DOI: 10.5455/msm.2020.32.127-130
Received: MAR 29 2020; Accepted: MAY 22, 2020

ORIGINAL PAPER Mater Sociomed. 2020 Jun; 32(2): 127-130

Progression Low Squamous Intraepithelial Lesion and Human Papillomavirus Infections

Mahira Jahic[1,2], Lejla Kameric[2,3], Azra Hadzimehmedovic[2,3]

[1]Gynecology Centre ,,Dr Mahira Jahic" Tuzla, Tuzla, Bosnia and Herzegovina

[2]Faculty of Medicine, University of Tuzla, Tuzla, Bosnia and Herzegovina,

[3]Department of Gynecology and Obstetrics, University Clinical Center Tuzla, Bosnia and Herzegovina

Corresponding author:
Prof. Mahira Jahic, MD, PhD. Gynecology Centre ,,Dr Mahira Jahic" Tuzla, University of Tuzla, Faculty of Medicine Tuzla. Bosnia and Herzegovina. Tel: +387 61 100 195. E-mail: mahira.j@bih.net.ba. ORCID ID: https//www.orcid.org/ 0000-0001-7551-5656.

ABSTRACT

Introduction: Infection with human papillomavirus is the main cause of cervical carcinoma. In Bosnia and Herzegovina (BIH) 556 cases of cervical carcinoma are diagnosed annually, and 141 women die from it. **Aim:** To determine the most common HPV type found in ASCUS and LSIL and progression, regression and persistence of lesions. M**ethods**: In a retrospective study, 11 051 PAP tests, performed in several private gynecological practices located in Tuzla Canton from January 2016 to December 2019, were analyzed. In processing of data , X^2 – statistical method was used. **Results**: 11051 PAP test were inspected. Normal findings were found in 90.48% (N-10002) and pathological findings in 9.49% (N-049). ASCUS was present in 4.9% (N-544), LSIL in 3.04% (N-337), HSIL in 0.74% (N-84), ASC-H in 0.27% (N-30) and AGC in 0.49% (N-55) of cases. The most common is HPV 16, found in 50.5% (N-44) of ASCUS and LSIL. Monoinfection with HPV 16 was found in 40.9% (N-18) ASCUS (N-3) and LSIL (N-15), and a combination of HPV 16 with other types like HPV 18, 31, 33, 39 in 59% (N-26). Progression of ASCUS lesion in HSIL 1.6% (N-2), and LSIL 9.6% (N-12). Progression of LSIL to HSIL was found in 9.0% (N-10). HSIL progresses significantly more frequent from LSIL ($p<0.05$) than from ASCUS changes. Lesions that progress into higher grade HSIL are HPV 16 positive. Progression into HSIL is not found in patients with low-risk HPV 6 and 11 infection. **Conclusion:** Women infected with HPV 16 have more a frequent progression of a lesion into higher grade HSIL. They should be intensively monitored because of the increased risk for development of cervical carcinoma.

Keywords: Cervical cancer, HPV 16, cervical lesions.

1. INTRODUCTION

Cervical carcinoma is the most common carcinoma in women of the age of 15 to 44. In Bosnia and Herzegovina (BIH) 556 cases of cervical carcinoma are diagnosed annually, and according to the report of ICO/IARC from 2019, 141 women die from it (1).

Human Papillomavirus infection is the main cause of cervical carcinoma. There are at least 15 high-risk HPV types that are significantly connected with progression of squamous intraepithelial lesion (SIL) into cervical carcinoma (2).

The most common high-risk HPV type that causes cervical carcinoma in BIH is HPV 16 in 59.3%, followed by HPV 18 in 8.8%, HPV 33 in 2.7% and HPV 31 in 2% of cases. Low risk HPV 6 and 11 are found in 0.0–1.3% of cases.

Cervical carcinoma can successfully be prevented if the changes that lead to it, like squamous intraepithelial lesion of low (LSIL) and high (HSIL) grade, including obligatory typing of HPV that caused such a change, are discovered in time.

According to the report of the ICO/IARC (HPV Information Centre), BIH has no data from 2019 about frequency of HPV infection in women with abnormal PAP test .

HPV 16 and HPV 18 are high-risk types and their prevalence is over 50% in HSIL and in 80-90% in cervical carcinoma (3). According to the existing literature, progression of ASCUS and LSIL in women that are HPV 16 positive is bigger than in women with same changes that are caused by other HPV high-risk types. Also, progression of lesion with HPV 16 infection is the same whether it is just a HPV 16 infection, or if the HPV 16 is combined with other types (4,5). Data about the frequency of the high-risk

HPV in low grade lesions, like ASCUS and LSIL, can help in establishing a strategy for monitoring and treating women with a high risk of developing cervical carcinoma. Simultaneously, it is a preventive measure against development of a large number of cervical carcinoma found in our country.

2. AIM

The aim of the study is to determine the most common HPV type found in ASCUS and LSIL and progression, regression and persistence of cervical lesions, ASCUS and LSIL, in the most commonly isolated HPV type.

3. PATIENTS AND METHODS

In a retrospective study, 11 051 PAP tests, performed in several private gynecological practices located in Tuzla Canton in a four year period from January 2016 to December 2019, were analyzed. The study was performed in Gynecological Centre "Dr. Mahira Jahic" Tuzla, Gynecological Practice "Dr Blitvic" Tuzla, Gynecological Practice "Prim Zukic" Srebrenik . PAP tests and HPV tests were analyzed using gynecological protocols.

Patients diagnosed with ASCUS and LSIL were reevaluated after local treatment with repeated PAP tests and were monitored in a 1 year period. ASCUS and LSIL management includes repeated cytology, HPV typing and colposcopy. Monitoring protocol depended on findings in repeated PAP test. PAP test was normal in 10 002 patients, so they were advised to do an annual control. ASCUS was found in 544 patients with 127 agreeing to monitoring, and LSIL was found in 337 patients with 111 agreeing to monitoring. In 145 monitored patients with ASCUS and LSIL, HPV typing was done, and after 12 months PAP test was evaluated. All cytological samples were screened in the same laboratory. PAP tests were done by a conventional method, dyed with Papanicolau method and examined by a Kruss microscope. Analysis of vaginal secretion was done by PAP test and HPV typing with HPV in situ hybridization and HPV Genotypes 14 Real-TM Quant (16,18,31,35,39,45,51,52,56,58,59,66,68). Gathered data were analyzed using X^2 test for statistical analysis of data.

4. RESULTS

In total 11051 PAP tests were examined. Normal findings were found in 90.48% (N-10002) and pathological findings in 9.49% (N–1049) of cases. ASCUS occurred in 4.9% (N-544), LSIL in 3.04% (N-337), HSIL in 0.74% (N-84), ASC-H in 0.27% (N-30) and AGC in 0.49% (N-55) of cases (Table 1).

The most common high-risk HPV type in ASCUS and LSIL is HPV 16 in 50.5% (N-44) of women. Monoinfection with HPV 16 was found in 40.9% (N-18) of women with ASCUS (N-3) and LSIL (N-15), and a combination of HPV 16 with other types (HPV 18, 31, 33, 39) was found in 59% (N-26).

The next high-risk type is HPV 18 found in 29.8% (N-26) of cases, that occurs combined with other types, and in a single form was not found in examined women. The next one is HPV 33 found in 24.1% (N-21), and HPV 31 in 16% (N-14). Other types like HPV 39, 45, 51, 56, 66 occur in a significantly smaller number (Table 2).

HPV 6 and 11 that belong to low-risk types are found in 22.9% (N-35) of cases and combined with high-risk types in 14.9% (N-13) of cases.

PAP tests	Results
Result of PAP smears (N,%)	11051(100%)
NILM	10002 (90.48%)
Abnormal PAP smears	1049 (9.49%)
Atypical	
ASC-US	544 (4,9%)
ASC-H	30 (0.27%)
Atypical glandular cells	55 (0.47%)
LSIL	337 (3.04%)
HSIL	84 (0.74%)

Table 1. Results of PAP tests

HPV type	ASCUS	LSIL	Total	%	P<0.05
6,11,16,18	2	6	8	9.1	no
6,11,16,18,31,33	0	3	3	3.4	no
16,18	4	10	14	16.0	no
31,33	0	8	8	9.1	no
6,11	5	15	20	22.9	no
6,11,31,33	0	2	2	2.2	no
16,39	0	1	1	1.1	no
18,39	0	1	1	1.1	no
31,56,66	0	1	1	1.1	no
39,45	0	1	1	1.1	no
39,66	1	0	1	1.1	no
51,56,66	0	1	1	1.1	no
16	3	15	18	20.6	no
33	3	5	8	9.1	no

Table 2. HPV types found in ASCUS (N-17) and LSIL (N-70)

In 544 patients with ASCUS lesions, 22.7% (N-124) were monitored. HPV typing was done in 27.4% (N-34). In 50% (N-17) of patients, HPV was positive, and in 50% (N-17 HPV) negative.

Progression of ASCUS lesion in HSIL was found 1.6% (N-2), and LSIL 9.6% (N-12), persistence of ASCUS in 58% (N-72), and a regression into a normal finding in 30.6% (N-38) (Table 3).

In 337 women with LSIL, 32.9% (N-111) HPV typing was done. HPV typing in 63.06% (N-70) was positive, and in 36.9% (N-41) negative.

Progression was found in 9.0% (N-10), persistence in 64.8% (N-72) and a regression into a lower grade or normal findings in 27%, ASCUS 12.6% (N-14) and normal findings in 13.5% (N-15) (Table 4).

Progression of ASCUS in HSIL was found in 1.6% (N-2) women with 1-HPV 16 and 1-HPV 16, 18, while progression of LSIL was found in 9% (N-10): 5-HPV 16, 4-HPV 16,18, 1-HPV Negative (Table 5).

HSIL progresses significantly more frequent from LSIL ($p<0.05$) than from ASCUS changes. Lesions that progress into higher grade HSIL are HPV 16 positive.

Regression of a lesion into normal findings is more frequent in ASCUS changes in 30.6% with 10.5% HPV 16

Observation ASCUS	NIML	ASCUS	LSIL	HSIL
124	38	72	12	2
%	30.6%	58.0%	9.6%	1.6%

Table 3. Results of the monitoring of women with ASCUS lesion during a 12-month period

Observation LSIL	NIML	ASCUS	LSIL	HSIL
111	15	14	72	10
%	13.5	12.6	64.8	9.0

Table 4. Results of monitoring of women with LSIL during a 12-month period

Progression	ASCUS	LSIL	P<0.05
HSIL	1.6% (N-2)	9% (N-10)	P<0.05 (X^2 -4.596)
HPV 16 pos	100% (N-2)	90% (N-9)	P>0.05

Table 5. Grade of progression of lesions in HSIL in regards to HPV16

Regression	ASCUS	LSIL	P<0.05
Normal findings	30.6% (N-38)	13.5% (N-15)	Exists (X^2-5.552)
HPV 16 positive	10.5% (N-4)	46.6% (N-7)	Exists (X^2-4.732)

Table 6. Regression of lesions in normal findings in regards to HPV 16

positive, and is statistically more significant in regards to regression from LSIL into normal findings in 13.5% with 46.6% positive HPV (Table 6).

Progression of ASCUS in LSIL is found in 9.6% (N-12), and regression from LSIL in ASCUS is 12.6% (N-14), which shows that a grade of regression of LSIL in ASCUS is bigger by 3%. Progression of ASCUS and LSIL into HSIL is not found in patients with low-risk HPV 6 and 11 infection.

5. DISCUSSION

The nature of history of cervical cancer contains reversible changes in the cervix tissue, in which there are no neoplastic changes in squamous epithelial, to different grades of abnormal changes in cells that conditionally lead to cervical carcinoma. Risk factors for progression of ASCUS and LSIL changes, that lead to a higher grade HSIL, are connected with high-risk HPV 16. Namely, many researches confirm a high percentage of HPV 16 in cervical carcinoma, so accordingly, ASCUS and LSIL can progress into a HSIL and invasive cervical carcinoma, or can regress to normal findings, depending on numerous factors, most important being a HPV 16 infection (6). Our research showed that HPV 16 is the most common type of virus found in ASCUS and LSIL in 50.5% of cases. HPV 16 is found in a single form in 40.9% (N-18) women with ASCUS (N-3) and LSIL (N-15), and combined with other high-risk types HPV 18, 31, 33, 39 in 59% (N-26). In researches HPV 16 and 18 were confirmed in over 70% of cervical cancers, 41% to 67% HSIL, 16% to 32% LSIL. HPV 16 and 18 are the most common types, followed by: HPV 31, 33, 45, 52 and 58 that are found in 20% of cervical carcinoma in the world (7,8).

Nicolas states that 32% ASCUS, LSIL 61%, and HSIL 71% are HPV positive (6). Manos finds 40 to 50% HPV in ASCUS, which is in accordance to our results, which are the positive HPV is found in ASCUS lesions in 50% and LSIL in 63% of cases. High-risk HPV is significantly more frequent to be found as the lesion grows. The percentage of representation of HPV is significantly more frequent in HSIL (90% to 100%). Untreated LSIL can progress in 13% of cases to HSIL during 2 years of monitoring (9,10). Women infected with HPV 16 have a transition of LSIL into HSIL in 9% of cases. We found a progression from ASCUS to HSIL in 1.6% (N-2) and LSIL in 9.6% (N-12). With similar researches during a 12-month period, a progression of ASCUS in LSIL and HSIL was monitored and found that a progression in LSIL occurs in 13.6% (N-11) and in HSIL in 2.5% (N-2) of cases (11). Results with a somewhat bigger percentage of progression were found by Barken, who states that 13% to 16% of untreated LSIL progresses into cervical carcinoma (12). Regression of HPV infection can occur spontaneously, but in 10-20% of women that infection persists and these women have a risk of developing LSIL, HSIL or cervical carcinoma (13). Monitoring data of untreated ASCUS and LSIL lesions state that LSIL regresses in 28.9%, and ASCUS in 29.8%. LSIL persists in 52.6%, and ASCUS in 58% of cases (14).

During analysis we found the persistence of ASCUS in 58%, a regression in 30.6% of cases. Persistence of LSIL was found in 64%, regression in 26%, ASCUS in 12.6% and normal findings in 13.6% of cases. In his study, Cortes found a bigger spontaneous regression of LSIL in 50% and a smaller progression of HSIL in 6% of cases during two years of monitoring. Other authors also found a bigger regression of LSIL in 57%, and a smaller persistence than ours in 32%, while progression to HSIL in 11% was similar to ours (15,16). A few authors wrote about a big regression of medically untreated LSIL (17,18,19).

From the above mentioned data, progression is higher in women with HPV 16 and LSIL than in women with ASCUS and HPV 16, but regression is faster in HPV negative women with ASCUS and LSIL than in HPV 16 positive.

Progression of lesions, ASCUS and LSIL, into HSIL did not occur in patients with low-risk HPV 6 and 11 infection.

According to research, intensive monitoring and treatment of women with ASCUS and LSIL and HPV 16 positive findings is needed. Colposcopy and minimal invasive methods of treatment are a choice for prevention of high-grade lesions and cervical carcinoma in these findings.

Cytology combined with HPV typing is the best method of choice which can direct a general practitioner in the sense of patient monitoring.

6. CONCLUSION

Women infected with HPV 16 have more a frequent progression of a lesion into higher grade HSIL. They should be intensively monitored because of the increased risk for development of cervical carcinoma.

- **Declaration of Patient Consent:** The authors certify that they obtained all appropriate patient consent forms.
- **Authors contribution:** Each author has been included in all steps of preparation this article. Final proof reading was made by the first author.
- **Conflict of interest:** None declared.
- **Financial support and sponsorship:** Nil.

REFERENCES

1. Bruni L, Albero G, Serrano B, Mena M, Gomez D, Munoz J, Bosch F, Sanjose S. ICO/IARC Information Centre on HPV and Cancer (HPV Information Centre). Human Papillomavirus and Related Disease in Bosnia &Herzegovina. Summary Report. 2019:1-64. https://www.hpvcentre.net/statistics/reports
2. Arslan E, Gokdagli F, Bozgad H, Vatansever D, Karsy M. Abnormal Pap smear frequency and comparison of repeat cytological follow-up with colposcopy during patient management: the importance of pathologist's guidance inthe managment. Opstet Gynecology. 2019;6(1):69-74.
3. Bassal R, Schejter E, Bachar R, Shapira H, Sanbank J, Supino Rosin J et al. Cervical pap screening among Israeli women, 2005-2010. Arch Gynecol Obstet. 2014; 289:615-622.
4. Gallo G,Bibbo M, Bagella L, Zamparelli A, Sanseverino F, Giovangoli M, Vecchione A, Giordano A. Study of viral integration of HPV-16 in young patients with LSIL. J Clin Pathol. 2003;56:532-536.
5. Kyeong S, Seon K, Yoo L, In L, at ol. Rissk factor for cytological progresion in HPV 16 infected women with ASC-US or LSIL:The Korean HPV cohort. Obstet Gynecol Sci. 2018;61(6):662-668.
6. Nicolas F, Schlecht R, Platt E, Maria C, Joa P, Jose M at al. Human Papilloma virus Infection and Time to Progression and Regression of Cervical Intraepithelial Neoplasia. Journalof the National Cancer Institute. 2003;95: 1336-1343.
7. Santos AL, Derchain SF, Sarian LO, et al. Performance of Pap smear and human papilloma virus testing in the follow-up of women with cervical intraepithelial neoplasia grade 1 managed conservatively. Acta Obstet Gynecol Scand. 2006; 85: 444.
8. Pretorius RG, Peterson P, Azizi F, Burchette RJ. Subsequent risk and presentation of cervical intraepithelial neoplasia (CIN) 3 or cancer after a colposcopic diagnosis of CIN 1 or less. Am J Obstet Gynecol. 2006; 195: 1260.
9. Poomtavorn Y, Suwannarurk K, Thaweekul Y, Maieang K. Risk factors for high-grade cervical intraepithelial neoplasia in patients with atypical squamous cells of undetermined significance (ASCUS) Papanicolaou smears. Asian Pac J Cancer Prev. 2011;12:235-238.
10. Jahić M, Jahić E, Mulavdić M, Hadžimehmedović A. Difference Between Cryotherapy and Folloe Up Low Grade Squamous lesion of Cervix Uteri. Med Arch. 2017; 71 (4):280-283.
11. Castle PE, Sider M, Jeronimo J, Solomon D, Schifman M. Risk assesment to guide the prevention of cervical cancer. Am J Opstet Gynecol. 2007;197:351-356.
12. Barken S, Rebolj M, Anderson E, Lynge B. Frequency of cervical intraepithelial neoplasia in weli-screened population. Int J Cancer. 2012;130:2438-44.
13. Cortes C, Gonzalez E, Morales J, Poblet E. Genotype as prognostic factor in cervical intraepithelial neoplasia grade I lesions. J Turk Ger Gynecol Assoc. 2017; 18: 1-8.
14. Jahic M, Jahic E. Diagnostic approach to patients with atypical squamous cells of undetermined significance cytological findings on cervix. Med Arch. 2016: 70 (4): 296-8.
15. Manos M, Kinney W, Hurley L, Sherman M, Shien-Ngai J, Kurman R, Fetterman B, Hartinger J, Mcintosh K, Pawlick G, Hiat R. Identifyng women with cervical neoplasia: using human papilloma virus DNA testing for equivocal Papanicolau results. JAMA. 1999;281:1605-1610.
16. Nomelini R, Guimaras P, Candido P, Campos A, Michelin M, Murta E. Prevention of cervical cancer in women with ASCUS in the Brazilian Unified National Health System: cost – effectiveness of the molecular biology method for HPV detection. Cad Saude Publico, Rio de Janeiro. 2012;28(11):2043-2052.
17. Jahić M. Infekcije grlića materice i vagine i krioterapija. Tuzla. Identity. 2017:222-223.
18. Ho GY, et al. Natural history of cervicovaginal papillomavirus infection in young women. N Engl J Med. 1998;338(7):423–428.
19. Yanofsky V, Patel R, Goldenberg G. Genital warts. J Clin Anesthet Dermatol. 2012;5(6):25-36.