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Research Article

# PATHOGENETIC ASPECTS OF CANCER ANOREXIA

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**Rakhimov Nodir Makhammatkulovich**
Samarkand State Medical University, Uzbekistan

**Shakhanova Shakhnoza Shavkatovna**
Samarkand State Medical University, Uzbekistan

**Tulanov Begzod Tulan Ugli**
Samarkand State Medical University, Uzbekistan

## ABSTRACT

Anorexia and malnutrition are the physiological response of the body to the development of cancer (i.e. activation of the immune system, increased energy consumption...). Initially, it is believed that all these changes help the body fight tumor growth. In this context, the effectiveness of anorexia treatment is related to several mechanisms. Firstly, the patient's body is not activated and is not in search of food and thus saves energy, it also reduces the heat loss that can occur due to increased convection. The stored temperature in this case is used by the body to fight the rapid growth of cancer. Second, eating less during illness also reduces the intake of nutrients needed by cancer cells, as well as reducing the energy intake needed for digestion. This effect of early anorexia is supported by a classic study in which force-feeding infected experimental mice resulted in increased mortality (1). However, despite the benefits of early anorexia, prolonged anorexia compromises the body's defenses and makes recovery more difficult.

## KEYWORDS

Body fight tumor growth, food and thus saves energy.

## INTRODUCTION

**Clinical significance of cancerous anorexia.**

The development of a cancerous tumor itself is often associated with the development of anorexia. Therefore, anorexia in cancer should not be confused with nausea and vomiting caused by radio-chemotherapy. Cancer patients may experience anorexia secondary to food refusal. In this case, anorexia is the result of the central integration of negative psychobiological, olfactory/taste sensations.

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Food aversion is an adaptive, powerful mechanism associated with the clinical state of the body, as it affects food choice and dysregulation of appetite (2). However, this mechanism appears to play a large role in chemotherapy-associated nausea and vomiting and has little effect on anorexia cancer.

**Degrees of prevalence and severity**

Anorexia and malnutrition are known to be common in cancer patients (3). The classic work of DeWys (4) helps estimate the prevalence of anorexia in cancer patients, showing that approximately 50% of cancer patients are malnourished at the time of diagnosis. In terminally ill patients, anorexia occurs in 60-64% of cases (5, 6). However, it should be clear that in some cases anorexia may also be due to prior therapeutic treatment. But not only the prevalence rate is high, especially in patients with a progressive cancer process. If anorexia is observed, it is usually of moderate severity (7), which is a problem for patients and their relatives (Fig. 1).

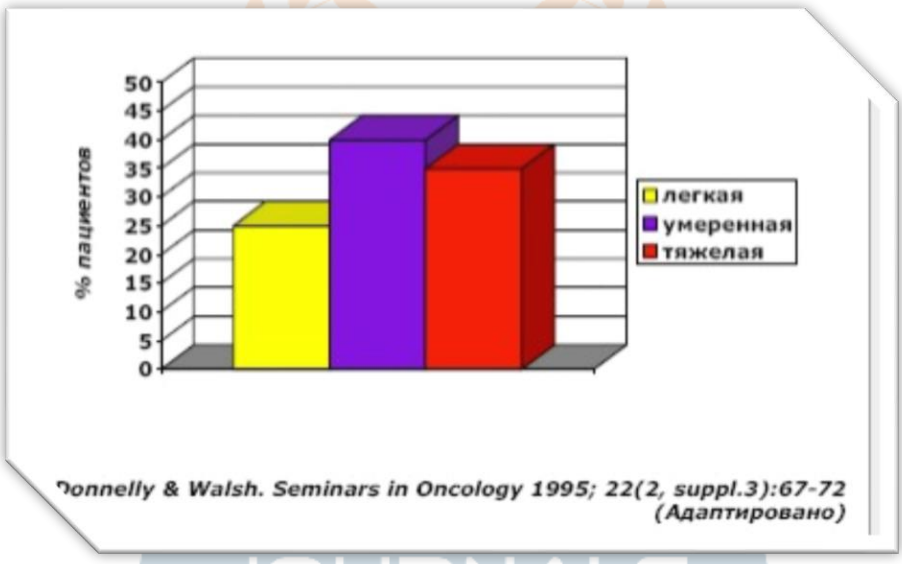


**Fig. 1 Severity of anorexia in cancer patients.**

**Pathogenetic mechanisms of cancerous anorexia.**

The pathogenesis of cancerous anorexia is multifactorial and is primarily associated with dysfunction of the central physiological mechanism that controls food intake, although the issue of specific neurochemical processes is still under discussion. Numerous factors are involved in the pathogenesis of anorexia; it significantly influences the development of the underlying disease, contributing to the onset of cachexia, increasing the incidence of complications and mortality, and worsening the quality of life (Fig. 2).

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**Fig.2 The pathogenesis of anorexia cancer is based on many factors and is of great clinical importance.**

Under normal conditions, energy consumption is controlled by the hypothalamus, where peripheral signals transmit information about energy and the state of adipose tissue (14) (Fig. 3). In the hypothalamus, the arcuate nucleus contains specific neuronal components that convert these signals into a neuronal response and then, via second-order signaling pathways, into a behavioral response (Fig. 4). Therefore, cancer anorexia may be secondary to defective signals coming from the periphery due to an erroneous transduction process or due to a disturbance in the activity of second-order neuronal signaling pathways.

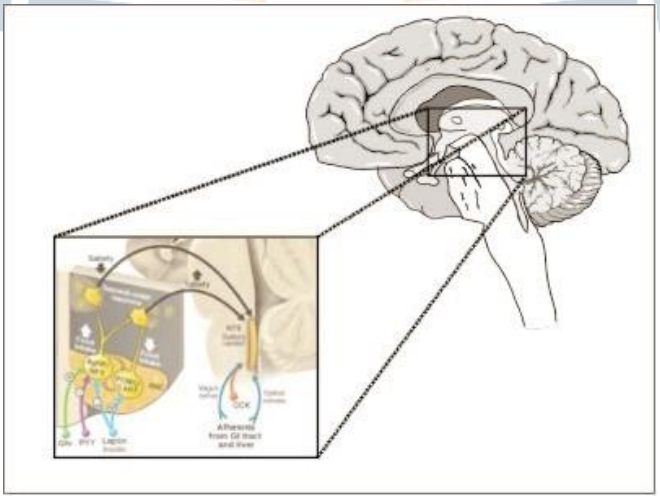

**Fig. 3 Food intake is regulated by the arcuate nucleus of the hypothalamus (ARC-arcuate nucleus)**

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**Role of Peripheral Signals**

The hypothesis that peripheral signals are involved in the pathogenesis of anorexia cancer is very interesting. Among the large number of peripheral signals, the hormones leptin and ghrelin are suitable candidates for discussion.

Leptin is produced primarily by adipocytes in proportion to body fat, and an increase in circulating levels of leptin leads to a decrease in energy intake. Thus, leptin is the most likely mediator of anorexia cancer. However, results from clinical and animal studies are conflicting (15, 16) and do not support this hypothesis. Later it was found that anorexia in both animals and humans develops without affecting the normal process of leptin synthesis (17, 18).

Ghrelin is a peptide produced primarily by the stomach in response to fasting (19). Increasing its levels in the circulation increases appetite and increases the need to eat (19). Therefore, cancerous anorexia may be associated, at least in part, with a decrease in ghrelin levels. However, animal and human data do not support this hypothesis, demonstrating elevated levels of ghrelin in both tumor-bearing animals and patients with cancer cachexia (see reference 20 for a more detailed discussion).

Putting these facts together, it follows from these data that cancerous anorexia is the result of "hypothalamic resistance," that is, the inability of the hypothalamic mechanisms for controlling food intake to adequately respond to peripheral signals.

**Energy signals**

Like changes in fat mass, changes in energy metabolism affect energy intake. Many studies suggest the existence of metabolic control over food intake, in which biochemical separation in hypothalamic neurons between fatty acid oxidation and synthesis is the main signal indicating catabolic and anabolic energy status [21]. Under normal physiological conditions, food intake increases the intracellular level of malonyl-CoA (22), which is a powerful signal that reduces food intake (Fig. 6). Therefore, energy signals may play a role in cancer anorexia, possibly due to the disturbed "feeling" of energy metabolism in cancer patients. This hypothesis is indirectly supported by the fact that during tumor development, fat metabolism changes and leads to a decrease in fatty acid oxidation (23) and possibly an increase in intracellular levels of malonyl-CoA. However, in order to reliably judge the participation of energy signals in the development of cancerous anorexia, additional studies are needed.

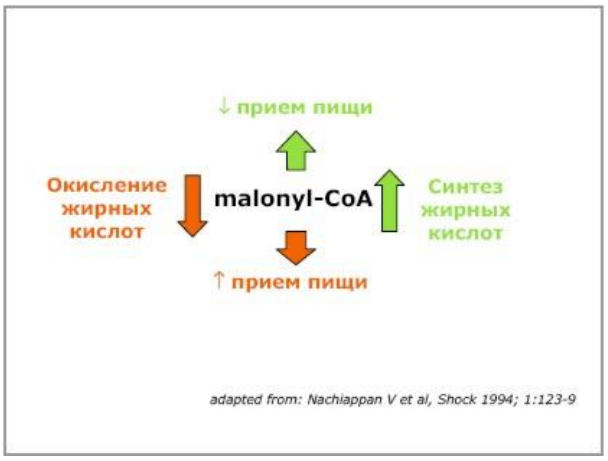

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**Fig. 4 Metabolic control of food intake.**

**Neuropeptides**

Consistent and convincing evidence suggests that cancerous anorexia is the result of a disorder in the hypothalamic system that converts peripheral signals into a neural response. Under normal conditions, peripheral signals interact with two distinct types of neuronal components in the arcuate nucleus: NPY/Agouti peptide (AgRP)-associated neurons and opiomelanocortin (ROMS)/cocaine and amphetamine (CART)-regulated neurons (for a detailed review, see section 14 of the literature list). These neurons create two pathways: first stimulation, and then slowing down the process of energy consumption. In an animal model of cancerous anorexia, it is clearly seen that NPY immunoreactivity is reduced (24) (Fig. 5), resulting in a reduced ability to stimulate food intake.

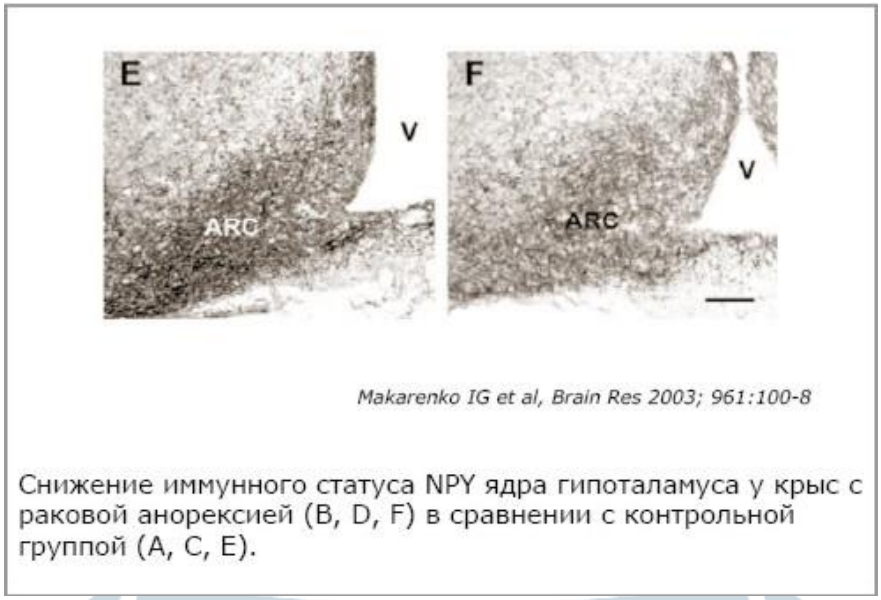


**Fig. 5 Arcuate nucleus NPY and cancerous anorexia (24).**

On the other hand, it has been repeatedly demonstrated that when the hypothalamic melanocortical system is blocked, either due to a physiological inhibitor (i.e., AgRP) or due to synthetic substitutes, food intake in cancerous animals resumes, which prevents the development of cachexia (25, 26). Similar results were achieved in experimental mice treated with melanocortin 4 (MC4R). In these mutants, POMC/CART neurons cannot be fully activated due to the absence of this class of receptors, and tumor development is not accompanied by the development of anorexia and cachexia, which is observed in normal mice (25) (Fig. 6).

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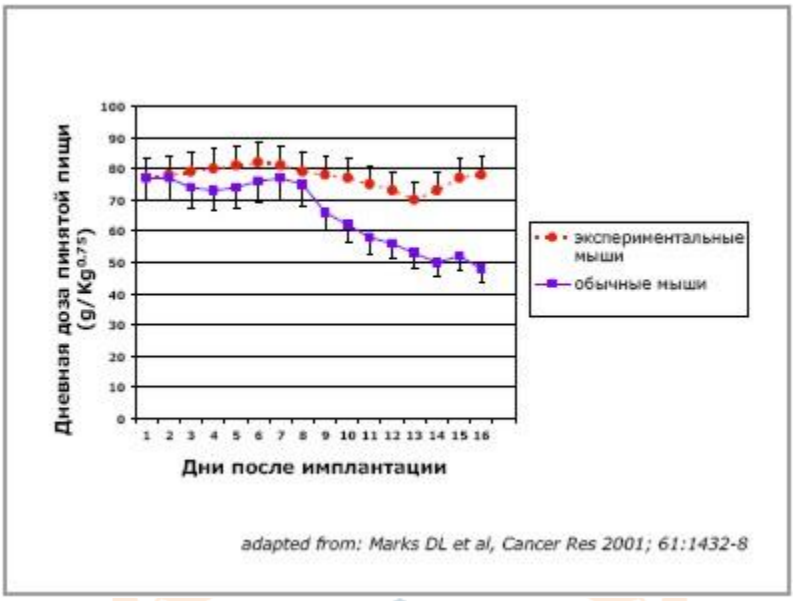


**Fig. 6 Melanocortin system in cancerous anorexia (25).**

Therefore, cancerous anorexia is associated with the inability of the hypothalamus to adequately respond to constant peripheral signals due to hyperactivation of the melanocortin system and partial slowing of NPY. This disorder may be caused by cytokines.

**The role of cytokines**

Many studies show that cytokines play a role in the process of anorexia cancer (27). In the Fisher/MCA rat model of cancer, interleukin-1 (IL-1) levels in the brain are inversely related to food intake (28), while microinjection of an IL-1 receptor antagonist inside the hypothalamus increases energy intake (29). In the same model, administration of recombinant soluble human tumor necrosis factor (TNF) receptor reduced anorexia and improved food intake (30) (Figure 7).

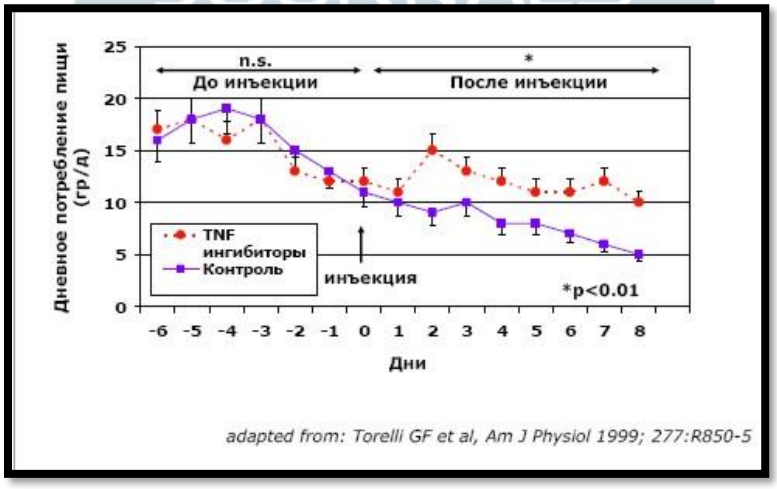

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**Fig. 7 TNF inhibitors and cancerous anorexia (30).**

In cancer patients, cytokines and anorexia are interrelated, although there is no indisputable evidence for this, since the biological effects of cytokines are largely mediated by paracrine and autocrine influences. Thus, the level of cytokine circulation does not reliably reflect their role in determining specific biological responses, but rather indicates their involvement. However, the role of interleukin-1 and other cytokines (interleukin-6 (IL-6), TNF-α, INF-γ (interferon-γ)) is noticeable in experimental models of cancer in the development of cancer anorexia. However, it should be noted that there are other studies that could not show a clear role of cytokines in experimental models of cancer anorexia and suggest the involvement of the nitric oxide system and systemic or local production of eicosanoids [3 1].

**The role of neuro-immune interactions of the hypothalamus**

Currently, the mechanisms of the negative effect of cytokines on energy consumption are being actively investigated. Inui has suggested that cytokines may play an important role in long-term nutritional suppression by mimicking the function of the hypothalamus to respond to negative signals (32). This occurs due to the suppression of the processes that stimulate the appetite NPY/AgRP and the stimulation of the anorexigenic processes POMC/CART.

Recent evidence indicates that hypothalamic serotonergic neurotransmission may be critical in the combination of cytokines and the melanocortin system. Fenfluramine increases serotonin levels in the hypothalamus, which activates the POMC/CART neurons in the arcuate nucleus and thus leads to anorexia and reduces food intake (33). On the other hand, it is known that cytokines, in particular IL-1, stimulate the release of serotonin in the hypothalamus [34]. Consequently, during tumor development, cytokines increase the serotonergic activity of the hypothalamus, which, in turn, activates POMC/CART neurons and leads to the development of anorexia and poor food intake (Fig. 10).

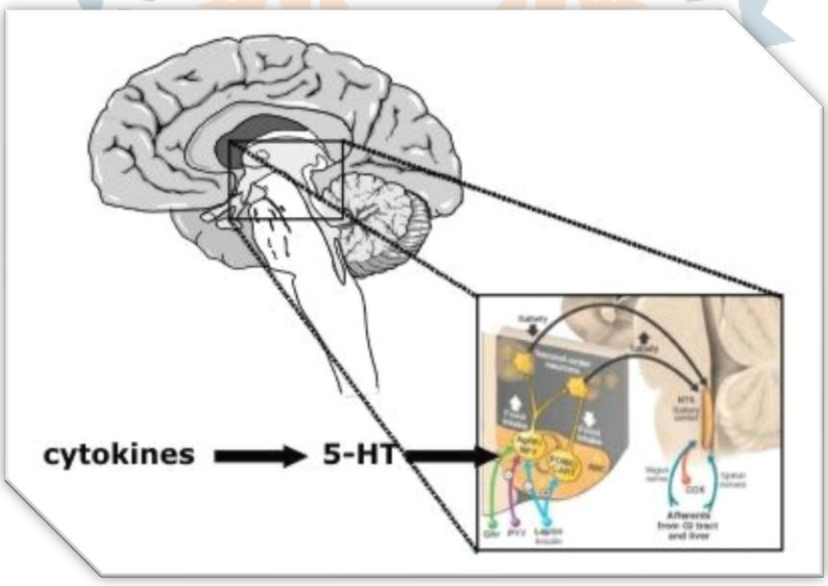

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**Fig. 8 Serotonin (5-HT) mediates the anorectic effect of cytokines on the hypothalamus.**

To prove the theory of the role of serotonin in the pathogenesis of cancerous anorexia in animals with cancer and anorexia, the level of serotonin in the hypothalamus was overestimated compared to the control group of rats, and after removal of the tumor, the level of serotonin in the hypothalamus returned to normal and the process of eating was normalized. consumption improved [35]. In cancer patients, the activity of the serotonergic system of the hypothalamus is activated by the level of tryptophan, a precursor of serotonin, in the cerebrospinal fluid (CSF). In patients with cancerous anorexia, tryptophan levels in the blood and cerebrospinal fluid are elevated compared with the control group (13, 36). Analysis of these data leads to the conclusion that the content of serotonin in the brain is a key factor in the pathogenesis of anorexia cancer.

In cancer patients, the appearance of anorexia contributes to the development of nutritional deficiencies and cachexia, as it reduces calorie intake, which leads to wasting of skeletal muscles. This exacerbates the detrimental effect of cancer-associated changes in protein metabolism on the patient's nutritional status and ultimately leads to increased morbidity and mortality (8). In addition, the clinical significance of anorexia is underlined by the fact that it serves as a factor closely associated with an increased risk of death in cancer patients (9) (Table 1), being as reliable in predicting survival as strong prognostic factors such as Karnofsky's performance status (Karnofsky Index) and Clinical prognosis of survival (Clinical prognosis of survival) (6, 9).

**Table 1 Factors associated with an increased risk of mortality. Anorexia is defined as early satiety.**

| Выживаемость после обращения (n=549) | HR | 95% CI | P |
|---|---|---|---|
| Настоящий статус (повышен на 1 единицу) | 1.4 | 1.3-1.6 | <0.001 |
| Пол (м/ж) | 1.3 | 1.1-1.6 | 0.012 |
| Дисфагия (есть/нет) | 1.3 | 1.0-1.6 | 0.05 |
| Раннее насыщение (есть/нет) | 1.3 | 1.1-1.5 | 0.01 |

As a result, anorexia and a decrease in energy intake negatively affect the quality of life of the patient (11) (Fig. 9).

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**Fig. 9 Negative impact of anorexia and reduced food intake on the quality of life of patients (11).**

## CONCLUSION

Anorexia is often mentioned by cancer patients and can be a symptom of the disease. Cancer anorexia is an important symptom because it affects malnutrition and ultimately cachexia, increases morbidity and mortality, and negatively affects quality of life. The pathogenesis of cancerous anorexia is multifactorial, but the main role is played by the inflammatory response of the body, provoked by a growing tumor, and the production of pro-inflammatory cytokines. Cytokines impair the function of the hypothalamus responsible for food intake, resulting in "hypothalamic resistance" to peripheral signals. These processes are mediated, at least in part, by serotonin. Due to the multifactorial nature of pathogenesis, it is difficult to find a sufficiently effective and reliable therapeutic approach. Although drug therapy can significantly improve appetite, in the first place, patients who lose their appetite should receive individualized nutritional advice, which can significantly affect the outcome of treatment.

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