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# FEATURES OF THE IMMUNE STATUS IN PRACTICALLY HEALTHY AND CANCER-AFFECTED RESIDENTS OF THE EUROPEAN NORTH WITH A HIGH CONTENT OF DOPAMINE IN PERIPHERAL VENOUS BLOOD

The study was conducted of 65 practically healthy people and 122 people suffering from oncological pathology of the gastrointestinal tract of various localization to study the immune status of practically healthy and oncological residents of the European region with an increased content of dopamine in peripheral venous blood. Thus, for the first time, it was established that the state of the immune status of residents of the European North with an increased content of dopamine in peripheral venous blood, in accordance with the state of health имеет, has significant deviations in people suffering from oncological pathology compared to practically healthy residents of the territories of the European North. Thus, the average dopamine content in practically healthy people and in people suffering from cancer pathology, is 33.1±3.93 and 133.66±8, respectively, чthe frequency of recording elevated dopamine concentrations in practically healthy people and in people suffering from cancer pathology is 7.69±0.23 % and 59.84±0.63 %, respectively. The average blood levels of transferrin and IgE in people suffering from oncological pathology are higher than in practically healthy people (119.89±35.77 and 53.34±7.21, respectively). The increase in the average content of other parameters studied was insignificant. The frequency of elevated concentrations of other immunological parameters was established, which was significantly higher in patients with oncological pathology. Thus, the appearance of immune responses is established, i.e. the interaction of the immune system with the tumor, which represents a balance between the processes of immune activation and immune suppression and violation of the mechanisms of regulation of components of the immune system that occur in people with malignant tumors.

**Keywords:** dopamine, immune status, oncological pathology, cytotoxic lymphocytes, transferrin, IgE, autoantibodies to DNA and RNA, CIC, autoantibodies to phospholipids (IgM), autoantibodies to phospholipids (IgG)

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A survey of 65 practically healthy people and 122 people suffering from oncological pathology of the gastrointestinal tract of various localization was conducted to study the immune status of practically healthy and oncological residents of the European North with elevated dopamine levels in peripheral venous blood. Thus, for the first time, it was established that the state of immune status in residents of the European North with an increased dopamine content in peripheral venous blood, in accordance with the state of health, has significant deviations in people suffering from oncological pathology compared with practically healthy residents of the European North. Thus, the average dopamine content in practically healthy people and in people suffering from oncological pathology is 33.1±3.93 and 133.66±8, respectively, the frequency of increased dopamine concentrations in practically healthy people and in people suffering from oncological pathology is 7.69±0.23% and 59.84±0.63%, respectively. The average blood transferrin and IgE levels in people suffering from cancer are higher than in practically healthy people (119.89±35.77 and 53.34±7.21, respectively). The increase in the average content of the other parameters studied was insignificant. The frequency of elevated concentrations of other immunological parameters was established, which was significantly higher in patients with oncological pathology. Thus, the appearance of immune reactions has been established, i.e. the interaction of the immune system with the tumor, representing a balance between the processes of immune activation and immune suppression and a violation of the mechanisms of regulation of the components of the immune system that occur in people with malignant tumors.

**Introduction.** Dopamine is interesting from the point of view of science because it performs various functions in the human body. It not only helps to think, move, form feelings, and make choices, but also

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contributes to the development of certain diseases. It is possible that dopamine affects the metabolism of cancer cells and promotes their progression and growth, and blocking dopamine receptors significantly slows down the growth of tumor formations. Researchers at Vanderbilt University Medical Center have identified the effects of dopamine on breast cancer growth. Studies conducted in mice have shown that inhibition of specific receptors contributes to the suppression of tumor development. This discovery opens up new opportunities for the development and implementation of effective cancer treatment methods. In some areas of science, dopamine is not well understood. It was necessary to find out whether the production of "stress dopamine" or any other factors that increase and accelerate the development of the disease, how they affect and change other immunological parameters of the blood, предстояло выяснить. It was of considerable interest to study elevated dopamine concentrations and compare them with immune responses in practically healthy and oncological patients of the European community with elevated dopamine content in peripheral venous blood. There is a well-known fact that in malignant neoplasms there is a violation of the immune defense.

Dopamine is a hormone and neurotransmitter, that cis synthesized from L-DOPA. This hormone is produced in the neurons of the brain located in the middle and medulla oblongata and is involved in the transmission of nerve impulses between cells. The dopaminergic system has a clear zonal distribution of dopamine neurons. Dopamine synthesized outside the central nervous system (adrenal glands, kidneys, and intestines) is not involved in the transmission of nerve impulses, but is involved in the regulation of the cardiovascular and other body systems. Up to 90% of dopamine is secreted in the gut [12,1-6]. Acting on the peristalsis of the ventricle and intestines, slows it down. It plays a significant role in the work of the pancreas, because it reduces the production of insulin by its cells (islets of Langerhans), kidneys, thereby accelerating the excretion of sodium and urine. Dopamine is involved in regulating the activity of the immune system and has a significant effect on the function of immune cells (reduces the activity of lymphocytes). Many immune cells express dopamine receptors that are bound to dopamine and this allows them to actively respond to dopamine and suggests that dopaminergic immune regulation is an important part of normal immune function. The dopamine concentration that immune system cells are exposed to in various anatomical regions is not yet clear [14]. So, бliterally, dopamine, as a key neurotransmitter , plays a huge role in the work of many body systems and a key role in a number of diseases, including cancer. All this suggests that dopamine plays an important role in the immune system.

**The aim** of the study is to study the features of the immune status in practically healthy and oncological residents of the European Region with a high content of dopamine in peripheral venous blood.

**Materials and methods.** An immunological examination of 65 practically healthy people living in the city of Arkhangelsk, who at the time of the examination had no history of acute and chronic pathology, was performed. As a comparison group, we took 122 people with a history of oncological pathology of the gastrointestinal tract of various localization. The age of the surveyed people was 41-70 years. The examination was carried out by a doctor in the medical company Biolam, Arkhangelsk. We have studied and analyzed the material carried out by employees of the laboratories of the Institute of Physiology of Natural Adaptations UB of the N. P. Laverov Federal State Budgetary Institution of the Russian Academy of Sciences of the Ural Branch of the Russian Academy of Sciences for several years. The study was conducted in accordance with the provisions of the Helsinki Declaration and was approved by the Ethics Committee of the N. P. Laverov Federal Research Center for Integrated Arctic Studies of the Ural Branch of the Russian Academy of Sciences (Protocol No. 5 of 27.11.2020). The survey was conducted with the written consent of respondents.

Blood sampling for the study was performed in the morning hours (8-10), on an empty stomach. Blood serum was separated from the formed elements (erythrocytes) by centrifugation (separation of the liquid part of blood from cells in order to prepare the biomaterial for subsequent analysis).

The complex of immunological research included the study of hemograms in blood smears stained by the Romanovsky-Giemse method. The concentrations of dopamine in the blood serum were studied by an enzyme-linked immunosorbent assay (IBL Hamburg, Germany). The level of cytotoxic lymphocytes (CD4+), transferrin (Bender MedSystems, Germany), immunoglobulin E (IgE) was evaluated using the test-kit 'Biosourse' (USA), circulating immune complex (CIC) using the test kit of the chemical company Reakompleks (Chita). The content of antibodies to double-stranded DNA (anti-dsDNA), ribonucleoprotein-(anti-RNP) (Bio-Rad, USA) was studied using Multiscan MS (Labsystems,-Finland) and Evolis (USA) analyzers and antibodies to phospholipids (IgM, IgG) using diagnostics of their production kits 'Biosourse' (USA).

Statistical analysis of the research results was carried out using the application software package "Microsoft Excel 2010" and "Statistica 7.0" (StatSoft, USA). The boundaries of the normal distribution of indicators were determined. The data distribution was compared with normal values using the Shapiro–Wilk test. The distributions of the results turned out to be similar to the normal one, so for describing the data the average arithmetic mean (*M*) and standard error of the mean *(m)* were calculated. Quantitative values between groups were compared using the Student's t-test. The differences were considered statistically significant at the significance level of the t-test $p < 0.05$-0.001.

**Results and discussion.** Changes in immunological parameters and the state of the immune status were found both in practically healthy people and in people suffering from oncological pathology of the gastrointestinal tract of various localization. Namely, an increase in the average blood content of dopamine, and immunoglobulin E and transferrin, both in practically healthy people and in people suffering from cancer (Table 1). Neurotransmitters are involved in many physiological and pathophysiological functions of the body, in the formation of the immune system, antimetastatic and antitumor resistance of the body. It is known from the literature that an imbalance in the system of excitatory and inhibitory neuro-transmitters affects the development and progression of malignant tumors [11]. Neurotransmitters can act as powerful regulators of many cell functions in the production of growth factors and factors that promote metastasis. They also modulate proliferation, migration, and the formation and development of new vessels in tumors, and, accordingly, their involvement in the formation and progression of oncological diseases cannot be excluded [15]. The average content of other immunological markers slightly exceeded the physiological limits. Immunoglobulin E (IgE) belongs to a class of immunoglobulins that are found in blood and in small amounts, but one of the most important factors of the immune

Table 1

**Average content of both dopamine and immunological parameters in peripheral venous blood in practically healthy and cancer-affected residents of the European North with a high content of dopamine in peripheral venous blood, (M±m)**

| Study parameters | Average content in practically healthy people, n=65, (M±m) | Average content in in people with oncological pathology of the gastrointestinal tract, n=122, (M±m) | Physiological limits |
|---|---|---|---|
| Dopamine, pg/ ml | 33.1±3.93 | 133.66±8.2*** | >30 пг/мл |
| Cytotoxic lymphocytes CD3+ CD8+, ×109 cells/l | 0.39±0.02 | 0.44±0.03* | 0.2-0.4 |
| Transferrin, g / l | 3.09±0.17 | 5.06±0.15** | 1.5-3.5 |
| Immunoglobulin E (IgE), u/ml | 53.34±7.21 | 119.89±35.77*** | <100 |
| CEC, g/ l | 2.97±0.64 | 4.03±0.38* | <2.0 |
| Anti-dsDNA , u/ ml | 53.95±7.47 | 68.0±13.66* | <50.0 |
| Anti-RNP, u/ml | 0.83±0.1 | 1.13±0.1* | <1.0 |
| Antiphospholipids IgM, u/ ml | 4.18±0.59 | 5.91±0.57* | <10.0 |
| Antiphospholipids IgG, u/ml | 6.54±1.25 | 7.16±0.9* | <10.0 |

Note: n is the number of people surveyed, ***p<0.001, **p<0.01, *p<0.05.

system. It reacts first to the penetration of a foreign antigen into the body and causes the development of an allergic reaction (type I). It also participates in the response to infection with parasites and at the same time directly interacts with the pathogen's antigens. In oncological diseases, the content of reagins increases. It is possible that the immune response to the complex of tumor antigens is accompanied by an antibody formation reaction with an increase in the m content of serum immunoglobulins and IgE, including [2]. Transferrin is a plasma protein that transports iron ions. Participates in the provision of innate immunity. It is known that in iron-deficient anemia, the level of transferrin in the blood increases [11-3]. The development of anemia is typical for patients with cancer [5]. Anemia occurs in 40-60 % of patients with malignant tumors of various localizations. The decrease in hemoglobin levels in cancer patients may be due to both the use of various methods of chemotherapy and radiation therapy, which have an overwhelming effect on hematopoiesis, and iron deficiency, which can be observed in chronic blood loss, reduced iron absorption and suppression of the process of red blood cell formation, which is typical for cancer patients. [6]. Iron deficiency occurs with blood loss, and transferrin transports iron ions in the body. Thus, the level of transferrin may be elevated in the blood.

The frequency of registration of elevated concentrations of cytotoxic lymphocytes, transferrin, immunoglobulin E,

Table 2

**Frequency of registration of elevated dopamine concentrations and immunological parameters in peripheral venous blood in practically healthy and cancer-affected residents of the European North with a high content of dopamine in peripheral venous blood. %**

| Parameters studied | Frequency of registration of elevated concentrations in healthy subjects. n=65 % | Frequency of registration of elevated concentrations in people with cancer pathology of the gastro- intestinal tract. n=122 % | Physiological limits |
|---|---|---|---|
| Dopamine. PG/ml | 7.69±0.23 | 59.84±0.63*** | >30 пг/мл |
| Cytotoxic lymphocytes CD3+ CD8+. ×109 cells/l | 23.08±0.39 | 90.77±0.78*** | 0.2-0.4 |
| Transferrin. g/l | 16.92±0.34 | 58.46±0.62*** | 1.5-3.5 |
| Immunogobulin E (IgE). IU/ml | 9.23±0.25 | 41.54±0.53*** | <100 |
| CEC. g/l | 15.39±0.32 | 96.92±0.8*** | <2.0 |
| Anti-dsDNA. IU/ml | 12.31±0.29 | 58.46±0.62*** | <50.0 |
| Anti-RNP. IU/ml | 1.54±0.1 | 49.23±0.57*** | <1.0 |
| Antiphospholipid IgM. u/ml | 4.62±0.18 | 12.31±0.29*** | <10.0 |
| Antiphospholipid IgG. IU/ml | 9.23±0.25 | 18.46±0.35*** | <10.0 |

circulating immune complexes, anti-dsDNA, anti-RNP, and autoantibodies to phospholipids was revealed depending on the increased content of dopamine in peripheral venous blood in practically healthy people and in people with malignant neoplasms of the gastrointestinal tract of various localization (Table 2). The obtained data were compared with the physiological limits. An increase in the frequency of registration of cytotoxic lymphocytes, transferrin, circulating immune complexes and *anti-RNP* in peripheral blood was found in practically healthy people. The content of other immunological parameters was slightly increased, but did not exceed the limits of the physiological norm. People suffering from cancer have a high frequency of elevated concentrations of all the studied parameters.

An increase in the concentration of cytotoxic lymphocytes can be observed in viral and bacterial infections, as well as during recovery from a severe infectious disease. But, in addition, an increased content of cytotoxic lymphocytes can also be observed in oncological pathology. Reactions to the antigen, in the form of graft rejection, cell-mediated cytotoxicity, as well as autoantigens and tumor, include lymphoproliferation and, as a result, an increase in the content of activated lymphocytes (CD25+, CD71+, HLA), NK (CD16+, CD56+), Th (CD4CD4+) and cytotoxic suppressors ((CD8+) [3]. T-cytotoxic lymphocytes cause lysis of tumor cells and spontaneous tumor breakdown. However, there is an opinion that these cells themselves are not related to the tumor cytotoxicity reactions; on the contrary, they are able to block activated specific cytotoxic T cells [11-0].

Circulating immune complexes (CICS) are compounds that are formed when antibodies meet antigens in the blood. Their role is to bind and neutralize foreign antigens and then eliminate them from the body. High concentrations of circulating immune complexes can be observed in practically healthy people [1]. An increase in CEC is also characteristic of autoimmune, infectious diseases and allergic reactions of type III. An increase in circulating immune complexes is also characteristic of oncological pathology [7]. The content of circulating immune complexes in the blood serum is constantly under the control of phagocytosis of blood mononuclears, and when the formation of CIC is out of control of phagocytes, respectively, an increase in the content of CIC is observed in the blood serum and this gives them toxic properties [8]. It is known from literature sources that a high frequency of phagocyte activity is recorded in oncological diseases [4].

It is known, that autoantibody concentrations are directly related to the activity of inflammation and are most pronounced in case of systemic complications [9]. Nearly always extremely high levels of autoantibodies, especially to dsDNA are detected in malignant neoplasms. It is possible that the main effect and purpose of increased concentrations of antibodies to nucleoproteins is to destroy tumor cells, since on proliferating cells the concentrations of various receptor structures that can bind antibodies to autoantigens, are much higher.

Phospholipid antibodies are proteins that the body produces in response to phospholipid antigens present in cells. It is possible that in the development of a number of diseases, antibodies to phospholipids IgM and IgG affect the appearance and development of certain diseases. The relatively high level of elevated concentrations of antiphospholipids IgM and IgG attracts attention, and it is possible that this process is somewhat more important in oncological pathology, since the most often detected increase in antibodies to antigens in other pathological conditions.

**Conclusion.** The state of the immune status of residents of the European North with a high content of dopamine in peripheral venous blood has significant deviations in people, with oncological pathology of the gastrointestinal tract of various localization, compared with practically healthy residents of the territories of the European North. Thus, the average dopamine content in practically healthy people and in people with oncological pathology, is 33.1±3.93 and 133.66±8, respectively; the frequency of registration of elevated dopamine concentrations in practically healthy people and in people with oncological pathology, is 7.69±0.23 % and 59.84±0.63 %, respectively. The average blood levels of transferrin and IgE in people with cancer are higher than in practically healthy people (119.89±35.77 and 53.34±7.21, respectively). The increase in the average content of other parameters studied was insignificant. The frequency of elevated concentrations of other immunological parameters was established, which was significantly higher in patients with oncological pathology. Thus, the appearance of immune responses, i.e., the interaction of the immune system with the tumor, which is a balance between the processes of immune activation and immune suppression, and a violation of the mechanisms of regulation of immune system components that occur in people with malignant tumors, is established.

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*The author declares that there is no conflict of interest.*

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SCIENTIFIC REVIEWS

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# RADIAL SCAR OF THE BREAST AS A MASK OF MALIGNANT NEOPLASMS

In order to study the radial scar as a mask of malignancy, a literature review was conduct-ed. It was found that the difficulty in diagnosing the radial scar is due to its morphological simi-larity to a malignancy and associated intraductal epithelial proliferations. To exclude a malignan-cy and intraductal proliferations, immunohistochemical visualization of the intact myoepithelial cell layer is used, as well as cellular heterogeneity of intraductal proliferations using markers such as p63, basal cytokeratins, smooth muscle actin, basal cytokeratins, and estrogen receptor. It was found that in the case of a combination of a radial scar with atypia or other high-risk lesions of the mammary gland, the likelihood of its transformation into malignant lesions of the mammary gland increases.

**Keywords:** radial scar, breast, radiation sclerosing lesion, B3 lesions, ductal carcinoma in situ

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Radial scar is part of a group of breast lesions [16] with uncertain malignant behavior [3], also known as high-risk or B3 lesions [9] with a borderline to variable histologic spectrum, risk of associated malignancy [7, 9, 15] and account for 5 to 12% of initial biopsy findings [27, 28].

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The most commonly used classification of breast lesions worldwide is the B-classification [28, 29], which was introduced in 1999 by a collaborative group of 23 European pathologists for the assessment of breast needle biopsy findings [14].

At the 3rd International Consensus Conference in 2022, six most relevant B3 lesions were discussed - benign but of uncertain biological potential [7], atypical ductal hyperplasia, squamous epithelial atypia, classic lobular neoplasia, radial scar, papillary lesions without atypia, and phyllodes tumors [29]. This group of breast lesions is difficult to classify histologically [3] and they are considered optional precursors to malignancy [9, 30]. In turn, the frequency of B3 lesions with a total risk of malignant development varies from 9.9% to 35.1% [7, 10, 14].

The main problem with B3 lesions is the possibility of underestimation of lesion malignancy [27, 33]. According to the study by Chou R et al., [14], the overall rate of transition to malignancy of B3 lesions was 26.4%, which is consistent with the data of other authors. Thus, according to Richter-Ehrenstein C. et al. [10], approximately a third of puncture biopsies of breast lesions classified as B3 detected during screening are precancerous or malignant after removal.

The diagnosis of a radial scar is problematic because of its morphological resemblance to malignancy and complicates differential diagnosis because of its association with other proliferative lesions.

Immunohistochemistry with visualization of the intact myoepithelial cell layer is of critical importance for differentiating the radial scar from invasive carcinomas and associated intraductal epithelial proliferations [33].

The prognosis of malignancy of a radial scar depends on the presence or absence of associated atypia. If atypia is absent on histological analysis, the probability of malignancy increases with larger lesions, the presence of calcifications, and advanced age [16, 21, 25].

The purpose of the study: analysis of publications devoted to the study of radial breast scar as a mask of malignancy.

In this review, we examined the literature sources devoted to the study of radial breast scar. A comprehensive search