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VEGFA GENE POLYMORPHISMS AND THE RISK OF MALIGNANCIES OF THE FEMALE REPRODUCTIVE SYSTEM: A META-ANALYSIS

Malignant neoplasms of the reproductive system are the leading cause of cancer mortality among women. Vascular endothelial growth factor (VEGF) is one of the most important factors in the malignancy process, but association of its gene polymorphisms with the risk of developing reproductive organ cancers remain contradictory. Polymorphisms in the *VEGFA* gene promoter region (rs2010963, rs699947) are functionally significant and associated with increased protein expression, which enhances angiogenesis. The rs3025039, located in the 3'-UTR, influences post-transcriptional regulation of the gene. **The aim of the study** was to compare the association of rs2010963, rs699947 and rs3025039 polymorphisms of the *VEGFA* gene with the risk of developing malignant neoplasms of the female reproductive system using a meta-analysis method. **Materials and Methods**. A systematic literature search of domestic and international databases identified 15 case-control studies. Statistical analysis was performed using a random-effects model. **Results.** A significant increase in the risk of female reproductive system cancers was associated with the minor alleles of *VEGFA* polymorphisms rs2010963 (OR = 1.24; 95% CI: 1.09–1.41; p = 0.0008) and rs699947 (OR = 1.16; 95% CI: 1.04–1.28; p = 0.0058). No such association was identified for rs3025039. The analysis indicated substantial heterogeneity among the included studies. **Conclusion.** The results of the meta-analysis confirm the role of *VEGFA* gene polymorphisms in modulating the risk of female reproductive system cancer and indicate the need to consider ethnic and nosological characteristics in further research.

Keywords: VEGFA, rs2010963, rs699947, rs3025039, polymorphism, meta-analysis, gynecologic malignancies.

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One gene whose protein product may potentially be involved in malignant growth is *VEGFA* (Vascular endothelial growth factor A) [16]. This gene is located on chromosome 6p21.1 and is over 16 kb in size; its coding region consists of 8 exons and 7 introns [26]. The VEGF family consists of five homologous members: VEGF-A (commonly known as VEGF), VEGF-B, VEGF-C, VEGF-D, and placental growth factor [12]. Vascular endothelial growth factor A (VEGFA), encoded by the *VEGFA* gene, plays a critical role in angiogenesis. Angiogenesis is a key process for tumor growth and metastasis. Therefore, the *VEGFA* gene and its products are of considerable interest in the context of oncology [7, 8]. Single-nucleotide polymorphisms of this gene may serve as potential markers of oncogenesis. The rs2010963 (c.-634C>G) polymorphism, located in the promoter region of the *VEGFA* gene, is functionally significant and may affect protein expression levels [9]. There is literature data on increased plasma VEGFA levels with this single-nucleotide substitution [13]. Experimental data indicate that genetic variability in the regulatory regions of the *VEGFA* gene can influence cancer risk and the progression of tumors that rely on angiogenesis. The c.-634C>G allele (rs2010963) can affect translation by potentially enhancing the efficiency of translation initiation, leading to increased VEGFA production [9]. The variable locus rs3025039 C>T of the *VEGFA* gene is located in the 3'-UTR region and can affect post-transcription processes and gene expression [27]. It has been reliably studied that rs3025039/*VEGFA* affects the secreted levels of VEGFA protein and in most studies has been identified as having a clear association with the risk of developing cancer [18]. The rs699947 is localized in the promoter region of the *VEGF* gene and is associated with the substitution of cytosine for adenine at position 2578 of cDNA. The presence of the A allele of rs699947 was found to be significantly associated with increased *VEGF* expression [11]. A number of studies have demonstrated the contribution of these polymorphisms to the development of malignant neoplasms of the female reproductive system [2,3,4,10,14, 17, 19, 21, 23, 24, 29]. However, the results of these studies remain contradictory. A meta-analysis summarizing the results of these studies is necessary to obtain a single statistically valid assessment.

The aim of the study was to compare the association of rs2010963, rs699947 and rs3025039 polymorphisms of the *VEGFA* gene with the risk of developing malignant neoplasms of the female reproductive system using a meta-analysis method.

Materials and Methods. Literature Search and Selection. For each polymorphism (rs2010963, rs699947, rs3025039), an independent systematic search was conducted in PubMed, Web of Science, Google Scholar, CyberLeninka, and Elibrary. Search queries included combinations of keywords related to the *VEGFA* gene and its polymorphisms (including alternative designations: *VEGF* -634G>C, *VEGF* -2578C>A, *VEGF* 936C>T) and gynecologic malignancies (ovarian cancer, endometrial cancer, cervical cancer). The search was limited to human studies with no language or publication date restrictions. Inclusion criteria: case-control studies containing data on genotype distribution in patients with gynecologic

Table 1

Main characteristics of the studies included in the meta-analysis

First author	Year	Nosology	Country	Population	Case (n)	Control (n)	Minor allele frequency	
							(cases)	(control)
rs2010963/*VEGFA*								
А.В. Рогалев [7]	2023	Cervical cancer	Russian Federation	Eastern European	120	112	41.25	30.8
A. Madrid-Paredes [23]	2020	Breast cancer	Spain	Mediterranean	80	123	32.50	33.33
Z. Li [22]	2021	Breast cancer	China	East Asian	259	273	45.75	37.36
Д.Р. Долгова [1]	2019	Ovarian cancer	Russian Federation	Eastern European	87	70	37.93	22.86
R. James [17]	2014	Breast cancer	India	South Asian	200	200	33.50	35.25
J. Rahoui [24]	2014	Breast cancer	Morocco	North African	70	70	39.29	27.14
Y.H. Kim [20]	2010	Cervical cancer	South Korea	East Asian	199	215	41.84	40.70
rs699947/*VEGFA*								
Z. Li [22]	2021	Breast cancer	China	East Asian	259	273	23.94	25.46
A. Madrid-Paredes [23]	2020	Breast cancer	Spain	Mediterranean	80	123	41.88	51.63
Al Balawi I.A. [10]	2018	Breast cancer	Saudi Arabia	Arabian	100	100	40.50	27.50
M. Rezaei [25]	2016	Breast cancer	Iran	Near Eastern	250	215	42.00	33.02
J. Rahoui [24]	2014	Breast cancer	Morocco	North African	70	70	34.29	44.29
S. Zidi [29]	2014	Cervical cancer	Tunisia	North African	86	124	40.70	31.05
В.И.Коненков [4]	2012	Breast cancer	Russian Federation	Eastern European	389	287	52.44	45.64
Y.H. Kim [20]	2010	Cervical cancer	South Korea	East Asian	199	215	24.37	25.83
Y. Li [21]	2010	Ovarian cancer	China	East Asian	303	303	25.91	22.44
rs3025039/*VEGFA*								
Андреева Е.А. [3]	2025	Ovarian cancer	Russian Federation	Eastern European	205	259	15.85	16.41
Bricia M Gutiérrez-Zepeda [14]	2024	Breast cancer	Mexico	Latin American	231	201	31.17	21.89
Z. Li [22]	2021	Breast cancer	China	East Asian	259	273	16.22	19.45
M. Rezaei [25]	2016	Breast cancer	Iran	Near Eastern	250	215	15.00	13.95
R. Kapahi [19]	2014	Breast cancer	India	South Asian	192	192	9.90	5.73
В.И. Коненков [4]	2012	Breast cancer	Russian Federation	Eastern European	389	241	16.58	15.56
Y.H. Kim [20]	2010	Cervical cancer	South Korea	East Asian	199	215	18.18	20.33
Y. Li [21]	2010	Ovarian cancer	China	East Asian	303	303	16.17	18.15

malignancies and in the control group. Exclusion criteria were duplicate data, lack of full text or required genotype frequency data, and non-compliance with Hardy-Weinberg equilibrium ($p<0.05$). The final analysis included 7 studies for the rs2010963 polymorphism, 9 studies for rs699947, and 8 studies for rs3025039. The main characteristics of the studies included in this meta-analysis are presented in Table 1.

Statistical Analysis of Study Results. An independent meta-analysis was conducted for each polymorphism using a random-effects model. Associations were assessed by calculating the pooled odds ratio (OR) with a 95% confidence interval (CI) within an additive model. Heterogeneity among studies was assessed using the I^2 statistic. Statistical analysis was performed in MC Office Excel.

Results and Discussion. The meta-analysis included data from 15 studies, comprising 2,771 cases of gynecological cancer and 2,698 controls. The results of the meta-analysis are presented in Table 2.

The meta-analysis revealed a statistically significant association with the risk of gynecological cancer for two polymorphic loci, rs2010963 and rs699947, of the *VEGFA* gene. The presence of the minor allele C of the rs2010963 polymorphism was associated with a 24% increased risk (OR = 1.24; 95% CI: 1.09–1.41; p = 0.0008). For the rs699947 polymorphism, the pooled OR was 1.16 (95% CI: 1.04–1.28; p = 0.0058), corresponding to a 16% increased risk. For the rs3025039 polymorphism, no statistically significant association was found (OR = 1.05; 95% CI: 0.92–1.18; p = 0.4487). Since the rs2010963 and rs699947 polymorphic loci are located in the promoter region, their effect on *VEGFA* expression and, consequently, on the intensity of angiogenesis seems to be the most likely mechanism for increasing the risk. The rs3025039, located in the 3'-UTR, may have a less significant regulatory effect. The available literature data are limited to meta-analyses focused on individual nosological forms [15,28]. The present study offers a comprehensive assessment of the associations of *VEGFA* polymorphisms for a heterogeneous group of malignant neoplasms of the reproductive system as a whole, which is a poorly studied area. Moderate to high heterogeneity (I^2 = 59.1% - 70.5%) was observed for all analyses, indicating variability in effect size between studies. The observed level of heterogeneity may be associated with ethnic differences in the populations and the diversity of disease entities in the pooled sample.

Table 2

Results of the meta-analysis of associations of *VEGFA* gene polymorphisms with the risk of gynecological malignancies

Polymorphism	Number of studies (case/control)	Pooled OR (95% CI)	P-value	I^2, %
rs2010963	7 (1015/1063)	1.24 (1.09–1.41)	0.0008	59.8
rs699947	9 (1736/1710)	1.16 (1.04–1.28)	0.0058	70.5
rs3025039	8 (2028/1899)	1.05 (0.92–1.18)	0.4487	59.1

Conclusion. The rs2010963 and rs699947 polymorphisms of the *VEGFA* gene are significant risk factors for female reproductive system cancers and can be considered candidate markers for the development of genetic predisposition profiles. The identified heterogeneity necessitates validation of the obtained data in large, homogeneous cohorts, separating the samples by disease entity and ethnicity.

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The authors declare no conflict of interest.

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S.K. Kononova

APPROACHES TO THE TREATMENT OF AUTOSOMAL DOMINANT SPINOCEREBELLAR ATAXIAS

This article is devoted to prospects for treating neurodegenerative diseases caused by dynamic mutations, based on published studies searching for therapeutic approaches to spinocerebellar ataxias. Although these diseases are incurable, research results show that some medications and physiotherapy can alleviate symptoms of cerebellar ataxia. Thanks to progress in the study of spinocerebellar ataxias in recent years, there is considerable hope that gene-therapy methods can be developed that will slow disease progression or even halt it.

Keywords: spinocerebellar ataxia, dynamic mutations, treatment, gene therapy, physiotherapy

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Introduction. Autosomal dominant spinocerebellar ataxias (ADSCA) represent a large heterogeneous group of hereditary ataxias, currently including about 40 types that differ by geno-phenotypic manifestations [18, 55]. ADSCAs are numbered chronologically as the genes responsible for the disease are discovered; for example, SCA47 was recently described by Gennarino V. et al., 2018 [5,30]. The most studied are SCA1, SCA2, SCA3, SCA6, SCA7, SCA17. Certain ADSCA forms are known to be concentrated in particular world populations: SCA1 in the Yakut population [3,31,63]; SCA2 in the Indian population [56]; SCA3 in Portuguese, Brazilian and Chinese populations [27].

Characteristic clinical signs of ADSCA are slowly or rapidly progressive dysarthria, oculomotor disorders and gait ataxia, and impaired coordination. The cerebellum, brainstem and spinal cord undergo neurodegeneration [1].

A common feature of all ADSCA subtypes is the presence of an unstable (dynamic) mutation caused by expansion of CAG repeats in the coding region of a gene, leading to formation of a polyglutamine (polyQ) tract in the encoded protein [43,55]. There is a relationship between age at onset and severity of neurological symptoms and the size of the polyQ-repeats expansion [45]. The expanded polyglutamine tract causes synthesis of a misfolded, aggregation-prone protein which, at advanced stages of aggregation, disrupts regulation of gene expression at the transcriptional level and leads to disturbance of neuronal homeostasis [26].

Table 1. Various ADSCA diseases with polyglutamine mutations.

The Republic of Sakha (Yakutia) is a region with the highest accumulation

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