

Correlation of human papilloma virus infection with cytology, colposcopy and histopathological examination of the bioptic tissue in low- and high-grade intraepithelial lesions

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Summary

Introduction: It is now believed that the majority of cervical cancer is preceded by long-term infection with high-risk types of the human papilloma virus (HPV). The presence of HPV high-risk types (HR-HPV) in the cells of intraepithelial change multiplies the possibility of its progressive development to high-grade cervical precancer and invasive disease. **Aim:** This study examined the correlation of HPV infection with cytology, colposcopy, and histopathological examination of the bioptic tissue in low- and high-grade cervical lesions. **Materials and Methods:** This research was conducted as a study section. Data collection was performed during a ten-year period, at the University Clinic of Gynecology and Obstetrics - Narodni Front in Belgrade (Serbia). The basic set included 1,927 patients. Colposcopy, cytology, histopathology, and HPV test verification was made in all patients. Statistical analysis was performed using the SPSS program, version 17.0. Contingency tables were used to assess the degree of correlation of variables and chi-square test was used to determine the level of statistical significance in this study. A p value < 0.05 was considered statistically significant. **Results:** Among 1,927 women studied, 635 (32.95 %) had abnormal cytological findings and among these, 272 (42.83%) were HR-HPV positive. There was a statistical difference between colposcopic and cytological findings in patients with HR-HPV ($\chi^2 = 35.33$, $p = 0.000$). There was also a statistically significant difference between histopathological and colposcopic findings in patients with HR-HPV ($\chi^2 = 10,171$, $p = 0.001$). Only HR-HPV types 16 and 18 showed a statistical significance compared to histopathological findings, unlike other HR-HPV. An important finding was that the authors found an abnormal colposcopy in 93.30% patients with low-grade intraepithelial neoplasia and 68.05% patients with low-grade squamous intraepithelial lesion (LSIL) had normal cytology and was 70.15 % HR-HPV negative. **Conclusion:** The findings imply that among high-grade intraepithelial neoplasias, the authors found a high presence of HPV type 16 and 18, and a statistical significant presence of HPV 16 in low-grade intraepithelial neoplasia, unlike other HR-HPV types in low-grade intraepithelial findings. The authors found a significant statistical correlation with abnormal cytology and presence of HPV type 16 in both groups (LSIL and high-grade squamous intraepithelial lesion (HSIL)). The authors also found an abnormal colposcopy in 93.30% of patients with low-grade intraepithelial neoplasia, while 68.05% of patients with LSIL had normal cytology and were HR-HPV negative in 70.15% of the cases.

Key words: Human papilloma virus (HPV); Colposcopy; Cytology; Histopathological examination.

Introduction

Cancer of the cervix is the second most common cancer among women worldwide [1]. Human papilloma virus (HPV) infection is a necessary cause of cervical cancer. It is now believed that the majority of cervical cancer is preceded by long-term infection with high-risk types of HPV, a sexually-transmitted infection [2, 3]. Considering the prognosis of these pathological changes, it is worth mentioning that their biological behavior is unpredictable. The presence of HPV high-risk types (HR-HPV) in the cells of intraepithelial change multiplies the possibility of its progressive development to invasive disease [3].

Persistent detection of HR-HPV types is a strong predictor of development of high-grade cervical precancer and invasive cancer [4]. The principle of preventive

actions should be respected, preventing already diagnosed intraepithelial change to develop into invasive cancer. Infection with HR-HPV types results in a complex of cellular abnormalities of the cervical epithelium and is an important early precursor event in carcinogenic progression to cervical cancer [5, 6]. Due to its simplicity and cost effectiveness, cytology is the most often used diagnostic method, representing the basis of the screening program in many countries worldwide. It must be pointed out that its sensitivity in discovering the intraepithelial stages of disease is limited. In histologically verified intraepithelial stages, the percentage of false-negative results of cytodiagnosics is considerable.

Other than cytodiagnosics, colposcopy is another method for detection of the cervical neoplasias, characterized by considerably higher sensitivity in detecting the lower stages of disease. For the verification and determination of pathological change extent detected by HPV testing, colposcopic and/or cytological examination, it would also be necessary to perform biopsy and histopathological examination.

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Table 1. — Correlation colposcopic findings with the results of HPV, cytological, and histopathological results.

	Colposcopy																	
	Normal n = 1,046						Abnormal n = 881											
	#	HPV-	%	#	HR-HPV+	%	#	LR-HPV+	%	#	HPV-	%	#	HR-HPV+	%	#	LR-HPV+	%
Cytology																		
Normal	732	69.98		105	10.04		24	2.29		94	10.67		260	29.51		84	9.53	
Abnormal	158	15.10		22	2.10		5	0.48		194	22.02		225	25.54		24	2.72	
Histopathological verification																		
LSIL	883	84.41		125	11.95		29	2.77		282	32.01		438	49.72		102	11.58	
HSIL	7	0.67		2	0.19		0	0		6	0.68		47	5.33		6	0.68	

tological verification [7, 8]. This study examined the correlation of HPV infection with cytology, colposcopy, and histopathological examination of the bioptic tissue in both low- and high-grade cervical lesions.

Materials and Methods

This research was conducted as a study section. Data collection was performed during the period from 2000 to 2010, in the University Clinic of Gynecology and Obstetrics - Narodni Front in Belgrade (Serbia). The basic set included 1,927 patients, aged 16-72 years (average age 33, SD = 9.60). Colposcopy, cytology, histopathology, and HPV test verification were made in all patients. Statistical analysis was performed using the SPSS program, version 17.0. Contingency tables were used to assess the degree of correlation of variables and chi-square test was used to determine the level of statistical significance in this study. A p value less than 0.05 ($p < 0.05$) was considered statistically significant.

Results

Altogether, 1,927 women were all examined with an adequate HPV test, cytology, colposcopy, and histopathological examination of the bioptic tissue. Of the subjects studied, 399 were < 24 years, 738 were 25-34 years, 790 were > 35 years. Altogether, 612 women (31.76%) were positive for one or more HR-HPV types. HPV 16 and HPV 33 were the most prevalent types found in 11.36% and 6.43%, respectively, with HPV 31 found in 5.24%; HPV 18 in 5.03%; and HPV 51 in 3.68%. Among 1,927 women, 635 (32.95%) had abnormal cytological findings and 272 (42.83%) among these were HR-HPV positive.

Concern regarding the low sensitivity of conventional cytology prompted research for new methods to either supplement or replace it. Testing for HPV has higher sensitivity but lower specificity than pap smear test [9, 10].

In Table 1 the authors found 612 patients with HR-HPV (16, 18, 31, 33, and 51) and carried out the correlation between the findings of colposcopy and cytology, as well as colposcopy correlation between the findings and histopathological examination of the bioptic tissue. There was a statistical difference between the findings of colposcopy and cytology in patients with HR-HPV ($\chi^2 = 35.33$, $p = 0.000$). Twenty-two normal subjects had colposcopic images and abnormal cytology (3.59%). Low-risk (LR) HPV was found in 137 patients and there was no statistically significant difference between colposcopic

Table 2. — Correlation between HPV and cytological findings (normal and abnormal).

	Normal cytology (n = 1292)		Abnormal cytology (n = 635)		Total (n = 1927)		p
	#	Total (%)	#	Total (%)	#	Total (%)	
HPV type							
HPV-	815	63.08	363	57.16	1178	61.13	
HPV+	477	36.92	272	42.83	749	38.87	0.000
HR HPV+	369	28.56	243	38.26	612	31.76	0.000
LR HPV+	108	8.35	29	4.57	137	7.11	0.002
HR infections							
16	113	8.75	106	16.7	219	11.36	0.000
18	57	4.41	40	6.3	97	5.03	0.075
31	68	5.26	33	5.2	101	5.24	0.951
33	83	6.42	41	6.3	124	6.43	0.978
51	48	3.71	23	3.62	71	3.68	0.919
Subtotal	369		243		612		
LR infections							
6	66	5.1	22	3.46	88	4.57	0.104
11	42	3.25	7	1.1	49	2.54	0.005
Subtotal	108		29		137		
Total infections	477		272		749		

Table 3. — Correlation of HPV in women with histopathological findings (LSIL and HSIL).

	Histopathological LSIL n = 1859			Histopathological HSIL n = 68		
	#	%	p	#	%	p
HPV type						
16	183	9.84	0.000	36	52.94	0.000
18	84	4.51	0.000	13	19.12	0.000
31	99	5.32	0.386	2	2.94	0.399
33	121	6.50	0.489	3	4.41	0.506
51	68	3.65	0.746	3	4.41	0.726

Table 4. — The correlation between HPV in women with LSIL and HSIL and normal cytology (PA II).

	HP LSIL PA II n = 1265			HP H-SIL PA II n = 27		
	#	%	p	#	%	p
HPV type						
16	100	7.90	0.000	13	48.14	0.000
18	50	3.95	0.003	7	25.92	0.000
31	68	5.37	0.715	0	0	0.218
33	82	6.48	0.907	1	3.70	0.560
51	46	3.64	0.877	2	7.40	0.301

and cytological findings ($\chi^2 = 0.394$, $p = 0.530$). Abnormal colposcopic images, abnormal cytology, and HR-HPV were found in 24 patients (17.52%). There was a statistically significant difference between histopathology and colposcopy in patients with HR-HPV ($\chi^2 =$



Table 5. — The correlation between HPV in women with LSIL and HSIL and pathological cytology (PA III).

HPV type	Histopathological LSIL PA III n = 594			Histopathological HSIL PA III n = 41		
	#	%	p	#	%	p
16	83	14.0	0.016	23	56.10	0.000
18	34	5.72	0.355	6	14.63	0.004
31	31	5.22	0.974	2	4.88	0.915
33	39	6.56	0.876	2	4.88	0.681
51	22	3.70	0.976	1	2.44	0.669

Table 6. — Distribution of HPV infected patients classified by age group, Belgrade, Serbia, 2000-2010.

HPV types	Age (years)						Total n = 1927	p	
	≤ 24 n = 399		25-34 n = 738		≥ 35 n = 790				
	#	%	#	%	#	%			
HPV 6	21	23.9	42	46.6	25	29.5	88	4.57	0.045
HPV 11	14	28.6	21	42.9	14	28.6	49	2.54	0.159
HPV 16	44	20.1	72	32.9	103	47.0	219	11.36	0.133
HPV 18	17	17.5	42	44.3	38	38.1	97	5.03	0.523
HPV 31	23	22.8	34	34.7	44	42.6	101	5.24	0.623
HPV 33	32	25.8	55	43.5	37	30.6	124	6.43	0.030
HPV 51	11	15.5	36	50.7	24	33.8	71	3.68	0.084
LR-HPV+	35	27.34	63	49.22	39	23.44	137	7.11	0.080
HR-HPV+	127	20.75	239	39.05	246	40.2	612	31.76	0.899

Table 7. — The correlation between colposcopic findings and histopathological verification.

Histopathological verification	Colposcopy				p
	Normal n = 1046		Abnormal n = 881		
	#	%	#	%	
LSIL	1037	99.14	822	93.30	0.000
HSIL	9	0.86	59	6.70	0.000

10,171, $p = 0.001$); 438 patients had abnormal colposcopic images and histopathological LSIL (71.57%), and only two patients had normal colposcopic images and histopathological HSIL. There was no statistically significant difference between histopathological and colposcopic findings in patients with LR-HPV ($x^2 = 1,718$, $p = 0.190$).

The results in Table 2 show that in 1,292 (67.04%) patients with normal cytology, 477 had HPV. The authors compared patients with HPV positive findings and cytology. There was a statistically significant difference between normal and abnormal cytology in both groups, with HR-HPV and LR-HPV. Unlike other viruses, the presence of the HPV 16 as HR-HPV and LR-HPV 11 indicated a statistical significance in patients with normal and abnormal cytology.

In Table 3 the authors found that in 1,927 patients, 1,859 had LSIL and 68 had HSIL, as confirmed by histopathological verification of the bioptic tissue. Only HR-HPV 16 and 18 showed a statistical significance compared to histopathological findings, unlike other HR-HPV. HPV testing found that HPV 16 were the most common viruses in HSIL as well as in LSIL histopathological findings.

Based on the results of cytology and biopsy as shown in Tables 4 and 5, the authors found 1,265 (65%) patients with histopathological LSIL and normal cytology and 27 (1.40%) patients with histopathological HSIL and normal cytology. In these patients, there was a statistically significant higher incidence of HR-HPV 16 and 18. Other HR-HPV viruses did not have a statistical significance compared to the histopathological exam and cytology. In the group of patients with abnormal cytology, the authors found after biopsy, 595 patients (30.83%) with LSIL and 41 patients (2.13%) with histopathological HSIL. The patients with HPV were divided according to three age groups.

Patients with HPV-positive results were divided into three age groups (Table 6). Of all LR-HPV, LR-HPV 6 occurred in 30.65% of the 25-34 year age group, while HR-HPV 16 was most prevalently found in the ≥ 35 year age group ($p < 0.05$). The second most common HPV virus was HR-HPV 33, which was significantly more common in the 25-34 year age group (43.55%) compared to other age groups ($p < 0.05$).

An examination of the colposcopic findings (Table 7) in relation to histopathological results, the authors found a statistical significance in both groups (LSIL and HSIL, $p < 0.05$). Abnormal colposcopy and HSIL were found in 59 patients (3.06%), which were significantly higher than in the nine patients (0.47%) with normal colposcopic results and histopathological HSIL findings.

Discussion

HPV is common sexually transmitted virus and a subset of high-risk types is integral to the development of cervical cancer and its cytologic precursors. HPV16 is the most common HPV type found in the cervix and cervical cancer is detected in over 50% of patients and has been reported to be the most common genotype in high-grade cervical intraepithelial neoplasia [10, 11]. Other HPV types commonly detected in cervical cancer include types 18, 31, and 45. The HPV genotypes 16, 18, 33, and 45 have been detected more frequently in invasive cervical carcinomas compared to premalignant lesions [12-14]. In this study, among high-grade intraepithelial neoplasia, the authors found in 52.94% the presence of HPV 16 and only 9.84% with HPV 16 in low-grade intraepithelial findings. Among HSIL, the authors found in 19.12% the presence of HPV 18, but other HR-HPV is present between 2.94% and 4.41%. These results are comparable with those of other studies and show that presence of HR-HPV (except for HPV 16) is low, between 3.65% and 6.50% in LSIL [11, 15-17].

In the natural history of HPV, most infections are transient, especially among younger women, and only a small fraction of infections that persist may progress to cervical cancer. In a prospective cohort of 1,075 women, Woodman demonstrated that, compared to HPV-women, women infected with HPV 16 and 18 had relative hazard ratios of 8.5% and 3.3%, respectively for the development of cervical intraepithelial neoplasia 2 (CIN 2) or 3 (CIN3) [17-20].





Due to its simplicity and cost-effectiveness, cytology and HPV tests are the most frequently used diagnostic methods, representing the basis of screening program in many countries worldwide [21-23].

As was expected, the authors found 48.14% HPV 16 with normal cytology and high-grade histopathological findings, while only 7.90% had HPV 16, LSIL, and normal cytology. Abnormal cytology showed that there was a higher statistically significant presence of HPV 16 in LSIL (14.0%) and HSIL (56.10%). These results confirmed that HPV infection is mostly a transient phenomenon resulting in no cervical lesions or mostly low-grade lesions that often regress spontaneously. The persistence of an HPV infection appears to be a prerequisite for the development of CIN 3 and cervical cancer. Viral, host, and environmental factors may influence the course of HPV infection [21, 24].

Other than cytodiagnosics, colposcopy is another basic method for detection of cervical neoplasias, characterized by a considerably higher sensitivity of detecting the lowest stages of disease. The baseline of colposcopy is the recognition of pathological changes of the cervical epithelium that are based on significant protein increase in dysplastic cells and a considerable loss of glycogen, as well as on the changes of the stromal vascular net regarding the number, appearance, and capillary arrangement. SIL undergoing a colposcopic examination are manifested as different pathological picture of acetowhite epithelium, mosaic, punctuation, leukoplaques or atypical blood vessels. They are a sign of the pathological events in the epithelium and need to be histologically explained [7, 22-24].

The study of Kulasingam et al. showed that all women with abnormal cytology resulted in colposcopy. The strategy of requiring two positive PCR tests for HPV was both more sensitive and specific than the referral of women with abnormal cytology results for colposcopy [25, 26]. The authors found normal colposcopy in only two patients (0.19%) with HR-HPV presence and HSIL and normal colposcopy in 11.95% patients with HR-HPV positive test and LSIL. Important findings include that 93.30% of the patients had LSIL and abnormal colposcopy, and only 6.70% of patients had HSIL and abnormal colposcopy. These results showed that colposcopy is effective for detecting the lowest stage of disease.

Conclusion

The findings in this study imply that among high-grade intraepithelial neoplasias, a high presence of HPV 16 and 18 was found and a statistically significant presence of HPV 16 was found in low-grade intraepithelial neoplasia, unlike other HR-HPV types in low-grade intraepithelial findings. The authors also found a significant statistical correlation between abnormal cytology and the presence of HPV 16 in both groups (LSIL and HSIL). The most prevalent HR-HPV 16 was found in the age group ≥ 35 years, while HPV 33 was more common in the age group of 25-34 years. Important findings include that abnormal

colposcopy was found in 93.30% of patients with low-grade intraepithelial neoplasia and 68.05% patients with LSIL that had normal cytology and that was 70.15% HR-HPV negative.

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