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Assessment of HPV DNA Test Value in Management Women with Cytological Findings of ASC-US, CIN1 and CIN2

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A B S T R A C T

The aim of this retrospective study was to answer the following questions: 1) is HPV DNA test for high-risk types able to predict lesion behaviour in women with cytological abnormalities lower than CIN3 (ASC-US, CIN1 and CIN2); 2) how to predict the histological diagnosis CIN3, and 3) is its use in diagnostic management in these patients justified or not? The study included 345 women (11 ASC-US, 312 CIN1 and 22 CIN2) that underwent conventional diagnostic management (repeat cytology and colposcopy with or without histology) and HPV testing for high-risk HPV types by PCR method. The value of HPV DNA test in predicting lesion regression/persistence was assessed in 275 subjects without histology. In 70 subjects, diagnostic accuracy (sensitivity, specificity, and positive and negative predictive value) of repeat cytology and HPV DNA test in predicting severe intraepithelial lesion (CIN3) was determined on the basis of colposcopy guided biopsy. The prevalence of persistent lesions was significantly higher in the group of HPV positive than in the group of HPV negative subjects (37.7% vs. *16.4%; p<0.001). Positive HPV test was associated with a 3.1-fold risk of lesion persistence [OR (95% CI) =3.095 (1.65–5.82)]. However, on screening to predict the outcome of cytologically diagnosed cervical lesion with sensitivity of 39.7% and positive predictive value of 37.7% showed that a positive test could not be considered a reliable indicator of lesion persistence. In contrast, the specificity of 82.5% and negative predictive value of 83.6% suggested that a negative test result could be taken as a good indicator of lesion regression. In comparison with repeat cytology, HPV test showed higher sensitivity (69.2%* vs. *61.5%) but significantly lower specificity (63.2%* vs. *93.0%) and positive predictive value (30.0%* vs. *66.7%), and comparable negative predictive value (90.0%* vs. *91.4%) in predicting histologically verified CIN3. In one patient with a histological diagnosis of squamous cell carcinoma with minimal invasion, repeat cytology indicated CIN3, whereas HPV test was negative. Due to authors experience in women with cytological abnormalities lower than CIN3, HPV testing is not a method to reliably predict lesion behaviour (regression, persistence) or presence of CIN3. HPV testing is of limited value in daily routine and should not be widely used until it is definitely demonstrated to be superior to conventional methods in improving the sensitivity, specificity and positive predictive value of CIN3 and invasive carcinoma detection.*

***Key words**: HPV testing, cytology, triage, cervical intraepithelial neoplasia*

Introduction

The main goal of cytological screening by Pap test is identification of women with cervical lesions at an increased risk of cervical carcinoma[1]. These women require regular follow up and/or treatment to prevent the lesion progression to invasive carcinoma. While there is general consensus that women with severe cytological lesions should be referred for additional testing without delay[2], the procedure for women with mild cytological lesions remains controversial[3]. Recommendations for women with atypical squamous cells of undetermined significance

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(ASC-US) and low-grade squamous intraepithelial lesions (LSIL) vary from conservative repeat cytology[4–7] through urgent referral for colposcopy and biopsy[8–11]. Such a scenario does not only increase healthcare cost considerably[12], but is also associated with unfavourable emotional effect[13].

The natural history of low-grade cytological lesions is difficult to predict on the basis of their cytomorphological appearance. These lesions may frequently undergo spontaneous regression, requiring no treatment[14–16]. Although the majority of women with ASC-US are free from clinically significant disease, some of them develop histologically verified high-grade cervical intraepithelial neoplasia (CIN3) or even a more severe disease[17–19].

In view of the evidence on the etiologic role of infection with the oncogenic human papillomavirus (HPV) in the development of cervical carcinoma and CIN[20–24], HPV testing has been proposed as a triage method to identify women at an increased risk of cervical carcinoma that should be referred for colposcopy[17,18]. However, results on the benefits of HPV triage in women with ambiguous cytology are quite controversial[25–27].

The aim of this retrospective study was to answer the following questions: 1) is HPV DNA test able to predict lesion behaviour in women with cytological abnormalities lower than CIN3 (ASC-US, CIN1 and CIN2); 2) predict histological diagnosis in CIN3 lesion; and 3) is its use in diagnostic work-up in these patients justified or not?

Subjects and Methods

The study included 345 women with cytological finding obtained on primary screening suggestive intraepithelial lesions lower than CIN3 (ASC-US, CIN1 and CIN2) that underwent HPV DNA testing for high-risk HPV types during subsequent diagnostic-therapeutic management including cytological and colposcopic follow up with or without histopathology analysis (from the beginning of 2005 to the end of 2008). All subjects were followed-up for 1–3 years.

Cytological smears were obtained by a spatula and cytobrush, applied onto the glass slide, fixed in 95% alcohol, and stained by the Papanicolaou method. The Croatian modification of the Bethesda 2001 system was used on classification of findings[28].

HPV DNA samples were obtained by a brush (Medscan, Malmö, Sweden) and referred for testing in a plastic cuvette with phosphate buffer (PBS). Quality control of DNA isolated from each individual sample was assessed by polymerase chain reaction (PCR) amplification of the β-globin gene. The presence of HPV in the samples was determined by the Roche PCR-ELISA method. The PCR-ELISA Dig-Labelling kit (Roche Diagnostics GmbH, Mannheim, Germany) with MY09 and MY11 consensus primers was used for PCR reactions[29]. HPV detection according to the risk level was done by use of the PCR ELISA DIG Detection kit (Roche Diagnostics GmbH, Mannheim, Germany), whereby a mix of L1, MY18/MY46 or GP1/GP2 consensus primers was used on group-specific genotyping to detect low-risk (6, 11) and high-risk (16, 18, 31, 33, 45, 52, 55, 59, etc.) HPV. Results obtained by PCR-ELISA were tested by amplification of the viral genome E6/E7 region. One pair of consensus primers (HPVpU-1M, HPVpU-2R) was used for E6/E7 gene amplification of high-risk HPV types (16, 18, 31, 33, 35, 52 and 58), whereas another pair of primers (HPVpU--31B, HPVpU-2R) was used for low-risk HPV types (6, 11). Amplified DNA fragments of L1-HPV, E6/E7-HPV and β-globin were determined by 1% agarose gel electrophoresis and visualized by an UV-transluminator (Pharmacia Biotech, Sweden).

In 275 subjects without histopathologic analysis, the natural history of the cytological diagnosed lesion was identified as regression (at least two follow up cytology findings within at least one year were negative) or persistence (at least two follow up cytology findings within at least one year were abnormal, irrespective of the level of abnormality). Colposcopy guided biopsy was performed in 70 subjects.

At the time of HPV testing, the following data were recorded in all study subjects: age, first abnormal cytological differential diagnosis, most severe cytological differential diagnosis, finding of HPV DNA test for high--risk types, time (months) elapsed between the first cytological finding and HPV DNA test, and time elapsed between HPV DNA test and histological analysis.

The value of HPV DNA testing for high-risk HPV types in predicting behaviour of a cytologically detected abnormality was assessed by comparison of the lesion natural history (regression or persistence) and HPV DNA test result.

Diagnostic accuracy (sensitivity, specificity, positive and negative predictive value) of repeat cytology and HPV DNA test for high-risk HPV types in the detection of histologically verified high-grade intraepithelial lesion (CIN3) as an immediate precancerous lesion and the main target of screening was assessed by comparison of histological finding with the most severe follow up cytology finding and HPV DNA test result.

Results

In the cohort of 345 women, the first abnormal cytological finding was ASC-US in 11, CIN1 in 312 and CIN2 in 22 women. The mean age of study subjects was 34± 10.1 (range 18–65) years. HPV test was performed at a mean of 20.7±5.2 months of the first abnormal cytological finding and 10.4±2.1 months before histology. Testing for high-risk HPV types showed positive result in 91 (26.4%) and negative result in 254 (73.6%) subjects.

In 275 subjects the natural history of lesion was determined without histological analysis and compared with HPV DNA test result (Table 1). Persistence of lesion was recorded in 58 (21.1%) and regression in 217 (78.9%) subjects.

TABLE 1
NATURAL HISTORY OF LESIONS IN RELATION TO RESULTS OF HPV DNA TESTING FOR HIGH-RISK TYPES (N=275)

Natural history of lesions		HPV DNA test for high-risk types		Total
		Positive	Negative	
Persistence	N	23	35	58
	%	37.7	16.4	21.1
Regression	N	38	179	217
	%	62.3	83.6	78.9
Total	N	61	214	275
	%	100.0	100.0	100.0

The prevalence of persistent lesions was significantly higher in the group of HPV positive women than in the group of HPV negative women (37.7% *vs.* 16.4%; p< 0.001). Positive HPV test for high-risk HPV types was associated with a 3.1-fold risk of lesion persistence [OR (95% CI)=3.095 (1.65–5.82)].

Assessment of the HPV DNA test value as a screening test to determine the likelihood of lesion persistence, which is an additional risk for the development of invasive carcinoma, yielded a sensitivity of 39.7% (23/58), specificity of 82.5% (179/217), positive predictive value of 37.7% (23/61) and negative predictive value of 83.6% (179/214).

In 70 subjects, follow up cytology finding and/or colposcopy finding indicated histological analysis, and samples were obtained by colposcopy guided biopsy. Out of 70 samples submitted for histological analysis, 16 (22.9%) were free from intraepithelial or invasive lesion, whereas squamous intraepithelial lesion was found in 53 (75.7%) samples (CIN1 in 23, CIN2 in 17 and CIN3 in 13 samples), and squamous cell carcinoma with minimal invasion in one (1.4%) sample (Table 2).

Diagnostic value of repeat cytology in predicting CIN3 was determined by comparison of histological finding with the most severe follow up cytological finding (Table 2). Cytological differential diagnosis of CIN3 in the detection of histologically verified CIN3 showed a sensitivity of 61.5%, specificity of 93.0%, positive predictive value of 66.7% and negative predictive value of 91.4%. In one patient with a histological diagnosis of squamous cell carcinoma with minimal invasion (CIM), cytological finding indicated CIN3.

Diagnostic value of HPV DNA test in the detection of CIN3 was determined by comparison of histological finding and HPV test result (Table 3). HPV DNA test was

TABLE 2
COMPARISON OF HISTOLOGICAL FINDING WITH THE MOST SEVERE FOLLOW UP CYTOLOGICAL FINDING (N=70)

Cytological finding		Histological finding					Total
		Benign	CIN1	CIN2	CIN3	CIM	
ASC-US	N	1	0	0	0	0	1
	%	6.3	0.0	0.0	0.0	0.0	1.4
CIN1	N	12	15	6	2	0	35
	%	75.0	65.2	35.3	15.4	0.0	50.0
CIN2	N	2	8	9	3	0	22
	%	12.5	34.8	52.9	23.1	0.0	31.4
CIN3	N	1	0	2	8	1	12
	%	6.3	0.0	11.8	61.5	100.0	17.1
Total	N	16	23	17	13	1	70
	%	100.0	100.0	100.0	100.0	100.0	100.0

CIM – carcinoma planocellulare cum invasione minimale

TABLE 3
HISTOLOGICAL FINDINGS IN RELATION TO RESULTS OF HPV DNA TESTING FOR HIGH-RISK TYPES (N= 70)

HPV DNA test for high-risk types		Histological finding					Total
		Benign	CIN1	CIN2	CIN3	CIM	
Positive	N	6	4	11	9	0	30
	%	37.5	17.4	64.7	69.2	0.0	42.9
Negative	N	10	19	6	4	1	40
	%	62.5	82.6	35.3	30.8	100.0	57.1
Total	N	16	23	17	13	1	70
	%	100.0	100.0	100.0	100.0	100.0	100.0

CIM – carcinoma planocellulare cum invasione minimale

positive in 30 (42.9%) and negative in 40 (57.1%) subjects.

In the detection of histologically verified CIN3, HPV DNA test showed a sensitivity of 69.2%, specificity of 63.2%, positive predictive value of 30.0% and negative predictive value of 90.0%. In one subject with a histological diagnosis of squamous cell carcinoma (CIM), HPV test was negative.

In comparison with differential cytology, HPV test showed higher sensitivity in the detection of CIN3, however, with a significantly lower specificity and positive predictive value, and a comparable negative predictive value (Table 4).

TABLE 4
DIAGNOSTIC VALUE OF REPEAT CYTOLOGY AND HPV DNA TESTING FOR HIGH-RISK TYPES IN DETECTION CIN3 LESIONS (N=13)

Diagnostic accuracy	Cytology	HPV DNA test for high-risk types
Sensitivity	61.5%	69.2%
Specificity	93.0%	63.2%
Positive predictive value	66.7%	30.0%
Negative predictive value	91.4%	90.0%

Discussion and Conclusion

Harald zur Hausen, a German virologist, was the first to point to the association between oncogenic HPV and cervical carcinoma in the early 1980s[20]. Subsequently, a large body of evidence has been published suggesting that persistent infection with oncogenic HPV is a primary risk factor and a necessary (yet not sufficient) cause of cervical carcinoma and its precursors.

The use of PCR in HPV testing has offered some hope to solve the dilemma concerning further procedures to be taken in women with Pap test indicating ASC-US or LSIL[30]. However, in spite of the large number of studies employing HPV test to discriminate patients that require urgent colposcopy and biopsy from those that can be cytologically followed up by Pap test alone, the potential benefits of the wide use of HPV screening have not yet been fully clarified[31,32]. Some studies point to the benefits of the large-scale use of HPV testing, whereas others are less enthusiastic, suggesting the use of this test to be for the time being restricted to the field of research[33–36].

In the present study, we retrospectively assessed the value of HPV test *versus* cytological and colposcopic follow up, and histology in indicated cases. Besides women with cytological findings of ASC-Us and CIN1 (LSIL), the study also included women with CIN2 because the protocol for CIN1 and CIN2 is the same in our setting[37].

The prevalence of HPV as detected by HPV DNA testing in the study population was 26.4% (91/345). Out of 275 women with cytological and colposcopic follow up alone, the lesion persisted in 58 (21.1%) and regressed in 217 (78.9%) subjects. The prevalence of persistent lesions was significantly higher in the group of HPV positive women than in HPV negative women (37.7% *vs*. 16.4%; $p<0.001$). Positive HPV test was associated with a 3.1-fold risk of lesion persistence [OR (95% CI)=3.095 (1.65–5.82)].

When the value of HPV test was assessed in the context of predicting the outcome of cytologically diagnosed cervical lesion, the sensitivity of 39.7% and positive predictive value of 37.7% showed that a positive test could not be considered a reliable indicator of lesion persistence. In contrast, the specificity of 82.5% and negative predictive value of 83.6% suggested that a negative test result could be taken as a good indicator of lesion regression.

Histological diagnosis made on colposcopy guided biopsy was used as a reference standard on assessing the value of HPV test; therefore, the possible errors that may have occurred on biopsy specimen collection should have been taken in consideration on result evaluation[38,39] and finding interpretation[40]. In addition, errors on cytological sample collection and interpretation may have also influenced assessment of the HPV test value.

CIN3 was found in 13 of 70 women that underwent cervical biopsy. HPV test showed a sensitivity of 69.2% and specificity of 63.2% in predicting CIN3. Test sensitivity and specificity are not independent measures because an increase in sensitivity with an apparent decrease in false-negative diagnoses may be accompanied by an increase in the rate of false-positive diagnoses, and *vice versa*. The connection between the test sensitivity and specificity is best illustrated by predictive values. The HPV test positive predictive value was 30.0% and negative predictive value 90.0%. In one subject with a histological diagnosis of squamous cell carcinoma with minimal invasion, HPV test was negative.

Kulasingam et al.[41] report on the HPV test sensitivity in predicting CIN2-3 to range from 55.7% to 93.3%. However, in another study reporting highest sensitivity, the positive predictive value varied from 17.3% to 28.3% and specificity from 24.2% to 66.8%[33]. In the study conducted by Hatch et al.[42], the HPV test sensitivity in predicting CIN2-3 in women with a cytological finding of LSIL was 67%, and in those with a cytological finding of ASC-US 60%, specificity 68% and positive predictive value 35%. HPV test was negative in 4 of 9 women with invasive squamous cell carcinoma.

In the present study, repeat cytology showed sensitivity of 61.5%, specificity of 93.0%, positive predictive value of 66.7% and negative predictive value of 91.4% in predicting CIN3. HPV test yielded a higher sensitivity, but its specificity and positive predictive value were significantly lower, whereas negative predictive value was comparable to that shown by repeat cytology. As more than 90% of study women had a primary cytological diagnosis of CIN1, the results could mostly be related to LSIL. In contrast to other studies, we separated CIN2 from the HSIL group, based on our national classifica-

tion of cytological findings, and were therefore able to directly compare cytological and histological grades of CIN.

In their meta-analysis of nine studies assessing the value of repeat cytology and HPV test in predicting HSIL when primary cytological finding indicated ASC-US or a more severe lesion, Arbyn et al.[43] found the sensitivity of cytology to range from 60.0% to 80.0%, specificity from 44.7% to 71.7%, positive predictive value from 3.8% to 22.2%, and negative predictive value from 93.4% to 97.8%. The sensitivity of HPV test ranged from 32.4% to 58.8%.

The results of our retrospective study revealed that HPV testing as a method of secondary screening in women with cytological abnormalities lower than CIN3 was not useful either to identify women whose lesions would regress or those with high-grade intraepithelial lesion (CIN3), or to obviate unnecessary colposcopy. While negative HPV test did indicate a higher likelihood of lesion regression, positive HPV test did not exclude lesion regression. In addition, positive HPV test suggested a higher likelihood of histologically verified CIN3, but negative HPV test did not exclude it. Due to our experience we would agree with the opinion that HPV testing has only a limited value in daily routine and should not be widely used before it is clearly demonstrated to be superior to conventional methods by increased sensitivity, specificity and positive predictive value in detecting CIN3 and invasive carcinoma.

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OCJENA VRIJEDNOSTI HPV DNA TESTA U OBRADI ŽENA SA CITOLOŠKIM NALAZOM ASC-US, CIN1 i CIN2

S A Ž E T A K

Cilj retrospektivne studije je bio odgovoriti na pitanja: može li HPV DNA test u žena s lakšim citološkim abnormalnostima (ASC-US, CIN1 i CIN2) prognozirati ponašanje lezije, može li predvidjeti histološku dijagnozu CIN3 i da li je njegova primjena u dijagnostičkom postupku kod tih žena opravdana ili ne. U studiju je uključeno 345 žena (11 ASC-US, 312 CIN1 i 22 CIN2) kojima je uz konvencionalni postupak (ponavljana citologija i kolposkopija sa ili bez histologije) učinjen i HPV DNA test na visokorizične tipove PCR metodom. Za 275 ispitanica bez histologije je određena vrijednost HPV testa u predviđanju regresije/perzistencije lezije. U 70 ispitanica je učinjena kolposkopski kontrolirana biopsija na temelju koje je određena dijagnostička točnost (osjetljivost, specifičnost, pozitivna i negativna prediktivna vrijednost) ponavljane citologije i HPV DNA testa u predviđanju teške intraepitelne lezije (CIN3). Učestalost perzistentnih lezija je bila značajno viša u skupini HPV pozitivnih (37,7%) nego u skupini HPV negativnih žena (16,4%) ($p<0,001$). HPV pozitivan test povećava rizik perzistiranja lezije za 3,1 puta. [OR (95% CI)=3,095 (1,65–5,82)]. Međutim, u predviđanju ishoda citološki dijagnosticirane cervikalne lezije, osjetljivost od 39,7% i pozitivna prediktivna vrijednost od 37,7% ukazuju da pozitivan test na visokorizične tipove nije valjani indikator za perzistiranje lezije, dok specifičnost od 82,5% i negativna prediktivna vrijednost od 83,6% ukazuju da je negativan test relativno dobar indikator za regresiju lezije.U odnosu na ponavljanu citologiju, HPV test ima za predviđanje histološki potvrđenog CIN3 višu osjetljivost (69,2% prema 61,5%), ali značajno nižu specifičnost (63,2% prema 93,0%) i pozitivnu prediktivnu vrijednost (30,0% prema 66,7%), te sličnu negativnu prediktivnu vrijednost (90,0% prema 91,4%). U jedne ispitanice s histološkom dijagnozom carcinoma planocellulare cum invasione minimale (CIM) ponovljeni citološki je nalaz bio CIN3, a HPV test je bio negativan. Prema našim rezultatima HPV testiranje u žena s citološkim abnormalnostima manjim od CIN3 nije metoda kojom bi se pouzdano moglo predvidjeti ponašanje lezije (regresija, perzistiranje) ili postojanje CIN3, pa za praktičara ima ograničenu vrijednost i ne bi ga trebalo široko primjenjivati sve dok se jasno ne dokaže da u odnosu na konvencionalne metode stvarno povećava osjetljivost, specifičnost i pozitivnu prediktivnu vrijednost detekcije CIN3 i invazivnog karcinoma.