Childhood leukemia
(Motor-vehicle exhaust)
Childhood leukemia & lymphoma
(Indoor air-pollutants)
Lung cancer Metastasis
(Nitric oxide)
Lung cancer
(Poly-aromatic hydrocarbon)
Childhood leukemia & lymphoma, brain tumors, Wilms' tumors, Ewing's sarcoma, germ cell tumors
(Pesticides)
Sarcoma & Lymphoma
(Dioxane, Incinerators)
Testicular cancer
(Env. Organic pollutants)
[In utero]
Bladder cancer
(Nitrate consumption)
Gastric cancer
(Radioactive nuclei)
[carbon, radium and uranium]

What biological barriers stand in the way of tumor cells?

- must resist attempts at self-correcting (p53) and self-destruction (resistance to apoptosis)
- must survive in hypoxic environment (requires oxygen und nutrients for growth and development) → angiogenesis, chronic inflammatory environment
- must resist destruction by immune attack (immune tolerance / immune escape)
- must master establishment and growth of tumor metastases

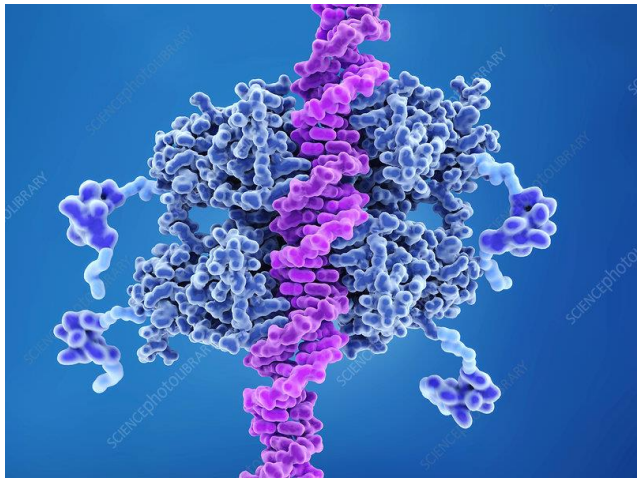


Guardian of the Genome

critical role of p53 in preventing the initiation and/or progression of cancer

The cancer cell must **resist the processes of repair (of DNA damage) or apoptosis**

tumor suppressor protein p53 plays a central role here



RUTGERS
Cancer Institute
of New Jersey
RUTGERS HEALTH

What does the psyche have to do with it?

⬇

glucocorticoids released during long-term stress decrease p53

High levels of cortisol **decrease p53 levels and function** → stimulating anti-apoptotic gene expression and contributing to tumor growth, metastasis, and chemotherapy resistance in cancer

The mechanism can be simplified as follows:

Chronic stress → expansion of glucocorticoids levels → binding to GR (glucocorticoid receptor) → induction of protein kinase SGK1 → increase of MDM2 activity → down-regulate p53 → tumorigenesis

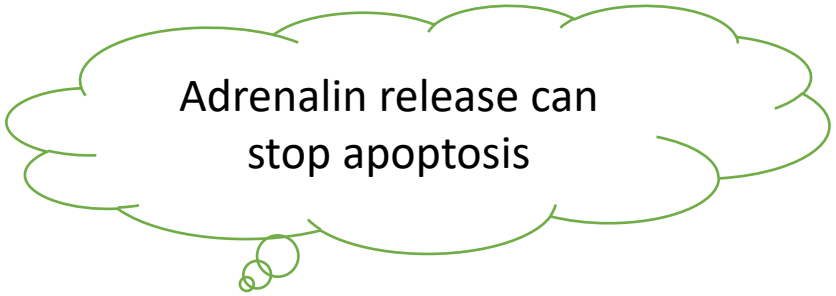
Feng (2012): Chronic restraint stress attenuates p53 function and promotes tumorigenesis
Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3345015/

Antiapoptotic signaling by epinephrine

The long-term release of adrenalin suppresses the process of apoptosis of cancer cells through interaction with beta(2)-adrenergic receptors in prostate and breast cancer cell

The mechanism can be simplified as follows:

Adrenalin → ADRB2 (beta-2 adrenergic receptor) → G-Protein (guanine nucleotide-binding proteins), PKA (protein kinase A) → influence of Bcl-2-proteins regulating mitochondrial membrane permeability → inhibition of apoptosis



Sastry (2007): Epinephrine protects cancer cells from apoptosis via activation of cAMP-dependent protein kinase and BAD phosphorylation
Source: https://pubmed.ncbi.nlm.nih.gov/17353197

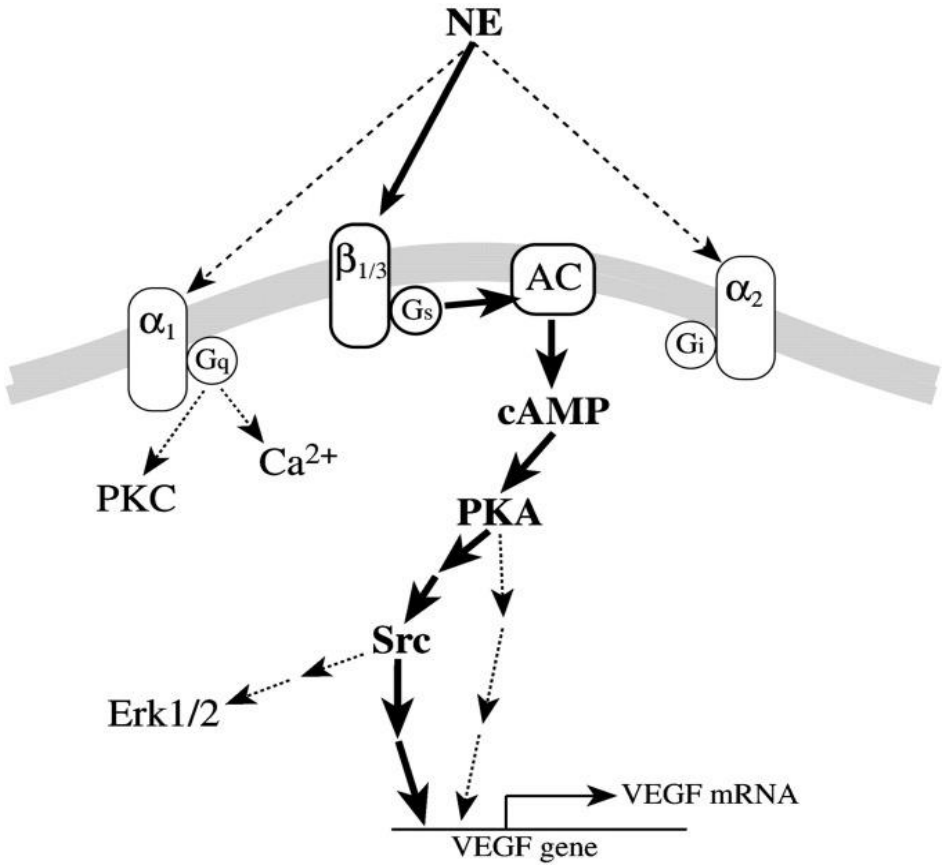
Activation of angiogenesis

Fredriksson (2000): Norepinephrine induces vascular endothelial growth factor gene expression in brown adipocytes through a beta - adrenoreceptor/cAMP/protein kinase A pathway involving Src but independently of Erk1/2

A study from Stockholm University points to connection between the stimulation of norepinephrine and the release of VEGF.

Pathway: Signaling was via a β-adrenoreceptor-induced increase in cAMP levels, further mediated by PKA (protein kinase A). Downstream of cAMP/PKA, the signal was mediated by Src tyrosine kinases.

Source: https://pubmed.ncbi.nlm.nih.gov/10788502



Angiogenesis

The psyche can also play a crucial role in this process

Feelings of intense loneliness in colorectal cancer patients were associated with stronger expression of VEGF and its stimulating vascularization in cancer

Nausheen (2010): Relationship between loneliness and proangiogenic cytokines in newly diagnosed tumors of colon and rectum
Source: https://pubmed.ncbi.nlm.nih.gov/20716709/

Antiangiogenic effect of neurotransmitter dopamine

In contrast, the preoperative experienced level of emotional support was associated with negative VEGF levels in ovarian cancer patients.

Lutgendorf (2002): Vascular endothelial growth factor and social support in patients with ovarian carcinoma
Source: https://pubmed.ncbi.nlm.nih.gov/12209725/

The Immune system and cancer

Cancer development can be controlled by cytotoxic innate and adaptive immune cells

Natural killers (NKs)
Cytotoxic T lymphocytes (CTLs)

How do cancer cells evade the destruction by immune attack?

Thanks to various mechanisms evolve cancer cells peripheral **immune tolerance**
There is the presence of inflammatory immune cells in tumor microenvironment
+
The physiologic effects of **chronic stress inhibit cellular immune responses**

Gonzales (2018): Roles of the immune system in cancer: from tumor initiation to metastatic progression
Source: https://pubmed.ncbi.nlm.nih.gov/ 30275043/

The Immune system and cancer

Chronic stress leads to decreased immune response

The Ohio State University

The data showed that the **physiologic effects of chronic stress inhibit cellular immune responses** including NK cell toxicity and T-cell responses.

Andersen (1998): Stress and Immune Responses After Surgical Treatment for Regional Breast Cancer
Source: https://www.ncbi.nlm.nih.gov/pmc/articles/ PMC2743254/

This study evaluated relations among optimism, depression, anger suppression and natural killer cell cytotoxicity in men treated for localized prostate cancer.

Results showed that **greater optimism and less anger suppression were associated with greater natural killer cell cytotoxicity**.

Penedo (2006): Anger suppression mediates the relationship between optimism and natural killer cell cytotoxicity in men treated for localized prostate cancer
Source: https://pubmed.ncbi.nlm.nih.gov/16581368/

Partial summary

- Substances released during prolonged stress may inhibit the process of self-destruction of potential cancer cells
- Substances released during long-term stress may stimulate tumor vascularization
- Substances released in states of calmness can suppress tumor vascularization
- Substances released during long-term stress can negatively affect the fighting ability of the immune system
- The feeling of insufficient support from close people can lead to the suppression of some parts of the immune system
- An optimistic approach to life can strengthen the fighting ability of some parts of the immune system
- The ability to share negative emotions can positively affect the immune system

Can chronic stress lead to a chronic inflammatory state through activation of the immune system?

chronic stress → a chronic inflammatory state

essential for tumor growth and development

THE OHIO STATE UNIVERSITY
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Relationship conflict (*in the absence of infection or injury*) and lower social support can effectively modulate **proinflammatory cytokine secretion**.

biological mechanisms

stress → catecholamine release + activation of nuclear factor kappa B → increased production of proinflammatory cytokines (IL-6, TNF-alpha, IL-1) in the absence of infection

Kiecolt-Glaser (2010): Close relationships, inflammation, and health
Source: https://pubmed.ncbi.nlm.nih.gov/ 19751761/

THE UNIVERSITY OF IOWA
ORGANIZED FEB. 25TH 1847.

Good social attachment of patients with ovarian cancer was associated with lower levels of **IL-6** (in peripheral blood).

Costanzo (2005): Psychosocial factors and interleukin-6 among women with advanced ovarian cancer
Source: https://pubmed.ncbi.nlm.nih.gov/ 15954082/

Proinflammatory cytokine secretion

The study showed that the stress **hormones norepinephrine and cortisol tended to increase IL-6 expression** in cells of oral squamous cell carcinoma and can affect oral cancer cells behavior.

Bernabe (2011): Stress hormones increase cell proliferation and regulates interleukin-6 secretion in human oral squamous cell carcinoma cells
Source: https://pubmed.ncbi.nlm.nih.gov/21187140/

Jaremka demonstrated that **lonelier healthy adults** exposed to acute stress exhibited **greater synthesis of TNF-alpha and IL-6** than their less lonely counterparts. And **lonelier posttreatment breast-cancer survivors** exposed to acute stress produced **more proinflammatory cytokines** (IL-6, IL-1β) than their counterparts who felt more socially connected.

Jaremka (2013): Loneliness promotes inflammation during acute stress
Source: https://pubmed.ncbi.nlm.nih.gov/23630220/

Summary

- Chronic inflammation can promote cancer growth
- Chronic stress can promote chronic inflammation
- Experiencing a state of contentment, calmness and good mood can lead to the suppression of substances that cause chronic inflammation
- Experiencing a state of contentment can lead to the support of the immune system
- The feeling of insufficient support from loved ones can promote the development of inflammatory environment

Paths to reduce cancer-related stress

- Ask for help / get informed / counseling / talk therapy
- Express yourself /share your feelings / support of loved ones
- Be kind to yourself
- Get moving / training in relaxation, meditation, or stress management

Because everything is manageable