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Genotyping of human papillomavirus DNA in Wielkopolska region

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ABSTRACT

Objectives: Human papillomavirus infection (HPV) is one of the most common sexually transmitted diseases. Long-term exposure to the HPV leads to development of high-grade squamous intraepithelial lesions that can eventually transform into cervical cancer.
The aim of the study was to assess the HPV genotype distribution in patients with abnormal pap smear and provide prospective study.

Material and methods: We obtained material from 674 women who registered to Specialist Medical Practice in the years 2008–2020. The sample for the molecular test was collected using combi brush and forwarded to the independent, standardized laboratory. HPV detection was done using PCR followed by DNA enzyme immunoassay and reverse hybridization line probe assay for virus genotyping. Sequence analysis was performed to characterize virus genotypes in HPV — positive samples.

Results: We found that 53% of patients tested positive for HPV. The percentage decreased with age. The following HPV types were the most common: HPV — 16 (24.5%), HPV — 53 (13.1%), HPV — 31 (10.3%), HPV — 51 (9.7%), HPV — 56 (9.5%).

Conclusions: Our results suggest that type-specific, high–risk HPV DNA — based screening should focus on HPV types 16, 31, 51, 56.

Key words: HPV; HPV genotypes; HPV screening; cervical cancer

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INTRODUCTION

Cervical cancer (Cc) remains the fourth most frequent cancer in women worldwide causing about 275,000 deaths annually [1, 2]. There are many factors affecting the development of this life-threatening disease, such as the socio-economic status, the age of first sexual intercourse, alcohol consumption or smoking, as well as genetic load, immunosuppression and a large number of pregnancies and births (especially for young women) [3]. However, the most important factor in developing cervical cancer is primarily persistent infection with high-risk HPV (HR HPV). It can lead to an uncontrolled course of infection and is the direct cause of the vast majority of cervical intraepithelial neoplasia and invasive cervical cancers. The oncogenic potential of particular HPV genotypes has been acknowledged since the discovery of the definitive association of HPV as the indubitable etiological agent for development of SIL and cervical cancer. The role of human papillomavirus in cervical cancer was established over 40 years ago [4, 5].

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Genotypes 16 and 18 are assumed to be responsible for about 70% of cc cases [6, 7].

A growing number of countries are replacing Pap-smears with molecular HPV testing as the primary screening modality. Both the American Cancer Society (ACS) and the European Society for Medical Oncology (ESCO) recommend a new pattern of cervical cancer screening [8, 9]. ACS recommends testing patients between 25 and 65 years of age every five years. Pap-smear has been the standard method for cervical cancer screening for over half of the century. It has reduced the incidence by 60–90% and the death rate by 90%. However, the limitation of Pap-smear is sensitivity (~50%) and a significant proportion of inadequate specimens. A pooled analysis of four randomized controlled trials of HPV-based cervical screening versus Pap-smear showed 60–70% greater protection against invasive cancer in favor of HPV-test [10]. Thirteen HPV genotypes are recognized to be oncogenes with high-risk potential by the International Agency for Research on Cancer [11].

On a global scale, HPV infections cause more than half of infection-linked cancers among women and barely 5% in males. Vaccines against the high-risk HPV types 16 and 18 represent the first prophylactic vaccines developed directly to prevent a major human cancer (cc). A significant decrease in the incidence of cervical cancer has been observed over the past several decades due to preventive measures and screening.

Objectives

This paper summarizes the results of HPV DNA genotyping in the Wielkopolska region. 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. Our aim is to provide distribution of particular HPV genotypes in specific age groups. This knowledge might enable estimating the potential effectiveness of HPV vaccines as primary prevention.

MATERIAL AND METHODS

This study included 674 patients who registered to Specialist Medical Practice in the years 2008–2020 for regular cervical screening. Parallel to the Pap-smear, the women were tested for the presence of HPV which genotypes were later determined. The sample for a molecular test (Linear Array HPV Genotyping-Roche Diagnostics) was collected from the external os of the cervix and vaginal wall with a use of combi brush. The obtained specimen was placed into a liquid-based medium Solution. An HPV test is a quality test that 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 result in molecular tests confirms the presence of DNA of at least one of the mentioned above oncogenic types of human papillomavirus in the collected specimens.

If needed, a following colposcopy and biopsy were performed. Specialist in gynecologic oncology with 10-year experience examined colposcopy with SmartOPTIC colposcope. Trial with a 5% aqueous solution of acetic acid as well as Schiller's test with Lugol's iodine were performed in all cases. The colposcopic images were evaluated according to Reid's Colposcopic Index which assesses the color, lesion boundaries and surface, blood vessels, and iodine test. All colposcopic images were archived. We used classification created by The International Federation of Cervical Pathology and Colposcopy and recommended by the Polish Society of Colposcopy and Cervical Pathophysiology.

Calculations were performed using the statistical package Statistica (ver. 13.3). Graphs were created with the help of Excel. Statistical hypotheses were verified at the level of significance of 0.05. The Shapiro-Wilk test was used to assess whether the data distribution is normal and Spearman's rho coefficient was used in order to analyze its correlation. The correlation between individual genotypes and age groups was analyzed with a Chi-square test.

RESULTS

The mean age of the entire population was 34. A total of 359 patients (53.3%) tested positive for HPV DNA. The quantitative and percentage distribution of individual genotypes is presented in Table 1. Figure 1 shows the percentage distribution of HPV-positive women in each age group. The HPV genotype 16 and 53 were the most common amongst HPV-positive women. They accounted for 24.5% and 13.4%, respectively. As far as both genotypes are concerned, the correlation between them and particular age groups was not found ($p > 0.05$). A detailed analysis is presented in Table 2 and 3.

The individual HPV genotypes have been allocated to three groups:

- Group A — carcinogenic to humans: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 64, 67, 68a, 68b, 73, 82;
- Group B — either probably or possibly carcinogenic to humans: 26, 53, 66, 69;
- Group C — unclassifiable as carcinogenic to humans: 6, 11, 40, 42, 44, 54, 55, 61, 62, 70, 71, 72, 81, 83, 84, 87, 90, CP6108.

Table 4 presents the basic descriptive statistics and the result of the normality distribution of the Shapiro-Wilk test (W). The result is statistically significant for all variables; therefore the distribution of the examined variables is highly deviating from normal ($p < 0.001$). The correlation of the

Table 1. The quantitative and percentage distribution of individual genotypes

HPV genotype	Presence n	Presence %	Deficiency n	Deficiency %
16	88	13.1	586	86.9
53	48	7.1	626	92.9
31	37	5.5	637	94.5
51	35	5.2	639	94.8
56	34	5.0	640	95.0
54	32	4.7	642	95.3
52	27	4.0	647	96.0
59	27	4.0	647	96.0
66	27	4.0	647	96.0
18	26	3.9	648	96.1
73	24	3.6	650	96.4
6	23	3.4	651	96.6
61	21	3.1	653	96.9
42	20	3.0	654	97.0
39	19	2.8	655	97.2
45	19	2.8	655	97.2
62	17	2.5	657	97.5
CP6108	15	2.2	659	97.8
33	14	2.1	660	97.9
84	14	2.1	660	97.9
67	11	1.6	663	98.4
68	11	1.6	663	98.4
90	11	1.6	663	98.4
35	10	1.5	664	98.5
58	10	1.5	664	98.5
82	8	1.2	666	98.8
81	8	1.2	666	98.8
83	7	1.0	667	99.0
11	5	0.7	669	99.3
40	5	0.7	669	99.3
55	5	0.7	669	99.3
70	5	0.7	669	99.3
87	3	0.4	671	99.6
44	2	0.3	672	99.7
68a	1	0.1	673	99.9
68b	1	0.1	673	99.9
72	1	0.1	673	99.9
64	0	0	674	100
26	0	0	674	100
69	0	0	674	100
71	0	0	674	100

n — number, HPV — human papillomavirus

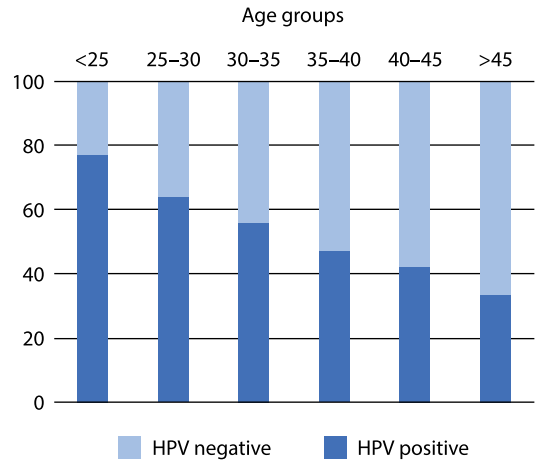

Figure 1. Distribution of HPV positive patients in specific age groups; HPV — human papillomavirus

occurrence of particular genotypes in specific age groups is statistically significant. This correlation is negative, so the frequency of occurrence of particular groups of HPV genotypes decreases with age (Fig. 1 and Tab. 4). The relationship calculated using Spearman's rho coefficient, however, is weak (Tab. 5).

For individual genotypes, the following relationships were found:

- genotype 51 (carcinogenic): significantly more frequent in patients under 25 years of age in comparison to all other age groups ($p = 0.001$), significantly more frequent in group 25–30 in comparison to group 30–35 ($p < 0.001$);
- genotype 56 (carcinogenic): significantly more frequent in groups 25–30 and 30–35 in comparison to group 40–45 ($p = 0.005$ and $p = 0.024$ respectively);
- genotype 59 (carcinogenic): significantly more frequent in patients under 25 years of age in comparison to groups 30–35, 35–40 and over 45 years ($p < 0.001$, $p = 0.0015$ and $p = 0.009$, respectively) and statistically significantly more frequent in patients in group 25–30 in comparison to groups 30–35, 35–40 and over 45 years of age ($p = 0.006$, $p = 0.015$ and $p = 0.049$, respectively);
- genotype 67 (carcinogenic): significantly more frequent in patients in group 25–30 in comparison to groups 30–35 and 35–40 ($p < 0.001$ and $p = 0.004$, respectively), significantly more frequent in group 25–30 in comparison to groups 30–35 and 35–40 ($p = 0.014$ and $p = 0.037$, respectively) and significantly more frequent in group 30–35 in comparison to group over 45 years of age ($p = 0.027$);
- genotype 73 (carcinogenic): significantly more frequent in patients in group under 25 years of age in comparison to groups 30–35 and 40–45 ($p = 0.016$ and $p = 0.008$, respectively) and significantly more frequent in group 25–30 in comparison to groups 30–35 and 40–45 ($p = 0.01$ and $p = 0.01$, respectively);
- genotype 66 (possibly carcinogenic): significantly more frequent in patients under 25 years of age in comparison to all other age groups ($p = 0.0035$).

There were also some significant interactions between other genotypes, such as 6, 52, 54 but because of their non-carcinogenic character, these were not mentioned.

In case of a positive HPV result, abnormal Pap-smear or a clinically suspicious cervix image, colposcopy with biopsy was performed. As a result, a biopsy was examined in 321 patients. In over half of the cases no pathology was found (NILM was diagnosed in 50% of patients). LSIL was present in 87 (27%) whereas HSIL in 71 (22%) samples. No squamous cervical cancer was histologically confirmed. However, what is noteworthy, two cases of adenocarcinomas were detected.

Table 2. Correlation between studied age groups and the presence of HPV genotype 16

Genotype 16	Group < 25	Group 25–30	Group 30–35	Group 35–40	Group 40–45	Group > 45	Line all	X2	p
Deficiency	43	129	156	120	70	68	586		
% Column	89.58	83.23	85.25	90.91	86.42	90.67			
% Line	7.34	22.01	26.62	20.48	11.95	11.60			
% All	6.38	19.14	23.15	17.80	10.39	10.09	86.94		
Presence	5	26	27	12	11	7	88		
% Column	10.42	16.77	14.75	9.09	13.58	9.33		5.41	0.368
% Line	5.68	29.55	30.68	13.64	12.50	7.93			
% All	0.74	3.86	4.01	1.78	1.63	1.04	13.06		
All	48	155	183	132	81	75	674		
% All	7.12	23.00	27.15	19.58	12.02	11.13	100		

HPV — human papillomavirus; p — p value

Table 3. Correlation between studied age groups and the presence of HPV genotype 53

Genotype 53	Group < 25	Group 25–30	Group 30–35	Group 35–40	Group 40–45	Group > 45	Line all	X2	p
Deficiency	42	142	171	122	77	72	626		
% Column	87.50	91.61	93.44	92.42	95.06	96.00			
% Line	6.71	22.68	27.32	19.49	12.30	11.50			
% All	6.23	21.07	25.37	18.10	11.42	10.68	92.88		
Presence	6	13	12	10	4	3	48		
% Column	12.50	8.39	6.56	7.58	4.94	4.00		4.29	0.508
% Line	12.50	27.08	25.00	20.83	8.33	6.25			
% All	0.89	1.93	1.78	1.48	0.59	0.45	7.12		
All	48	155	183	132	81	75	674		
% All	7.12	23.00	27.15	19.58	12.02	11.13	100		

HPV — human papillomavirus; p — p value

Table 4. Correlation between age groups and the oncogenic potential of the studied HPV genotypes

HPV type	M	SD	LMod.	Min.	Max.	Skew.	W	p
Group A	0.60	0.84	394	0	5	1.53	0.713	p < 0.001
Group B	0.11	0.35	606	0	2	3.20	0.348	p < 0.001
Group C	0.29	0.63	529	0	4	2.70	0.511	p < 0.001

HPV — human papillomavirus; M — mean; SD — standard deviation; p — p value

DISCUSSION

This study provides comprehensive information on the HPV prevalence and genotype distribution among a cohort of Polish women who were referred to a single center for HPV genotyping following either a diagnosis of abnormal cytology or for screening. We have not found such a database of one roof patients.

In comparison to another recent study conducted in Poland, we have noticed some discrepancies. As expected, the most frequent HPV genotype was 16. It was present in 26% of all HPV-positive patients compared to 20% in mentioned study. On the other hand, negative patients constituted 46.7%, and in the cited study 32.1%. According to Smolarz et al. HPV genotype 18 was found in about 14% of women, while in our observation, it was in 10th place and occurred twice less often (7.2%) [12]. Contrary to the literature, we did not observe genotype 18 occurring frequently. That, however, could the result of our focus on a heterogeneous group, where neither SIL nor cervical cancer was the criterion. In line with previous studies, HPV 16, 31, and 45 genotypes were most often detected in patients diagnosed with ASC-US or LSIL, whereas in patients with HSIL, genotypes 16, 33, 18, 31, 56 were the most common [13, 14]. We also provide data for the HPV types that are phylogenetically classified as oncogenic, such as HPV types 26, 67, 69, and 82, but seldomly described in epidemiological studies [15]. Little is known about the exact mechanism of HPV-associated carcinogenesis of these rare types due

Table 5. Correlation between age groups and HPV genotypes divided into three groups

	rho Spearman	p
Age group & Group A	–0.23	0.000
Age group & Group B	–0.08	0.033
Age group & Group C	–0.17	0.000

HPV — human papillomavirus; p — p value

to insufficient epidemiological evidences. The biological properties of the rare high-risk HPV types have only been investigated in a few studies, which included mostly cervical intraepithelial neoplasms lesions and a few cases of invasive cervical cancer [16].

As far as prevention is concerned, it is both important to detect lesions in the early stage and to identify risk-factors of carcinogenesis. Early diagnosed HPV-positive patients will be eligible for a high risk of cancer development. As a consequence, they will be subjected to tighter inspection and follow-up visits. The prevalence of HPV infection among women with subclinical or latent disease leads to different results. It depends on the studied population and used method of HPV detection. The highest percentage of infections is diagnosed using a PCR method which is recognized to have the highest sensitivity among all molecular biology techniques. It allows to detect the presence of one copy of HPV in 105–106 cells. PCR is now becoming a common diagnostic technique that is used in numerous laboratories. The results obtained from PCR are comparable and allow to avoid their false interpretation. The introduction of DNA testing has increased the effectiveness of screening programs in women over 30 years of age with the NILM (negative for intraepithelial lesion or malignancy) and reduced the number of unnecessary colposcopies and treatment in younger patients [17–20].

What is noticeable, the correlation of the appearance of particular genotypes in specific age groups is statistically significant — the frequency of occurrence of particular groups of HPV genotypes decreases with age. Over the past four to five decades the assessment of the distribution of HPV types in cervical cancer has been crucial for determining the cause of age-related differences. If the reason is the cohort effect, that could allow us to predict changes in the distribution of HPV types in the upcoming years, resulting in improvement of implementing preventive HPV-vaccination.

Originally, risk stratification in cervical screening based on the underlying HPV genotype was suggested in 2003 when the primary clinical HPV assays for screening indicated the detection of high-risk HPV genotype was performed either in a research setting or as an in-house test. Clifford et al. [21], suggested that HPV genotypes 16, 18, and 45 would merit closer surveillance than infection with other high-risk HPV genotypes. Subsequently, large-scale studies of cervical cancers displayed the contribution of different HPV genotypes to squamous cell carcinoma and adenocarcinoma. It served as a foundation to determine the hierarchy of high-risk HPV genotypes [22]. Throughout the next decade, studies showed that genotypes 31, 33, 52, and 58 confer risks similar to HPV 18 and 45, thereby establishing impetus for contemplating more complex screening algorithms using genotype-specific risk stratification. That resulted in forming more precise colposcopy referral recommendations and allowed to reduce [23–26] overtreatment. Thus, today's application of HPV diagnostics in screening distinguishes between a partial genotyping result for reporting of HPV 16 and 18, with the remaining high-risk HPV genotypes as a pooled result. A recent expert review by Xu et al., [27] assessing the accuracy of HPV 16/18 genotyping to triage LSIL cytology, points out that although the partial genotyping strategy increases the positive predictive value, the specificity declines compared with cytology. A more complete differentiation between genotypes may improve this strategy.

This work provides estimates of the important contribution of HPV types 16, 31, 51, 56, 52, 59, and 18. These types might be considered while developing new vaccines with a wider efficacy range. The early detection of cancers associated with HPV types 16, 31, and 51 could be considered in screening programs aimed at clinical management based on the HPV genotype. Our results indicate which HPV types should be emphasized on when the cross-protective effects of current vaccines are assessed. What is more, they could come as applicable while preparing recommendations for HPV vaccines usage. According to our findings those type-specific, high-risk, HPV-DNA-based screening tests and protocols should be focused on HPV types 16, 18, 31, 51, 52, 56, and 59.

CONCLUSIONS

Cervical cancer screening is recommended by clinical practice guidelines for being effective cancer preventive method. HPV 16 and 18 partial genotyping is implemented in several clinical screening guidelines. Evidence, that have been accumulated for over a decade, suggests that the definition should be expanded to include risk stratification on the full spectrum of high-risk HPV genotypes of women undergoing screening.

In the future, follow-up and vaccination status of patients may indicate a trend related to the extinction of some HPV genotypes in the vaccinated population. The advantage of our research is the long duration of the study. Close follow-up should last two years as up to 25% of relapses are observed within that period of time. During follow-up, both LSIL and HSIL were detected in 158 patients. It is a proof of

necessity of supervision over the patients. Two cases of adenocarcinoma furtherly confirm that statement. That is why it is essential to build trust in the doctor-patient relationship, conduct social campaigns reminding about regular check-ups and expand diagnostics beyond the exclusive cytology.

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Conflicts of interest

The authors declare no conflict of interest.

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