VIA MEDICA

ORIGINAL PAPER / GYNECOLOGY

Ginekologia Polska
2022, vol. 93, no. 1, 11–17

ISSN 0017–0011, e-ISSN 2543–6767

DOI 10.5603/GP.a2021.0167

Human papillomavirus genotyping in high-grade squamous intraepithelial lesion

Marcin Przybylski[1, 2], Sonja Millert-Kalinska[1, 3], Andrzej Zmaczynski[4], Rafal Baran[4], Lucja Zaborowska[4], Robert Jach[4], Dominik Pruski[1, 5]

[1]Department of Obstetrics and Gynecology, District Public Hospital in Poznan, Poland
[2]Marcin Przybylski M.D. Gynecology Specialised Medical Practice Poznan, Poland
[3]Poznan University of Medical Sciences, Poland
[4]Department of Gynecology and Obstetrics, Jagiellonian University Collegium Medicum, Cracow, Poland
[5]Dominik Pruski M.D. Gynecology Specialised Medical Practice Poznan, Poland

ABSTRACT

Objectives: Human papillomavirus infection is one of the most common sexually transmitted infections. Long-term exposure to the HPV leads to high-grade squamous intraepithelial lesions affecting cervical cancer. Knowledge about the distribution of HPV genotypes is crucial to guide the introduction of prophylactic vaccines. We aimed the genotype distribution in patients reporting due to abnormal Pap — smear tests.

Material and methods: We provide a prospective observational cohort study. We obtained material from 428 women registered to Provincial Hospital in Poznan and Specialist Medical Practice in 2018–2021. In the current study, we analyze results from the first 110 inclusions with the diagnosis of HSIL from a cervical biopsy.

The probe for the molecular test was collected with a combi brush and passed to an independent, standardized laboratory. HPV detection was done using PCR followed by DNA enzyme immunoassay and genotyping with a reverse hybridization line probe assay. Sequence analysis was performed to characterize HPV-positive samples with unknown HPV genotypes. The molecular test detected DNA of 41 HPV genotypes. We performed statistical analyzes using the STATISTICA package 13.3.

Results: We found that 98.2% of patients received HPV-positive test results. The most frequent HPV genotype was 16, which assumed for 54.1%. In patients negative for HPV 16, the percentage decreased with increasing age. We detected that the following HPV types are next most common: HPV 31 (16.2 %), HPV 52 (11.7%), HPV 51 (9.9%), HPV 18 (9.0%), HPV 33 (9%). Moreover, thyroid diseases were the most common comorbidities and occurred in 15 patients.

Conclusions: To our knowledge, this study is the most extensive assessment of HPV genotypes in HSIL diagnoses in Poland.

Key words: HPV genotyping; HSIL; high-grade lesion; cervix biopsy

Ginekologia Polska 2022; 93, 1: 11–17

INTRODUCTION

Cervical cancer remains the fourth most common cancer in women worldwide, causing about 275,000 deaths annually [1, 2]. Cervical cancer mortality has decreased significantly in recent decades, especially in developed countries. Since the '90s, we have observed the same tendency in Poland, reflecting the improvement in the epidemiological situation. However, to achieve tremendous success, both preventive and therapeutic activities must be continued step by step. In Poland in 2014, cervical cancer was diagnosed in nine women a day, and nearly 50% died from it [3]. This direction of change is undoubtedly related to thriving preventive programs. In most countries, it is based on a typical Pap smear. The American College of Obstetricians and Gynecologists included the hrHPV DNA test in the screening guidelines in 2003 for the first time. Since 2013, subsequent reports, including current European guidelines, have shown the advantage of human papillomavirus (HPV) tests over traditional Pap-smear in women aged 30–65 [4, 5].

An abnormal cytology, a positive HPV test, or a suspicious cervical image indicate extended diagnostics. It comprises a colposcopy with a biopsy to look for precan-

Corresponding author:
Robert Jach
Department of Gynecology and Obstetrics, Jagiellonian University Collegium Medicum, Cracow, Poland
e-mail: jach@cm-uj.krakow.pl

Received: 8.06.2021 Accepted: 1.07.2021 Early publication date: 6.10.2021

cerous lesions. A biopsy diagnosis of high grade squamous intraepithelial lesion (HSIL) is the current threshold for excision of a precancerous lesion [6]. However, most HSIL will not progress to invasive cervical cancer (ICC) if not treated [7]. HSIL are heterogeneous and include both productive hrHPV infections and early and advanced transforming hrHPV lesions. Productive infections and early transforming infections may regress spontaneously [8]. In contrast, we should treat advanced transforming lesions without delay because of the risk of progression in a short time. Therefore, it is essential to select among HSIL patients those at increased risk so as not to expose everyone to invasive treatment. It especially concerns women in productive age, whose interventions may impact the future pregnancy.

The factor that has a significant impact on the development of cervical cancer is primarily persistent infection with high-risk HPV (hrHPV), leading to an uncontrolled course of the disease. The oncogenic potential of particular HPV genotypes has already been acknowledged. HPV is the indubitable etiological agent for SIL development and cervical cancer. Over 40 years ago, the role of human papillomavirus (HPV) in cervical cancer was established [9, 10]. Persistent infection with hrHPV is the direct cause of the majority of cervical intraepithelial neoplasia and invasive cervical cancers. Moreover, current data indicate that genotypes 16 and 18 are assumed to be responsible for about 70% of cervical cancer cases [11, 12].

This paper summarizes the results of HPV DNA genotyping in women diagnosed with HSIL in Poznan, Poland. So far, we do not have reliable data on the contribution of selected oncogenic HPV types in the formation of cervical pathology in the Polish population. To our knowledge, it is the most extensive analysis that has been described in Poland to date. We aim to provide distribution of particular HPV genotypes concerning age groups in women diagnosed with HSIL. This knowledge might enable estimating the potential effectiveness of primary prevention, which is HPV vaccination. Additionally, we aim to analyze the risk factors for developing HSIL lesions and the variables that may affect its more frequent occurrence.

MATERIAL AND METHODS

We present a prospective observational cohort study conducted in Provincial Hospital in Poznan and Specialist Medical Practice, Poland. Inclusion criteria were: 1) an abnormal cytological test result (≥ ASC-US), positive HPV test result or abnormal cervix image, 2) 18 years of age or older. The exclusion criteria were: 1) the previous diagnosis of ICC, 2) current pregnancy or pregnancy in the previous three months, 3) insufficient material for HPV genotyping.

We collected the data on relevant medical history, the number of sexual partners, parity and living status, using a standardized questionnaire from each subject. In the current study, we analyze results from the first 110 inclusions with the diagnosis of HSIL from a cervical biopsy.

We recruited 428 patients registered to Provincial Hospital in Poznan and Specialist Medical Practice between 2018 and 2021 because of either an abnormal Pap-smear result (≥ ASC-US) and positive HPV test result or abnormal cervix image resulting in the collection of material for histopathological examination. From all women, we distinguished those diagnosed with high-grade squamous intraepithelial lesions.

The follow-up schedule for all women included cytology every six months — close supervision for two years, then return to the routine screening program. Following colposcopy and LEEP conization was done in most cases. Women diagnosed with either negative for intraepithelial lesion (NILM), a negative result for HPV infection, or a typical cervix image did not require extended diagnosis and returned to the regular screening program.

Pap-smear and HPV genotyping

Parallel to the Pap-smear, we tested those women for the presence of HPV and determined their genotypes. The test material was obtained using a cervex-brush from the external os of the cervix and vaginal wall. The obtained specimen was placed into a liquid-based medium, ThinPrep PreserCyt Solution. An HPV test is a quality test. It serves to identify high- risk HPV DNA of the following genotypes: 6, 11, 16, 18, 26, 31, 33, 35, 39, 40, 42, 43, 44, 45, 51, 52, 53, 54, 55, 56, 58, 59, 61, 62, 64, 66, 67, 68, 68a, 68b, 69, 70, 71, 72, 73, 81, 82, 83, 84, 87, CP6108, 90 in vitro. A positive test in molecular test confirms the presence of DNA of at least one of the abovementioned oncogenic types of human papillomavirus in the collected specimens.

The probe for a molecular test (Linear Array HPV Genotyping-Roche Diagnostics) was collected with a combi brush and passed to an independent standardized laboratory. HPV detection was done using PCR followed by DNA enzyme immunoassay with a reverse hybridization line probe assay. Sequence analysis was performed to characterize HPV-positive samples with unknown HPV genotypes. The molecular test detected DNA of 41 HPV genotypes.

Colposcopy and LEEP-conization

If needed, following colposcopy and LEEP-conization were performed. A specialist in gynecologic oncology with 10-year experience examined colposcopy with SmartOPTIC colposcope. In all cases, a trial with a 5% aqueous solution of acetic acid was performed, as well as Schiller's test with Lugol's iodine. According to Reid's Colposcopic Index, the colposcopic images were evaluated, assessing the colour, lesion boundaries and surface, blood vessels, and iodine

Table 1. Descriptive characteristics of the study groups, means or n (%)

n	110
Age [yrs]	33.3
Living status	
City > 100,000 inh.	51 (46.4%)
Town or city < 100,000 inh.	59 (53.6%)
Parity	
0	50 (45.5%)
1–2	49 (44.5%)
≥ 3	11 (10.0%)
Comorbidities	40 (36.4%)
Thyroid disease	15 (13.6%)
PCOS/ prediabetes/DM type 1	6 (5.5%)
Fertility issues	5 (4.6%)
CVD	3 (2.8%)
Endometriosis	3 (2.8%)
HPV status	
(+)	108 (98.2%)
(–)	2 (1.8%)

PCOS — polycystic ovary syndrome; DM — diabetes mellitus; CVD — cardiovascular disease; HPV — human papillomavirus infection

test. All colposcopic images were archived. We used the International Federation of Cervical Pathology and Colposcopy classification and recommended by the Polish Society of Colposcopy and Cervical Pathophysiology.

Excisions were done with colposcopic guidance after application of acetic acid 5% and Lugol's iodine. The sizes of the loops were selected according to the size of the lesions. Finally, the curettage of the cervical canal was performed to obtain endocervix material. 12 to 16 paraffin blocks were created from each cervical specimen, and four to five sections were examined from each block. Histopathological analysis was performed in an independent laboratory by experienced pathologists.

All patients gave informed consent to participate in the study. The Bioethics Committee approved the study of the Medical Chamber of Wielkopolska on the 17th of March 2021 (95/2021).

Statistical analysis

We performed calculations using the statistical package Statistica (ver. 13.3) and graphs — using Excel. Statistical hypotheses were verified at the level of significance of 0.05. We performed the Pearson's Chi-square test to analyze the correlation between individual genotypes and age groups. We searched for other correlations between risk factors, and the occurrence of individual diagnoses using Pearson's Chi-square or Yates corrected Chi-square tests.

Table 2. The quantitative and percentage distribution of individual genotypes

HPV genotype	Presence n	Presence %	Deficiency n	Deficiency %
16	60	54.1	51	45.9
31	18	16.2	93	83.8
52	13	11.7	98	88.3
51	11	9.9	100	90.1
18	10	9.0	101	90.0
33	10	9.0	101	90.0
53	7	6.3	104	93.7
56	6	5.4	105	94.6
59	6	5.4	105	94.6
45	5	4.5	106	95.5
66	5	4.5	106	95.5
6	5	4.5	106	95.5
58	4	3.6	107	96.4
73	4	3.6	107	96.4
82	4	3.6	107	96.4
39	3	2.7	108	97.3
67	3	2.7	108	97.3
42	3	2.7	108	97.3
54	3	2.7	108	97.3
62	3	2.7	108	97.3
35	2	1.8	109	98.2
68	2	1.8	109	98.2
61	1	0.9	110	99.1
70	1	0.9	110	99.1
81	1	0.9	110	99.1
83	1	0.9	110	99.1

HPV — human papillomavirus

RESULTS

The mean age of the entire population was 33. Most patients had less than three children, and more than half lived in the town or city with less than 100,000 inhabitants. More than one-third of patients had comorbidities. The most frequent were the thyroid diseases, comprising hypothyroidism, Hashimoto's disease and Graves' disease. Thyroid diseases were the most common comorbidities and occurred in 15 patients, although we did not find statistical significance. We also observed cases of fertility issues, polycystic ovaries syndrome and Diabetes Mellitus type 1. Table 1 presents descriptive characteristics of the study group.

A total of 108 patients (98.2%) were positive for HPV DNA. The quantitative and percentage distribution of individual genotypes is presented in Table 2. Six genotypes were the most frequent in the study group- 16, 31, 52, 51, 18 and 33. They all belong to high-risk oncogenic HPV types.

Table 3. Relation between presence of HPV genotype 16 and age groups

Age groups	HPV genotype 16 presence					
	no		yes		all	
	n	%	n	%	n	%
< 30	21	43.7%	13	21.7%	34	31.5%
30–40	18	37.5%	37	61.7%	55	50.9%
> 40	9	18.8%	10	16.6%	19	17.6%
All	48	100.0%	60	100.0%	108	100.0%

HPV — human papillomavirus

The HPV genotype 16 accounted for 54.1% of all HPV-positive patients, and the result turned out to be statistically significant for the age groups (p = 0.027). Table 3. presents the relation between the presence of HPV genotype 16 and age groups. Among women who do not have the HPV genotype 16, the percentage of women under 30 years of age is twice as high as those of patients with HPV 16. In contrast, there were more women with the HPV genotype 16 than people without it in the group between 30 and 40 years of age.

The most frequent HPV genotypes in women below 30 years of age were: 16 (47%), 31 (26.5%), 51 (14.7%), 52 (14.7%), 53 (11.8%).

The most frequent HPV genotypes in women between 30 and 40 years of age were: 16 (67.3%), 31 (12.7%), 33 (10.9%), 51 (10.9%).

The most frequent HPV genotypes in women above 40 were: 16 (47.6%), 52 (14.3%).

We have found that single HPV infections are more common in women over 30 than infections with multiple HPV types. Only the youngest patients are more likely to be infected with more than one type of virus. In the youngest patients, infections with a single genotype of the virus occurred in 30.3% of HPV-positive patients and infections with at least two types- in 69.7% of patients. In women between 30 and 40, infection with a single virus type occurred in 57.4% of HPV-positive patients and multiple infections in 42.6% of patients. 76.2% of HPV-positive women were infected with a single HPV type in the oldest age group, and 23.8% had multiple infections.

The most frequent Pap-smear results in women below 30 years of age were: LSIL, HSIL and ASC-H. The most frequent Pap-smear results in women above 30 years of age were: ASC-H, HSIL and LSIL. The percentage distribution of Pap-smear diagnoses of HSIL, LSIL and ASC-H was similar (29%, 29% and 28%, respectively). Moreover, 12% of women administered to the hospital with a diagnosis of atypical squamous cells of undetermined significance and 2% — AGC. We have compiled all Pap-smears in Figure 1.

Figure 2 presents the scheme of recruiting patients for the study and the follow-up results. As far as follow up is concerned, we performed LEEP-conization in most cases. In 11.8% of patients, it was not possible to perform LEEP-conization due to various reasons. We present the results of excised lesions in Figure 3. Two-thirds of cases of the high-grade squamous intraepithelial lesion in the biopsy was confirmed in LEEP-conization. Three women heard the diagnosis of invasive cervical cancer — one of them — squamous cell carcinoma and two — adenocarcinoma. In 30% of patients, the final diagnosis was milder — in 8%, LSIL and 22% of women had a correct result of a histopathological examination.

The most frequent LEEP-conization result in women below 30 years of age was HSIL (16/34), accounting for 47.1%. In patients between 30 and 40 years of age, HSIL accounted for 69.1% (38/55). It was also the most common final diagnosis in the oldest women — 52.4% (11/21).

Among the diagnoses of NILM and LSIL in LEEP-conization 96.6% (28/29) of patients were HPV (+), including 37.9% (11/29) HPV 16 (+). The most common Pap-smear result was LSIL 41.4% (12/29) and HSIL 27.6% (8/29). Among the diagnoses of HSIL and ICC in LEEP-conization 98.5%

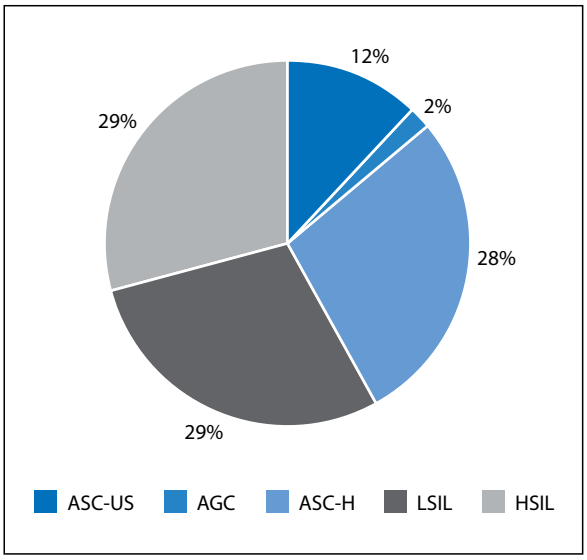

Figure 1. Pap-smear results; ASC-US — atypical squamous cells of undetermined significance; AGC — AGC — atypical glandular cells; ASC-H — atypical squamous cells cannot exclude HSIL; LSIL — low-grade squamous intraepithelial lesion; HSIL — high-grade squamous intraepithelial lesion

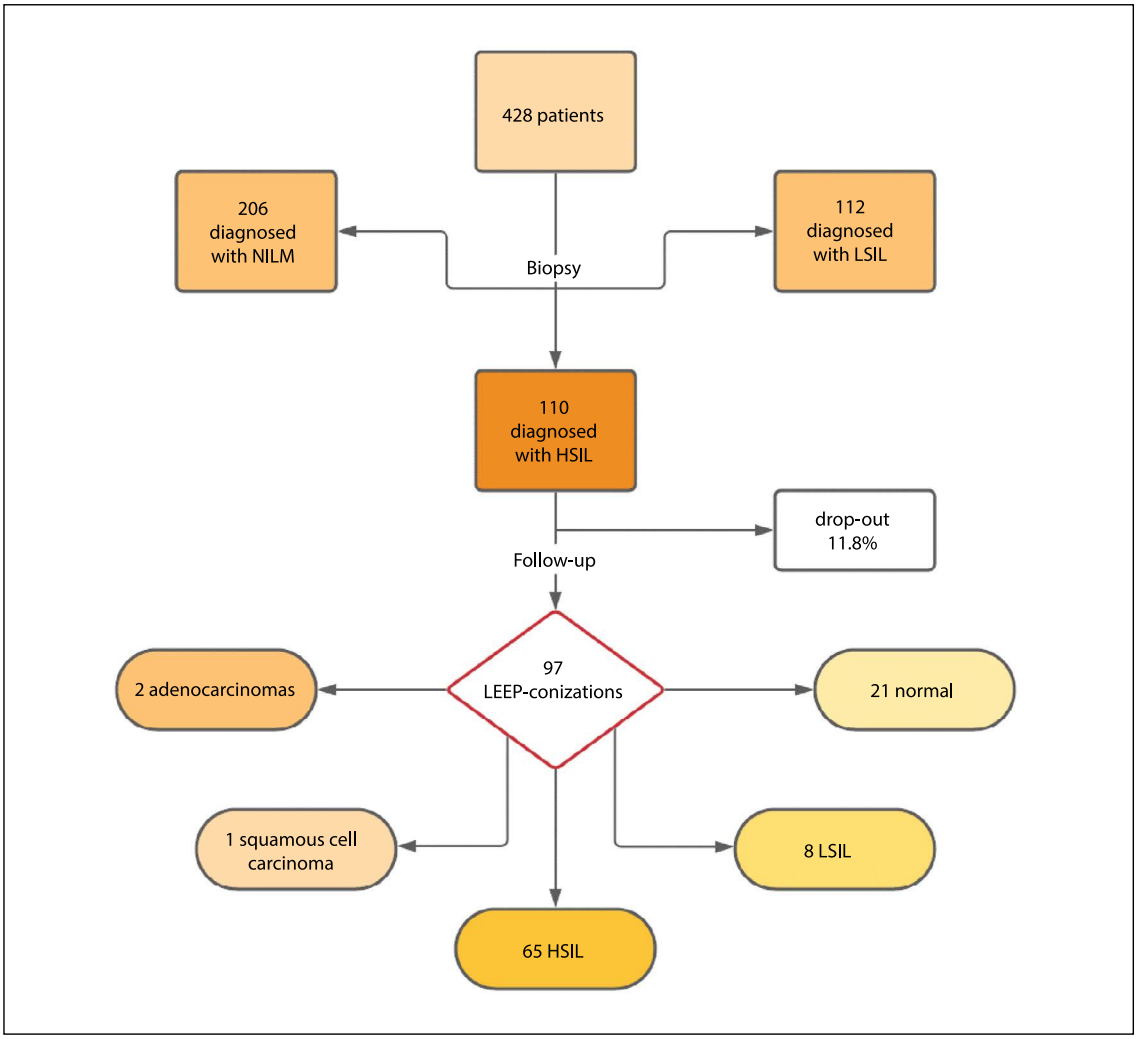

Figure 2. The scheme of recruiting patients for the study

(67/68) of patients were HPV (+), including 60.3% (41/68) HPV 16 (+). The most common Pap-smear result was ASC-H 32.4% (22/68) and HSIL 29.4% (20/68).

DISCUSSION

We designed this study to define the distribution of HPV genotypes within HSIL. To our knowledge, it is the most extensive assessment of HPV genotype in HSIL in Poland to date. Additionally, we have not found such a database of one roof patients.

There were twenty-six HPV genotypes present in our study group out of 40 possible. Of these, 16 belonged to high-risk HPV, 2 to low-risk HPV, and eight had unknown oncogenic potential. The analysis confirmed a significant relationship between HPV 16 genotype and age groups. Six genotypes were the most frequent in the study group — 16, 31, 52, 51, 18 and 33. They all belong to high-risk oncogenic HPV types. The HPV genotype 16 accounted for 54.1% of all HPV-positive patients. Interestingly, in the age group

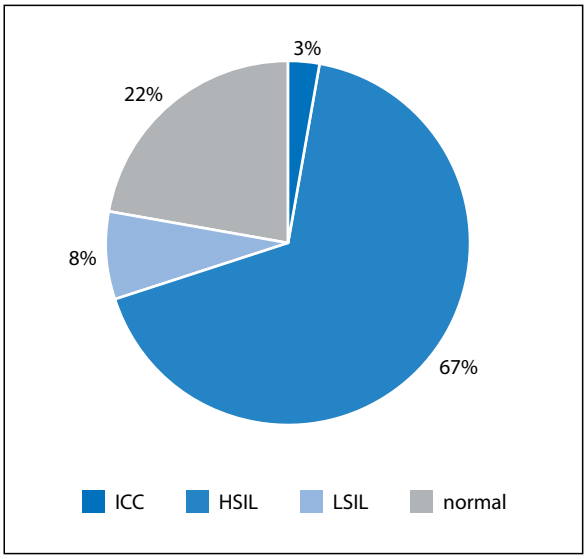

Figure 3. LEEP-conization results; ICC — invasive cervical cancer; HSIL — high-grade squamous intraepithelial lesion; LSIL — low-grade squamous intraepithelial lesion

between 30 and 40 years of age, genotype 16 accounted for 67.3%.

A study conducted over a decade ago in the same region of Poland showed that the most common viruses detected in women diagnosed with HSIL are: 16, 33, 18, 31, 56. They accounted for 75.86% (88/116) of all detected HPV genotypes [13].

According to Clifford GM et al. [14] of 15 HPV types that are considered oncogenic, HPV type 16 and 18 accounts for about 70% of cervical cancers while HPV types 31, 33, 35, 45, 52 and 58 are associated with an additional 15% of cervical cancer. In the study group, 16 and 18 HPV genotypes constituted 59% (65/110). We noticed that the HPV 18 genotype is not detected as often compared to other databases. The abovementioned differences may result from the fact that only 3 of our patients had finally been diagnosed with ICC. Most women were finally diagnosed with HSIL. However, the next common genotypes were mainly similar to the results of other researchers. In our study, HPV types 31, 33, 35, 45, 52 and 58 occurred in 38% of all HPV-positive patients.

It was beyond the scope of our study, but we noticed a high incidence of autoimmune diseases and, in particular, thyroid diseases. All autoimmune diseases accounted for 37.5% (15/40) of all possible comorbidities. Interestingly, we observed that thyroid diseases, including hypothyroidism, Graves' disease, and Hashimoto's disease, occurred in 15 patients. This finding may contribute to new research and extended observations. So far, various meta-analyses and prospective studies have focused on demonstrating the safety of vaccines against HPV in people suffering from autoimmune diseases. These studies did not show a relationship between the increased number of cases, exacerbations, or progression of autoimmune diseases [15, 16]. Perhaps now is the time to look for the relationship between the increasing incidence of autoimmune diseases, especially autoimmune thyroiditis (AT), and greater exposure to HPV infections. So far, we have not been able to find such studies in the available databases.

The paper presented by Aubin F. et al. [17] is the only one relating to the incidence of HPV infections in patients suffering from autoimmune diseases. Different studies have demonstrated a link between genital HPV infection and systemic lupus erythematosus (SLE). The prevalence of genital HPV infection was increased in SLE women compared to the general population (12 to 20% vs 7%) [18, 19], and the increase was statistically significant for multiple HPV infections and infections with some of the HR-HPV types such as HPV16 [20]. In a prospective observational study of 144 SLE patients, the prevalence of HPV infection increased significantly, from 12.5% at baseline to 25% after three years [21]. In patients with Sjögren's syndrome and rheumatoid arthritis, no significant differences were found regarding either Pap smear results or HPV status [22, 23]. Researchers from Canada reported an increased prevalence of abnormal Pap smears in 320 women with systemic sclerosis than the general population (25.4% vs 13.8%) [24]. We did not find in the literature data describing the relationship between other autoimmune diseases and HPV infection. Future studies should take into the account abovementioned relation.

Of all the patients diagnosed by biopsy as HSIL, 70% at the final diagnosis of LEEP-conization resulted from HSIL or ICC. In the other patients, the result was typical, or they had LSIL. Proper identification of women with confirmed HSIL among those with abnormal Pap smear results before colposcopy and biopsy is essential to avoid over investigation and over-treatment. Not every cytologically diagnosed HSIL will progress to histological HSIL or ICC. From follow-up and LEEP-conization results, we see that even with biopsy-confirmed HSIL, only 68/97 women still had high-grade lesions or developed cancer. hrHPV testing has shown high sensitivity for HSIL detection. More and more Western countries use hrHPV testing either as a stand-alone screening test or in combination with cytology or triage.

The large meta-analysis compiled by Smith JS et al. [12] proves that HPV16/18 prevalence was 70% overall and varied from 65% in South/Central America to 76% in North America. Combined HPV16/18 prevalence in all HSIL cases constituted 52%. HPV16 was the predominant type in HSIL from all continents. This meta-analysis concluded that more than two-thirds of cervical cancers and half of HSIL could be prevented after using HPV 16/18 vaccines.

Analyzing the obtained data, we noticed that the percentage of multiple HPV infections decreases with increasing age, and the incidence of only one HPV genotype rises significantly. Referring to Sukasem C. et al. [25], the presence of a single HPV-genotype infection was more common than multiple infections (77.27% and 22.73%, respectively). The hrHPV infections were eight times more frequent than lrHPV. The most common genotypes by decreasing order of frequency were HPV16, 58, 18, 33, 68, 31 and 66 (7/167; 4.19%).

Persistent HPV infections may progress into high-grade cervical lesions and ICC. Therefore, the analysis of the frequency of HPV genotypes in large groups of patients may contribute to the development of new preventive strategies. Information on the occurrence of genotypes in different countries will help implement protective vaccinations against specific, most virulent genotypes of HPV [26–28]. Nonetheless, these data on the prevalence and distribution of HPV genotypes in the population may raise the understanding of the HPV molecular epidemiology in Poland. Lastly, the limitation of our publication is the relatively small number of patients with ICC examined.

CONCLUSIONS

To our knowledge, this study is the most extensive assessment of HPV genotypes in HSIL diagnoses in Poland.

Funding

This research received no external funding.

Institutional review board statement

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Bioethics Committee of the Medical Chamber of Wielkopolska (protocol code 95/2021, date of approval: 17.03.2021).

Informed consent statement

Informed consent was obtained from all subjects involved in the study.

Data availability statement

The data presented in this study are available on request from the first and second author. The data are not publicly available due to sensitive information regarding both the health and epidemiological status of the study group.

Conflict of interest

The authors declare no conflict of interest.

REFERENCES

1. Dijkstra MG, Snijders PJF, Arbyn M, et al. Cervical cancer screening: on the way to a shift from cytology to full molecular screening. Ann Oncol. 2014; 25(5): 927–935, doi: 10.1093/annonc/mdt538, indexed in Pubmed: 24445150.
2. Rees I, Jones D, Chen H, et al. Interventions to improve the uptake of cervical cancer screening among lower socioeconomic groups: A systematic review. Prev Med. 2018; 111: 323–335, doi: 10.1016/j.ypmed.2017.11.019, indexed in Pubmed: 29203349.
3. Didkowska J. Zachorowania i zgony na nowotwory złośliwe w Polsce. Krajowy Rejestr Nowotworów. Centrum Onkologii - Instytut im. Marii Skłodowskiej - Curie .
4. Saslow D, Solomon D, Lawson HW, et al. American Cancer Society, American Society for Colposcopy and Cervical Pathology, American Society for Clinical Pathology. American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. Am J Clin Pathol. 2012; 137(4): 516–542, doi: 10.1309/AJCPTGD94EVRSJCG, indexed in Pubmed: 22431528.
5. Karsa Lv, Arbyn M, Vuyst HDe, et al. European guidelines for quality assurance in cervical cancer screening. Summary of the supplements on HPV screening and vaccination. Papillomavirus Research. 2015; 1: 22–31, doi: 10.1016/j.pvr.2015.06.006.
6. Santesso N, Mustafa RA, Schünemann HJ, et al. Guideline Support Group. World Health Organization Guidelines for treatment of cervical intraepithelial neoplasia 2-3 and screen-and-treat strategies to prevent cervical cancer. Int J Gynaecol Obstet. 2016; 132(3): 252–258, doi: 10.1016/j.ijgo.2015.07.038, indexed in Pubmed: 26868062.
7. McCredie MRE, Sharples KJ, Paul C, et al. Natural history of cervical neoplasia and risk of invasive cancer in women with cervical intraepithelial neoplasia 3: a retrospective cohort study. Lancet Oncol. 2008; 9(5): 425–434, doi: 10.1016/S1470-2045(08)70103-7, indexed in Pubmed: 18407790.
8. Kyrgiou M, Mitra A, Arbyn M, et al. Fertility and early pregnancy outcomes after conservative treatment for cervical intraepithelial neoplasia. Cochrane Database Syst Rev. 2015(9): CD008478, doi: 10.1002/14651858.CD008478.pub2, indexed in Pubmed: 26417855.
9. zur Hausen H. Similarities of papillomavirus infections with tumor promoters. Princess Takamatsu Symp. 1983; 14: 147–152, indexed in Pubmed: 6097579.
10. zur Hausen H. Papillomaviruses in the causation of human cancers - a brief historical account. Virology. 2009; 384(2): 260–265, doi: 10.1016/j.virol.2008.11.046, indexed in Pubmed: 19135222.
11. Wilkinson DE, Baylis SA, Padley D, et al. Collaborative Study Group. Establishment of the 1st World Health Organization international standards for human papillomavirus type 16 DNA and type 18 DNA. Int J Cancer. 2010; 126(12): 2969–2983, doi: 10.1002/ijc.25039, indexed in Pubmed: 19904756.
12. Smith JS, Lindsay L, Hoots B, et al. Human papillomavirus type distribution in invasive cervical cancer and high-grade cervical lesions: a meta-analysis update. Int J Cancer. 2007; 121(3): 621–632, doi: 10.1002/ijc.22527, indexed in Pubmed: 17405118.
13. Kedzia W, Pruski D, Józefiak A, et al. [Genotyping of oncogenic human papilloma viruses in women with HG SIL diagnosis]. Ginekol Pol. 2010; 81(10): 740–744, indexed in Pubmed: 21117301.
14. Clifford GM, Smith JS, Plummer M, et al. Human papillomavirus types in invasive cervical cancer worldwide: a meta-analysis. Br J Cancer. 2003; 88(1): 63–73, doi: 10.1038/sj.bjc.6600688, indexed in Pubmed: 12556961.
15. Genovese C, LA Fauci V, Squeri A, et al. HPV vaccine and autoimmune diseases: systematic review and meta-analysis of the literature. J Prev Med Hyg. 2018; 59(3): E194–E199, doi: 10.15167/2421-4248/jpmh2018.59.3.998, indexed in Pubmed: 30397675.
16. Grimaldi-Bensouda L, Rossignol M, Koné-Paut I, et al. PGRx-AD Study Group. Risk of autoimmune diseases and human papilloma virus (HPV) vaccines: Six years of case-referent surveillance. J Autoimmun. 2017; 79: 84–90, doi: 10.1016/j.jaut.2017.01.005, indexed in Pubmed: 28190705.
17. Aubin F, Martin M, Puzenat E, et al. Genital human Papillomavirus infection in patients with autoimmune inflammatory diseases. Joint Bone Spine. 2011; 78(5): 460–465, doi: 10.1016/j.jbspin.2011.03.002, indexed in Pubmed: 21570889.
18. Tam LS, Chan AYK, Chan PKS, et al. Increased prevalence of squamous intraepithelial lesions in systemic lupus erythematosus: association with human papillomavirus infection. Arthritis Rheum. 2004; 50(11): 3619–3625, doi: 10.1002/art.20616, indexed in Pubmed: 15529372.
19. Klumb EM, Pinto AC, Jesus GR, et al. Are women with lupus at higher risk of HPV infection? Lupus. 2010; 19(13): 1485–1491, doi: 10.1177/0961203310372952, indexed in Pubmed: 20605875.
20. Nath R, Mant C, Luxton J, et al. High risk of human papillomavirus type 16 infections and of development of cervical squamous intraepithelial lesions in systemic lupus erythematosus patients. Arthritis Rheum. 2007; 57(4): 619–625, doi: 10.1002/art.22667, indexed in Pubmed: 17471531.
21. Tam LS, Chan PKS, Ho SC, et al. Natural history of cervical papilloma virus infection in systemic lupus erythematosus - a prospective cohort study. J Rheumatol. 2010; 37(2): 330–340, doi: 10.3899/jrheum.090644, indexed in Pubmed: 20032093.
22. Cirpan T, Guliyeva A, Onder G, et al. Comparison of human papillomavirus testing and cervical cytology with colposcopic examination and biopsy in cervical cancer screening in a cohort of patients with Sjogren's syndrome. European Journal of Gynaecological Oncology. 2007; 28(4).
23. Contreras WR, Fuentes HM, Gámez Na, et al. Prevalence and cervical human papilloma virus associated factors in patients with rheumatoid arthritis. Ginecología y Obstetricia de México. 2008; 76(1).
24. Bernatsky S, Hudson M, Pope J, et al. Canadian Scleroderma Research Group. Reports of abnormal cervical cancer screening tests in systemic sclerosis. Rheumatology (Oxford). 2009; 48(2): 149–151, doi: 10.1093/rheumatology/ken442, indexed in Pubmed: 19074957.
25. Sukasem C, Pairoj W, Saekang N, et al. Molecular epidemiology of human papillomavirus genotype in women with high-grade squamous intraepithelial lesion and cervical cancer: will a quadrivalent vaccine be necessary in Thailand? J Med Virol. 2011; 83(1): 119–126, doi: 10.1002/jmv.21948, indexed in Pubmed: 21108348.
26. Muñoz N. Human papillomavirus and cancer: the epidemiological evidence. J Clin Virol. 2000; 19(1-2): 1–5, doi: 10.1016/s1386-6532(00)00125-6, indexed in Pubmed: 11091143.
27. Castellsagué X, Díaz M, de Sanjosé S, et al. International Agency for Research on Cancer Multicenter Cervical Cancer Study Group. Worldwide human papillomavirus etiology of cervical adenocarcinoma and its cofactors: implications for screening and prevention. J Natl Cancer Inst. 2006; 98(5): 303–315, doi: 10.1093/jnci/djj067, indexed in Pubmed: 16507827.
28. Clifford GM, Smith JS, Aguado T, et al. Comparison of HPV type distribution in high-grade cervical lesions and cervical cancer: a meta-analysis. Br J Cancer. 2003; 89(1): 101–105, doi: 10.1038/sj.bjc.6601024, indexed in Pubmed: 12838308.