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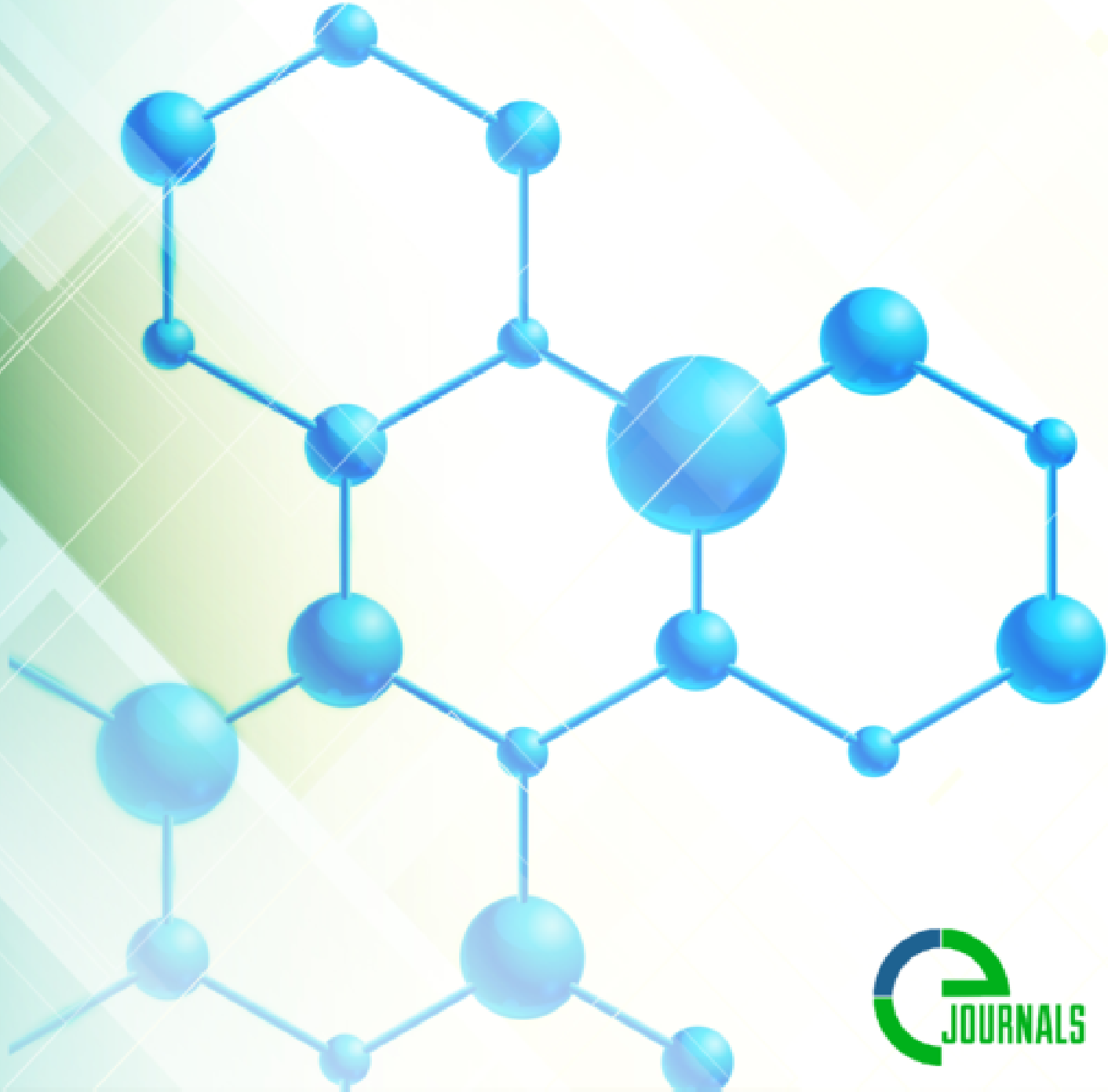

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MOLECULAR-GENETIC POLYMORPHISMS IN PATIENTS WITH CERVICAL INTRAEPITHELIAL NEOPLASIA

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Relevance.

The main causative factor in the development of cervical intraepithelial neoplasia in women is considered to be infection with the high-risk human papillomavirus (HPV). HPV infection and integration of its genome into the chromosomal apparatus of cervical epithelial cells serve as an early key mechanism in the progression of cervical tumor lesions.

Among the genes that influence the risk of developing cervical neoplasia, the attention of researchers is focused on studying variants of the TGFβ genes RAP1 (rs17687727), MKI67 (rs10764749) and BCL2 (rs2279115)

However, the relationship between overexpression of these genes and the risk of cervical intraepithelial neoplasia continues to be studied due to conflicting results.

Objective

To study the features of molecular genetic polymorphism in patients with cervical intraepithelial neoplasia infected with the human papillomavirus.

Material and methods of research.

The main group consisted of 100 patients with CIN II and cervical cancer. Of these, there were 40 (40%) with CIN II and HPV "-", 46 (46%) with CIN II and HPV "+", and 14 (14%) with cervical cancer. The control group consisted of 92 women without cervical pathology. The characteristics of the polymorphic genes TGFBRAP1 (rs17687727), MKI67 (rs10764749) and BCL2 (rs2279115) were studied using standard allele-specific PCR. For a variational assessment of the frequency of genotypes of the studied gene polymorphisms, we analyzed the correspondence of the expected (He) and observed (Ho) frequencies of their distribution in groups of women with cervical intraepithelial neoplasia (CIN) of the cervix and comparative controls of healthy women, in accordance with the Hardy equilibrium Weinberg (RHV, $p>0.05$).

Research results

Analyzing the differences between the distribution of He and Ho frequencies of genotypes G/C, G/A and A/A according to the genetic marker TGFβ RAP1 (rs17687727) taking into account the exact criterion coefficient ($\chi 2$) and reliability (P), their statistically insignificant nature was established as in the main group women with CIN 2 ($\chi 2=0.69$; $P=0.385$) and in the healthy group ($\chi 2=0.69$; $P=0.387$).

Based on the structural analysis of the TGFβ RAP1 gene (rs17687727), a number of features were identified between the groups of examined patients and healthy ones. In the main group with cervical intraepithelial neoplasia, the main functionally favorable (G) and minor functionally unfavorable (A) alleles were identified in 60.0% and 40.0% of cases, while the main genotype G/G was detected in 38.0% of patients with CIN 2, and cases carriage of functionally unfavorable variants G/A and A/A were detected in 44.5% and 18.0% of women in this group, respectively.

Moreover, analyzing the structure of the TGFβ RAP1 gene (rs17687727) in the group of women with CIN 2, depending on the negative and positive results for HPV, in the group of women with HPV "-" CIN 2, carriage of the major G and minor A alleles was found in 66.3% and 33.7% cases, and the main G/G, heterozygous G/A and minor A/A genotype variants, respectively, in 45.0%, 42.5% and 12.5% of cases.

At the same time, in the group of CIN 2 women with HPV "+" result, the main G and minor A alleles were identified in 56.5% and 45.3% of cases, and the main G/G, heterozygous G/A and minor A/A genotype variants were identified in 26.6 %, 50.0% and 21.4% of cases, respectively.

Functional analysis of the TGFβ RAP1 gene (rs17687727) in the main group of patients with CIN 2 and healthy

Alleles and genotypes	Allele and genotype frequencies				χ^2	P	RR	95%CI	OR	95% CI
	Main		Control							
	n	%	n	%						
G	120	60.0	147	79.9	17.9	0.01	0.8	0.53-1.07	0.4	0.24-0.6
A	80	40.0	37	20.1	17.9	0.01	1.3	0.76-2.34	2.6	1.69-4.16
G/G	38	38.0	60	65.2	14.2	0.01	0.6	0.33-1.02	0.3	0.18-0.58
G/A	44	44.0	27	29.3	4.4	0.05	1.5	0.89-2.52	1.9	1.04-3.43
A/A	18	18.0	5	5.4	7.2	0.01	3.3	1.97-5.57	3.8	1.43-10.2

Moreover, among patients with CIN2, a statistically significant increase in the frequencies of heterozygous and mutant genotypes G/A was found in 1.9 ($\chi2$=4.4; P=0.05; OR=1.9; 95%CI: 1.04-3.43) and A/A in 3.8 ($\chi2$=7.2; P=0.01; OR=3.8; 95%CI: 1.43-10.2) times with a decrease in carriage of the main genotype G/G ($\chi2$=14.2; P=0.01; 95%CI: 0.18-0.58) compared with those in a healthy group.

The results of a comparative analysis of differences in the distribution of the TGFβ RAP1 gene (rs17687727) between patients with CIN 2 in the main group and healthy women showed high functional activity of the gene in relation to the risk of CIN 2 formation. In particular, the risk of the disease is statistically significantly increased among carriers of the unfavorable allele A in 2.6 times ($\chi2$=17.9; P=0.01), heterozygous G/A in 1.9 ($\chi2$=4.4; P=0.05) and mutant A/A genotypes in 3.8 ($\chi2$=7.2; P=0.01; OR=3.8; 95% CI: 1.43-10.2) times.

Analysis between groups of CIN 2 women with HPV "-" and healthy ones revealed the presence of statistically significant differences in the frequencies of the weakened allele A, the proportion of which among patients was 2.0 times higher ($\chi2$=5.6; P=0.03; OR=2.0; 95%CI: 1.13 -3.62), which was accompanied by a decrease in the frequencies of the protective main allele G ($\chi2$=5.6; P=0.03; 95%CI: 0.28-0.88) and genotype G/G ($\chi2$=4.7; P=0.05; 95%CI: 0.21-0.92) among the sick group. Differences in the proportions of genotypes G/A ($\chi2$=2.2; P=0.2; OR=1.8; 95%CI: 0.83-3.83) and A/A ($\chi2$=2.0; P=0.2; OR=2.5; 95%CI: 0.7 -8.82) were characterized by the presence of an unexpressed tendency towards a decrease in their frequencies in the group of patients in relation to healthy ones.

Thus, the differences in the distribution of the TGFβ RAP1 gene (rs17687727) in the group with CIN 2 HPV "-" compared to healthy people were statistically significant only in relation to the frequency of the weakened allele A, which indicated a significant increase in the risk of CIN2 with HPV "-" in carriage of this allele by 2.0 times ($\chi2$=5.6; P=0.03). Whereas, when carrying genotypes G/A and A/A, there was a tendency to increase the risk of CIN2 formation in HPV "-" women by 1.8 ($\chi2$=2.2; P=0.2) and 2.5 ($\chi2$=2.0; P=0.2) times, respectively .

In parallel, between the groups of CIN2 women with HPV "+" and healthy ones, there were statistically significant differences in the frequencies of the weakened allele A by 3.1 times ($\chi2$=16.7; P=0.01; OR=3.1; 95%CI: 1.79 - 5.23) and genotype A /A by 4.8 times ($\chi2$=8.4; P=0.01; OR=4.8; 95%CI: 1.67-14.01) exceeding their shares among patients. Along with this, a statistically significant decrease in the protective effect of the main G allele ($\chi2$=16.7; P=0.01; 95%CI: 0.19 - 0.56) and the G/G genotype ($\chi2$=11.5; P=0.01; 95%CI: 0.14 - 0.59) regarding the risk of disease. In terms of the frequency of the heterozygous genotype G/A, there was a tendency to increase its frequency among the sick group by 1.9 times ($\chi2$=2.7; P=0.1; OR=1.9; 95%CI: 0.89 - 3.85).

Thus, differences in the distribution of the TGFβ RAP1 gene (rs17687727) in the group with CIN 2 HPV "+" compared to healthy people showed a statistically significant increase in the frequencies of the weakened A allele and the A/A genotype, which was associated with an increased risk of CIN2 with HPV "+ "by 3.1 ($\chi2$=16.7; P=0.01) and 4.8 ($\chi2$=8.4; P=0.01) times due to a significant decrease in the protective effect of the main allele G ($\chi2$=16.7; P=0.01) and genotype G/G ($\chi2$= 11.5; P=0.01). At the same time, the presence of a tendency to increase the frequency of G/A heterozygotes also shows an increase in the risk of CIN 2 among its carriers with HPV "+" by 1.9 times ($\chi2$=2.7; P=0.1).

Analyzes conducted between groups of women with cervical cancer and healthy ones revealed the presence of an associative relationship between the risk of developing the disease and weakened allele A and genotype A/A, among carriers of which, the chance of developing cervical cancer was statistically significantly increased by 3.4 ($\chi2$ = 9.3; P=0.01; OR=3.4; 95%CI: 1.56-7.61) and 4.7 times ($\chi2$=4.5; P=0.05; OR=4.7; 95%CI: 1.12-20.15), respectively. An increase in the unfavorable effect of these markers was associated with a significant decrease in the protective effect of the main G allele ($\chi2$=9.3; P=0.01; 95%CI: 0.13-0.64) and the G/G genotype ($\chi2$=6.8; P=0.01; 95%CI: 0.07 - 0.68) regarding the risk of disease. Moreover, a tendency towards a 2.4-fold increase in the risk of the disease was also observed among carriers of the G/A heterozygote ($\chi2$=2.4; P=0.2; OR=2.4; 95%CI: 0.79 - 7.35).

Assessing the functional activity of the TGFβ RAP1 gene (rs17687727) in a group of women with cervical cancer compared with healthy ones, a significant associative relationship was revealed between an increased risk of the disease and carriage of weakened allele A in 3.4 ($\chi2$=9.3; P=0.01) and genotype A/A by 4.7 ($\chi2$=4.5; P=0.05) times, as well as a tendency to increase the risk of the disease among carriers of the G/A heterozygote by 2.4 times ($\chi2$=2.4; P=0.2).

Analyzing the correspondence of the distribution of actually observed (He) to theoretically expected (Ho) frequencies of genotypes of the MKI67 gene variant (rs10764749) in groups of healthy women ($\chi2$=1.0; P=0.305) and with cervical intraepithelial neoplasia ($\chi2$=2.51; P=0.112), no cases of deviation from the canonical distribution of genotypes were found, which indicated their correspondence at Hardy-Weinberg equilibrium (HW, p>0.05).

Analyzing the structural features of the MKI67 gene (rs10764749) to study the distribution of frequencies of its alleles and genotypes in the main group of patients with CIN 2, the percentage of the dominant main allele C corresponded to 70.5%, and the weakened variant T - 29.5%. Among patients with CIN 2, the main C/C genotype also occupied a dominant place and amounted to 53.0%, while unfavorable variants C/T and T/T were determined in 35.0% and 12.0% of the examined women in this group.

By studying the functional features of the TGFβ RAP1 gene (rs17687727) in the main group of women with CIN2 in comparison with those among healthy women, a statistically significant associative relationship was established between the risk of developing CIN2 and the studied genetic marker. In particular, this proved the presence of statistically significant differences between the frequencies of unfavorable allele A ($\chi2$=13.1; P=0.01; OR=2.5; 95%CI: 1.54-4.21) and genotypes C/T ($\chi2$=4.5; P=0.01; OR =1.9; 95%CI: 1.02-3.67) and T/T ($\chi2$=5.1; P=0.03; OR=4.0; 95%CI: 1.2-13.64), the frequencies of which were higher in CIN 2 at 2.5, 1.0 and 4.0 times respectively. Moreover, the increase in the activity of unfavorable loci was accompanied by a statistically significant decrease in the protective effect of the favorable allele C ($\chi2$=13.1; P=0.01; 95%CI: 0.24-0.65) and genotype C/C ($\chi2$=10.0; P=0.01; 95% CI: 0.21-0.69).

Functional analysis of the MKI67 gene (rs10764749) in the main group of patients with CIN 2 and healthy women

Alleles and genotypes	Allele and genotype frequencies				χ^2	P	RR	95%CI	OR	95% CI
	Main		Control							
	n	%	n	%						
C	141	70.5	158	85.9	13.1	0.01	0.8	0.57-1.18	0.4	0.24-0.65
T	59	29.5	26	14.1	13.1	0.01	1.2	0.63-2.36	2.5	1.54-4.21
C/C	53	53.0	69	75.0	10.0	0.01	0.7	0.42-1.18	0.4	0.21-0.69
C/T	35	35.0	20	21.7	4.1	0.05	1.6	0.96-2.71	1.9	1.02- 3.67
T/T	12	12.0	3	3.3	5.1	0.03	3.7	2.07-6.54	4.0	1.2- 13.64

Thus, functional analysis of the TGFβ RAP1 gene (rs17687727) between patients with CIN 2 in the main group and healthy women allowed us to establish a statistically significant relationship between this genetic marker and the risk of CIN2 formation. In particular, when carrying unfavorable allele T and genotypes C/T and T/T, the risk of CIN 2 is statistically significantly increased by 2.5 ($\chi2$=13.1; P=0.01), 1.9 ($\chi2$=4.1; P=0.05) and 4.0 ($\chi2$= 5.1; P=0.03) times, respectively.

Functional analysis between groups of CIN2 women with HPV "-" and healthy ones made it possible to determine a statistically significant association with an increase in the risk of developing the disease when carrying the minor T allele by 2.3 times ($\chi2$=6.7; P=0.01; OR=2.3; 95%CI: 1.22-4.34) and genotype T/T by 4.2 times ($\chi2$=4.2; P=0.05; OR=4.2; 95%CI: 1.06-16.92). At the same time, a significant decrease in the frequencies of the main allele C ($\chi2$=6.7; P=0.01; 95%CI: 0.23-0.82) and genotype C/C ($\chi2$=4.0; P=0.05; 95%CI: 0.21-0.98) proved a decrease in their protective actions regarding the risk of developing the disease. Differences in the frequencies of the G/A genotype ($\chi2$=2.2; P=0.2; OR=1.8; 95%CI: 0.83-3.83) between the studied groups did not differ at a significant level.

Established statistically significant differences in the frequencies of the minor T allele and the T/T genotype for the MKI67 gene (rs10764749) between women with CIN 2 HPV "-" and healthy women prove the presence of their associative relationship with an increase in the risk of the disease by 2.3 times ($\chi2$=6.7; P= 0.01) and 4.2 ($\chi2$=4.2; P=0.05) times, respectively.

In the groups of CIN2 women with HPV "+" and healthy ones, statistically significant differences were established in relation to all variants of alleles and genotypes. In particular, it was found that the risk of the disease is increased among carriers of unfavorable allele A by 3.1 times ($\chi2$=14.3; P=0.01; OR=3.1; 95%CI: 1.72 - 5.54), genotype C/T by 2.5 times ($\chi2$=5.8 ; P=0.03; OR=2.5; 95%CI: 1.19-5.4) and A/A 4.5 times ($\chi2$=4.8; P=0.05; OR=4.5; 95%CI: 1.17-16.9). It is also important to note that among women with CIN 2 HPV "+" there was a significant decrease in the protective effect of the main allele C ($\chi2$=14.3; P=0.01; 95%CI: 0.18-0.58) and genotype C/C ($\chi2$=11.6; P=0.01; 95%CI: 0.13-0.58) regarding the risk of disease.

Consequently, carriage of unfavorable alleles and genotypes of the MKI67 gene (rs10764749) is statistically significantly associated with an increased risk of CIN2 with HPV "+" by 3.1 ($\chi2$=14.3; P=0.01), 2.5 ($\chi2$=5.8; P=0.03) and 4.5 ($\chi2$ =4.8; P=0.05) times.

Comparative analyzes of the functional features of the MKI67 gene (rs10764749) between groups of women with cervical cancer and healthy women made it possible to establish the absence of an independent associative connection between the studied marker and the risk of developing the disease, which is proven by the presence of statistically insignificant differences in the distribution of allele frequencies (C - $\chi2$=1.0; P= 0.4; OR=0.6; 95%CI: 0.23 - 1.62 and T - $\chi2$=1.0; OR=1.7; 95%CI: 0.62 - 4.44) and genotypes (C/C - $\chi2$=0.7; P=0.4 ; OR=0.6; 95%CI: 0.18 - 1.96; =2.3; 95%CI: 0.23-22.25).

Comparing the differences in the distribution of the MKI67 gene (rs10764749) in the groups of women with CIN 2 HPV "-" and CIN 2 with HPV "+" in the distribution of allele frequencies (C - $\chi2$=0.8; P=0.4; OR=1.3; 95%CI: 0.7 - 2.57 and T - $\chi2$=0.8; P=0.4; OR=0.7; 95%CI: 0.39-1.43) and genotypes (C/C - $\chi2$=1.2; P=0.3; OR=1.6; 95%CI: 0.69 -3.78; C/T - $\chi2$=1.2; OR=0.6; 95%CI: 0.25-1.49) also no statistically significant values have been established.

At the same time, for the MKI67 gene (rs10764749) in groups of women with CIN 2 HPV "+" and cervical cancer, differences in allele frequencies (C - $\chi2$=1.5; P=0.3; OR=0.5; 95%CI: 0.2 - 1.45 and T - $\chi2$=1.5; P=0.3; OR=1.9; 95%CI: 0.69-5.02) and genotypes (C/C - $\chi2$=1.5; P=0.3; OR=0.5; 95%CI: 0.14-1.59 ; C/T - $\chi2$=0.4; OR=1.8; 95%CI: 0.48-6.39 and T/T - $\chi2$=0.6; OR=2.0; did not reach a statistically significant level.

Thus, the results of the analysis of the structural and functional features of the MKI67 gene (rs10764749), carried out in groups of women with CIN 2 and healthy ones, show the presence of a statistically significant role of the studied genetic marker in increasing the risk of cervical intraepithelial neoplasia.

Analysis of the correspondence between the canonical distribution of actually observed (He) genotypes of the BCL2 gene (rs2279115) to their theoretically expected (Ho) frequencies in a group of healthy women and with cervical intraepithelial neoplasia showed no deviation in Hardy-Weinberg equilibrium (HW, p>0.05). Compliance with RHV proved the presence of statistically insignificant differences between He and Ho frequencies of genotypes C/C, C/A and A/A for the studied marker in the healthy ($\chi2$=2.09; P=0.15) and the main groups ($\chi2$=3.55; P=0.06).

Studying the structural features of the BCL2 gene (rs2279115) in the main group with cervical intraepithelial neoplasia, it was found that the dominant allele variant was the C allele (56.0%), and among the genotypes, the C/A variant (40.0%). The proportion of the minor allele was 44.0%, while homozygous wild C/C and mutant A/A genotypes were identified in 36.0% and 24.0% of women in this group.

The results of the analysis carried out between the main group of women with CIN2 and healthy ones made it possible to establish an increase in the functional activity of the BCL2 gene (rs2279115) in relation to an increase in the risk of CIN 2. Proof of this was the observed statistically significant differences in the polymorphic loci of the gene, characterized by an increase in the frequency of unfavorable allele A by 3.6 times ($\chi2$ =30.2; P=0.01; OR=3.6; 95%CI: 2.28 - 5.68), genotypes C/A in 2.0 ($\chi2$=4.9; P=0.05; OR=2.0; 95%CI: 1.08 - 3.7) and A/ And by 5.5 ($\chi2$=12.9; P=0.01; OR=5.5; 95%CI: 2.17-13.93) times, which was simultaneously accompanied by a decrease in the frequency of the wild allele C ($\chi2$=30.2; P=0.01; 95%CI: 0.18 - 0.44) and genotype C/C ($\chi2$=21.6; P=0.01; 95%CI: 0.14 - 0.44) among patients with CIN 2 compared with the same in a healthy sample

Functional analysis of the BCL2 gene (rs2279115) in the main group of patients with CIN 2 and healthy women

Alleles and genotypes	Allele and genotype frequencies				χ^2	P	RR	95%CI	OR	95% CI
	Main		Control							
	n	%	n	%						
C	112	56.0	151	82.1	30.2	0.01	0.7	0.48- 0.97	0.3	0.18 - 0.44
A	88	44.0	33	17.9	30.2	0.01	1.5	0.8 - 2.69	3.6	2.28 - 5.68
C/C	36	36.0	64	69.6	21.6	0.01	0.5	0.29- 0.92	0.2	0.14 - 0.44
C/A	40	40.0	23	25.0	4.9	0.05	1.6	0.96- 2.68	2.0	1.08 - 3.7
A/A	24	24.0	5	5.4	12.9	0.01	4.4	2.79- 6.98	5.5	2.17-13.93

Consequently, assessing the degree of participation of the BCL2 polymorphic gene (rs2279115) in the risk of CIN 2 compared to healthy women, statistically significant differences in the distribution of the studied genetic marker were established. The results provide evidence that for the BCL2 gene (rs2279115), carriage of the unfavorable allele A, as well as genotypes C/A and A/A, significantly increases the risk of CIN 2 by 3.6 ($\chi2$=30.2; P=0.01), 2.0 ($\chi2$=4.9; P=0.05) and 5.5 ($\chi2$=12.9; P=0.01) times.

The study of the structural features of the BCL2 gene (rs2279115) between groups of CIN2 women with HPV "-" and healthy ones also made it possible to observe differences in the distribution of the gene that were statistically significant. Thus, if among a group of patients the frequencies of unfavorable allele A, genotypes C/A and A/A increased significantly by 3.2 times ($\chi2$=16.2; P=0.01; OR=3.2; 95%CI: 1.82 - 5.68), genotypes C/A at 2.7 ($\chi2$=6.5; P=0.03; OR=2.7; 95%CI: 1.26 - 5.85) and A/A at 3.7 ($\chi2$=4.9; P=0.05; OR=3.7; 95%CI: 1.16 - 11.72) times, then the activity of the main allele C ($\chi2$=16.2; P=0.01; 95%CI: 0.18 - 0.55) and genotype C/C ($\chi2$=13.8; P=0.05; 95%CI: 0.11 - 0.51) was significantly different from their significant decrease compared to their values in the healthy group.

Analysis of the structural features of the BCL2 gene (rs2279115) between groups of CIN2 women with HPV "+" and healthy ones also showed the presence of statistically significant differences between the distribution of unfavorable allele A and genotype A/A, the frequencies of which among patients were 4.0 times higher ($\chi2$=25.5; P=0.01; OR=4.0; 95%CI: 2.34 - 6.89) and 7.6 ($\chi2$=16.1; P=0.01; OR=7.6; 95%CI: 2.83-20.5) times, as well as between the frequencies of the main allele C ($\chi2$ =25.5; P=0.01; 95%CI: 0.15 – 0.43) and genotype C/C ($\chi2$=13.5; P=0.01; 95%CI: 0.12 – 0.53), the protective activity of which, on the contrary, decreased among patients. Meanwhile, despite the more frequent occurrence of heterozygote C/A among patients by 1.5 times ($\chi2$=0.9; P=0.4; OR=1.5; 95%CI: 0.67 – 3.15), there were no statistically significant differences in its distribution between groups.

Thus, according to the BCL2 gene (rs2279115), the risk of developing CIN 2 with HPV "+" is significantly increased among carriers of the unfavorable allele A by 4.0 ($\chi2$=25.5; P=0.01) and genotype A/A by 7.6 ($\chi2$=7.6; P= 0.01) times, which makes it possible to classify the studied gene as a prognostic marker for the development of this pathology.

The results of the structural and functional features of the BCL2 gene (rs2279115) obtained in a comparative analysis between groups of women with cervical cancer and healthy ones showed a significant relationship between the increased risk of cervical cancer among carriers of the mutant allele A in 3.4 ($\chi2$=9.0; P=0.01; OR= 3.4; 95%CI: 1.54 - 7.67) and genotype A/A by 4.7 ($\chi2$=4.5; P=0.05; OR=4.7; 95%CI: 1.12-20.15) times, observed in connection with a decrease in the protective effect in these women wild variants of the C allele ($\chi2$=9.0; P=0.01; 95%CI: 0.13 - 0.65) and genotype C/C ($\chi2$=6.1; P=0.03; 95%CI: 0.08 - 0.74). Along with this, it was found that heterozygous carriage of C/A was accompanied by a tendency to increase the risk of the disease by 2.3 times ($\chi2$=1.9; P=0.2; OR=2.3; 95%CI: 0.72 - 7.02).

Assessing the functional activity of the BCL2 gene (rs2279115) in a group of women with cervical cancer compared with healthy ones, a significant associative relationship was revealed between an increased risk of the disease and the carriage of a weakened allele A in 3.4 ($\chi2$ = 9.3; P = 0.01) and genotype A/A in 4.7 ($\chi2$=4.5; P=0.05) times, as well as a tendency to increase the risk of the disease among carriers of the G/A heterozygote by 2.4 times ($\chi2$=2.4; P=0.2).

The results of the structural and functional analysis of the BCL2 gene (rs2279115) indicate its important contribution to the mechanisms of implementation of CIN 2. The risk of the disease is associated with the carriage of unfavorable loci of this gene: allele A, genotypes C/A and A/A are statistically significantly associated with an increase of 3.6 times ($\chi2$=30.2; P=0.01), 2.0 ($\chi2$=4.9; P=0.05) and 5.5 ($\chi2$=12.9; P=0.01) times the risk of developing CIN 2.

Along with this, it was found that unfavorable allele A, as well as genotypes C/A and A/A, are independently significantly associated with an increase in the risk of CIN 2 with HPV "-" by 3.2 ($\chi2$=16.2; P=0.01), 2.7 ($\chi2$= 6.5; P=0.03) and 3.7 ($\chi2$=4.9; P=0.05) times, respectively, and with HPV "+" allele A and genotype A/A increase the risk of developing CIN 2 by 4.0 ($\chi2$=25.5; P=0.01) and 7.6 ($\chi2$=7.6; P=0.01) times. Moreover, a significant associative relationship was identified with an increase in the risk of cervical cancer with the carriage of weakened allele A by 3.4 ($\chi2$=9.3; P=0.01) and genotype A/A by 4.7 ($\chi2$=4.5; P=0.05) times.

Conclusion

Thus, concluding the discussion of the results of a study on the study of the structural and functional features of the TGFβ RAP1 (rs17687727), MKI67 (rs10764749) and BCL2 (rs2279115) genes in cervical intraepithelial neoplasia, the presence of a significant associative connection between them has been proven, and therefore the TGFβ RAP1 (rs17687727) markers, MKI67 (rs10764749) and BCL2 (rs2279115) can be considered as prognostic genetic predictors of a high risk of developing CIN 2, and TGFβ RAP1 (rs17687727) and BCL2 (rs2279115) - cervical cancer.

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