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Hyperhomocysteinemia and Distribution Features of Allelic Polymorphism of Folate Group Genes in Patients with Malignant Neoplasms

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ABSTRACT

INTRODUCTION: Malignant neoplasms (MNs) are currently widespread in the population. The study of the etiology of various tumor diseases is an important field of medical science. In recent years, elevated level of homocysteine (HC) in blood has been shown to be closely associated with cancer, as well as with unfavorable course after surgical interventions and during chemotherapy.

AIM: To assess the role of hyperhomocysteinemia (HHC) and polymorphism of folate cycle genes in the development of tumor processes and venous thromboembolic complications (VTEC).

MATERIALS AND METHODS: The PubMed and eLibrary.ru databases were searched for publications for the period from January 1, 2005 to December 31, 2024, including abstracts and articles with the results of original studies (primary sources), meta-analyses and reviews (secondary sources), foreign and Russian clinical guidelines (tertiary sources) using the keywords 'malignant neoplasms', 'hyperhomocysteinemia', 'folate cycle gene polymorphism', 'folic acid', 'venous thromboembolic complications'. The role of HHC, folate cycle gene polymorphism in the development of tumor processes and venous thrombosis was analyzed and assessed.

RESULTS: This review analyzes the relationship between elevated plasma HC levels and the risk of developing malignant neoplasms of various locations and discusses clinical prospects. The article presents evidence of interaction between allelic polymorphism of folate cycle genes involved in HC metabolism, and the risk of development and course of cancer in humans. The article systematizes data on the role of HHC in the development of VTEC in patients with cancer.

CONCLUSION: The content of HC in blood plasma can be used as a potential tumor biomarker for various types of MNs, and HHC can be an important prognostic marker for the course of tumor processes and a risk factor for the development of VTEC. Understanding the effect of HC levels on the growth and proliferation of tumor cells will allow the creation of new promising strategies to combat MNs. Further clinical studies are needed for a more accurate assessment of these positions.

Keywords: malignant neoplasms; hyperhomocysteinemia; polymorphism of folate cycle genes; folic acid; venous thromboembolic complications; vitamin B_{12} deficiency.

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Гипергомоцистеинемия и особенности распределения аллельного полиморфизма генов фолатной группы у больных со злокачественными новообразованиями

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АННОТАЦИЯ

Введение. Злокачественные новообразования (ЗНО) в настоящее время широко распространены в популяции. Изучение этиологии различных опухолевых заболеваний является важным звеном в медицинской науке. В последние годы было показано, что повышенный уровень гомоцистеина (ГЦ) в крови тесно связан с раком, а также неблагоприятным течением после оперативных вмешательств и на фоне химиотерапии.

Цель. Оценить роль гипергомоцистеинемии (ГГЦ) и полиморфизма генов фолатного цикла в развитии опухолевых процессов и венозных тромбоэмболических осложнений (ВТЭО).

Материалы и методы. В базах данных PubMed и eLibrary.ru выполнен поиск публикаций за период с 1 января 2005 по 31 декабря 2024 года, включая тезисы и статьи с результатами оригинальных исследований (первичные источники), метаанализы и обзоры (вторичные источники), зарубежные и российские клинические рекомендации (третичные источники) по ключевым словам «злокачественные новообразования», «гипергомоцистеинемия», «полиморфизм генов фолатного цикла», «фолиевая кислота», «венозные тромбоэмболические осложнения». Проанализирована и оценена роль ГГЦ, полиморфизма генов фолатного цикла в развитии опухолевых процессов и венозных тромбозов.

Результаты. В этом обзоре анализируется взаимосвязь между повышенным уровнем ГЦ в плазме и риском развития ЗНО различной локализации и обсуждаются будущие клинические перспективы. Приводятся доказательства взаимодействия между аллельным полиморфизмом генов фолатного цикла, участвующих в метаболизме ГЦ, и риском развития и течения ЗНО у человека. Систематизируются сведения о роли ГГЦ в развитии венозных ВТЭО у пациентов со ЗНО.

Заключение. Содержание ГЦ в плазме крови можно использовать в качестве потенциального опухолевого биомаркера при различных видах ЗНО, а ГГЦ может являться важным прогностическим маркером течения опухолевых процессов и фактором риска развития ВТЭО. Понимание влияния уровня ГЦ на рост и пролиферацию опухолевых клеток позволит создать новые многообещающие стратегии борьбы с ЗНО. Для более точной оценки этих позиций необходимы дальнейшие клинические исследования.

Ключевые слова: злокачественные новообразования; гипергомоцистеинемия; полиморфизм генов фолатного цикла; фолиевая кислота; венозные тромбоэмболические осложнения; дефицит витамина B_{12}.

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INTRODUCTION

Malignant neoplasms (MNs) are currently widespread in the population. They are characterized by the appearance of uncontrollably dividing cells capable of invading adjacent tissues and metastasizing to distant organs. The study of the etiology of various tumor diseases is an important aspect in medical science and, in particular, in oncology. Evidence has recently been presented that the development of tumors is influenced by environmental factors rather than genetic predisposition [1]. Researchers have assessed 30 major cell mutations leading to cancer of the colon, lung, bladder, thyroid gland and other organs. It turned out that only 10–30% of them are caused by internal factors, such as heredity, while 70–90% of mutations are directly related to exposure to hazardous environmental factors.

Understanding and identifying the etiologic risk factors that influence the development of tumors in humans, is a necessary prerequisite for their prevention. Along with the known causes of MNs, the relationships between the content and metabolism of homocysteine (HC) in blood and the development of cancer processes in humans have been actively discussed. A particularly promising direction may be the assessment of the cause-and-effect relationships of the HC content with various risk factors involved in the metabolism of HC, including polymorphism of folate cycle genes, concentration of B vitamins, which may provide insight into the development of new forms of complex treatment and diagnostics of cancer.

The **aim** of this study explores the role of hyperhomocysteinemia (HHC) and polymorphism od folate cycle gene polymorphism in the development of tumor processes and venous thromboembolic complications (VTEC).

MATERIALS AND METHODS

The PubMed and eLibrary.ru databases were searched for publications for the period from January 1, 2005 to December 31, 2024, including abstracts and articles with the results of original studies (primary sources), meta-analyses and reviews (secondary sources), foreign and Russian clinical guidelines (tertiary sources) by the keywords 'malignant neoplasms', 'hyperhomocysteinemia', 'folate cycle gene polymorphism', 'folic acid', 'venous thromboembolic complications'. The role of HHC, folate cycle gene polymorphism in the development of tumor processes and venous thrombosis was analyzed and assessed.

Homocysteine Metabolism and Pathological Effects of its Disorder

Homocysteine is a naturally occurring sulfur-containing amino acid, produced in metabolism of *methionine*, one of the eight essential amino acids in an organism [2]. Metabolism of HC involves a number of enzymes. The main enzymes include methylenetetrahydrofolate, reductase, methionine synthetase, methionine synthetase reductase and a number of others (Figure 1). In addition to enzymes, a key role in HC metabolism is played by folic acid, and also by vitamins B_6 and B_{12}. Under normal conditions, about 50% of HC undergo remethylation to form methionine. The remaining HC is catabolized through transsulfuration processes into cysteine, which is a precursor of glutathione, the main cell redox buffer that protects cells from oxidative damage [1–4].

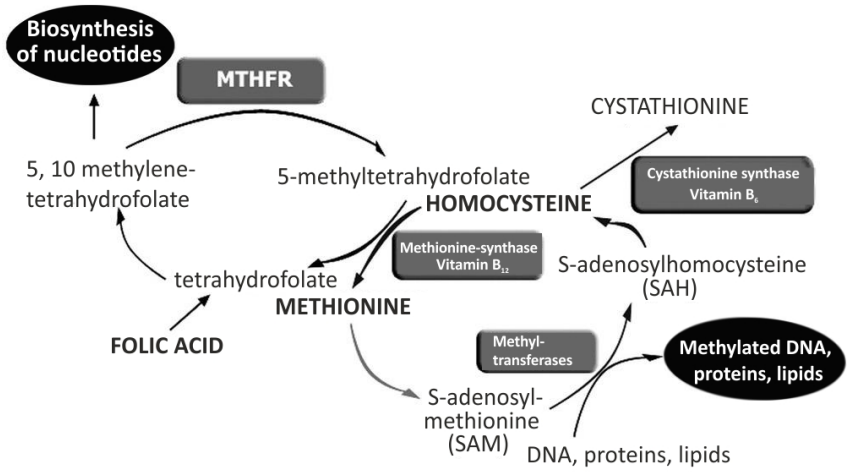

Fig. 1. Homocysteine metabolism: MTHFR — methylenetetrahydrofolate reductase.

The reference interval of normal HC values in Western Siberia varies from 5.0 to 11.0 μmol/l [5]. To note, the upper limit of HC norm may vary depending on the territory, consumption of vitamins in the population, genetic characteristics and a number of other factors [1].

The most common causes of HHC are low activity of folate cycle enzymes as a result of genetic polymorphism, a certain lifestyle and diet, existence of diseases and drug effects [6–10]. When HC metabolism is disrupted and it accumulates in the cell, a mechanism of release of excess of this amino acid into the bloodstream is triggered, which protects the cell from the cytotoxic effect of HC. HHC in the bloodstream contributes to endothelial damage and is accompanied by the development of endothelial dysfunction [2, 6, 11], which in turn leads to the formation and progression of cardiovascular diseases, atherosclerosis, VTEC [2, 12–14].

Relationship between Folate Cycle Genes and Homocysteine Metabolism in Malignant Neoplasms

Polymorphism of the *MTHFR 677 C→T* gene is known to be quite common in the general population. When studying the polymorphism of folate cycle genes, 9-point mutations were identified in the *MTHFR* gene, the most significant being *replacement of allele C with T in position 677*, which, in turn, leads to replacement of alanine with valine in the enzyme protein molecule [9]. In individuals with the genetic defect, the thermolabile *MTHFR* enzyme is synthetized. At the same time, its activity is reduced from the average value by approximately 35% in heterozygous carriage and by 65% in homozygous carriage [9]. The *MTHFR 677 C→T* mutation is transmitted by an autosomal recessive pattern. The adverse effects of the T allelic variant of the *MTHFR* gene depend significantly on external factors — low levels of folic acid in food, smoking, alcohol consumption, etc.

The *MTR* gene codes for amino acid sequence of methionine synthetase enzyme and catalyzes the conversion of homocysteine to methionine. The best studied polymorphic locus of *MTR* is A2756G, which leads to replacement of aspartic acid with a glycine residue (D919G) [15]. As a result, HC level increases and S-adenosylmethionine level decreases. To generate the active form of *MTR*, the methionine synthetase-reductase enzyme is required, which is encoded by the *MTRR* gene. The polymorphic substitution *66 A→G* results in the replacement of amino acids (I22M), which reduces the functional activity of the enzyme, and vitamin B_{12} deficiency further aggravates this effect.

Elevated levels of HC are often found in patients with various MNs. A correlation has been established between HHC, genetic polymorphism of folate cycle enzymes and MNs. In patients with malignant neoplasms and with disturbed methylation, both primary (caused by a genetic defect in the genes of folate cycle enzymes) and secondary (secondary to methylation disorders) HHC is observed [16].

It is known that surgical intervention or chemotherapy are associated with a sharp rise of HC level in plasma, which leads to higher incidence of thromboembolic events [16–18]. The risk factors for venous thrombosis are surgical interventions, chemotherapy, hormonal adjuvant therapy, central venous catheters, prolonged immobilization, hereditary thrombophilias and some other factors [16]. Since the most commonly used clinical chemotherapeutic agents (alkylating agents, antimetabolites, methotrexate, hormones and antagonists) are antifolate drugs, their use causes a decrease in plasma folate concentrations [19]. Another study showed that elderly cancer patients are at higher risk of developing HCC than younger ones [14].

All types of cancer at late stages demonstrated high plasma HC levels, whereas at early cancer stage, no significant changes in HC concentration in plasma were observed (Table 1) [20].

A number of studies revealed high HC levels in some malignant neoplasms [21]. In the study by D. Tastekin et al. (2015), the average HC level in patients with lung cancer was (15.3±7.3) μmol/l, while in the control group of healthy individuals it was (9.8±2.6) μmol/l [22]. Y. Qiang et al. (2018) showed that in patients with esophageal cancer, the average HC concentration was 15.6 μmol/l, while in the control group it was less than 11.0 μmol/l [23]. In patients with colorectal cancer, the HC content exceeded 12.2 μmol/l, and in the control it was less than 7.9 μmol/l [24]. In patients with gastric cancer, the average HC level was 13.2 μmol/l, and in the control group it was 6.1 μmol/l. It has been found that every 5 μmol/l increase in serum HC levels increases the incidence of gastrointestinal cancer by 7% [22, 24]. HC can disrupt the methionine cycle and alter cytosine methylation in DNA CpG islands, leading to the suppression of tumor suppressor genes and activation of proto-oncogenes, which may contribute to the development of malignant neoplasms. Inflammatory remodeling of the gastrointestinal tract due to high HC levels increases the production of reactive oxygen species, which can cause several disorders, including carcinogenesis when they accumulate excessively [25].

In patients with malignant neoplasms, polymorphism of folate cycle genes has been studied: *MTHFR 677*, *MTHFR 1298*, *MTR 2756*, *MTRR 66*. Carriage of *MTHFR 677 CT* and *MTHFR 677 TT* gene alleles are the most common genetic causes of HHC [26, 27], which significantly increases the risk of developing malignant neoplasms, in particular gastric cancer [26, 28]. In carriers of the *MTHFR 677 TT* allele, gastric cancer was encountered 1.5 times more often than in the control group. At the same time, low folic acid intake increased the risk of developing gastric malignant neoplasms 2 times or more, which once again confirms the protective effect of folic acid on the development of tumors of various locations [22, 29, 30]. The presence of *H. pylori* in patients with the *MTHFR C677T* gene polymorphism was accompanied by a 1.8-fold increase in the risk of gastric

Table 1. Relationship of polymorphism of some genes involved in homocysteine metabolism with malignant neoplasms [20]

Gene	Polymorphism	Replacement of amino acid	Type of malignant neoplasm	Relative risk
Methylenetetrahydrofolate-reductase	677C→T	A226V	Endometrial carcinoma	1.10
			Esophageal squamous cell carcinoma	1.47
			Breast cancer	1.00*/1.12/1.00*
			Acute lymphocytic leukemia	0.99/0.23
			Prostate cancer	0.78
			Colorectal cancer	1.78/1.001/0.76
			Prostate cancer	0.58
	1298A→C	E443A	Acute myeloid leukemia	0.33/1.00
			Endometrial cancer	0.88
	1793G →A	R1793E	Colorectal cancer	0.17
			Acute myeloid leukemia	1.00
Methionine synthase reductase	66A→G	I22M	Leukemia	1.00*
			Colorectal cancer	2.77/1.07
			Gastric cancer	0.74/1.39
			Breast cancer	4.45
			Head and neck cancer	1.10
Methionine synthase	2756A→G	D919G	Colorectal cancer	1.03/0.65/2.04
			Lung cancer	1.34
			Hepatocellular carcinoma	1.01
			Cervical cancer	0.27
			Glioblastoma multiforme	1.00*
			Breast cancer	1.00*
			Squamous cell carcinoma	1.00*
			Gastric cancer	1.06/1.35
			Pancreatic cancer	1,08/3,35
Methylenetetrahydrofolate dehydrogenase	1958G→A	A653G	Gastric cancer	2.05
			Leukemia	0,80
	401G→A	R134K	Gastric cancer	1,43
			Leukemia	0,89
			Ovarian cancer	0,97

Note: * — documents that did not report a lack of connection were given a value of 1.00

cancer [31]. The *MTHFR A1298C* gene polymorphism did not affect the risk of developing gastric adenocarcinoma [7].

When studying esophageal squamous cell carcinoma and polymorphism of the *MTHFR 677* gene, the following data were obtained: carriage of the pathological allele *MTHFR 677 CT* or *677 TT*, 2.2 times increases the risk of esophageal squamous carcinoma [7], which considerably rises with smoking [32], while the genotype of *C* allele

of the *MTHFR 1298* gene practically has no effect on the development of esophageal squamous cell cancer [32]. At the same time, consumption of folic acid had a significant protective effect, reducing these risks.

Individuals with *MTHFR 677 CT* and *MTHFR 677 TT* allelic variants had a 70–80% higher risk of developing lung cancer than individuals with the *MTHFR 677 CC* genotype. Alcohol consumption, tobacco smoking, and folate deficiency increase this risk [10]. *MTHFR 677 CT/TT* allelic variants reduce enzyme activity by 60% or more [21]. Therefore, these *MTHFR* gene variants correlate with the risk of developing esophageal, gastric, and lung cancer. For carriers of the homozygous *CC* genotype of the *MTHFR* gene and normal *MTHFR* enzyme activity, high serum levels of vitamins B_2 and B_{12} were associated with a reduced risk of developing esophageal squamous cell carcinoma [30].

The relationships and influence of methionine synthetase and methionine synthetase reductase gene polymorphism on the development of malignant neoplasms were studied. Q. Shi et al. (2005) confirmed in their study that the *MTR A2756G* gene polymorphism is associated ith a 30% increase in the risk of lung cancer [33]. In particular, the risk of developing lung cancer increased 1.3 times in the carriage of the AG allele of the *MTR 2756* gene and 1.4 times in the carriage of the *MTRR 66 A→G* allele [10, 34]. However, the risks decreased with increased intake of folic acid and vitamin B_{12} with food [33, 35, 36]. Simultaneous carriage of the *MTR 2756 A→G* and *MTRR 66 A→G* gene polymorphisms increased the risk of lung cancer by 40% or more [33].

The *MTRR A66G* gene variant, both in the dominant and codominant states, increased the risk of gastric cancer 1.4 times [37, 38], and esophageal cancer 1.6 times [39]. However, the influence of other pathological variants of the *MTR* gene alleles was not revealed.

It has been proven that hyperhomocysteinemia correlates with low levels of folic acid, vitamins B_6 and B_{12} and with a higher risk of developing cancer [20, 30, 40–42]. An interesting observation is the fact that in heavy smokers, folic acid enhances the carcinogenic effect of smoking, promotes accelerated proliferation of cancer cells [16, 43], increasing the risk of lung cancer 1.5 times [44]. Treatment of cancer patients with folic acid and vitamin B_{12} increases mortality from cancer [45].

Low levels of vitamin B_{12} are known to lead to pernicious anemia, which increases the risk of developing gastric tumors 6–8 times [46], hypopharyngeal cancer [47] and lung cancer [44] 2.0 times, and breast cancer by 30% [28]. At the same time, an inexplicably high level of vitamin B_{12} can be considered a possible marker of solid cancer. In this case, the risk of developing cancer increases 2.0 times, and of MN with metastases 4.2 times [48].

Hyperhomocysteinemia is a Risk Factor f or Venous Thromboembolic Complications in Patients with Malignant Neoplasms

Patients with cancer often have an increased risk of developing VTEC, which is the second most common cause of death in cancer patients [49, 50]. Patients with cancer are at 4–7 times increased risk of VTEC compared to the general population, and with some types of cancer, the likelihood of developing venous thrombosis is even higher [51–53]. VTEC can often be the first symptom indicating a neoplastic process [51, 54]. Deep vein thrombosis (DVT) is diagnosed in 60% of patients with cancer. In many patients, DVT often becomes a source of pulmonary embolism (PE). It has been proven that from the moment of diagnosis of malignant neoplasms, up to 24.2% of patients die from VTEC within 30 days, 66.3% of patients die within 1 year, and 75.6% of patients die within 5 years [54, 55].

The incidence VTEC is highest in the first months after the diagnosis and then gradually decreases [56]. It is known that about 50.0% of thromboses associated with MNs are observed within 6 months before the diagnosis of cancer and 2 years after [57]. In the MEGA population study (2005), the incidence of venous thrombosis was calculated from the moment of detection of the main oncological disease. After the diagnosis, in the first 3 months it was 53.5%, in the period from the 3rd to the 12th month — 14.3%, and after 10 years the probability of development decreased almost completely [58].

Currently, a large number of risk factors associated with thrombotic complications in patients with neoplastic processes are known. These include causes directly related to the tumor process (localization, stage of the disease, prevalence of the process and degree of tumor differentiation), patient characteristics (demographic parameters, concomitant diseases, immobilization, hereditary thrombophilia, obesity, etc.) and treatment (use of chemotherapy drugs, hormonal adjuvant therapy, surgery, central venous catheters, etc.) [50, 54].

In the body, with the underlying tumor growth, multidirectional changes occur in the hemostasis system, and a number of biochemical parameters that are markers of thromboembolic complications, changes significantly [59]. According to the Vienna Cancer and Thrombosis Study (CATS; 2014), the group of VTEC biomarkers includes increased levels of leukocytes, platelets, D-dimer, soluble P-selectin, decreased hemoglobin levels, the presence of cancer procoagulant and tissue factor (TF), which are produced by activated malignant cells and become predictors of venous thrombosis [54, 59, 60]. Significant risk factors also include increased concentrations of proinflammatory cytokines (tumor necrosis factor, interleukin-1), as well as microvesicles in some tumor processes, which are involved in the activation of hypercoagulation and expression of tissue factor of monocytes, which contributes to thrombus formation [61, 62].

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Several decades ago, it was established that hereditary and acquired thrombophilia are significant risk factors for the development of VTEC [50, 63, 64]. The pathogenesis of thrombophilia in cancer patients includes risk factors associated with the response to the tumor (inflammation, acute phase reaction, dysproteinemia, focal necrosis, hemodynamic disturbances), as well as specific factors caused by the tumor cells themselves and tumor-associated macrophages. In this case, procoagulant and fibrinolytic activity of cancer cells, their interaction with platelets, mononuclear macrophages and endothelium, neoangiogenesis, and therapeutic measures (chemotherapy, hormone therapy) are observed. Tumor cells activate the coagulation or fibrinolysis system, creating conditions for their further spread, stimulation of angiogenesis, increased vascular permeability, which in turn contributes to metastasis [64–66].

The combination of genetic forms of thrombophilia and circulation of reactive oxygen species are of great clinical importance. The following are significant: mutation of FV Leiden 1691 and FII 20210 prothrombin, hyperhomocysteinemia in combination with the *MTHFR C677T* gene polymorphism, PAI-1 G4/G5 and platelet glycoprotein polymorphism, antithrombin III deficiency, and disorders in the protein C and S system [6, 63, 64]. However, at present, there are practically no serious cohort studies showing the frequency of occurrence and the relationship of genetic significant forms of thrombophilia in cancer patients with the development of thrombotic manifestations. Most published studies are usually low in power, and their results vary depending on the region, tumor type, stage of the disease and treatment.

HHC is an established independent risk factor for cardiovascular diseases. Negatively affecting blood vessels, it leads to the development of atherosclerosis and coronary heart disease, thrombotic complications (heart attack, stroke, VTEC), including those in combination with genetic polymorphism of folate cycle genes [49]. The fact of increased HC content in patients with tumor diseases is also indisputable today [63, 64]. In particular, HHC is often observed in women with progressive breast cancer [49, 67], which helps explain the high frequency of VTEC in women with metastatic breast cancer [68]. According to other data, the presence of the *MTHFR C677T* gene polymorphism in combination with HHC can be a serious risk factor provoking clinically expressed thrombotic complications and especially latent thromboses, which are detected as pathoanatomical findings 3–4 times more often. The presence of the *MTHFR* gene polymorphism allows the inclusion of folic acid and B vitamins in the therapeutic regimen to correct homocysteine levels [68].

Since HHC is the most common condition, being an independent risk factor for the development of venous and arterial thrombosis in the population, the study of its role and contribution to the development of thrombotic events in cancer patients seems to be very interesting. The role of folic acid metabolism in the development of tumor processes initiating HHC is of great scientific interest [16, 49]. The relationship with the stage of the process and metastasis, survival and the absence of tumor relapses, long-term prognosis and prospects with underlying surgical, combined and comprehensive treatment of patients with malignant neoplasms taking into account the content of HC in plasma in combination with polymorphism of folate cycle genes, as well as personalized correction of HHC with folates and B vitamins according to the feedback principle, seems to be a promising direction today. Therefore, new comprehensive clinical studies are needed in this direction.

CONCLUSION

To date, the effect of homocysteine levels on the growth and proliferation of tumor cells remains poorly understood. However, there is a close relationship of impaired homocysteine metabolism in malignant neoplasms with the underlying genetic and acquired risk factors, among other things, with the development of thrombotic events. It is logical to assume that patients with an established diagnosis of a malignant neoplasm should not be prescribed drugs that increase homocysteine levels, and after radiation, adjuvant chemotherapy or hormone therapy, surgery, it is advisable to monitor its content in the long term.

Understanding the effect of homocysteine on the growth and proliferation of cancer cells will allow us to create new promising strategies to combat cancer. Plasma homocysteine levels can be used as a potential tumor biomarker for various types of malignant neoplasms, and hyperhomocysteinemia can be an important prognostic marker for the course of tumor processes and a risk factor for the development of venous thromboembolic complications.

The development of methods for correcting elevated homocysteine levels in cancer patients appears to be a promising direction. Further clinical studies are needed to more accurately assess these positions.

ADDITIONAL INFORMATION

Author contributions. A.S. Petrikov — concept and design of the study, collection and processing of material, editing; V.I. Belykh— concept and design of the study, collection and processing of material, writing the text; A.D. Rybnikova— collection and processing of material, writing the text. All authors approved the manuscript (the publication version), and also agreed to be responsible for all aspects of the work, ensuring proper consideration and resolution of issues related to the accuracy and integrity of any part of it.

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