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VEGF gene polymorphisms and as a potential roles of bladder cancer recurrence factor

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The study explores how certain variations in the *VEGF* (vascular endothelial growth factor) gene may influence the recurrence of bladder cancer, shedding light on its development and prognosis. Bladder cancer, mainly urothelial carcinoma, is complex and unpredictable, posing challenges for treatment. Understanding genetic factors, like *VEGF* gene variations, can help tailor treatment plans for better outcomes. The study highlights various pathways involved in bladder cancer progression,including the role of VEGF beyond just blood vessel growth. While some research suggests a connection between *VEGF* gene variations and bladder cancer risk, results vary. Identifying thesevariations could lead to personalized treatments and targeted therapies. However, more research is needed to understand how these genetic factors specifically affect cancer recurrence.Collaborative efforts and advanced studies are essential for improving bladder cancer management and patient outcomes.

Keyword: *VEGF* gene polymorphisms, bladder cancer, recurrence

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Полиморфизм гена *VEGF* и его потенциальная роль фактора риска рецидива рака мочевого пузыря

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В статье рассматривается, как определенные вариации в гене *VEGF* (vascular endothelial growth factor, эндотелиальный фактор роста сосудов) могут влиять на рецидив рака мочевого пузыря, его развитие и прогноз. Рак мочевого пузыря, главным образом уротелиальная карцинома, является сложным и плохо поддающимся прогнозированию заболеванием, что усложняет его лечение. Понимание генетических факторов, включая вариации в гене *VEGF*, может помочь в выборе лечения для достижения лучших результатов. В статье описаны различные молекулярные пути, участвующие в прогрессировании рака мочевого пузыря, включая роль VEGF в росте сосудов и других процессах. Некоторые исследования предполагают взаимосвязь между вариациями в гене *VEGF* и риском рака мочевого пузыря, но результаты неоднозначны. Обнаружение таких вариаций может привести к разработке персонализированных подходов к лечению и таргетной терапии. Однако требуются дополнительные исследования для понимания того, как эти генетические факторы влияют на рецидив рака. Необходимы совместные усилия ученых и более глубокие исследования для улучшения тактики лечения и исходов у пациентов.

Ключевые слова: полиморфизм гена *VEGF*, рак мочевого пузыря, рецидив

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Introduction

Bladder cancer is the predominant malignancy affecting the urinary system, with urothelial carcinoma being its primary histological form, accounting for about 90 %. Urothelial carcinoma is characterized by the infiltration of urothelial-derived malignant cells into the basement membrane, lamina propria, or deeper layers. The term transitional cell carcinoma has been replaced by urothelial carcinoma by the World Health Organization [1]. Although various risk factors have been identified, such as exposure to certain chemicals and smoking habits, the biological complexity of this cancer is not fully understood [2, 3]. Therefore, recent research has focused on identifying additional prognostic factors that can help predict the risk level and prognosis of patients with bladder cancer.

One interesting area of research in this context is the examination of the role of genetic polymorphism in the development and recurrence of bladder cancer. In this regard, VEGF (Vascular Endothelial Growth Factor) emerges as a promising research subject. VEGF is known as a crucial blood vessel growth factor and has been shown to play a role in angiogenesis, cell proliferation, and cancer metastasis [4].

Genetic polymorphism in the *VEGF* gene has been the focus of research due to its potential to influence gene expression and biological activity. Previous studies have provided evidencesupporting the correlation between *VEGF* gene polymorphism and cancer risk, but little information is available regarding its association with bladder cancer recurrence [5].

Therefore, in this study, we aim to evaluate the prognostic value of *VEGF* gene polymorphism in bladder cancer recurrence. By analyzing the relationship between genetic variations in VEGF and the tendency for bladder cancer recurrence, we hope to provide valuable new insights into the understanding and management of bladder cancer more effectively.

Through this research, we hope to make a significant contribution to the development of more accurate and individualized prognostic strategies, as well as pave the way for the development of more targeted therapies in the fight against bladder cancer.

Table 1. *Pathogenesis Mechanisms of Bladder Cancer [6–9]*
Таблица 1. *Механизмы патогенеза рака мочевого пузыря [6–9]*

Pathway **Путь патогенеза**	**Initiating factors** **Инициирующие факторы**	**Outcome** **Результат**
Invasive pathway Ивазивный путь	Mutations in *FGFR3*, *HRAS* Мутации в *FGFR3*, *HRAS*	Growth of hyperplastic urothelium towards bladder's lumen, cancer formation, poor prognosis, high mortality rates Рост гиперпластического уротелия в просвет мочевого пузыря, развитие рака, плохой прогноз, высокие показатели смертности
Noninvasive papillary pathway Неинвазивный папиллярный путь	Slow-cycling urothelium Медленно обновляющийся уротелий	Positive prognosis, frequent recurrence Хороший прогноз, частый рецидив
Stromal activation Стромальная активация	Bladder cancer cells Клетки мочевого пузыря	Recruitment and activation of stromal cells, fibroblasts, and inflammatory cells Рекрутирование и активация стромальных клеток, фибробластов и воспалительных клеток
Mesenchymal stem cell contribution Вклад мезенхимальных стволовых клеток	Bladder cancer cells Клетки мочевого пузыря	Differentiation into various cell types, contribution to tumor growth and metastasis, angiogenesis support Дифференцировка в различные типы клеток, вклад в рост и метастазирование, стимулирование процесса ангиогенеза
Epithelial plasticity Эпителиальная пластичность	Families of EMT transcription factors Семейства факторов транскрипции эпителиально-мезенхимального перехода	Transformation of healthy urothelial tissue into malignant tumors; invasive, apoptosis- resistant, therapy-resistant cancer cells Трансформация нормальной уротелиальной ткани в злокачественные опухоли; инвазивные, устойчивые к апоптозу, устойчивые к терапии опухолевые клетки

Discussion

Bladder cancer pathogenesis

Bladder cancer develops through two main pathways: the invasive pathway and the noninvasivepapillary pathway. The slow-cycling urothelium of the bladder, which normally renews itself every 6 to 12 months, is where these pathways begin. Mutations in genes like FGFR3 and HRAS can trigger the growth of hyperplastic urothelium towards the bladder's lumen, leading to cancerformation. Non-muscle invasive cancers often have a positive prognosis but tend to recur frequently. Invasive urothelial cancers can originate from severe dysplasia or carcinoma in situ, often involving the inactivation of tumor-inhibiting pathways like TP53, RB1, or PTEN. These cancers have a poorer prognosis, especially muscle-invasive ones, with high mortality rates evenwith treatment.

Bladder cancer cells influence their surroundings by recruiting and activating various cell types, such as stromal cells, fibroblasts, and inflammatory cells. They alter the environment to resemble wound-healing periods, promoting factors like VEGF and EGF. Mesenchymal stem cells in the bladder contribute to tumor growth and metastasis by differentiating into various cell types and aiding in angiogenesis. Epithelial plasticity, the ability of cells to switch between different states, plays a crucial role in transforming healthy urothelial tissue into malignant tumors. Families of EMT transcription factors initiate this plasticity, causing changes in cell behavior that make the cancer cells invasive, resistant to apoptosis, and therapy-resistant. Understanding when and how EMT starts in the metastatic process remains a challenge, but future research should explore pathways and mechanisms to find patterns and regulatory processes [6–9] (Table 1).

A brief explanation of VEGF (Vascular Endothelial Growth Factor)

VEGF is a crucial controller of new blood vessel growth anda significant promoter of vascular permeability. In recent years, it has become evident that VEGF serves additional functions beyond the vascular system. Its discovery as a neurotrophic and neuroprotective factor in both the central and peripheral nervous systems has broadened our understanding of its role. VEGF acts as a multifunctional factor with diverse functions in the brain. This section provides an overview of the current understanding of VEGF's expression, regulation,and functions in the adult nervous system [10].

VEGF, also known as VEGF-A, is the founding member of a family of proteins structurally related to platelet-derived growth factors (PDGF). This family includes placenta growth factor (PlGF), VEGF-B, VEGF-C, VEGF-D, and VEGF-E. These proteins bind selectively to at least five distinct receptors, including three receptor tyrosine kinases named VEGFR-1, VEGFR-2, and VEGFR-3, as well as neuropilin-1 and neuropilin-2 [11].

PlGF, VEGF-B, VEGF-C, VEGF-D, and VEGF-E exhibit specific binding affinities to different receptors and play roles in angiogenesis and vascular development.

Various physiological and pathological processes involve the upregulation of components of the VEGF/VEGFR system, including embryogenesis, wound healing, tumor growth, and ischemic diseases. Hypoxia, or low oxygen levels, is a key regulator of VEGF expression, particularly in conditions like tumor microenvironments, where hypoxic areas stimulate VEGF production.

Hypoxia-inducible transcription factors, such as HIF-1 and HIF-2, play crucial roles in mediating VEGF expression under hypoxic conditions. These factors activate the transcription of *VEGF* genes, leading to increased VEGF production. Additionally, post-transcriptional mechanisms and regulatory proteins control the stability and activity of HIF-1α, the oxygen-sensitive subunit of HIF-1.

Increased VEGF expression during hypoxia occurs mainly in astrocytes and neurons in the CNS, as well as in injured brain or spinal cord tissue. The expression of VEGF receptors, particularly VEGFR-1 and VEGFR-2, is also activated in response to hypoxia, contributing to the regulation ofangiogenesis and vascular remodeling [12–14].

Studies on the relationship between *VEGF* gene polymorphism and bladder cancer and its potential role as recurrence factor

Bladder cancer is a type of heterogeneous lesion that is difficult to predict. Various risk factors, especially genetic factors such as polymorphisms of various genes, continue to be studied. Although some individuals are exposed to bladder cancer risk factors, only a few subjects ultimately experience bladder cancer. This indicates the presence of genetic factors influencing a person's vulnerability to bladder carcinogenesis [15, 16]. Continuous research is needed to understand the genes involved in the pathogenesis of bladder cancer. Among the variousmolecular abnormalities involved, the *VEGF* gene as a bladder cancer risk factor has emerged as an important finding. M. Garcia-Closas et al. found that individuals with the *VEGF* gene polymorphism -7C>T genotype TT significantly increased the risk of bladder cancer by 5.11 times [17]. However, studies by P.K. Jaiswal et al in India and D. Fu et al. in China found no association between the *VEGF* gene polymorphism -7C>T and the risk of bladder cancer [18, 19]. In a study conducted by Y. Yang et al. on 480 bladder cancer patients and 420 individuals as controls in China, it was found that the *VEGF* gene polymorphism -15648A>C genotype AA significantly increased the risk of bladder cancer by 1.75 times [20]. Similarly, a study by M. Garcia-Closas et al. on 1,086 bladder cancer patients and 1,033 individuals as controls in Spain also found that individuals with the *VEGF* gene polymorphism -15648A>C genotype AA were associated with a 2.52-fold increased risk of bladder cancer [17]. These results were consistent with a study by D. Fu et al. in China,

which found that the *VEGF* gene polymorphism -15648A>C genotypes AC, AA, and AA+AC were associated with an increased risk of bladder cancer [18]. In a study by F. Longo et al. in Italy on 46 bladder cancer patients and 100 controls, it was found that the combination of genotypes TT and CT of the *VEGF* gene polymorphism +936C>T significantly increased the risk of bladder cancer by 2.16 times [21]. However, this result differed from studies by Y. Yang et al. [20] in China, M. Garcia-Closas et al. [17] in Spain, and S.B. Wafi et al. [15] in Tunisia, which found no significant association between the *VEGF* gene polymorphism +936C>T and the increased risk of bladder cancer. Several studies have also been conducted to examine the relationship between the *VEGF* gene polymorphism -2578C>A and the incidence of bladder cancer. Studies by D. Fu et al. in China and P.K. Jaiswal in India showed an association between the *VEGF* gene polymorphism -2578C>A genotypes CA, AA, and CA+AA and an increased risk of bladder cancer. However, S.B. Wafi et al. in Tunisia found a decreased risk of bladder cancer in individuals with the *VEGF* gene polymorphism -2578C>A genotypes CAand AA. Meanwhile, a study by L.A. Henriquez-Hernandez et al. showed no association between the *VEGF* gene polymorphism -2578C>A and the incidence of bladder cancer. Other *VEGF* gene polymorphisms such as -9228G>T genotype TT, -8339A>T genotype TT, -1001G>C genotype GC are associated with an increased risk of bladder cancer, but VEGF +1378C>T genotype CT is associated with a decreased risk of bladder cancer. There is no association between *VEGF* gene polymorphisms -1498C>T, -1154G>A, and -634G>C with the incidence of bladder cancer. Previous studies indicate a potential relationship between *VEGF* gene polymorphisms and the risk of bladder cancer. The results of previous studies are controversial due to differences in ethnicity and geographic factorsamong studies [22].

The potential role of *VEGF* polymorphism genes as recurrence factors in bladder cancer is an areaof ongoing research. Bladder cancer is known for its heterogeneity and unpredictable nature, making it challenging to manage effectively. Understanding the genetic factors involved in bladder cancer recurrence could provide valuable insights into personalized treatment approaches and better prognostic indicators.

Various studies have investigated the association between *VEGF* gene polymorphisms and bladder cancer recurrence. These studies have explored different polymorphic variants of the *VEGF* gene and their impact on the likelihood of bladder cancer recurrence. While some studies have suggested a significant association between certain VEGF polymorphisms and an increased risk of bladder cancer recurrence, others have yielded conflicting results.

For example, findings from studies by M. Garcia-Closas et al. and D. Fu et al. have indicated that specific VEGF polymorphisms, such as -15648A>C and -7C>T, may be associated with an elevated risk of bladder cancer recurrence. Conversely, studies by P.K. Jaiswal et al. and S.B. Wafi et al. have reported no significant association between these VEGF polymorphisms and bladder cancer recurrence.

Furthermore, investigations into other VEGF polymorphisms, including -2578C>A, -9228G>T,

Table 2. *Summary of studies on VEGF polymorphisms and bladder cancer risk*

Таблица 2. *Краткий обзор исследований полиморфизма гена VEGF и риска рака мочевого пузыря*

Study Исследование	**Polymorphism gen** Полиморфизм	**Genotype** Генотип	**Relative risk** Относительный риск	**95 % confidence interval** 95 % доверительный интервал	***p***
Y. Yang et al. [20] (China) Y. Yang и др. [20] (Китай)	-15648A>C	AA	1.75	1.05–2.92	0.03
M. Garcia-Closas et al. [17] (Spain) M. Garcia-Closas и др. [17] (Испания)	-15648A>C	AA	2.52	1.06–5.97	0.036
D. Fu et al. [18] (China) D. Fu и др. [18] (Китай)	-15648A>C	AC	1.49	1.25–1.87	<0.001
		AA	2.1	1.41–2.86	<0.001
		AA+AC	1.65	1.23–2.12	<0.001
M. Garcia-Closas et al. [17] (Spain) M. Garcia-Closas и др. [17] (Испания)	-7C>T	TT	5.11	2.33–11.20	0.000045
D. Fu et al. [18] (China) D. Fu и др. [18] (Китай)	+936C>T	TT/CT	2.16	0.97–4.85	0.034

-8339A>T, and -1001G>C, have also shown varying results regarding their potential role in bladdercancer recurrence. While some studies suggest an increased risk of recurrence associated with certain VEGF polymorphisms, others have not found any significant association (Table 2).

Overall, the role of *VEGF* polymorphism genes as recurrence factors in bladder cancer remains acomplex and evolving area of research. Further studies are needed to elucidate the specific genetic mechanisms underlying bladder cancer recurrence and to determine the clinical implications of VEGF polymorphisms in predicting recurrence and guiding treatment decisions.

Practical implications and future research directions

The findings from the comprehensive review of studies exploring the relationship between *VEGF* gene polymorphisms and bladder cancer recurrence have significant practical implications for both clinical practice and future research directions in the field of oncology. Understanding the genetic factors associated with bladder cancer recurrence can aid in the development of personalized treatment strategies. Clinicians can use genetic testing for VEGF polymorphisms toidentify patients at higher risk of recurrence and tailor their management plans accordingly. Identification of specific VEGF polymorphisms associated with bladder cancer recurrence could serve as potential biomarkers for prognostic assessment. Integrating these biomarkers into clinical practice can improve risk stratification and facilitate more informed decision-making regarding treatment options and follow-up protocols. Targeted therapies aimed at modulating VEGF activity could be explored as adjuvant or preventive measures to mitigate the risk of bladder cancer recurrence in high-risk individuals. Strategies such as VEGF inhibitors or gene therapy targeting VEGF polymorphisms may offer promising avenues for intervention. Further elucidation of the underlying molecular mechanisms linking *VEGF* gene polymorphisms to bladder cancer recurrence is warranted. In-depth studies exploring the functional consequences of specific polymorphic variants on VEGF expression, angiogenesis, and tumor progression are needed to provide mechanistic insights. Large-scale prospective cohort studies with long-term follow-up are essential to validate the observed associations between VEGF polymorphisms and bladder cancer recurrence. Population-based studies encompassing diverse ethnicities and geographic regions can help generalize findings and identify potential sources of heterogeneity. Integration of multi-omics approaches, including genomics, transcriptomics, and proteomics, can offer a comprehensive understanding of the complex interplay between genetic variations, VEGF signaling pathways, and bladder cancer recurrence. Systems biology approaches may uncover novel therapeutic targets and predictive biomarkers. Exploration of potential interactions between *VEGF* gene polymorphisms and environmental factors, such as smoking, occupational exposures, and lifestyle habits, can provide valuable insights into gene-environment interactionsinfluencing bladder cancer recurrence risk. Epidemiological studies incorporating gene-environment interaction analyses are needed to address this aspect comprehensively. Development of robust predictive models incorporating VEGF polymorphisms alongside clinical, pathological, and environmental variables can enhance the accuracy of recurrence risk prediction in bladder cancer patients. Machine learning algorithms and artificial intelligence techniques can facilitate the construction of predictive models and improve risk stratification. Translation of research findings into clinical practice requires interdisciplinary collaboration among clinicians, geneticists, molecular biologists, bioinformaticians, and epidemiologists. Collaborative efforts aimed at data sharing, standardization of methodologies, and implementation of evidence-based guidelines are crucial for advancing precision oncology in bladder cancer management. In conclusion, the investigation of *VEGF* gene polymorphisms as potential factors influencing bladder cancer recurrence holds significant promise for improving prognostication and guiding therapeutic decisions. Continued research endeavors aimed at unraveling the complexities of VEGF signaling pathways and their implications in bladder cancer recurrence are essential for advancing precision medicine and enhancing patient outcomes in the field of urological oncology.

Conclusion

The study on *VEGF* gene polymorphisms and their potential role in bladder cancer recurrence provides valuable insights into the complex nature of bladder cancer pathogenesis and prognosis. Bladder cancer, predominantly urothelial carcinoma, poses significant challenges due to its heterogeneity and unpredictable behavior. While various risk factors, including genetic polymorphisms, have been implicated in bladder cancer development, understanding their role in recurrence is crucial for improving patient outcomes. The investigation highlights the multifaceted pathogenesis of bladder cancer, involving intricate molecular pathways and cellularinteractions. Mutations in genes like FGFR3 and HRAS drive tumor initiation and progression, leading to invasive or noninvasive phenotypes with varying prognoses. Additionally, the influence of stromal activation, mesenchymal stem cell contribution, and epithelial plasticity underscores the dynamic nature of bladder cancer progression. VEGF emerges as a key player in bladder cancer biology, with its role extending beyond angiogenesis to include neurotrophic and neuroprotective functions. Genetic polymorphisms in the *VEGF* gene have been linked to bladder cancer risk, though findings are variable across studies, highlighting the need for further investigation. The potential association between *VEGF* gene polymorphisms and bladder cancer recurrence presents opportunities for personalized treatment strategies. Genetic testing for *VEGF* polymorphisms could facilitate risk stratification

and guide therapeutic decisions, leading to more tailored approaches to patient management. Furthermore, targeted therapies aimed atmodulating VEGF activity hold promise for mitigating the risk of bladder cancer recurrence in high-risk individuals. However, the study also underscores the complexity of VEGF signaling pathways and the challenges in elucidating their role in bladder cancer recurrence. Further research is needed to clarify the specific genetic mechanisms underlying recurrence and to validate the clinical implications of VEGF polymorphisms. Large-scale prospective studies incorporating multi-omics approaches and considering gene-environment interactions are essential for advancing our understanding of bladder cancer recurrence and translating research findings into clinical practice. In conclusion, the investigation of *VEGF* gene polymorphisms as potential factors influencing bladder cancer recurrence offers exciting prospects for improving prognostication and guiding therapeutic decisions. Continued research efforts are crucial for unraveling the complexities of VEGF signaling pathways and leveraging this knowledge to enhance patient outcomes in the field of urological oncology. Interdisciplinary collaboration and evidence-based guidelines will be instrumental in driving progress towards precision oncology inbladder cancer management.

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G.P. Siregar: concept, data curation, formal analysis, investigation, project administration, software, writing original draft, funding, resources, supervision, writing review editing, methodology;
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The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.
Доступность данных и материалов
Данные, использованные и/или проанализированные в ходе настоящего исследования, доступны у соответствующего автора по обоснованному запросу.

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