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The Importance of Other HPV in High-Grade CIN

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ABSTRACT

Background & Objective: High-risk (HR) HPV infection is the major cause of cervical cancer, which is still one of the most common cancers among women. Based on some not-published results, it seems that some of the other HR HPVs might be as important as HPV 16, and 18 in developing high-grade CIN. This study was conducted to determine the relationship between Other HPV and high-grade CIN.

Materials & Methods: In this prospective study from 2019 to 2022 (approved by the ethics committee), all women with positive HPV based on the COBAS method were invited to participate in the study (N=646). For all the patients, colposcopy was done, and then the liquid-based samples of women with Other HPV positives were reanalyzed by HPV typing.

Results: All the patients who were infected with HPV18 were involved in CIN1. On the other hand, 50% of patients who were infected with HPV18 were involved in CIN2. 50% of patients with HPV45 were involved in CIN2. There is also a significant relationship between HPV31 and CIN3.

Conclusion: Because in our study there was a significant relationship between CIN3 and HPV31; and CIN2 with HPV45, and in the COBAS method, HPV31 and HPV45 are only reported under the general title of Other HPV, because of the possibility of the importance of other HPV with high-grade neoplasias, it is recommended to analyze the other HPV with HPV typing. Further studies are needed to confirm our findings.

Keywords: Other HPV, CIN, HPV Typing, COBAS, Diagnosis

Introduction

The high prevalence of HPV is an important public health concern **(1)**. The causal role of HPV in all cancers of the uterine cervix has been firmly established biologically and epidemiologically **(2)**. Globally, cervical cancer remains one of the most common cancers among women and is the fourth most common cancer after breast, colorectal, and lung cancer. **(3)**. Nowadays, more than 100 types of HPV have been identified, which are classified into two categories: low-risk types and high-risk types **(4)**. This virus is the most common STIs and an essential factor in CIN **(5, 6)**. Cervical cancer is very deadly, but it can be prevented and diagnosed early. Most of the countries that have an organized screening program to be able to control this cancer well **(7, 8)**. It should be noted that approximately 77% of cervical cancer patients in Iran are infected with the HPV virus **(9, 10)**. Management of cervical cancer is primarily done with surgery or radiation therapy, and chemotherapy is a valuable supplement **(11)**. There are two main approaches to controlling cervical cancer: HPV vaccination and screening **(12)**. There is evidence of the effectiveness of vaccination among young women in terms of a reduction in the prevalence of high-risk HPV types. Screening for several decades. The priority will remain the prevention of cervical cancer **(13)**. In our study, we want to evaluate the importance of the other HPV types in patients with HG-CIN because the result of their HPV test was reported to be just another HPV.

Methods

Study sampling

A prospective study on 646 patients with an average age of 34.5 years, after receiving the ethics code (IR.SBMU.RETEC.REC.1400.1196) from the research unit of SBMU, it was performed on patients who met the conditions for entering the study,

including obtaining informed consent, having an abnormal pap smear and abnormal examination, and having risk factors for cervical neoplasia during 2019–2022. For all women with positive HPV based on the COBAS method, colposcopy was done, then the liquid-based samples of women with Other HPV positive were reanalyzed by HPV typing (Real Time PCR technique) in the laboratory of one of the hospitals under SBMU. The information from the files included: age, marital status, education of the patient, employment status, number of sexual partners, age of onset sexual relationship, number of pregnancies and delivery method, type of contraception, menstrual status, tobacco and hookah consumption, genital warts, immune deficiency, pap smear test, colposcopy and HPV type. In this study, the data in the files especially the information related to HPV diagnostic tests were recorded in the questionnaire.

Data analysis

The data collected through SPSS software; version 26 (IBM, USA) was subjected to statistical analysis with chi-square tests. The relationship between HPV types and CIN types was determined, which is reported in the study findings section.

Results

Demographics

This prospective study was conducted on 646 patients with an average age of 34.5, among whom 328 cases of CIN1, 122 cases of CIN2, and 99 cases of CIN3 were detected with colposcopy, among which 348 cases of HPV18, 145 cases of HPV16, and 53 cases of Other HPV types were detected. Wife, 85 cases with a history of hookah consumption, and 80 cases with a history of alcohol consumption were recorded among patients and their spouses. In the evaluation of patients and their spouses in terms of the number of sexual partners, 290 cases reported more than one sexual partner and 332 cases of more than one sexual partner were reported in their wives. In the use of contraceptive methods, 106 cases of condoms, 360 cases of withdrawal (WD), and 180 cases of other methods were reported. 137 cases of the studied population had a history of one pregnancy, 101 had a history of two pregnancies, 76 had more than two pregnancies, and 332 had no pregnancy. 122 had a history of miscarriage, and 5 had a history of ectopic pregnancy. Of the total number of patients who had a history of childbirth, 126 had a natural birth and 162 had a cesarean delivery. 13 patients had a history of STIs, and 34 of their wives also reported a history of STIs. For the age of menopause, 15 cases were postmenopausal, and in terms of menstrual problems, 55 cases mentioned various menstrual problems (Table 1).

Table1. Demographics Data

Average age (years)		**34.5**	
CIN	CIN1	N=328	50.77%
	CIN2	N=122	18.88%
	CIN3	N=99	15.32%
HPV	HPV18	N=348	53.86%
	HPV16	N=145	22.44%
	Other HPV	N=53	8.20%
Smoking history	Patient	N=98	15.17%
	Spouse	N=72	11.14%
History of hookah use		N=85	13.15%
History of alcohol	Patient	N=80	12.38%
	Spouse	N=80	12.38%
More than one sexual partner	Patient	N=290	44.89%
	Spouse	N=332	51.39%
Contraceptive methods	Condom (26)	N=106	16.40%
	Withdrawal (26)	N=360	55.72%
	Other methods	N=180	27.86%
Gravid	1	N=137	21.20%
	2	N=101	15.63%

Average age (years)		**34.5**	
History of abortion	>2	N=76	11.76%
	Nulligravid	N=332	51.39%
		N=122	18.88%
History of ectopic pregnancy		N=5	0.77%
Childbirth history	Normal vaginal delivery	N=126	19.50%
	Cesarean section	N=162	25.07%
History of venereal disease	Patient	N=13	2.01%
	Spouse	N=34	5.26%
Menopause		N=15	2.32%
Menstrual problems		N=55	8.51%

Findings

Of the 646 patients studied, 303 Pap smear results were reported as normal, 32 cases did not perform the Pap smear test, 152 ASCUS cases, 21 ASC-H cases, 71 LSIL cases, 26 HSIL cases, 37 inflammation cases, and 6 atrophy cases were reported (Table 2).

Table 2. Result of pap smear

	Frequency	Percent
Normal	303	46.8%
ASCUS	152	23.5%
ASC-H	21	3.2%
LSIL	71	10.9%
HSIL	26	4%
Inflammation	37	5.7%
Atrophy	6	0.92%
None	32	4.9%

All the patients who were infected with HPV18 were involved in CIN1. On the other hand, 50% of patients who were infected with HPV18 were involved in CIN2 (Figure 1). 50% of patients with HPV45 were involved in CIN2. There is also a significant relationship between HPV31 and CIN3 (Figure 2,3). Its significance level is 0.029 less than the error rate of 0.05. 33.3 people with HPV31 are involved in CIN3 at the same time. The findings between HPV39 and CIN showed that there is a significant relationship between HPV39 and CIN1 (0.026) because it is lower than the value of 0.05, which indicates that 16.7% of infected people with HPV39 at the same time have grade CIN1. In the evaluation of HPV45 patients with types of CIN, it was found that there is a significant relationship between HPV45 and CIN2 (0.004), which is less than the error rate of 0.05, which means that 50% of people who have HPV45 (Figure 4) are also involved in CIN2 at the same time. The evaluation of patients with HPV51 (Figure 5) and simultaneous involvement with CIN1 showed that 20% of patients who have HPV51 are also involved in CIN1. The findings obtained from patients with HPV58 and suffering from CIN types showed that there is a significant relationship between HPV58 and CIN1 because the significant amount is 0.046 less than the error coefficient 0.05. This means that 14.3% of people who have HPV 58 are also involved in CIN1 at the same time. In the evaluation of patients who have HPV 16 and 18 at the same time, there is a significant relationship between the grade of CIN1; 37.5% of those who have HPV 16 and 18 are also involved in CIN1 disease. 25% of people who have this type of HPV also have a CIN3 grade. 15.2% of people with HPV16+HPV Others and 26.8% of people with HPV Others have CIN2, and 30.3% of people with HPV Others have CIN2, 3 and 19.3% have CIN3.

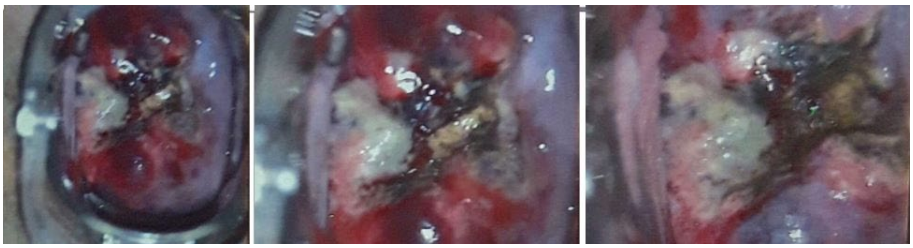

Figure 1. **HPV 18, ASCUS**

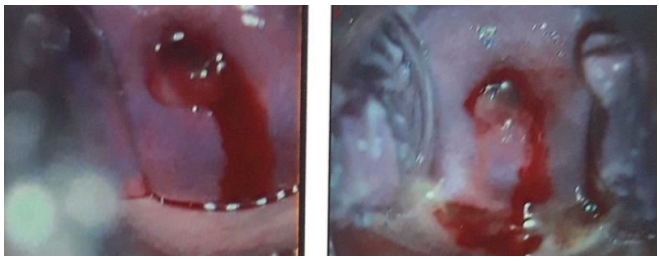

Figure 2. **HPV 31**

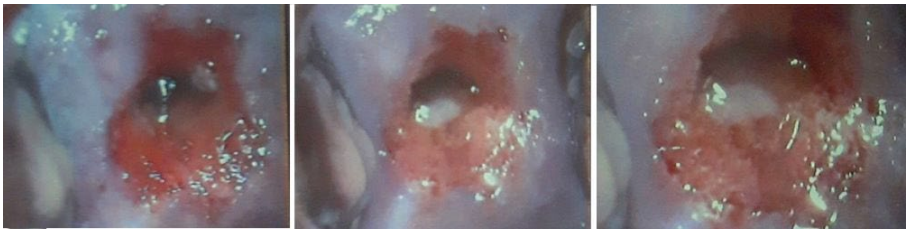

Figure 3. **HPV 31, HPV 11, LSIL**

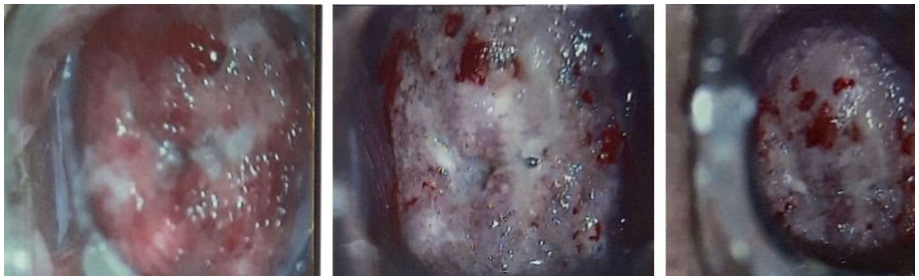

Figure 4. **HPV 45, ASCUS**

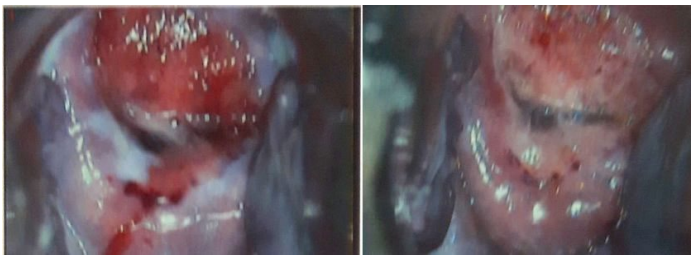

Figure 5. **HPV 51**

33.3% of patients with normal pap smears had HPV31; 11.1% of patients with ASCUS and ASC-H pap smears had HPV45; and 33.3% with positive LSIL had HPV31 (Table 3).

Table3. **Result of pap smear and HPV31**

		HPV 31		
		Yes	No	None
Pap Smear	Normal	%33.3	%48.7	%35.9
	ASCUS	%11.1	%24.1	%21.9
	ASC-H	%11.1	%3.2	%1.6
	LSIL	%33.3	%10.7	%4.7
	HSIL	0	%2.8	%15.6
	Inflammation	%0.0	%5.6	%7.8
	Atrophy	0	0	1.6
	None	%11.1	%4.4	%9.4

The results showed that 33.3% of patients with a normal pap smear were infected with HPV45, 33.3% of patients with ASCUS were infected with HPV45, and 33.3% of patients with positive ASC-H were infected with HPV45 (Table 4).

Table 4. Result of pap smear and HPV45

		HPV 45		
		Yes	No	None
Pap Smear	Normal	%33.3	%48.5	%35.9
	ASCUS	%33.3	%23.8	%21.9
	ASC-H	%33.3	%3.1	%1.6
	LSIL	0	%11.1	%4.7
	HSIL	0	%2.8	%15.6
	Inflammation	0	%5.6	%7.8
	Atrophy	0	0	%1.6
	None	0	%4.5	%9.4

Discussion

In a study on 400 patients with pap smear samples, the frequency of HPVs was: 16 with 19.1%, 39 with 12.5%, and 18 with 8.9%, respectively.

But in our study, the most common types of HPV were HPV18 (53%), HPV16 (22%), and other types of HPV (8.2%). In their study, the highest rate of HPV infection was at the age of 36 (7.7%). In our study, the average age of HPV patients was 33.5 years. In their study, most of the women with HPV had a diploma (34.6%), and 60.9% of these women were housewives **(14)**. But in our study, 63.2% of the women with HPV had a university education, and 57% were working people. In a 2014 study on women referred to hospitals of SBMU in Tehran over 10 years, the results showed that both in women with invasive CIN and in women with high-grade SIL, the most common type of HPV is HPV16, followed by HPV18, HPV31 and HPV26 **(15)**. However, in our study, the most common types of HPV were: HPV18 in 348 cases, HPV16 in 145 cases, and Other HPV types in 53 cases, and there is a significant relationship between HPV31 and CIN3. According to another study in 2018 on 2453 women with an average age of 35.1, the overall prevalence of HPV is 10.3%. Similar to our study, it was concluded from their study that HPV typing and detection of common HPV genotypes should be considered in CIN prevention programs in Iran **(16)**, but in our study it was recommended due to the importance of other HPVs with high-grade neoplasias, in order to speed up the diagnosis and economic savings, only the HPV typing method should be used instead of COBAS from the beginning. In a 2013 study, high-risk HPV was identified as the strongest risk factor for high-grade cervical pre-cancer **(17)**. and there is CIN2. The chi-square value was 4.856 with a significance of 0.028, which is less than the

significance level of 0.05. A 2021 study found that HPV-16 was the most common type of HPV in high-grade CIN lesions. After that, Other HPVs are in the next rank in terms of frequency, which indicates the importance of Other HPV types. HPV-18 was also observed in people with CIN (2). In our study, the importance of Other HPVs was also emphasized, and the majority of our patients, that is about a quarter of the patients (22.5%), were infected with (HPV16), and 50% of the patients were simultaneously infected with HPV18 and low-risk HPV types. were also involved in CIN2. A systematic review was conducted in 2017 to determine the estimates and persistence of HPV in women after treatment for CIN. A total of 45 studies provided data on HPV persistence after treatment among 6106 women. This systematic review provided evidence for significant heterogeneity in post-treatment HPV DNA testing methods and stability estimates **(18)**. This point expresses the importance of our study in relation to the HPV detection method, which from the beginning only uses the HPV typing method instead of COBAS, apart from speeding up the diagnosis and saving money. In a study in 2013, the persistence of HPV was significantly dependent on the study area and HPV type. Approximately half of HPV infections last 6 to 12 months. Repeat HPV testing at one-year intervals can identify women who are at high risk of cervical precancer due to persistent HPV infections. In our study, a 3- to 4-year follow-up of patients showed that in those with CIN1, 2, counseling, strengthening the immune system, reducing high-risk relationships, quitting smoking, alcohol and hookah, and following health tips, the persistence of HPV in 6 months to one year of follow-up was reduced, and in some cases (55 cases), they became negative. In Mousavi et al.'s cross-sectional study, the INNO-LiPA® HPV Genotyping Extra-II and Aptima HPV assay kits were used in DNA- and E6/E7 mRNA-based methods for detection of HR-HPV **(19)**. It should be noted that a great advantage of real-time PCR (HPV typing) assays is the possibility of quantifying the HPV in the specimen **(20)**. Several studies have shown that the amount of HR-HPV present in a cervical smear (the "viral load") as measured by real-time PCR (HPV typing) is predictive for the presence or development of high-grade cervical lesions **(21-25)**.

Conclusion

Because in our study there was a significant relationship between CIN3 and HPV31, and CIN2 with HPV45, and in the COBAS method, HPV31 and HPV45 are only reported under the general title of other HPV, because of the possibility of the importance of other HPV with high-grade neoplasias, it is recommended to analyze the other HPV with HPV typing. Further studies are needed to confirm our findings. If other studies with a larger sample size in the future also confirm the importance of HPV 31 and HPV 45 with high-grade neoplasias like our study, in order to speed up the diagnosis and save money, these two HPVs, along with HPV16 and HPV18, should be tested separately even in the COBAS method.

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Author's Contributions

Conceived and designed the analysis: Farah Farzaneh, Afsaneh Hosseini, Elanz Ghaffari, collected the data: Afsaneh Hosseini, contributed data or analysis tools: Tahereh Ashraf Ghanjouee, Maryam Sadat Hosseini, performed the analysis: Farah Farzaneh, wrote the paper: Farah Farzaneh, Afsaneh Hosseini, Elanz Ghaffari.

Conflict of Interest

The authors declare no conflict of interest.

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