REVIEWS

Review article
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Genetic polymorphism associated with cervical cancer: a systematic review

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Abstract

Introduction. Cervical cancer (CC) is one of the most common cancers in women. The CC etiological agent is the high-risk oncogenic human papillomavirus. In the meantime, not all women infected with this virus can develop cancer, thus suggesting that there is genetic predisposition to CC.

The **aim** of the study was to analyze information about single nucleotide polymorphisms associated with the CC risk.

Materials and methods. The performed search was focused on genome-wide association studies (GWAS) and meta-analyses conducted over the last 10 years and addressing the genetic risk of CC in the Caucasian population.

Results. The most significant associations with CC were found in the following single nucleotide polymorphisms. Based on the GWAS data, they involve risk alleles *rs138446575-T* (OR = 2.39) *TTC34*; *rs73728618-T* (OR = 1.48) *HLA-DQA1*; *rs3130196-C* (OR = 1.4) *HLA-DPB1*; *rs2516448-T* (OR = 1.39 and 1.44) *MICA* and protective alleles *rs9271898-A* (OR = 0.64) and *9272143-C* (OR = 0.65) between *HLA-DRB1* and *HLA-DQA1*, *rs55986091-A HLA-DQB1* (OR = 0.66). Based on the meta-analysis data, they involve genotype *rs4646903-CC* (OR = 4.65) *CYP1A1* and protective alleles *rs1801133-T* (OR = 0.77) *MTHFR*, *rs2333227-AA* (OR = 0.57) *MPO*.

Conclusion. The obtained data are critically important for development of laboratory techniques and reagent kits allowing for a personalized approach to identification of risk groups, which could benefit from compulsory vaccination and screening for pre-cancers of the cervix.

Keywords: *meta-analysis, high-risk oncogenic human papillomavirus, single nucleotide polymorphism, genome-wide association study, cervical cancer*

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Научный обзор
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Генетические полиморфизмы, ассоциированные с раком шейки матки: систематический обзор

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Аннотация

Введение. Рак шейки матки (РШМ) является одним из самых распространённых онкологических заболеваний у женщин. Этиологический агент РШМ — вирус папилломы человека высокого канцерогенного

риска. При этом не у всех женщин, инфицированных этим вирусом, развивается рак, что позволяет предположить наличие генетической предрасположенности к РШМ.
Цель работы заключалась в анализе информации об однонуклеотидных полиморфизмах, ассоциированных с риском развития РШМ.
Материалы и методы. Выполнен поиск исследований по полногеномному скринингу ассоциаций (GWAS) и метаанализов за последние 10 лет, посвящённых генетическому риску РШМ в европеоидной популяции.
Результаты. Наиболее значимые ассоциации с РШМ были найдены у следующих однонуклеотидных полиморфизмов. По данным GWAS — с аллелями риска *rs138446575-T* (ОШ = 2,39) *TTC34*; *rs73728618-T* (ОШ = 1,48) *HLA-DQA1*; *rs3130196-C* (ОШ = 1,4) *HLA-DPB1*; *rs2516448-T* (ОШ = 1,39 и 1,44) *MICA* и протективными аллелями *rs9271898-A* (ОШ = 0,64) и *9272143-C* (ОШ = 0,65) между *HLA-DRB1* и *HLA-DQA1*, *rs55986091-A HLA-DQB1* (ОШ = 0,66). Для метаанализов — с генотипом *rs4646903-CC* (ОШ = 4,65) *CYP1A1* и протективными аллелями — *rs1801133-T* (ОШ = 0,77) *MTHFR*, *rs2333227-AA* (ОШ = 0,57) *MPO*.
Заключение. Использование полученных данных является важным этапом создания лабораторных методик и наборов реагентов, направленных на персонализированный подход к определению групп риска с целью рекомендации таким пациенткам обязательной вакцинации и скрининга предраковых заболеваний шейки матки.

Ключевые слова: *метаанализ, вирус папилломы человека высокого канцерогенного риска, однонуклеотидный полиморфизм, полногеномный скрининг ассоциаций, рак шейки матки*

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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Introduction

Cervical cancer (CC) is the fourth most common cause of cancer incidence and mortality in women worldwide, with an estimated more than 340,000 deaths in 2020, accounting for 7.7% of all cancer-related deaths[1]. The number of new CC cases continues to rise in Russia, having increased almost by 22% (from 14,000 to 17,000 cases over 10 years (from 2009 to 2019), thus demonstrating the social significance of this disease. It is notable that women aged 30 to 44, falling into the group of socially active and reproductive age, account for 32.4% of CC cases [1]. The Russian cancer care statistics data for 2019 show that the established preventive methods for precancerous conditions of the cervix lack efficiency (absence of universal vaccination program, poor awareness of the importance and availability of cervical cancer screening, lack of motivation for routine examinations). As a result, the CC-related death rates remain almost unchanged [1].

Infection with high-risk oncogenic human papillomavirus (HR-HPV) is a proven carcinogenic factor of CC. It has been found that the relationship between HPV and CC is stronger than the relationship between smoking and lung cancer [2]. On the other hand, the existing literature data show that among women with an HPV infection rate of 15-40%, the CC incidence accounts only for 0.015%, implying that susceptibility can be genetic [3]. Identification of single nucleotide polymorphisms (SNPs) associated with the disease makes it possible to detect potential inherited predisposition to development of pathological conditions during the pre-symptomatic period for timely diagnosis or prevention of the disease [4]. As most women experience a long asymptomatic period, develop CC due to infections most often transmitted through sexual intercourse and are most vulnerable at their reproductive age, the assessment of the genetic risk of CC development is an important clinical task, especially when women from risk groups, including HIV-infected women, are involved [5].

The **aim** of the study was to summarize the information about SNPs associated with the risk of CC development in the Caucasian population.

Materials and methods

The study protocol was prepared following the PRISMA guidelines [6] and registered with PROSPERO — an international database of registered reviews in public health with a health-related outcome [7]. At the same time, our study does not meet some of the registration criteria on PROSPERO: For example, it is not connected directly with any treatment based on the review results. The identification of genetic risks offers an additional tool aimed to improve the awareness of healthcare providers so that they could use a personalized approach to disease prevention at the pre-symptomatic stage [4].

The literature search was conducted using such Internet resources as PubMed, Web of Science, Scopus,

[1] WHO. Global Cancer Observatory. Cancer Today: Data visualization tools for exploring the global cancer burden in 2020. URL: https://gco.iarc.fr/today

and GWAS Catalog[2]. The search was performed in English using such keywords as cervical cancer, gene variants, polymorphism, single nucleotide polymorphism, meta-analysis, GWAS from November 17 through December 12, 2021.

Inclusion and exclusion criteria

Inclusion criteria:

- the review included the assessment of the SNP association with CC;
- the publication date was not earlier than 2011;
- the study design is consistent with the genome-wide association study (GWAS) or meta-analysis.

Exclusion criteria:

- the review did not address the Caucasian population, which in this study referred to the population of Europe and the white population of the United States;
- neither odds ratio (OR) or 95% confidence interval (95% CI) was specified;
- OR and 95% CI did not point at any statistically significant association with CC for the Caucasian population;
- the meta-analysis included fewer than 2 studies, which analyzed the Caucasian population.

Statistical analysis

The recalculation of the variables for Caucasian populations described in the meta-analyses was performed using the RevMan 5.0 software (Cochrane Collaboration).

The statistical heterogeneity of the samples was measured using the heterogeneity index (I^2) and Cochran's Q test. I^2 shows the percentage of variation across studies, which is caused by heterogeneity rather than by chance (at $I^2 > 50\%$, samples are considered heterogeneous). Cochran's Q test is used to check whether the effects are the same across studies; at $p > 0.1$, the effect was considered identical, as the meta-analysis included a small number of studies with a small sample size [8, 9].

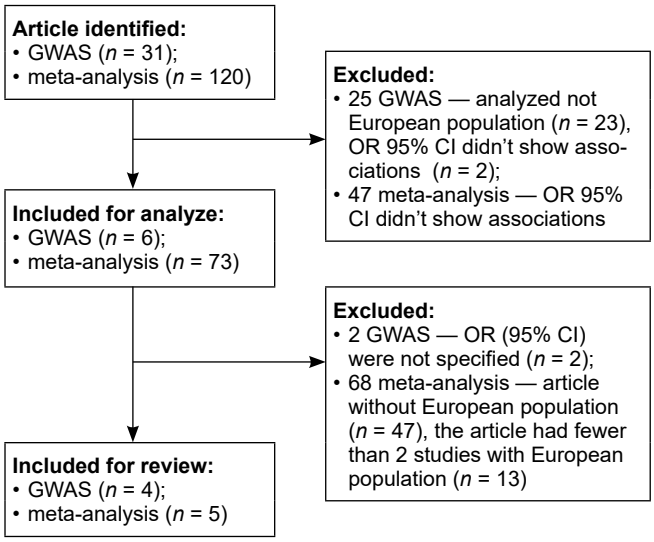
The data are provided both for the fixed-effects model and random-effects model [12].

Results

The search resulted in 4 GWAS and 5 meta-analyses, where the analysis of 40 SNPs was conducted (**Figure**).

In total, GWAS combined the results of the analyses of 34 SNPs; in 17 SNPs, rare alleles were associated with the disease, while in 15 SNPs, they were protective. The CC-associated alleles and OR values calculated in GWAS are presented in **Table 1**.

Based on 5 meta-analyses that met the specified criteria, we found 6 SNPs in 4 genes. Out of them, 4 SNPs were associated with the CC risk and 2 SNPs had a protective effect. **Table 2** presents detailed information and calculated OR values for Caucasian populations analyzed in the above meta-analyses.



Flow chart of study selection.

The data presented in Table 2 can be backed up by the following calculations.

After the data on allele and genotype frequencies had been retrieved from the studies and summarized with the reference to Caucasian populations, the association of the *rs1801133-CC* genotype was no longer significant (OR = 0.79; 95% CI = 0.53–1.12; $p > 0.05$); however, it was found that the association of the *rs1801133-T* (OR = 0.77; 95% CI = 0.66–0.89; $p < 0.01$) was statistically significant both in the fixed-effects and random-effects model.

For *rs5742909*, the association shown in the second column in Table 2 was no longer significant both for the allelic and recessive model (*CC* compared to *CT* + *TT*): OR = 1.19; 95% CI = 0.98–1.45; $p > 0.05$ and OR = 1.19; 95% CI = 0.96–1.47; $p > 0.05$, respectively. At the same time, the parameters used to measure homogeneity of studies exceeded the specified values, thus being indicative of heterogeneity of the studies ($I^2 > 50\%$; $p < 0.1$).

For *rs4646903*, the OR values reached statistically significant levels in the homozygous model (*CC* compared to *TT*): OR = 4.14; 95% CI = 1.24–13.81; $p < 0.05$ for the random-effects model and OR = 4.65; 95% CI = 1.51–14.43; $p < 0.05$ for the fixed-effects model. At the same time, for the associations in the recessive model (*TT* compared to *CT* + *CC*), the calculations showed heterogeneity of the studies ($I^2 > 50\%$; $p < 0.1$). After the study [29], together with its data that had an impact on heterogeneity coefficients, had been excluded from the analysis, the association lost its significance: OR = 1.14; 95% CI = 0.81–1.62; $p > 0.05$ in the ran-

[2] GWAS Catalog (2020). URL: https://www.ebi.ac.uk/gwas/home

Table 1. SNP associated with cervical cancer for GWAS

Sample size — case/control [source]	Gene	SNP	Allele (frequency, %)*	OR (95% CI)**
4769/145545 [10]	*PAX8*	***rs10175462***	*A* (39)	**0,87 (0,84–0,91)**
	CLPTM1L	***rs27069***	*T* (43)	**0,88 (0,84–0,92)**
	HLA-B	***rs9272245***	*C* (31)	**1,26 (1,21–1,31)**
	MICA	***rs6938453***	*A* (25)	**0,79 (0,75–0,83)**
	HLA-DQA1	***rs9272050***	*G* (37)	**1,27 (1,21–1,32)**
	HLA-DQB1	***rs55986091***	*A* (15)	**0,66 (0,60–0,72)**
	TTC34	***rs138446575***	*T* (3)	**2,39 (1,75–3,27)**
	ACACB	***rs117960705***	*G* (1)	**1,22 (1,04–1,44)**
1140/1058 [11]	*MICA*	***rs2516448***	*T* (39)	**1,44 (1,30–1,58)**
	HLA-DRB1, HLA-DQA1	***rs9272143***	*C* (46)	**0,65 (0,59–0,72)**
	HLA-DPB2	*rs3117027*	*A* (34)	1,73 (1,38–2,19)
48961/408786 [12]	*LINC00339*	*rs2473290*	*T* (21)	1,08 (1,05–1,12)
	PARP1	*rs2793381*	*C* (84)	1,08 (1,05–1,11)
	PAX8	***rs10175462***	*G* (61)	**1,15 (1,10–1,19)**
	HCG27	***rs3869114***	*G* (87)	**1,20 (1,12–1,29)**
	HLA-B	***rs3016018***	*C* (51)	**1,13 (1,10–1,17)**
	AIF1	***rs34451818***	*C* (4)	**0,79 (0,73–0,85)**
	AGER	***rs2070600***	*C* (95)	**0,78 (0,73–0,84)**
	HLA-DQA1	***rs73728618***	*T* (90)	**1,48 (1,39–1,58)**
	HLA-DQB1	***rs9273501***	*T* (61)	**0,9 (0,88–0,92)**
	HLA-DMA, HLA-DMB	***rs2395296***	*A* (31)	**1,09 (1,06–1,12)**
	COL11A2P1	***rs3117245***	*C* (88)	**1,17 (1,11–1,24)**
	HLA-DPB2	***rs3129270***	*C* (89)	**0,87 (0,83–0,92)**
	AHR	*rs9639279*	*A* (37)	0,93 (0,9–0,95)
	CASC8	*rs78449170*	*T* (95)	1,18 (1,11–1,25)
	MLLT10	*rs55990219*	*T* (99)	0,83 (0,78–0,89)
	FGFR2	*rs3096763*	*A* (39)	0,95 (0,94–0,97)
	MYEOV	*rs35637432*	*G* (98)	0,81 (0,75–0,88)
	KANSL1	*rs2532389*	*G* (77)	1,07 (1,05–1,1)
	NSF	*rs199533*	*G* (78)	1,06 (1,04–1,08)
	CCNE1	*rs997669*	*T* (64)	0,96 (0,94–0,97)
	ZBTB46	*rs4809367*	*C* (87)	0,92 (0,89–0,95)
1034/3948 [13]	*HLA-DRB1, HLA-DQA1*	***rs9271898***	*A* (49)	**0,64 (0,59–0,70)**
	MICA	***rs2516448***	*T* (61)	**1,39 (1,28–1,52)**
	HLA-DPB1, HLA-DPA1	***rs3130196***	*C* (12)	**1,40 (1,26–1,57)**
	HLA-DRB1, HLA-DQA1	***rs115625939***	*G* (11)	**0,58 (0,51–0,67)**

Note. *Allele frequency for European population in Ensemble[3] database [14, 15]. **$p < 10^{-6}$ for choices marked.

[3] URL: https://www.ensembl.org/index.html

dom-effects model and OR = 1.15; 95% CI = 0.83–1.59; $p > 0.05$ in the fixed-effects model.

For *rs1048943*, the OR values reached statistically significant levels in the recessive model (*TT* compared to *CC* + *CT*): OR = 2.52; 95% CI = 1.08–5.86; $p < 0.05$ in the random-effects model and OR = 2.52; 95% CI = 1.83–3.47; $p < 0.05$ in the fixed-effects model. However, the calculations revealed heterogeneity of the studies ($I^2 > 50\%$, $p < 0.1$). After the study data [26] contributing to heterogeneity had been removed from the calculations, the OR values decreased both for the random-effects and fixed-effects model, while remaining statistically significant: OR = 1.63; 95% CI = 1.08–2.45; $p < 0.05$; at the same time, in the allelic model (*C* compared to *T*), the association was no longer significant: OR = 1.31; 95% CI = 0.89–1.93; $p > 0.05$.

For *rs1800629*, both in the allelic model (*A* compared to *G*) and in the recessive model (*GG* compared to *AA* + *AG*), the coefficients showed heterogeneity of the studies ($I^2 > 50\%$; $p < 0.1$). After the study data

Table 2. SNP associated with cervical cancer for meta-analysis

SNP, risk genotype or risk allele (rare allele frequency, %)*	Meta-analysis, sample size — case/control [source]	OR (95% CI)	Sample size case/control, country, source	OR (95% CI)	Calculated OR (95% CI), *p*-value	An heterogeneity index, Cochran's Q test
MTHFR, rs1801133, T (36)	1898/2678 [16]	0,64 (0,45–0,89)	21/91, Greece [17]	0,79 (0,38–1,66)	0,77 (0,66–0,89); $p < 0,01$	$I^2 = 0\%$; $p = 0,83$
			636/592, Netherlands [18]	0,75 (0,63–0,89)		
			124/168, Poland [19]	0,84 (0,59–1,20)		
CTLA4, rs5742909, T (8)	1665/1502 [20]	1,72 (1,07–2,77)	140/216, Poland [21]	1,07 (0,86–1,33)	1,19 (0,98–1,45); $p > 0,05$	$I^2 = 82\%$; $p = 0,02$
			1281/808, Sweden [22]	1,99 (1,25–3,17)		
CYP1A1, rs4646903, CC (11)	2148/2252 [23]	2,16 (1,45–3,21)	43/121, Israel [24]	0,87 (0,03–21,98)	4,65 (1,51–14,43); $p < 0,05$	$I^2 = 0\%$; $p = 0,49$
			405/337, Sweden [25]	8,69 (1,11–68,35)		
			104/124, Portugal [26]	3,87 (0,73–20,54)		
CYP1A1, rs1048943, CT + CC (3)	1466/1690 [23]	2,22 (1,48–3,33)	85/202, Turkey [27]	5,66 (3,27–9,80)	2,52 (1,83–3,47); $p < 0,05$	$I^2 = 84\%$; $p = 0,02$
			43/121, Israel [24]	1,73 (0,84–3,56)		
			456/495, Poland [28]	1,59 (0,97–2,60)		
TNF-α, rs1800629, AA + GA (13)	4146/4731 [29]	1,47 (1,08–2,00)	127/107, USA [30]	0,85 (0,48–1,49)	1,18 (1,01–1,37); $p > 0,05$	$I^2 = 81\%$; $p = 0,0002$
			143/194, USA [31]	0,92 (0,57–1,48)		
			195/244, Portugal [32]	3,20 (2,0–5,12)		
			154/228, USA [33]	0,89 (0,59–1,34)		
			1263/804, Sweden [22]	1,14 (0,94–1,39)		
MPO, rs2333227, AA (24)	1125/1150 [34]	0,60 (0,36–0,99)	149/126, Germany [35]	0,28 (0,01–6,93)	0,57 (0,34–0,95); $p < 0,05$	$I^2 = 0\%$; $p = 0,91$
			100/122, Portugal [36]	0,59 (0,19–1,78)		
			476/493, Poland [37]	0,58 (0,32–1,03)		

Note. *Allele frequency for European population (EUR) in Ensemble database [15].

responsible for heterogeneity [33] had been excluded from the analysis, the association became insignificant both for the allelic and the recessive model: OR = 1.04; 95% CI = 0.91–1.20; $p > 0.05$ and OR = 1.05; 95% CI = 0.89–1.23; $p > 0.05$, respectively.

For *rs2333227*, the OR values reached statistically significant levels in the recessive model (*AA* compared to *GG* + *AG*) both for fixed and random effects: OR = 0.57; 95% CI = 0.34–0.95; $p < 0.05$ and OR = 0.57; 95% CI = 0.34–0.95; $p < 0.05$, respectively. In the homozygous model (*AA* compared to *GG*), the association was significant only for the fixed-effects model: OR = 0.60; 95% CI = 0.36–0.99; $p = 0.05$; for random effects, the association failed to reach statistical significance: OR = 0.60; 95% CI = 0.36–1.0; $p = 0.05$.

Discussion

In GWAS, the highest OR values were found for *rs138446575* (OR = 2.39) near the *TTC34* gene, *rs73728618* (OR = 1.48) in *HLA-DQA1* and *rs3130196* in the intergenic region between *HLA-DPB1 and HLA-DPA1* (OR = 1.4). In two GWAS, relatively high OR values of 1.44 [12] and 1.39 [14] were replicated for *rs2516448* near the *MICA* gene. In two other GWAS, an association with CC for the common allele *G* (OR = 1.15) [13] and a protective effect for the rare allele *A* (OR = 0.87) was found for *rs10175462* (*G* > *A*) in the *PAX* gene [11].

The highest protective effect was demonstrated by *rs9271898-A* (OR = 0.64) and *rs9272143-C* alleles (OR = 0.65) between *HLA-DRB1* and *HLA-DQA1*, and *rs55986091* near *HLA-DQB1* (OR = 0.66).

The meta-analyses demonstrated a much higher value of OR, reaching 4.65 for *rs4646903* in *CYP1A1*. The high value of OR compared to the data presented in Table 1 can be caused by the limited focus of GWAS calculating OR values only for the allelic model. The OR values calculated for *rs5742909*, *rs1048943* and *rs1800629* (Table 2) cannot be used for assessing the association with the risk, as the values of the heterogeneity indices and Q test fell outside the interval range showing the heterogeneity of studies. Using an in-depth analysis such as a meta-regression analysis for these data [38] is impossible due to a small number of publications covered by our meta-analysis. At the same time, the meta-analyses showed statistically significant OR values for the *rs1801133-T* protective allele (OR = 0.77) and the *rs2333227-AA* genotype (OR = 0.57).

The previously published meta-analyses [16, 20, 23, 29, 34] that form the core of this study did not address Caucasian populations specifically. The recently published GWAS review by Ramachandran et al. did not include the analysis of all the loci found during the literature search for the publication [39]. This study combines the data on genetic factors identified in GWAS and meta-analyses associated with CC in the Caucasian population, thus contributing to the scientific novelty of this study.

The diagnosis of multifactorial diseases during the prehospital phase results in a 20% decrease in the costs due to the reduced number of laboratory and instrumental tests and examinations, outpatient visits and better selected therapies matching patients' needs and pharmacological responses (through pharmacogenetic testing) [4, 40]. The systematization and analysis of data from different published studies are important for developing laboratory techniques and reagent kits aimed at identification of risk groups for multifactorial diseases and, consequently, at a personalized approach to therapeutic or diagnostic actions [4, 41].

Information about the most significant SNPs, which, based on the obtained data, include *rs138446575*, *rs73728618*, *rs3130196*, *rs2516448*, *rs10175462*, *rs9271898*, *rs9272143*, *rs55986091*, *rs4646903*, *rs1801133* and *rs2333227*, is critically important for development of laboratory techniques aimed at identification of individual risks of CC. The identification of both individual and population risks of CC development will enhance the effectiveness of monitoring of individuals infected with HR-HPV, as they will be motivated to be vaccinated and examined, thus contributing significantly to the downward trend in the CC-related deaths. .

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