

Age and Cervical Histology, the Most Important Factors to Predict Human Papilloma Virus Clearance

Fariba Behnamfar, Fatemeh Ahmadi Solush, Tajossadat Allameh*

Department of Obstetrics & Gynecology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran



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Corresponding Information:

Tajossadat Allameh,
Department of Obstetrics & Gynecology,
School of Medicine, Isfahan University of
Medical Sciences, Isfahan, Iran
Email: t_allameh@med.mui.ac.ir

ABSTRACT

Background and Objective: Cervical Cancer (CC) is a common cancer which is associated with HPV-infection. The aim of this study is to investigate the risk factors which affects HPV-clearance.

Methods: This study was carried out on women with high risk HPV infection. All the patients underwent pap smears and cervical biopsy. Demographic data, marital status, vaccination history and consumption of tobacco, alcohol, opium and oral contraceptive pills were asked through a questionnaire.

Results: The results showed that in one year follow-up, 142 (67.1%) patients showed HPV clearance. The HPV clearance decreased by increasing age ($P=0.028$) or higher CIN grades ($P=0.017$). In case of parity, there was no significant difference in univariate analysis ($P=0.147$), but it was significant in multiple logistic regression analysis (95% CI: 0.413-0.941, OR=0.624, $P=0.024$).

Conclusion: It seems that age and cervical histology at the start of HPV infection are the most important factors for HPV clearance.

Keywords HPV, Persistence, Clearance, Cervical cancer

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Introduction

Cervical Cancer (CC) is the fourth most common cancer and the fourth leading cause of female cancer deaths among women on a world-wide scale with 569,847 new cases and 311,365 deaths in 2018 due to the most recent Globocan report (1).

It is confirmed that infection with high-risk persistent human papillomavirus (HPV) which is a common sexually transmitted disease (STD), has been involved in 99.7% of cervical squamous cell cancer cases (2, 3). Therefore, launching a CC screening using primary high-risk HPV testing is an efficient tool to decrease incidence, burden and mortality of this disease (4). Predominantly, HPV infection is clear within 1-2 years after infection and only a few cases show persistence or progression from normal or CIN1 lesions to CIN2 and CIN3 (5).

Besides, existing evidence suggest that numerous risk factors affect CC development and its clinical course. Age, marital status, tobacco

smoking, alcohol or drugs use, oral contraceptive use, low socioeconomic status and HPV vaccination are among the relevant factors (6-9). On the other hand, a number of studies have not shown this relationship (10-13). Due to the controversies about affecting HPV clearance and importance of high-risk HPV in cervical cancer, which is an important cause of death in women especially in developing countries, this study was done.

Materials and Methods

This prospective cohort study was carried out on women with high-risk HPV infection being referred to Gynecology clinic from June 2020 to March 2022. All the patients underwent pap smears and cervical biopsy. Women with \geq CIN2 were excluded from the study, so the study included women with positive HR HPV test and CIN 1 or

less on cervix. Also, women with HIV infection, pregnancy, immunosuppression, cervical neoplasia history, chronic comorbidity or genital tract cancer were excluded from the study.

When doing colposcopy, punch biopsy was taken from suspicious areas. Two to three biopsies were taken from the squamocolumnar junction (SCJ) randomly in patients with normal colposcopy. Demographic data, marital status, vaccination history and consumption of tobacco, alcohol, opium, and oral contraceptive pills were asked through a questionnaire. A year later, patients were re-examined by Co-test (HPV (cobas®) and pap smear) and all the questions were asked again.

The mean and standard deviation are used for description of quantitative variables, and frequency was used for description of qualitative variables. The analysis was performed using IBM SPSS software, version 24, through independent-t, Chi-squared, ANOVA, logistic regression and Fisher's exact tests. P value less than 0.05 was considered as significant.

Results

At the beginning of the study, all women with high-risk HPV underwent colposcopy and biopsy. The results showed that in 100 cases (43.4%) cervical histology showed CIN1 and in 130 cases (56.6%) the result was normal. Fifteen patients had \geq CIN2 on their cervix and were excluded from the study, so 230 patients were included.

The questionnaire including age, parity, education level, cigarette smoking, opium use, alcohol use, OCP use, marital status, HPV vaccination and comorbidities was completed. After one year, all participating patients were visited and the co-test (including pap-smear and HPV test) was performed. The mean age of participants was 35.6 ± 8.4 years.

Comparing the co-test results with the initial assessment, the results showed that in one year follow-up, 142 (67.1%) patients showed HPV clearance. Also, clearance rate was checked for each of the factors. Baseline characteristics were summarized in [Table 1](#).

Table 1. Baseline characteristics

		Total (n=230)	Clearance group (n=142)	No clearance group (n=88)	P-value
		Number (%)	Number (%)	Number (%)	
Parity	0	100 (43.5%)	60 (60%)	40 (40%)	0.147
	1	75 (32.5%)	51 (68%)	24 (32%)	
	2	39 (17%)	19 (48.7%)	20 (51.3%)	
	≥ 3	16 (7%)	12 (75%)	4 (25%)	
Education	High school	21 (9.1%)	14 (66.7%)	7 (33.3%)	0.705
	Diploma	50 (21.7%)	32 (64%)	18 (36%)	
	Associate's degree	20 (8.7%)	14 (70%)	6 (30%)	
	Bachelor's degree	100 (43.5%)	62 (62%)	38 (38%)	
	Master's degree	32 (13.9%)	17 (53.1%)	15 (46.9%)	
	PhD	7 (3%)	3 (42.9%)	4 (57.1%)	
Cigarette smoking	No smoking	196 (85.2%)	123 (62.8%)	73 (37.2%)	0.451
	Smoker	34 (14.8%)	19 (55.8%)	15 (44.2%)	
Opium use	Yes	1 (0.4%)	0 (0%)	1 (100%)	0.383
	No	229 (99.6%)	142 (61.7%)	88 (38.3%)	
Alcohol use	Yes	42 (18.3%)	25 (59.5%)	17 (40.5%)	0.744
	No	188 (81.7%)	117 (62.2%)	71 (37.8%)	
OCP use	Never	207 (90%)	125 (60.4%)	82 (39.6%)	0.205
	Now or before	23 (10%)	17 (73.9%)	6 (26.1%)	
Marital status	Married	166 (72.1%)	104 (62.6%)	62 (37.4%)	0.653
	Unmarried	64 (27.9%)	38 (59.3%)	26 (40.7%)	
HPV vaccination*	Yes	47 (20.4%)	26 (55.3%)	21 (44.7%)	0.310
	No	183 (79.6%)	116 (63.4%)	67 (36.6%)	

* Vaccination after positive HPV test is considered

The number of patients who had positive result for HPV16, HPV18 and other high risk HPV subtypes at the first visit was 100, 39 and 141, respectively. In one year follow-up, these numbers changed to 28, 8 and 61.

One hundred and twenty women (52.2%) had normal cytologic study (pap smear) in the first-visit

and the number of ASC-US and LSIL results was 57 (24.8%) and 53 (23%), respectively. After one year, 186 patients had normal results and the number of ASC-US and LSIL results was 25 and 18, respectively. Only one patient was presented with ASC-H+HSIL result ([Table 2](#)).

Table 2. Type-specific HPV persistence, cytologic and histopathologic outcomes

		Total (n=230)	Clearance group (n=142)	No clearance group (n=88)	P-value
		Number (%)	Number (%)	Number (%)	
Type-specific HPV persistence outcomes	HPV16+	100 (43.4%)	59 (59%)	41 (41%)	0.453
	HPV16-	130 (56.6%)	83 (63.8%)	47 (36.2%)	
	HPV18+	39 (16.9%)	20 (51.3%)	19 (48.7%)	0.140
	HPV18-	191 (83.1%)	122 (63.9%)	69 (36.1%)	
	Other	141 (61.3%)	90 (63.8%)	51 (36.2%)	0.412
	hrHPV*+ Other hrHPV-	89 (38.7%)	52 (58.4%)	37 (41.6%)	
Cytologic outcomes	Normal	120 (52.1%)	77 (64.2%)	43 (35.8%)	0.483
	ASC-US	57 (24.7%)	36 (63.2%)	21 (36.8%)	
	LSIL	53 (23.2%)	29 (54.7%)	24 (45.3%)	
Histopathologic outcomes	Normal	130 (56.6%)	89 (68.5%)	71 (31.5%)	0.017
	CIN1	100 (43.4%)	53 (53%)	47 (47%)	

* High-risk HPV

Moreover, histologic study of the patients showed that 130 (56.5%) patients were normal and 100 (43.5%) had CIN1 result. One hundred and eight patients underwent punch biopsy in 12 months follow-up, and the number of normal, CIN1 and CIN2 results was 64, 43 and 2, respectively.

Although in case of parity, there was no significant difference in univariate analysis ($p=0.147$), clearance and no-clearance groups showed a significant difference in multiple logistic regression analysis (95% CI: 0.413-0.941, OR=0.624, $p=0.024$).

The mean age in the clearance and no-clearance groups was 34.6 ± 8.5 and 37.1 ± 8.0 , respectively; so the difference was significant ($p=0.028$). As mentioned in Table 2, the HPV clearance rate was significantly higher in patients with normal histopathologic result compared with CIN1 ($P=0.017$); but there was no dramatic difference between HPV types or various cytologic results.

Discussion

In this study, high-risk HPV patients were selected and prospectively evaluated to find clearance and factors affecting clearance. Age, parity, education, smoking, opium use, alcohol use, OCP use, marital status, HPV vaccination, primary cytologic and histopathologic outcomes were included in this study as possible risk factors of HPV persistence. In this study, the overall HPV clearance rate was 67%. Age, cervical histopathology and parity were showed to be the most important risk factors for persistence of HPV infection.

Current studies believe that about 70 % of sexually active women are contaminated with HPV and clear in the coming weeks or months (14, 15). Over time, various articles have introduced different factors about the lack of HPV clearance, which we

discussed in this article. We evaluated 230 women of whom 142 (67.1%) were cleared and 88(38.3%) were not. 59% of HPV16 cases, 51.3% of HPV18 cases, and 63.8% of High-risk HPV cases were cleared. Type-specific HPV investigations represented a notable role in some studies (16, 17), especially about HPV16 (18-20). In our study, this difference was not significant.

Present study showed that with increasing age, non-regression of HPV becomes more probable. One possible reason is that with increasing age, the immune system becomes weak, so the clearance of HPV is more difficult (21). Several authors have studied about the effect of age on HPV clearance. Sammarco *et al.*, (22) represented that females aged 22–27 years have a higher risk for persistent high risk HPV, which is in line with Li *et al.*, (23) who believe that this risk is higher in limits of age in comparison with middle-aged women. Some studies showed that early age at first sexual intercourse is also effective in HPV persistence (6, 24).

About 20% of our patients had been vaccinated after positive HPV result, but it was shown that post-HPV-infection vaccination doesn't seem to be effective in HPV regression. After all, there are still some challenges about efficacy of therapeutic vaccines against HPV infection (25).

In the present study, multiparity was associated with increased risk of HPV persistence, which is coordinated with Kim *et al.* study (7). They believed the trauma during childbirth could be the probable reason. Cervical histopathology in our study was significantly different between the two groups of normal and CIN1 ($P=0.017$), which was consistent with the study of Kim *et al.*, (7), but some other studies denied this relationship (26, 27). A possible reason for the negative effect of multiparity on HPV-clearance is the high prevalence of squamous

metaplasia in pregnancy (28). Further studies are needed to investigate the pathophysiology of these outcomes.

There are some biological and epidemiological evidence about tobacco carcinogens that affects cervical tissue (29-33), in the present study tobacco and opium users showed no significant difference compared to never-smokers. It should be noted that passive smoking has even shown to cause HPV non-clearance (34). It should be noted that due to some social issues, patients may not report the exact number of parity and their smoking status correctly.

In spite of the findings of our study, alcohol (35) and also hormonal contraceptive (36) consumers might be at higher risk to longer-term HPV infection in other studies. There is also some evidence about synergistic effect of viral load (37) or smoking (34) with alcohol use. Also, sexual behavior (number of lifetime sexual partners, having non-monogamous male partners, etc.) and marital status seems to be important. Previous studies, but not ours show these risk factors are effective in HPV persistence and also in genital warts (8, 38).

Although cytology has been associated with HPV in some studies (11, 39), our study didn't show this relevance.

In this study with respect to social and cultural issues, many patients did not honestly answer questions about smoking and marital status. It seems that further studies with more follow-up periods could provide more complete findings. In this study, some possible risk factors such as viral load were not checked. Due to the expansion of potential risk factors and heterogeneity of the present studies, future studies are expected to conduct more comprehensive reviews in this case. Due to the possibility of progression to cervical cancer with HPV persistence, next studies with more cases are recommended.

Conclusion

It seems that age, cervical histology and parity at the start of HPV infection are the most important factors for HPV clearance.

In other words, higher age and the histopathology result of CIN1 compared to normal result and multiparity are associated with HPV persistence or even progression.

Acknowledgment

None.

Conflict of interest

The authors declare no conflict of interest. The ethical code is IR.MUI.MED.REC.1399.358.

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