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Practical application of modified ASCCP 2019 algorithms in the diagnosis and early detection of cervical pathology

Klaudyna Madziar, Witold Kedzia

Division of Gynecology, Department of Perinatology and Gynecology, Gynecology and Obstetrics Clinical Hospital, Karol Marcinkowski University of Medical Sciences, Poznan, Poland

ABSTRACT

Objectives: We assessed the risk for the high-grade precancerous CIN 2 (+) in women with HSIL and ASC-H depending on HPV status.

Material and methods: A retrospective analysis of results of cervical cancer screening following the current ASCCP recommendations by co-testing (LBC and molecular HPV DNA HR) performed between 2018 and 2022 in the Laboratory of Cervical Pathology, Obstetrics and Gynecology Hospital of Poznan University of Medical Sciences. Patient ages ranged from 22 to 72 years.

Results: The analysis of abnormal results of liquid-based cytology revealed the following: 1 suspicion of cervical carcinoma, 49 HSIL, 97 ASC-H, 95 LSIL, 92 ASCUS, and 4 AGC cases. Histopathological verification of the biopsy samples revealed a total of 288 abnormal results. CIN 2 (+) lesions were found in 127 women. ASC-H was the most common abnormal cytologic finding. Of the 338 molecular test results for HPV DNA HR, 85% were confirmed positive. A positive molecular signal confirming the presence of human papillomavirus on PAP smear was not homonymous with simultaneous histopathological diagnosis of cervical pathology.

Conclusions: There is a high risk for CIN 2 (+) in patients with HSIL and HPV 16 (+) and/or HPV DNA HR (+), as well as ASC-H and HPV 16 (+). HSIL is rarely observed in women with HPV 16 (–). The risk for CIN 2 (+) in women with ASC-H and HPV (–) is low.

Key words: cervical intraepithelial neoplasia; uterine cervical neoplasms

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INTRODUCTION

Cervical cancer is the fourth most common malignancy among women globally [1]. It is significantly more often detected in developing countries. Unlike in the case of other malignant neoplasms, the etiology of cervical cancer is associated with a chronic viral infection. Human papillomavirus (HPV), with its 100 subtypes, is predominantly a sexually transmitted disease. The risk factors for HPV include the following: promiscuity, high gravidity and parity, early age at sexual initiation, lower immunological response, smoking, and long-term use of contraceptives [2].

Currently, equal attention is being paid to developing active primary and secondary prevention of cervical cancer through screening programs. Finland and Switzerland have been the two pioneers among the European countries with national screening programs for cervical cancer prevention, which minimized morbidity and mortality rates for that malignancy. As far as Poland is concerned, the National Population-Based Cervical Cancer Screening Program was suspended in 2015, ten years since its launch. While the program was still operational, personalized invitations for a PAP smear were issued to Polish women. Canceling the program has resulted in meager attendance rates for screening tests and low awareness about cervical cancer prevention and early detection methods.

Data from the International Agency for Research on Cancer on morbidity rates for malignant neoplasms illustrate the current epidemiological situation regarding cervical cancer. According to the 2020's report, cervical cancer was diagnosed in 1.9 % of the population. It was the sixth most

Corresponding author:
Klaudyna Madziar
Division of Gynecology, Department of Perinatology and Gynecology, Gynecology and Obstetrics Clinical Hospital, Karol Marcinkowski University of Medical Sciences,
33 Polna St, 60–535 Poznan, Poland
e-mail: klaudyna.madziar@gmail.com

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prevalent malignancy among Polish women, with 3862 absolute cases per year and 2137 deaths in 2020 alone [3].

In the USA, where screening programs have been active since the 50s of the previous century [4], liquid-based cytology (LBC) is used in the diagnostic process, and molecular testing for HPV is a standard medical procedure. In 2019, the new guidelines of the American Society for Colposcopy and Cervical Pathology (ASCCP) for the management of abnormal cervical cancer screening test results and cancer precursors were introduced in the USA [5]. Their goal is to calculate the risk for developing at least high-risk intraepithelial neoplasia of the cervix, cervical intraepithelial neoplasia (CIN) 3 (+), based on medical history as well as current and previous screening test results [6]. High-risk HPV molecular test (HPV DNA HR), which can identify 14 highly oncogenic HPV types (16,18,31,33,35,39,45,51,52,56,58,59,66,68) [7], has replaced the PAP smear as the main screening tool. Also, the time gap between the diagnosis of high-grade squamous intraepithelial lesion (HSIL) to cervical conization with LEEP (Loop Electrosurgical Excision Procedure) has been shortened, allowing to defer colposcopy-directed biopsy in special cases. The new guidelines, designed based on the Kaiser Permanente prospective cohort in North California, including 1.5 million women, have been built on the assumption that the number of women with CIN grade 3 (+) in the USA decreases as a consequence of high rates of attendance for vaccine and screening test appointments [6].

Objectives

The study aimed to assess the risk for the following:

1. high-grade precancerous CIN 2 (+) (CIN 2 and CIN 3) in women with HSIL, HPV 16 (+) and women with HSIL, HPV 16 (+) and/or HPV HR (+);
2. high-grade precancerous CIN 2 (+) in women with HSIL, HPV (–);
3. high-grade precancerous CIN 2 (+) in women with ASC-H, HPV 16 (+) and/or HPV HR (+);
4. high-grade precancerous CIN 2 (+) in women with ASC-H, HPV (–).

MATERIAL AND METHODS

A total of 338 results of liquid-based cytology, performed between 2018 and 2022, were retrospectively analyzed. The patients reported for routine screening in the Laboratory of Cervical Pathology, Obstetrics and Gynecology Hospital of Poznań University of Medical Sciences. Patient ages ranged from 22 to 72 years. Following the current ASCCP recommendations, all patients underwent cervical cancer screening by co-testing (LBC and molecular HPV DNA HR) [8, 9].

As far as HPV DNA HR detection was concerned, the material obtained from the ectocervix and vaginal fornix using a Cervex-Brush® was placed in a liquid Roche Cell Collection Medium without the brush. The Cobas® 4800 Human Papillomavirus (HPV) Roche Diagnostics qualitative test was used for the analysis. Target amplification was used for DNA analysis by polymerase chain reaction (PCR) and nucleic acid hybridization. That method allowed for HPV 16/18 genotyping, irrespective of other highly oncogenic types.

All smears graded as HSIL and ASC-H (Atypical Squamous Cells, Cannot Rule Out High-Grade Squamous Intraepithelial Lesion) were re-evaluated for this study. The local Bioethics Committee approved this retrospective study to be included in a Ph.D. dissertation. PQStat Software was used for statistical analysis [10].

RESULTS

The analysis of 338 abnormal results of liquid-based cytology (LBC) revealed the following: 1 suspicion of cervical carcinoma, 49 HSIL, 97 ASC-H, 95 LSIL (Low-grade Squamous Intraepithelial Lesion), 92 ASCUS (Atypical squamous cells of undetermined significance), and 4 AGC (Atypical Glandular Cells) cases. Histopathological verification of the biopsy samples obtained from the 338 women with abnormal smear results is presented in the second part of Table 1. A total of 288 abnormal results were detected on histopathology. Cervical carcinoma was confirmed in 15 patients; HSIL — CIN 2 (+) lesions were found in 127 women.

ASC-H was the most common (29%; 97/338) abnormal cytologic finding, followed by LSIL (28%; 95/338) and ASCUS (27%; 92/338). Histopathological verification detected cervical carcinoma in 5% (15 out of the 288 abnormal histopathology findings) of the investigated women. Pathomorphological diagnosis of HSIL was most often confirmed for cytologic findings of HSIL (76%; 37/49) and ASC-H (43%; 42/97). Cervical carcinoma was confirmed in two and disconfirmed in two of the four women with AGC cytology.

Of the 338 molecular test results for HPV DNA HR, 293 (85%) were positive. The correlation between abnormal cyto-oncologic findings and HPV DNA HR status is presented in Table 2. A positive molecular signal confirming the presence of oncogenic human papillomavirus on PAP smear was not homonymous with simultaneous histopathological diagnosis of cervical pathology. The presence of at least CIN 1/LSIL was histologically confirmed in only 77% (261/338) of the investigated women with a positive HPV DNA HR test result. The highest rate of positive molecular tests (100%) was found for cases with the diagnosis of cervical carcinoma at cytology, followed by HSIL (94%; 46/49).

Of the 338 smears, 288 were further analyzed, with the cyto-oncologic diagnosis of HSIL or ASC-H as the threshold criterion for further analysis. Each eligible patient underwent an obligatory molecular test for 14 oncogenic HPV types.

The results of the histopathological correlation between patients with HSIL, HPV 16 (+), HSIL, HPV HR (+), and HSIL,

Table 1. Histopathological verification of the following smear results: high-grade squamous intraepithelial lesion (HSIL), atypical squamous cells cannot rule out high-grade squamous intraepithelial lesion (ASC-H), low-grade squamous intraepithelial lesion (LSIL), atypical squamous cells of undetermined significance (ASCUS), atypical glandular cells (AGC), n = 338

Abnormal cytology result		[%]	Abnormal histopathology result	Carcinoma	[%]	Hist. HSIL (CIN 2 +)	[%]	Hist. LSIL	[%]	Koilocytes	[%]	Normal Histopathology result	[%]
Carcinoma	1/338	1		0/1		1/1	100	0/1		0/1		0/1	
HSIL	49/338	14		4/49	8	37/49	76	2/49	4	3/49	6	3/49	6
ASC-H	97/338	29		6/97	6	42/97	43	18/97	19	17/97	18	14/97	14
LSIL	95/338	28		0/95		29/95	31	40/95	42	16/95	17	10/95	10
ASCUS	92/338	27		3/92	3	18/92	20	26/92	28	24/92	26	21/92	23
AGC	4/338	1		2/4	50	0/4		0/4		0/4		2/4	50
Total	n = 338	n = 100	n = 288	15/288	5	127/288	44	86/288	30	60/288	21	n = 50	

Values are expressed as a percentage, rounded to the nearest integer

Table 2. Correlation between abnormal cytology result and molecular human papillomavirus (HPV) DNA HR test, n = 338

Abnormal cytology result		[%]	HPV DNA HR (+)	[%]	HPV DNA HR (-)	[%]
Carcinoma	1/338	1	1/1	100	0/1	
HSIL	49/338	14	46/49	94	3/49	6
ASC-H	97/338	29	81/97	84	16/97	16
LSIL	95/338	28	86/95	91		9
ASCUS	92/338	27	75/92	82	17/92	18
AGC	4/338	1	4/4	100	0/4	
Total	n = 338	n = 100	n = 293		n = 45	

Values are expressed as a percentage, rounded to the nearest integer; HSIL — high-grade squamous intraepithelial lesion; ASC-H — atypical squamous cells, cannot rule out high-grade squamous intraepithelial lesion; LSIL — low-grade squamous intraepithelial lesion; ASCUS — atypical squamous cells of undetermined significance; AGC — atypical glandular cells

Table 3. Histopathological correlation between cervical intraepithelial neoplasia (CIN) 2 (+) and high-grade squamous intraepithelial lesion (HSIL) cytology and molecular human papillomavirus (HPV) DNA HR testing

Histopathology result	HSIL, HPV 16 (+)	[%]	HSIL, HPV 16 (+) i/lub HR (+)	[%]	HSIL, HPV DNA HR (-)	[%]
Carcinoma	4/33	12	4/46	9	0/3	
CIN 3	13/33	40	18/46	39	0/3	
CIN 2	11/33	33	17/46	37	2/3	67
CIN 1	1/33	3	2/46	4	0/3	
Koilocytes	2/33	6	3/46	7	1/3	33
Normal histopathology result	2/33	6	2/46	4	0/3	
Total	n = 33	100	n = 46	100	n = 3	100

Values are expressed as a percentage, rounded to the nearest integer

HPV DNA HR (-) are presented in Table 3. Notably, in a group of 49 patients with the cyto-oncologic diagnosis of HSIL, HPV was detected in all but three women. CIN 2 on histopathology was found in two, and only koilocytes were detected in one out of the three women.

The results of histopathological correlation between the patients with the diagnosis of ASC-H, HPV DNA HR (+) and ASC-H, HPV DNA HR (–) are presented in Table 4.

A statistical analysis was conducted to correlate the results of cytology, the molecular HPV test, and histopathological evaluation. Relative risk (RR) for CIN 2 (+) lesions in different clinical situations was assessed. Data are presented in Table 5.

The highest statistically significant relative risk for CIN 2 (+) was calculated for HSIL, HPV 16 (+) and/or HR (+) (RR = 2.578), as well as for HSIL, HPV 16 (+) (RR = 2.328).

Table 4. Histopathological correlation between cervical intraepithelial neoplasia (CIN) 2 (+) and ASC-H [Atypical squamous cells, cannot rule out high-grade squamous intraepithelial lesion] cytology and molecular human papillomavirus (HPV) DNA HR testing

Histopathology result	ASC-H, HPV DNA HR (+)	[%]	ASC-H, HPV DNA HR (–)	[%]
Carcinoma	3/81	4	0/13	
CIN 3	22/81	27	0/13	
CIN 2	16/81	20	3/13	23
CIN 1	16/81	20	2/13	15
Koilocytes	15/81	19	1/13	8
Normal histopathology result	9/81	10	7/13	54
Total	n = 81	100	n = 13	100

Values are expressed as a percentage, rounded to the nearest integer

Table 5. Statistical analysis of relative risk for cervical intraepithelial neoplasia (CIN) 2 (+) lesion

Objectives	CIN 2 (+) lesion and	RR	95% CI	p value
1. Risk assessment for high-grade precancerous CIN 2 (+) in women with HSIL, HPV 16 (+) and women with HSIL, HPV 16 (+) and/or HPV HR (+)	HSIL, HPV 16 (+)	2.328	1.827–2.968	< 0.00001
	HSIL, HPV 16 (+) and/or HPV HR (+)	2.578	2.068–3.215	< 0.00001
2. Risk assessment for high-grade precancerous CIN 2 (+) in women with HSIL, HPV (–) cytology	HSIL, HPV (–)	Such assessment cannot be performed		
3. Risk assessment for high-grade precancerous CIN 2 (+) in women with ASC-H, HPV 16 (+) and/or HPV HR (+) cytology	ASC-H, HPV 16 (+)	1.3286	0.959–1.841	0.0438
	ASC-H, HPV HR (+)	1.1283	0.587–2.169	0.3587
4. Risk assessment for high-grade precancerous CIN 2 (+) in women with ASC-H, HPV (–) cytology	ASC-H, HPV (–)	0.7215	0.263 – 1.976	0.6351
	ASC-H, HPV HR (+), HPV 18 (+)	1.0867	0.712–1.658	0.3499
	ASC-H, HPV 16 (–)	0.953	0.638–1.424	0.4071
	HPV 16 (+) and/or HPV 18 (+)	1.4367	1.153–1.790	0.0006
	HPV 16 (+)	1.4724	1.175–1.845	0.0004
	HPV 18 (+)	2.297	0.661–7.98	0.0953
	HPV HR (+)	0.9343	0.772–1.130	0.2423

RR — relative risk; CI — confidence interval; p value — probability value; r; HSIL — high-grade squamous intraepithelial lesion; HPV — human papillomavirus; ASC-H — atypical squamous cells, cannot rule out high-grade squamous intraepithelial lesion

Statistically, significantly the lower relative risk for CIN 2 (+) was detected for ASC-H, HPV 16 (+) (RR = 1.3286). Statistical analysis revealed high relative risk of CIN 2 (+) lesions for HPV 16 (+) and/or HPV 18 (+), as well as only HPV 16 (+). Notably, a low relative risk of CIN 2 (+) was detected for HPV 18 (+).

DISCUSSION

The latest 2019 ASCCP guidelines introduce the so-called 'expedited pathway' between cytological diagnosis and treatment of patients with HSIL HPV 16 (+), HPV HR (+), and ASC-H/HPV (+). The path offers a shortcut between cyto-molecular findings and cervical conization, with colposcopy and biopsy being deferred altogether. In that way, the cyto-molecular results approach the gold-standard level, *i.e.*, the pathomorphological findings, which, until the 2019 ASCCP recommendations, had been the only indispensable eligibility criterion for cervical conization.

Attempts are being made to implement that algorithm in Poland, but severe concerns surrounding the issue should not be ignored. The diagnostic value of cyto-diagnosis, the basis of the new modification according to ASCCP, is high and surpasses the sensitivity and specificity of Polish diagnostic standards. Liquid-based cytology offers a significantly higher diagnostic quality than conventional cytology used most often in Poland, not to mention the technicians' assessment standards, experience, and qualification. In Poland, molecular diagnostics is not included in standard algorithms for prevention programs that the National Health Fund reimburses. In light of the above, there is cause for concern regarding a swift one-to-one transfer of the ASCCP standards to Poland without making allowances for the local standards of diagnostic testing.

In this study, we aimed to verify the accuracy and safety of the ASCCP management guidelines for women with the cyto-oncological diagnosis of HSIL and HPV 16 positive mo-

lecular test in Polish conditions. As was already mentioned, the issue's core is the quality of cyto-diagnostics. In this study, maximum sensitivity and specificity of the cytologic assessment were ensured by using LBC and employing skilled and experienced cytotechnologists accustomed to the high standards of prevention and early detection of cervical cancer. As a result, the correlation between cytology findings and the final histopathological assessment was 85%. Also, it is possible to detect certain regularities in the analyzed sample, typical for the results reported by long-term British screening programs. The number of abnormal results in each category is inversely proportional to the intensity of the morphological changes. The lowest number of detections was associated with carcinoma (1/338) and HSIL (49/338), while the highest with cytology findings of low clinical significance: LSIL (95/338) and ASCUS (92/338).

The scale of histopathological verification is yet another proof of the high sensitivity of the cytologic findings. Higher correlation rates between cyto-diagnostics and histopathology correspond to a more reliable quality of the diagnostics [11]. In this study, special care was taken when analyzing the cytological findings of HSIL and carcinoma, and the correlation scale was the highest for those cases — 100% for carcinoma and 76% (37/49) for HSIL CIN 2 (+). The lower clinical significance of the cytological results corresponds to lower correlation rates with histopathological HSIL abnormalities — 31% (29/95) for LSIL and 20% (18/92) for ASCUS cytology.

The obtained results demonstrate a distinct correlation between statistically significantly higher risk for CIN 2 (+) lesion, *i.e.*, pathomorphological HSIL, and cytology result defined as HSIL and the presence of DNA HPV in a molecular test performed on the liquid base used for cytology.

For this study, the threshold for clinical analysis was set at CIN 2 (+) instead of CIN 3 (+), meaning the investigation estimated relative risks and correlations between CIN 2/CIN 3 and carcinoma versus HSIL, ASC-H cytology, and the molecular test result, with genotyping. Lowering the threshold to CIN 2 (+) was based on the assumption that CIN 2 and CIN 3 are jointly defined as pathomorphological HSIL. Immunohistochemical identification of protein p16 suppressor might constitute an objective boundary, separating the two precancerous stages into high- and low-risk. As the new guidelines do not mention the need to categorize the advancement of the lesion and its prognostic importance using immunohistochemistry, differentiation between CIN 2 and CIN 3 is subjective, and the clinical significance of both changes is comparable, as is the recommended therapeutic management. The highest relative risk for correlation between HSIL cytology and CIN 2 (+) was detected for cases when the molecular test was positive for HPV 16 and/or any other 13 genotypes analyzed in this study. A slightly lower risk was found for HSIL cytology and positive type 16 HPV. Rebecca B. Perkins has presented identical proportions for the relative risk scale. According to that author and data from 2019 ASCCP guidelines, the correlation between CIN 3 (+) and HSIL cytology and molecular DNA HPV HR testing is the highest and amounts to 65% [6]. Notably, the term "DNA HPV HR" encompasses all 14 types of HPV, together with 16 and 18. According to Perkins, a lower correlation is found if HSIL cytology is combined with a positive HPV 16 (+) test. Both high relative risk ratio and statistical significance of the observed correlations support the validity of the new updated 2019 ASCCP recommendation to perform LEEP conization in the affected patients, provided they are 25 years or older, without the unnecessary delay due to colposcopy, biopsy, and pathomorphological testing. According to ASCCP, the risk for CIN 3 (+) in those women has been estimated at 60–100%.

The correlations detected in this study demonstrate a possibility of expanding the 2019 ASCCP recommendations about immediate excision in women with HSIL/HPV 16 (+) cytology and patients with HSIL/HPV HR (+) cytology, with or without HPV 16. Further research is necessary, with a larger sample size, to test and verify that modification. The relevance and purpose of performing molecular tests are additionally validated by not a single case of HSIL cytology but a negative molecular test found in the group of 288 women in our study. Also, it bears evidence of the quality of the cyto-diagnostics performed in this study.

Such a scenario was considered by Perkins, who estimated the risk of CIN 3 (+) at 25%. The author mentions two alternative paths: colposcopy or expedited treatment, i.e., LEEP conization. This study found a low probability of cases when patients with HSIL cytology have negative molecular test results. Such a situation may occur due to the limitations of the molecular testing method, which typically identifies 'only' 14 most common HPV types. The low-risk HPV types have meager oncogenic potential and rarely correlate with CIN 3 (+) lesions. We believe that the diagnostic algorithm in such situations should be based on colposcopy and not expedited treatment. Interesting results were obtained for CIN 2 (+) risk in cases with ASC-H cytology and either positive or negative DNA HPV HR molecular test result. The highest relative risk ratio for CIN 2 (+) was calculated for ASC-H cytology and DNA HPV 16. The correlation in question was statistically significant, and it is the only clinical situation with ASC-H cytology that reaches statistical significance. It needs to be emphasized that the relative risk ratio for ASC-H cytology does not exceed half of the relative risk value demonstrated for HSIL/HPV 16 (+) cytology. The abovementioned Perkins has estimated the risk for CIN 3 (+) in ASC-H, HPV (+) and ASC-H, HPV (–) women at 26% and 25%, respectively, suggesting either colposcopy or expedited treatment for both scenarios. In our study, only one clinical situation has

remarkable results, namely ASC-H cytology and positive molecular HPV 16. We believe that the relative risk value and statistical significance are reason enough to recommend expedited treatment, i.e., LEEP conization. We recommend the traditional diagnostic-therapeutic algorithm (colposcopy and treatment after biopsy results, if necessary) for the remaining clinical situations with ASC-H cytology. Those remaining clinical situations with ASC-H cytology — ASC-H/HPV 16 (–) and ASC-H HPV HR (+) — have a low relative risk for CIN 2 (+), and the correlations lack statistical significance. Also, the correlation between ASC-H cytology and the presence of CIN 2 (+) does not exceed 43%.

To sum up, the 'expedited pathway' between cytology and conization in the context of the molecular test result, recommended by ASCCP, is feasible for the CIN 2 (+) threshold established in our study and certain clinical situations, namely: HSIL cytology with DNA HPV 16 (+), HSIL cytology with DNA HPV 16 (+) and/or DNA HPV HR (+), ASC-H cytology with DNA HPV 16 (+).

The value of the relative risk for CIN 2 (+) in the context of the molecular test alone, without the cyto-diagnostics, should not be overlooked either. The high relative risk for CIN 2 (+) was detected in two clinical situations, both of which reached statistical significance, namely DNA HPV 16 (+) and DNA HPV 16 and/or HPV 18 (+). The latest ASCCP guidelines took note of that correlation and recommend colposcopy for women with positive HPV 16 or 18 molecular test. Our findings also support the validity of these recommendations.

CONCLUSIONS

1. High risk for CIN 2 (+) is found in patients with HSIL and positive molecular test for HPV 16 and/or high-risk oncogenic HPV.
2. HSIL is rarely observed in women with negative molecular DNA HPV 16 test results.
3. High risk for CIN 2 (+) is associated with the diagnosis of ASC-H cytology and HPV 16 (+). The risk is lower than the correlations presented in the first conclusion for HSIL cytology.
4. The risk for CIN 2 (+) in women with ASC-H cytology and HPV (–) is low.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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