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ЗНАЧЕНИЕ ПОЛИМОРФИЗМА ГЕНОВ В РАЗВИТИИ КОЛОРЕКТАЛЬНОГО РАКА

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Цель. Определить значение полиморфизма генов *MTHFR (Ala222Val), XPD (Lis751Gln), XRCC1 (Arg194Trp), XRCC1 (Arg399Gln), XRCC1 (Arg208His), APE1 (Asp148Glu), hOGG1 (ser326Ces), P53 (Pro47Ser), VEGF (C654G), EGFR(A2073T), TNF(G308A), CHEK2 (Ile157Thr), MMP1 (1607 1G>2G), TIMP1(C53CT)* в развитии колоректального рака.

Материалы и методы. Проанализированы 106 случаев колоректального рака у пациентов, проходивших лечение в ГБУ РО Областной клинический онкологический диспансер (Рязань). Генотипирование всем больным выполнялось методом выделения ДНК из лейкоцитов венозной крови с последующей полимеразной цепной реакцией (ПЦР) с электрофоретической детекцией результата.

Результаты. Взаимосвязи между возрастом пациентов на момент верификации диагноза и полиморфизмом ни для одного из исследуемых генов зарегистрировано не было ($p>0,05$). Статистически значимая связь выявлена между полиморфизмом гена *TNF* (*G308A*) и стадией рака: его гомозиготный мажорный генотип *G/G* гораздо чаще встречался в группе пациентов с III-IV стадией ($p=0,047$). При наличии аллеля *G/G TNF (G308A)* совместно с гомозиготным мутантным аллелем гена *MMP1 (1607 1G/2G)* отмечается прямая связь с возрастанием доли пациентов, диагноз которым был поставлен на III-IV стадии. Данное сочетание двух полиморфизмов статистически значимо различалось в обследуемых группах ($p=0,025$). У 8 из 10 больных с IV стадией отмечено наличие полиморфизма *G/G* в гене *VEGF (C654G)*. Данный мутантный гомозиготный вариант встречался значительно реже у пациентов с I (37,5%), II (40%) или III стадией (37,5%) ($p=0,0147$).

Выводы. Исследованные гены не влияют на возрастной критерий манифестации колоректального рака и встречаются одинаково часто у пациентов обоих полов вне зависимости от возрастной группы. Локализация и степень дифференцировки опухоли также не зависят от полиморфизма исследуемых генов. Наличие полиморфизма *G/A* гена *TNF (G308A)* следует считать благоприятным критерием, способствующим меньшей агрессивности опухоли ($p<0,05$). Выявление же мажорного генотипа *G/G* особенно в сочетании с гомозиготным мутантным аллелем гена *MMP1 (1607 1G/2G)* является неблагоприятным фактором ($p<0,05$). Наличие гомозиготного мутантного генотипа G/G *VEGF (C654G)* может напрямую коррелировать с быстрой прогрессией опухолей и активным метастазированием ($p<0,05$).

Ключевые слова: *полиморфизм генов; колоректальный рак; инвазивный рост; метастазирование.*

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SIGNIFICANCE OF GENE POLYMORPHYSM IN DEVELOPMENT OF COLORECTAL CANCER

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Aim. To determine the significance of polymorphism of *MTHFR (Ala222Val), XPD (Lis751Gln), XRCC1 (Arg194Trp), XRCC1 (Arg399Gln), XRCC1 (Arg208His), APE1 (Asp148Glu), hOGG1 (ser326Ces), P53 (Pro47Ser), VEGF (C654G), EGFR(A2073T), TNF (G308A), CHEK2 (Ile157Thr), MMP1 (1607 1G>2G), TIMP1(C53CT)* genes in development of colorectal cancer.

Materials and Methods. 106 Cases of colorectal cancer in patients who were on treatment in Ryazan Clinical Oncological Dispensary (Ryazan) were analyzed. Genotyping in all patients was performed using the method of isolation of DNA from leukocytes of venous blood with subsequent polymerase chain reaction (PCR) with electrophoretic detection of the result.

Results. No interrelation between the age of patients and polymorphism of any studied gene was recorded at the moment of verification of the diagnosis ($p>0.05$). Statistically significant relationship was identified between polymorphism of *TNF* (*G308A*) gene and the stage of cancer: its homozygous major genotype *G/G* more commonly occurred in the group of patients with III-IV stage ($p=0.047$). In the presence of allele of *G/G TNF (G308A)* gene together with homozygous mutant allele of *MMP1 (1607 1G/2G)* gene, a direct relationship with increase in the number of patients diagnosed with III-IV stage was noted. This combination of two polymorphisms showed a statistically significant difference in the studied groups ($p=0.025$). In 8 out of 10 patients with IV stage, the presence of *G/G* polymorphism in *VEGF (C654G)* gene was noted. This mutant homozygous variant was much more rare in patents with I (37.5%), II (40%) or III stages (37.5%) ($p=0.0147$).

Conclusions. The studied genes do not influence the age of manifestation of colorectal cancer and occur at the same frequency in patients of both genders irrespective of the age group. Localization and the extent of differentiation of the tumor do not depend on polymorphism of the studied genes either. The presence of *G/A* polymorphism of *TNF (G308A)* gene should be considered a favorable criterion associated with lower aggressiveness of the tumor ($p<0.05$), whereas identification of the major *G/G* genotype especially in combination with homozygous mutant allele of *MMP1 (1607 1G/2G)* gene is an unfavorable factor ($p<0.05$). The presence of G/G mutant genotype of *VEGF (C654G) gene* may directly correlate with rapid progression of tumor and with active metastatic spreading ($p<0.05$).

Keywords**:** *polymorphism of genes; colorectal cancer; invasive growth; metastatic spreading.*

Colorectal cancer (CRC) is the third most common type of cancer in Russia. Annually 60,000 cases of CRC are newly diagnosed. In total, in our country more than 350,000 patients with this pathology are under regular medical check-up.

With this, the results of treatment of this category of patients are unsatisfactory in a large extent due to advanced stage of the process at the moment of verification of the diagnosis. Late identification of CRC (III-IV stages) is the result of absence of screening programs of diagnosis, insufficient knowledge of the causes and risk factors for initiation of this pathology, and peculiarities of the course of the disease that in some cases may be very rapid.

Currently, CRC is treated with combined or complex approach using surgical, radiation and medicinal methods [1].

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Peculiarities of initiation of cancer, response to the conducted treatment may be largely determined by the individual patient's genotype that codes for mechanisms that both participate in the carcinogenesis and oppose it [2,3]. In this context, many scientific works are devoted to identification of the connection of polymorphism of genes with pathological processes [4,5] and with different localizations of the tumor [6,7].

The *aim* of work was to determine the significance of polymorphism of *MTHFR (Ala222Val), XPD (Lis751Gln), XRCC1 (Arg194Trp), XRCC1 (Arg399Gln), XRCC1 (Arg208His), APE1 (Asp148Glu), hOGG1 (ser326Ces), P53 (Pro47Ser), VEGF (C654G), EGFR(A2073T), TNF(G308A), CHEK2 (Ile157Thr), MMP1 (1607 1G>2G), TIMP1(C53CT)* genes in development of colorectal cancer.

In accordance with the set aim, interrelation of polymorphism with gender, age of patients, localization of tumor process; the degree of tumor differentiation, stage of the disease, depth of invasion and metastatic spread of the tumor was evaluated.

Materials and Methods

The study was carried out on the base of RyazSMU and Ryazan Regional Clinical Oncological Dispensary and was approved by Local Ethic Committee (Protocol №5 of 06.11.15). The patients' data were used in the work after signing of Informed consent.

Genotyping for polymorphism of the following genes was conducted: *MTHFR (Ala222Val), XPD (Lis751Gln), XRCC1 (Arg194Trp), XRCC1 (Arg399Gln), XRCC1 (Arg208His), APE1 (Asp148Glu), hOGG1 (ser326Ces), P53 (Pro47Ser), VEGF (C654G), EGFR (A2073T), TNF (G308A), CHEK2 (Ile157Thr), MMP1 (1607 1G>2G), TIMP1 (C53CT).*

Genotyping was conducted in the Central Research Laboratory of Ryazan State Medical University by isolation of DNA from leukocytes of venous blood of the examined patients with subsequent PCR with electrophoretic detection of the result using SNP-EXPRESS» (SPC «Litech», Russia).

The study involved 106 patients receiving treatment for colorectal cancer. The gender composition of the examined patients was approximately equal: 58 men (55%) and 48 women (45%). By the age the patients were divided to 3 groups according to the full amount of years at the moment of manifestation of the disease. I group included patients with relatively early manifestation – before 55 years (the mean age 45.7 years – 24 patients), II - from 55 to 65 years (60.1 – 48 patients) and III group above 65 years (71.6 years – 43 patients). The mean age of all patients at the moment of diagnosis was 61.5 years.

76 Patients (72%) had the diagnosis of colorectal cancer and in 30 patients (28%) tumors were localized in other parts of the large intestine.

The diagnosis was verified in 100% of patients. Histologically, all tumors were represented by adenocarcinomas, mostly with moderate differentiation (G-2, 81%).

The stage of the disease was determined according to the International TNM classification of 8th revision (2018). By the extent of spread of the process, a share of patients with I-II stage (without metastatic lesion of regional lymph nodes) was 45.3% (48 patients), with III stage – also 45.3% (48 patients), and 10 patients (9.6%) had IV stage at the moment of making diagnosis.

Statistical processing of the results was conducted using Excel 2007 (MS, USA), Statistica 10.0 (Stat Soft Inc., USA) software package and online calculators (for Hardy-Weinberg equilibrium – https://wpcalc.com/en/equilibrium-hardy-weinberg/). Description and comparison of differences in frequencies of qualitative characteristics in the independent groups were based on Pearson chi-squared test, with Yates correction if the quantity of expected events was from 5 to 9, or with Fischer exact test if the quantity was less than 5. The prognostic significance of the characteristic was evaluated with determination of relative risk

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(RR) with 95% confidence interval (CI). In groups of patients deviation of allele frequency from Hardy-Weinberg equilibrium was also evaluated. In the analysis, statistically significant were considered differences at $p<0.05$.

Results and Discussion

No statistically significant gender differences were found in the population of individuals of male and female gender ($p>0.05$). No interrelation was established between the age of patients and polymorphism of a single studied gene in the groups at the moment of verification of the diagnosis ($p>0.05$). Besides, in all the age groups Hardy-Weinberg equilibrium was preserved which shows reliability of distribution of allele frequency inside age population groups.

In the analysis of relationship between polymorphism of the studied genes and localization of the tumor process, no statistically significant differences were recorded ($p>0.05$), as well as in the evaluation of the influence of polymorphism of the studied genes on the extent of tumor differentiation ($p>0.05$).

The relationship with the stage of tumor process at the moment of diagnosis was evaluated. For the majority of polymorphic genes no direct relationship with increase in stage was noted ($p>0.05$). A statistically significant relationship was found for polymorphism of *TNF G308A* gene coding for tumor necrosis factor: its homozygous major genotype *G/G* was more common in the group of patients with newly identified III-IV stage of the disease (in 69% of patients) in comparison with the group of patients diagnosed at I-II stage (40% of patients, $\chi^2=3.96$, $p=0.047$, RR=1.45 [1.0; 2.03], Table 1).

Table 1

Relationship of Polymorphism of TNF and MMP1 Genes with Stage of Disease

Genotype/allele	I-II stage	III-IV stage	χ^2, p	RR [95% CI]
TNF(G308A)				
G/G	18	33	3.96, *p=0.047*	1.45 [1.0;2.03]
G/A	30	25		
A/A	0	0	-	-
G	66	91	2.57, *p=0.11*	0.77 [0.57;1.04]
A	30	25		
TNF(G308A) + MMP1 (1607 2G/2G)				
G/G	3	16	5.04, *p=0.025*	1.85 [1.13;3.05]
G/A	12	10		

Besides, relationship of polymorphism of the given gene with other genes was analyzed. It was found that in the coexistence of *G/G TNF (G308A)* allele with homozygous mutant allele of *MMP1 (1607 1G/2G)* gene a direct relationship was noted with increase in the number of patients who were first diagnosed at III-IV stage. Proteins encoded by these genes are similar in their biological role and interrelated in terms of potentiating each other. This combination of two polymorphisms showed a statistically significant difference in the studied groups ($\chi^2=5.04$, $p=0.025$, RR=1.85 [1.13; 3.05], Table 1).

Despite a small share of patients with IV stage of the disease included into the study, in 8 of 10 patients of this group *G/G* polymorphism in *VEGF (C654G)* gene was noted. This mutant homozygous variant was relatively rare in patients with I (37.5%), II (40%) or III stages (37.5%) ($p=0.0147$, RR=5.42 [1.21; 24.32], Table 2).

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Table 2

Stage of Tumor and Polymorphism of VEGF Gene

Genotype/Allele	I-II Stage	III-IV Stage	p	RR [95% CI]
VEGF (C654G)				
C/C	10	1	*p=0.0147*	5.42 [1.21;24.30]
C/G	49	1		
G/G	37	8		
C	69	3	*p=0.1*	2.90 [0.88;9.62]
G	123	17		

On the basis of frequency of genetic polymorphism, no differences in dependence on age of the patient at the moment of manifestation of CRC were revealed. It is quite possible that development of cancer at younger age has genetic substantiation, but it was not shown in the given study.

Localization and the extent of differentiation of the tumor neither depend on polymorphism of the studied genes.

Polymorphic genes *MTHFR (Ala222Val), XPD (Lis751Gln), XRCC1 (Arg194Trp), XRCC1 (Arg399Gln), XRCC1 (Arg208His), APE1 (Asp148Glu), P53 (Pro47Ser), EGFR (A2073T), CHEK2 (Ile157Thr), TIMP1 (C53CT)* did not show any influence on the tendency of the tumor to more aggressive invasive growth and to metastatic spreading.

With this, a direct relationship was revealed between carriage of major homozygote of *TNF (G308A) G/G* gene and a high capacity of the tumor to rapid invasion manifested in identification of the disease already in III-IV stage. Carriers of at least one mutant allele of *TNF (G308A)* gene probably have a weakened function of this cytokine, and, accordingly, its reduced biological influence. These data confirm the known relationship between the activity of cytokine TNF-α and tumor progression due to its ability to enhance cell proliferation, stimulate neoangiogenesis and also to potentiate other factors of inflammation accelerating growth of tumor [8]. Identification of heterozygous condition of the given gene (G/A) may be of favorable prognostic significance due to a longer time required by the tumor for lymphogenic and remote metastasis.

It was also noted that the presence of mutant homozygous allele *MMP1 (1607 2G/2G)*, besides *TNF (G308A) G/G* genotype, leads to a more aggressive and rapid growth of tumor and is a poor prognostic criterion. This is probably associated with excessive inducing influence of TNF-α cytokine on matrix metalloproteases coded for by *MMP1* gene which, in turn, promote early metastatic spread of tumor [9].

Mutation of vascular endothelial growth factor VEGF is a reliable aggressive risk factor of rapid progression of tumor. In our study we did not qualitatively determined expression of this gene in tumor cells, however, it is quite possible that mutant genotype of this allele (G/G) is associated with enhanced growth of vessels and rapid progression of tumor. A small amount of patients with IV stage of tumor process involved into the study did not permit a unambiguous interpretation of the obtained results, but the revealed sharp increase in the mutation of the given gene in this group requires further investigation and probably an additional immune-histochemical examination of tumorous tissues of these patients.

Conclusion

The significance of polymorphism of *MTHFR (Ala222Val), XPD (Lis751Gln), XRCC1 (Arg194Trp), XRCC1 (Arg399Gln), XRCC1 (Arg208His), APE1 (Asp148Glu), hOGG1 (ser326Ces), P53 (Pro47Ser), VEGF (C654G), EGFR (A2073T), TNF(G308A), CHEK2*

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(Ile157Thr), MMP1 (1607 1G/2G), TIMP1 (C53CT) genes in development of colorectal cancer was analyzed.

The studied genes were equally common in both genders irrespective of the age and did not produce any influence on the age criterion for manifestation of colorectal cancer, neither on localization and the extent of differentiation of tumor.

A reliable connection between polymorphism of *TNF (G308A)* gene and a tendency of the tumor to rapid invasion into the deeper lying tissues was established that was reflected in identification of the disease at III-IV stage. The existence of G/A polymorphism should be considered a favorable factor promoting a lower aggressiveness of tumor ($p<0.05$). The existence of G/G major genotype, especially in combination with homozygous mutant allele of *MMP1 (1607 1G/2G)* gene is an unfavorable factor that is most common in patients with the newly diagnosed colorectal cancer at III-IV stage ($p<0.05$).

The presence of homozygous mutant G/G genotype of *VEGF (C654G)* gene may correlate with rapid tumor progression and active metastatic process.

Extension of knowledge of the nature of cancer, peculiarities of its treatment in a particular patient in future will help improve the results of patients' treatment and to transition of personalized therapy.

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Дополнительная информация [Additional Info]

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