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ORIGINAL ARTICLE

Geotropism and Oncogenic Potential of HPV Infections in Cohort Study Populations in Vojvodina, North Region of Serbia

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Abstract

Background/Aim: Geotropism of the human papillomavirus (HPV) represents the heterogeneous distribution of different genotypes worldwide. Aim of this study was to evaluate the prevalence of the HPV infection in women from Vojvodina, Serbia, according to cytological status and pathological changes of cervix - dysplasia and cancer.

Methods: The research was conducted as a retrospective study at the Oncology Institute of Vojvodina and the Institute of Public Health of Vojvodina (IPHV). Data from the medical records of female patients treated for cervical intraepithelial neoplasia or cervical cancer at the Department of Gynaecology, Clinic for Surgical Oncology, Oncology Institute of Vojvodina in Sremska Kamenica in the period from 2016 to 2021 were used, as well as the laboratory findings of the IPHV for a group of patients with normal cytological results of the Papanikolau (PAPA) smear.

Results: A total of 731 women, from 20 to 82 years of age, with different cytological results were enrolled. 567 samples were classified as NILM, while 164 samples belong to a group of abnormal histopathology (LSIL/HSIL/cervical cancer). The HPV genotyping assay was performed using the EUROArray HPV test to detect 30 HPV genotypes. In the overall number with normal cytological findings, HPV infection was verified in 242 (42.7 %) patients, of which 135 (55.8 %) were verified with high risk HPV, while 76 (31.4 %) were verified with a mixed group of HPV (Low risk/High risk HPV). Most prevalent genotypes were HPV 16, 31, 53, 51 and 18 in NILM cytological status. In the samples with the abnormal histopathology, the most prevalent genotypes were HPV 16, 33, 31 and 56, while 18 and 39 were equally verified. Genotype 16 was the most prevalent in the examined sample, with a higher prevalence in higher-grade histopathological findings: 18.8 % in LSIL, 31.9 % in HSIL and 75.0 % in cervical cancer samples. Infection with multiple associated genotypes of HPV was not correlated with histopathology. By comparing histopathological diagnosis and age, older patients had higher-grade lesions.

Conclusion: Based on the estimated oncogenic potential of HPV genotypes as well as their prevalence in presented sample, it can be concluded that the nine-valent HPV vaccine for genotypes 6, 11, 16, 18, 31, 33, 45, 52 and 58 would have the potential to prevent HPV infection and the incidence of precancerous lesions and cervical cancer in about 85 % of women. Observing trends in the prevalence of HPV, especially HR HPV genotypes, can be important in the further strategy of applying secondary and primary prevention, as well as the application of HPV detection as part of co-testing or considering the introduction of HPV testing in the initial screening program.

Key words: HPV infections; Geotropism; Precancerous lesions; Prevention.

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Introduction

Geotropism of the human papillomavirus (HPV) represents the heterogeneous distribution of different genotypes worldwide. The aetiology of intraepithelial lesions and carcinoma of the cervix is, in most cases, of an infectious nature and the hypothesis about the role of the human papillomavirus in the pathogenesis of these lesions is well known.[1] HPV infection is the most common sexually transmitted disease today, the transmission of which requires contact with the genital skin, mucous membrane or bodily fluids of the partner.[2] The highest prevalence of this infection was observed in women in their early twenties. Spontaneous elimination of the virus within the first two years occurs in 90 % of women under the age of 30, while the remaining 10 % have the possibility of developing condyloma, dysplasia and even invasive cervical cancer, depending on the virus genotype.[1] The infection develops very quickly after sexual intercourse with a carrier of the HPV, but the progression of the infection to cervical intraepithelial neoplasia (CIN) and cancer takes years. Genital HPV infection is multifocal, often involving several organs of the lower reproductive tract. Any neoplasia associated with HPV infection increases the risk of neoplasia in other places, such as the vulva, vagina and anal region.[2] According to current estimates in Serbia, 1327 women get cervical cancer every year and 551 die from cervical cancer. Cervical cancer is the 4th most common cancer among women in Serbia and the second most common cancer among women between the ages of 15 and 44.[3, 4] Modern approaches to comprehensive screening and primary prevention of cervical cancer with the prophylactic HPV vaccine led to a global call by the World Health Organization (WHO) to initiate the idea of eradicating this disease by 2030.[5] The aim of this study was to examine the prevalence and distribution of different HPV genotypes in a cohort of female patients with normal cytological findings, as well as the oncogenic potential of HPV infection genotypes in a group of patients with histopathologically verified dysplasia and cervical cancer in Vojvodina, the northern region of Serbia.

Methods

The research was conducted as a retrospective study at the Oncology Institute of Vojvodina (IOV) and the Institute of Public Health of Vojvodina (IPHV). It used data from the medical records of female patients treated for cervical intraepithelial neoplasia or cervical cancer at the Department of Gynaecology, Clinic for Surgical Oncology, Oncology Institute of Vojvodina in Sremska Kamenica in the period from 2016 to 2021, as well as the laboratory findings of the IPHV for a group of patients with normal cytological results of the Papanikolau (PAPA) smear. The source of the material was the archival material of the IOV and IPHV obtained from the medical documentation on the histopathological material from operation and cytological findings, the identified genotypes of the HPV and the age of the patients. The use of medical documentation was approved by the competent Ethics Committee.

Inclusion criteria:
- group of female patients with regular cytological PAPA test and verified HPV typing of cervical smear;
- female patients older than 18 years with histopathological verified cervical intraepithelial neoplasia or cervical cancer;
- female patients with cervical smear HPV typing.

Non-inclusion criteria:
- female patients with histopathologically verified cervical intraepithelial neoplasia or cervical cancer in whom HPV typing was not performed;
- female patients with other malignant diseases or immunocompromised diseases;
- female patients with recurrent cervical dysplasia;
- pregnant women.

By analysing the documentation of IOV and IPHV and applying the criteria for sample selection, 164 patients with pathological changes on the cervix and 567 patients with a regular cytological smear were included in further data processing. Cytology findings that were collected and included in the analysis were obtained by conventional PAPA smear.

The histopathological data that were collected resulted from the analysis of the tissue obtained by biopsy of the cervix under the control of the colposcope from the fields that showed the highest degree of abnormality or by one of the excision methods on the cervix. The material obtained in this way was placed in 4 % formalin and further sent for standard processing in the pathological histological laboratory.

Genotyping of HPV DNA in cervical swab samples for all group was performed using a qualitative amplification and hybridisation test. Viral DNA extraction was performed using the commercial SaMag STD DNA Extraction Kit, using the SaMag-12 Automatic Nucleic Acids Extraction System (*Sacace Biotechnologies*, Como, Italy) in accordance with the manufacturer's instructions. In each EUROArray HPV test 5 µL of the extracted DNA was used. If amplification was not performed on the same day as extraction, the processed samples were stored at 2–8 °C for a maximum of five days or frozen at – 80 °C for longer periods. The HPV genotyping assay was performed using the EUROArray HPV test (*EUROIMMUN*, Luebeck, Germany) according to the manufacturer's instructions. The test uses panel of specific primers and probes, to detect 30 HPV genotypes in single reaction, among them, 18 high-risk HPVs (HR HPV) genotypes (16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73, 82) and 12 low-risk HPVs (LR HPVs) (6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81, 89). Amplification and hybridisation steps allowed identification of both the target viral genetic material (E6/E7 genes) and the human *HSP90* gene used as endogenous controls for valid sample extraction and amplification.

The obtained results of genotyping were considered valid if the test results of all controls were satisfactory according to the manufacturer's instructions.

Statistical analyses

Qualitative data were described using frequencies and percentages. Quantitative data were described using range (minimum and maximum), mean and standard deviation. Differences in mean values of continuous variables were analysed by Student's t-test or ANOVA test for more than two samples and the difference between non-continuous variables was analysed by χ^2 test, using the software package JASP (University of Amsterdam, Amsterdam, the Netherlands). The p-value < 0.05 was used as the cut-off for statistical significance.

Results

The study included 567 patients with a normal cytological smear according to Bethesda classification (negative for intraepithelial lesion or malignancy, NILM) in which the presence of HPV was examined (Table 1).

In the overall number the presence of HPV infection was verified in 242 (42.7 %) female patients, of which 135 (55.8 %) were verified with high-risk (HR) HPV, while 76 (31.4 %) were verified with a mixed group of HPV (low-risk (LR)/HR HPV).

Based on gene typing in the mentioned group, the distribution of HPV genotypes is shown in Figure 1.

Based on the results obtained in the group of women with the negative cytological results, NILM, HPV genotype 16 (39.6 %) was the most represented, followed by genotype 31 (20.0 %), 51 (10.0 %) of highly oncogenic, while genotype 18 ranks fourth in the high-risk group with 5.2 %. Of the HPV genotypes with low oncogenic potency, HPV genotype 6 was verified in 96.7 %.

In patients with histopathological verification, a total of 164 patients were treated. The average age of the patients was 40.5 ± 12.5 years. The oldest patient was 82 and the youngest was 20 (Table 2).

A total of 49 (29.9 %) patients with low-grade squamous intraepithelial lesion (LSIL), 90 (54.9 %) with high grade squamous intraepithelial lesion (HSIL) and 25 (15.3 %) with cervical cancer were included in the analysis.

In patients with histopathological changes on the cervix (LSIL/HSIL/cancer), HPV infection was verified in 125 (76.2 %) patients, while in 39 (23.8 %), HPV was negative (Figure 2).

Table 1: Distribution of human papillomavirus (HPV) infection with normal cytological findings

Cytology	HPV negative	HPV positive	HR HPV positive	LR HPV positive	HR+LR HPV positive	Total
NILM	325 (57.3 %)	242 (42.7 %)	135 (55.8 %)	31 (12.8 %)	76 (31.4 %)	567 (100.0%)

HR HPV – High-risk HPV; LR HPV – Low-risk HPV; NILM – Negative for intraepithelial lesion or malignancy.

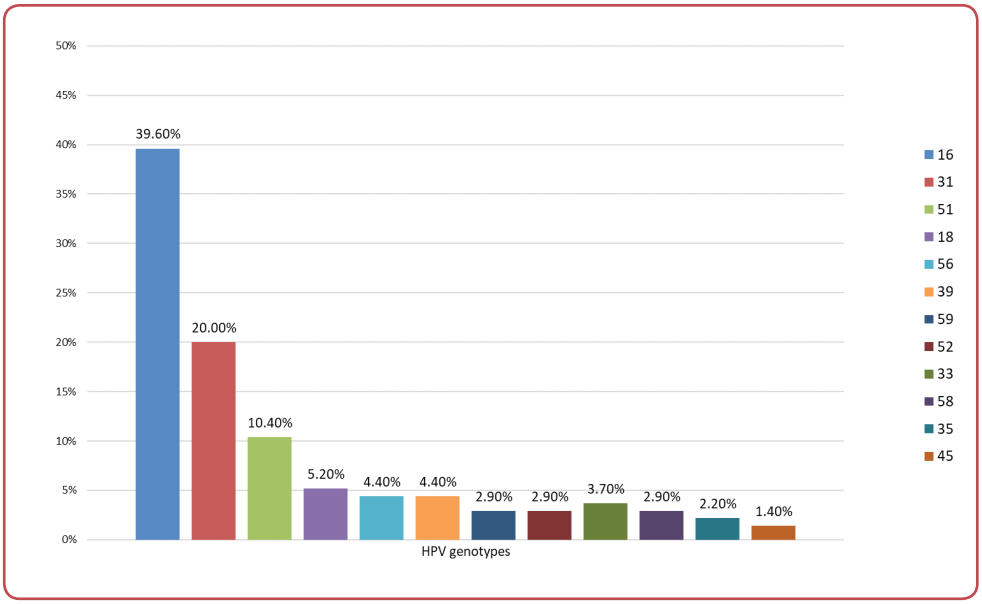

Figure 1: Distribution of human papillomavirus (HPV) genotypes in female patients with NILM cytological findings

IARC – International Agency for Research on Cancer (HPV classification); HR HPV – high risk human papillomavirus (genotype: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59); LR HPV – low risk human papillomavirus (genotype: 6, 11); NILM – Negative for intraepithelial lesion or malignancy;

Table 2: General characteristics of the examined group

Histopathology	N	%
LSIL	49	29.87
HSIL	90	54.87
Cervical cancer	25	15.26
Overall	164	100.00
Age: mean ± SD (range)	40.5 ± 12.5 (20 – 82 years)	

LSIL – Low-grade squamous intraepithelial lesion; HSIL -High grade squamous intraepithelial lesion;

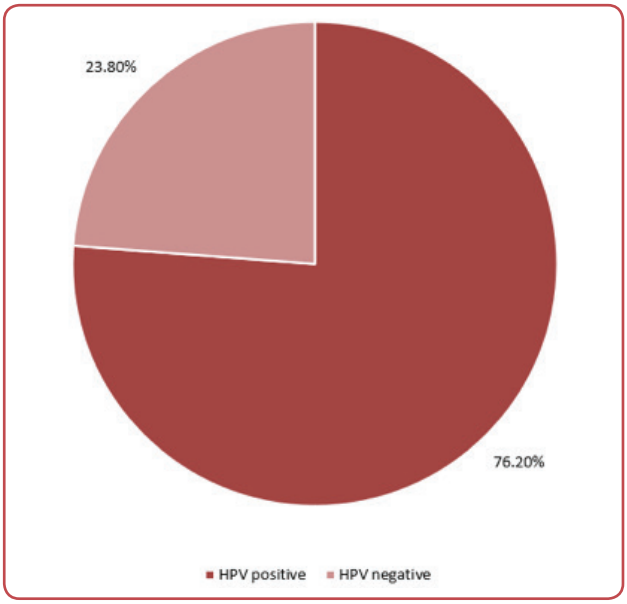

Figure 2: Prevalence of human papillomavirus (HPV) infection in LSIL/HSIL/cervical cancer samples

LSIL – Low-grade squamous intraepithelial lesion; HSIL -High grade squamous intraepithelial lesion;

In patients with LSIL changes, 32 (65.3 %) were positive and 17 (34.7 %) were negative for HPV infection. In patients with HSIL, 69 (76.7 %) were positive and 21 (23.3 %) were negative for HPV infection. In patients with cervical cancer, a total of 24 (96.0 %) were positive and (4.0 %) were negative for HPV infection (Figure 3).

In patients with LSIL/HSIL/cancer of the cervix concerning the distribution of HPV genotypes, the most represented verified HPV was genotype 16 (36.8 %), 33 (7.2 %), 31 (5.6 %) and genotype 56 (4.8 %). Multiple HPV infection with several genotypes was verified in 29.6 % patients (Figure 4).

Observing of HPV genotypes concerning the histopathological findings in patients with LSIL changes, the majority of patients with multiple HPV infections were verified 40.6 %, HPV genotype 16 was confirmed in 18.8 %, 31 in 9.45 % and genotypes 39 and 51 in 6.2 %, respectively. In female patients with HSIL changes, multiple HPV infections and HPV genotype 16 were equally verified; 31.9 % of the other genotypes, HPV genotype 33 prevailed; 11.6 % and genotype 56; 7.2 %. In patients with cervical cancer, HPV genotype 16 was the most prevalent (75.0 %), while the next was genotype 18 (8.3 %) and genotypes 45 and 35 (4.2 %). Multiple HPV infection was present in 8.3 % patients with cervical cancer (Table 3).

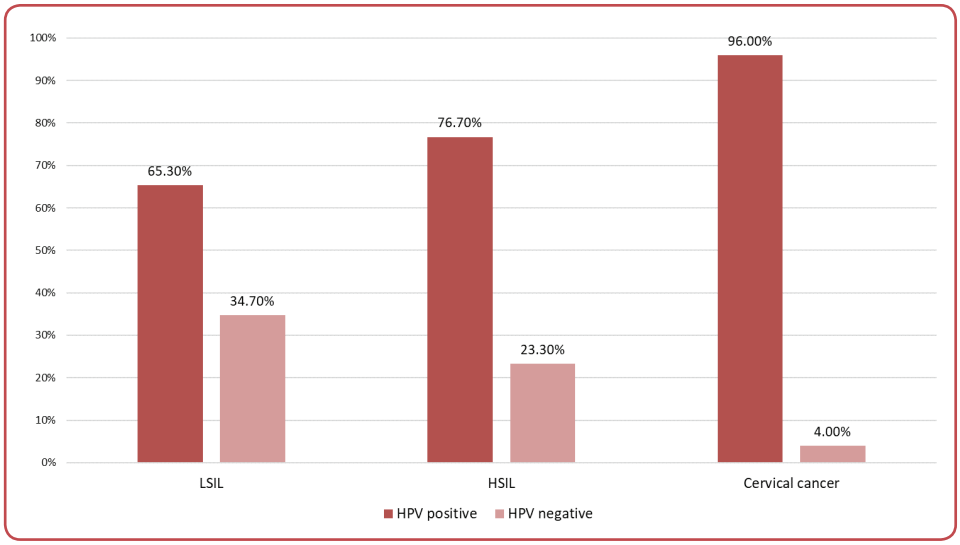

Figure 3: Prevalence of human papillomavirus (HPV) infection obtained by cytological swabs in histopathology confirmed diagnosis (LSIL/HSIL/cancer) of the cervix

LSIL – Low-grade squamous intraepithelial lesion; HSIL -High grade squamous intraepithelial lesion;

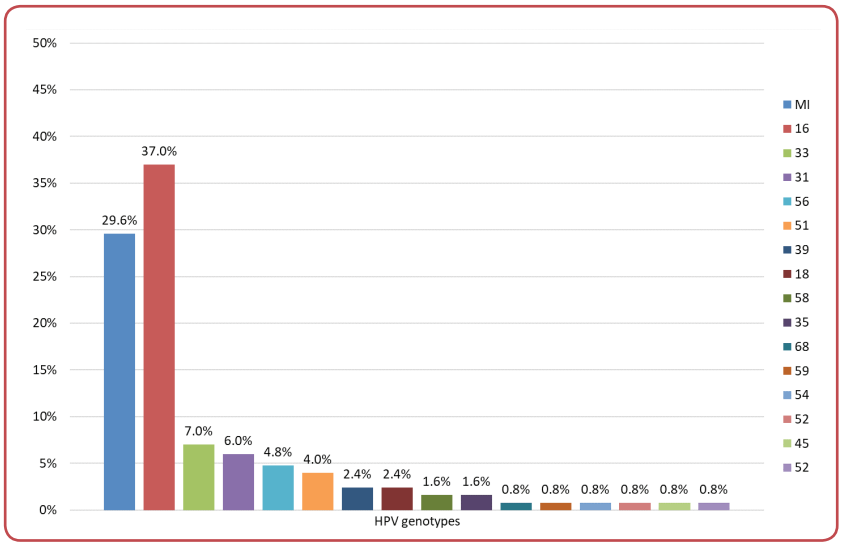

Figure 4: Prevalence of human papillomavirus (HPV) infection obtained by cytological swabs in histopathology confirmed diagnosis (LSIL/HSIL/cancer) of the cervix

LSIL – Low-grade squamous intraepithelial lesion; HSIL - High grade squamous intraepithelial lesion; MI – multiple infections; IARC – International Agency for Research on Cancer (HPV classification): HR HPV – high risk human papillomavirus (genotype: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59); LR HPV – low risk human papillomavirus (genotype: 6, 11);

Using the χ^2 test, a statistically significant difference (χ^2 = 18.024, df = 2; p < 0.001) was established in the prevalence of HPV genotype 16 between patients with histopathological findings of LSIL, HSIL and cancer. This highly oncogenic genotype of the virus is significantly more often present in histopathological findings of a higher degree, that is, in HSIL and cervical cancer. Using the same methods of statistical processing, no statistically significant difference was found in the prevalence of multiple associated genotypes of HPV between patients with histopathological findings of LSIL, HSIL and cancer (χ^2 = 4.371, df = 2; p = 0.112). Data processing and the Student's t-test did not establish a statistically significant difference (p = 0.914) between years of life and the presence of highly oncogenic HPV 16. Using the same methods, it was determined that there was a statistically significant difference (p < 0.001) in the presence of multiple associated genotypes of HPV in different age groups of patients. In younger female patients, more combined genotypes of the HPV were isolated more often than in older patients (Figure 5).

Table 3: Prevalence of human papillomavirus (HPV) genotypes obtained by cytological swabs in histopathology confirmed (LSIL/HSIL/cancer) of the cervix

HPV genotype	Pathological cervical cytology					
	LSIL		HSIL		Cervical cancer	
	N	%	N	%	N	%
Multiple infection	13	40.62	22	31.88	2	8.33
16	6	18.75	22	31.88	18	75.00
31	3	9.35	4	5.80	0	0.00
39	2	6.25	1	1.45	0	0.00
51	2	6.25	3	4.35	0	0.00
18	1	3.13	0	0.00	2	8.33
33	1	3.13	8	11.59	0	0.00
56	1	3.13	5	7.25	0	0.00
58	1	3.13	1	1.45	0	0.00
59	1	3.13	0	0.00	0	0.00
68	1	3.13	0	0.00	0	0.00
35	0	0.00	1	1.45	1	4.17
45	0	0.00	0	0.00	1	4.17
52	0	0.00	1	1.45	0	0.00
54	0	0.00	1	1.45	0	0.00
Total	**32**	**100.00**	**69**	**100.00**	**24**	**100.00**

LSIL – Low-grade squamous intraepithelial lesion; HSIL -High grade squamous intraepithelial lesion;

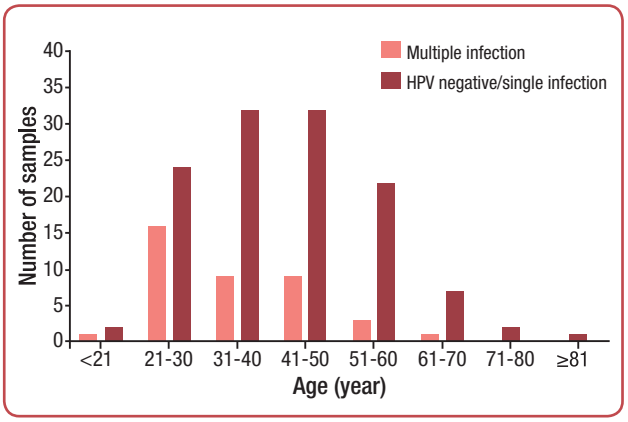

Figure 5: Frequency of multiple human papillomavirus (HPV) infection according to age

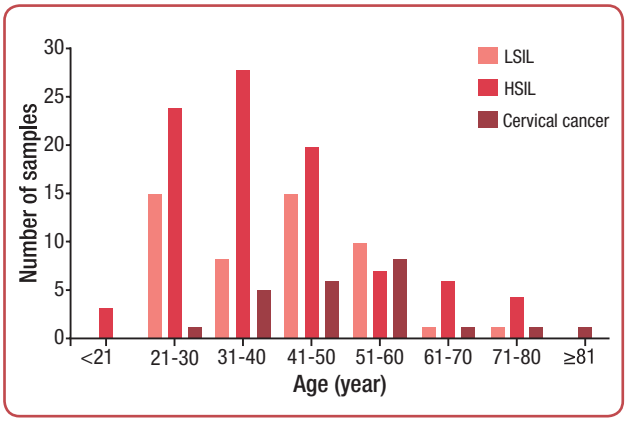

Figure 6: Correlation of age and histopathological findings

LSIL – Low-grade squamous intraepithelial lesion; HSIL -High grade squamous intraepithelial lesion;

Using the ANOVA test, statistical significance was confirmed in the existence of a significant correlation ($p < 0.001$) between age and histopathological findings. Older patients had lesions of a higher degree (Figure 6).

Discussion

Geotropism of HPV represents the heterogeneous distribution of different genotypes worldwide. Positive for HPV in patients with normal cervical findings range from 12-49 %.[6, 7] Worldwide, HPV 16 is the most common genotype of HR HPV found in 60 % of cervical cancer cases. In comparison, HPV genotype 18 is found in about 10 %, genotypes 45 and 31 in 4 % each and genotypes 33, 52 and 58 each in another 2 %.[10] HPV 16 and 18 genotypes are also associated with about 25 % of LSIL and 50 % to 60 % of HSIL.[6] The HPV genotype 16 is represented by 32.3 % in South Asia, 28.9 % in Southern Europe, 24.4 % in Western Europe, 24.3 % in North America and 12 % in Africa.[8] However, a low prevalence was recorded in the Middle East or in Qatar, where an HPV prevalence of 6.1 % was presented in the general population with normal or pathological cytology, especially HPV genotype 81.[9] Considering the presence of certain genotypes of HPV in the region of Vojvodina, the HPV genotype 16 (39.6 %) predominates in ex-

amined group with normal cytological findings, followed by genotype 31 (20.0 %), 51 (10.4 %) of the highly oncogenic ones, while genotype 18 was on fourth place in the high-risk group with 5.2 %. HPV 6 as the low-risk was detected in 96.7 %. It is important to note the presence of HPV genotype 56 (4.4 %) were seen, which warrants further monitoring of this type in terms of their oncogenetic since it is not among vaccine genotypes. In the study of Kaliterna et al, in Split and Dalmatia, Republic of Croatia, out of the total number of women tested, 200 (35 %) were positive for HR HPV. Polymerase chain reaction (PCR)-based assays were used for HR HPV genotyping in positive specimens. The following frequency was observed: HPV 16 in 10.0 %, HPV 18 in 6.1 %, HPV 31 in 2.6 %, HPV 33 in 1.9 %, HPV 52 in 1.4 %, HPV 59 in 0.7 %, HPV 45 in 0.4 % of samples.[10] In the study by Milutin-Gasperov et al, it was determined that the most frequent genotype was HPV 16, with a frequency of 15.9 %, including single and multiple infections. It was followed by HPV genotypes: 31, 6/11, 33, 18, 52, 45 and 58 with 8.7 %, 7.1 %, 4.5 %, 3.8 %, 2.3 %, 1.8 % and 1.1 %, respectively.[11]

In monitoring the oncopotentiality of HPV genotypes, this study included 164 female patients, average age 40.5 ± 12.5 years, with a histopathologically verified diagnosis (dysplasia or cervical cancer). Observing the prevalence of high-risk genotypes of the HPV in certain groups of histopathological findings, it can be concluded that genotype 16 was the most prevalent in the examined sample, with a higher prevalence in higher-grade pathohistological findings. Namely, of all patients with LSIL, this high-risk genotype was identified in 18.8 %, HSIL in 31.9 % and in cervical cancer, it was detected in even 75.0 %. The results match the literature data. It is characteristic that in total cohort, in contrast to literature data, HPV genotype 18 was not so represented, only 2.4 %. In the de Sanjos study, HPV genotypes 16 and 18 were present in 71 % of cancers.[12, 13] Martins et al obtained similar results in their study conducted in São Paulo between 2009 and 2011, analysing the data of 665 female patients. In their examined sample, HPV 16 was also the most prevalent high-risk genotype, with a prevalence of 38.1 % among HSIL findings and 66.7 % among invasive cervical cancer findings.[14] A meta-analysis of 85 studies including 10,058 patients with cervical cancer, also confirmed the predominant prevalence of HPV genotype 16 in squamous histological genotypes of cervical cancer ranging from 46 % in Asia to 63 % in North America. Another common genotype was HPV genotype 18, with about 10 % – 14 % in squamous cell carcinoma.[7] In presented cohort, HPV 16 and 18 were also prevalent in the group with cervical cancer, 75.0 % and 8.3 %, respectively. It should be noted that the subgroup with cervical cancer in this study was too small to determine the presence of other genotypes of viruses. Still, HPV 16 is predominant in the Vojvodina region as well. Based on the before mentioned meta-analysis, which included 133 studies and a total of 14,595 patients, the combination of HPV 16 and 18 was verified in 74 % – 77 % of squamous cell carcinomas in Europe and North America and 65 % – 70 % in Africa, Asia and South/Central America.[2, 7] Using the same methods of statistical processing (χ^2 test), no statistically significant difference was found in the prevalence of multiple associated genotypes of HPV between patients with pathohistological findings of LSIL, HSIL and cancer ($p = 0.112$). Schmitt et al also concluded that infection with multiple virus genotypes does not have a higher prevalence among high-grade cytological findings than low-grade ones.[15] Also, infections with multiple genotypes of viruses are more prevalent in the younger population and milder lesions, 40.62 % in LSIL vs 8.33 in carcinoma in presented material. Similar results were shown in the study by Milosevic et al, where the prevalence of multiple HPV infection in younger patients under the age of 35 was 43 % and NILM cytological findings were 30 % vs 13.9 % in HSIL-a cytological findings.[16]

The above data support the hypothesis that these are more transient infections that resolve spontaneously in most cases and that the oncogenesis initiates mainly one virus genotype. In the examined sample, a statistically significant difference between the age and the presence of several associated genotypes of the HPV was determined. In younger female patients, more combined genotypes of the HPV were isolated more often than in older patients. In their work, De Vuyst et al interpreted the results of the eighteen most extensive studies on the prevalence of the HPV in the countries of Northern and Western Europe. Each study showed the highest prevalence of high-risk genotypes among young women in the age group between 25 and 30 years, with a decline in the frequency of this infection after that.[17] Presented results showed no significant correlation between HPV 16 prevalence and age. By comparing patients' histopathological diagnosis and age,

it was observed that older female patients had higher-grade lesions. Kamineni et al came to the same results. They observed that the largest number of female patients with invasive cervical cancer were in the over 65 age category.[18] Observing the representation of HPV genotypes in the examined population of Vojvodina with regular cytological findings, the predominant genotypes of high-risk genotypes were genotypes 16 (27.3 %), 31 (16.5 %), 51 (11.2 %), genotype 53 (11.6 %) and only in fifth place was HPV genotype 18 (8.3 %). Concerning the oncogenic potential represented in the examined group with pathological changes on the cervix in Vojvodina, the prevalence of HPV genotype 16 prevails in HSIL changes and cancer. The obtained results correspond to literature data from several regions.[7, 15, 19, 20] Although the distribution of other genotypes is similar to other study, observing the relationships of geotropism and oncopotential in precancerous lesions in the examined cohort, it should be emphasised that the prevalence of HPV genotypes 31 (16.5 %) is higher in the population with regular findings, while in HSIL changes genotype 33 and 56 prevail, 11.6 % and 7.25 %, respectively. The obtained results contribute to understanding the transition of the HPV, but also the oncogenic potential of specific genotypes that are not included in the prophylactic vaccine, such as HPV genotype 56, which was verified in HSIL lesions (7.25 %) in this study and is similar to its prevalence in a healthy population.

In presented cohort, in patients with pathological changes on the cervix (LSIL/HSIL/cervical cancer), HPV infection was not verified by the available method in 39 (21.78 %) patients and HPV negativity decreased with the severity of the lesion, LSIL (34.69 %), HSIL (23.33 %) and in cervical cancer (4.00 %).

According to worldwide data, it is estimated that 5.5 % – 11 % of cervical cancers are HPV negative.[21-23] A decrease in HPV negative cases was observed in a meta-analysis of 243 studies that included 30,848 female patients with invasive cancer. The incidence of HPV positive cases ranged from 1990–1999, 2000–2005 and 2006–2010: 85.9 %, 87.9 % and 92.9 %, respectively. This trend is explained by better and more sensitive methods of detecting HPV infection and better classification of non-cervical cancers.[24] The cause of this group can be seen through the prism of false negative results and inadequate cancer classification.[25] Observing the histological genotype, real negative HPV cancers are often adenocarcinomas of unclear aetiology. For cervical adenocarcinoma, the HPV negative finding ranges from 15 % – 38 %.[13, 24, 26] Petry et al confirmed that about 68 % of HPV negative tumours were incorrectly diagnosed as primary cervical cancer.[27] However, in a study that used next-generation sequencing (NGS), HPV negative cervical cancer was around 5 % and a rare number of histopathological genotypes of cervical cancer that are HPV negative were verified. Still, they should be taken into account.[28-31]

Conclusion

In cervical intraepithelial neoplasia and cervical cancer, HPV 16 had the highest oncogenic potential, along with genotypes 33, 31, 18 and 56. Genotype 16 was most often associated with pathohistological changes on the cervix. Infection with multiple associated genotypes of the HPV was not correlated with histopathology. Observing trends in the prevalence of HPV, especially HR HPV genotypes, can be important in the further strategy of applying secondary and primary prevention, as well as the application of HPV detection as part of co-testing or considering the introduction of HPV testing in the initial screening program.

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Conflict of interest

None.

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