Type-Specific Persistence/Clearance Results in Human Papillomavirus Infections in Turkish Women

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ABSTRACT

OBJECTIVE: The persistence of high-risk human papillomavirus (HPV) infections, most of which are known to be transient is of critical importance for the development of precursor lesions and cancer in the cervix. The aim of the present study is to investigate the persistence and clearance of genotype-based HPV infections and also some cofactors that could be effective in persistence.

STUDY DESIGN: Data of 115 patients whose human papillomavirus and genotype detection was made with multiplex PCR (Polymerase chain reaction), and capillary electrophoresis were categorized as low-risk HPV (LR-HPV)/high risk HPV (HR-HPV) and single/multiple HPV infections, and clearance/persistence data of two years were investigated.

RESULTS: While 82 (71.3%) out of 115 patients (mean age 40.1 years) had a single HPV infection, the remaining had two or more HPV infections. Of all HPV infections, 81.5% (128/157) were HR-HPV. Clearance rates of HPV infections during the first two years was 85.4% (134/157), persistence was 14.6% (23/157). The most frequently persisted HR-HPV genotypes were 31, 52, 68, 16, and 35, respectively. A statistically significant difference was not found in HPV persistence with regard to the infection's being single/multiple or LR/HR. A significant difference was not found between age groups and persistence.

CONCLUSIONS: Of HPV infections, 85.4% are cleared during the first two years while the most frequently persisted HR-HPV genotypes were 31, 52, 68, 16, and 35, respectively. Being aware of population-based clearance/persistence results of type-specific infections may specify screening strategies.

Keywords: Cervical cancer, Clearance, Human papillomavirus, Persistence

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Introduction

Human papillomavirus (HPV) infection is the most frequently diagnosed sexually-transmitted disease. The persistence of oncogenic high-risk HPV (HR-HPV) is responsible for all cervical cancers, many anal, and some vulvar/vaginal cancers (1,2). Most of them are transient after detection of the first infection, and 90% are spontaneously cleared in 24 months (3-8). The same woman may be re-infected with the same HPV type, although most of the type-specific HPV infections are cleared. This may occur from a new partner, re-infection of the same partner, or reactivation of the initial infection (9).

In cervical carcinogenesis, the most important step of HPV infection is the persistence of HPV infection, progression to precancerous lesions, and invasion (10,11). Persisted infection is defined as "finding the same genotype positive in two consecutive HPV tests"; however, the screening interval of type-specific infection may widely vary among different reports (12,13).

The co-existence of sexually-transmitted infections and immune-response disorders were detected to increase HPV persistence (14). High parity, smoking, long term use of oral contraceptives (OC) were also accused as cofactors for persistence (15-18). However, the factors that regulate progression could not be fully explained yet. Human immune deficiency virus (HIV) positivity is a strong risk factor for HPV persistence (8,14).

Although environmental and genetic factors are considered to contribute to the progression of cervical cancer as a cofac-

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tor, the role of these risk factors in the natural course of precursor lesions has been questioned in rare studies. Researches about the natural persistence/clearance of HPV infection has gained importance in recent years. Incidence, genotype frequency, and prevalence of HPV infection may vary among geographic regions (19,20). Sufficient knowledge is not available about the persistence and clearance of geographic region and population-specific HPV infections (21-27).

The aim of the present study was to investigate the persistence/clearance of HPV genotype-specific infections in our region during a 2-year period.

Material and Method

The patients aged between 23-70 years who were detected to have HPV positivity on routine gynecologic examination and genotype detection was made between December 2015 and December 2019 were included in this retrospective cohort study. Pregnant women, the patients who had a macroscopic mass lesion in the cervix, and the diagnosis of cancer were excluded from this study. The study was conducted in accordance with the ethical guidelines, including the World Medical Association (1975) Declaration of Helsinki 2008, and the legal requirements of the Ethics Committee of Canakkale Onsekiz Mart University (Date:29.01.2020; approval no:2020/02).

The second cervical sample was obtained within 18-24 months, and the same assessment procedure was applied. The tests were done before the 18th month and after the 24th month was not included. The patients were also excluded if they were performed a surgical procedure to cervix like conization after the first test.

"Persistence" was defined as detection of the same HPV genotype of the type-specific persistent HPV infection, and "clearance" was defined as a negative test for the individual HPV type following a positive test for that type. Colposcopic biopsy results of patients were not given in our study because the main subject of the study was the persistence and clearance of HPV.

DNA isolation and HPV genotyping

Total genomic DNA was extracted from cervicovaginal smear samples by using the commercial QIAamp Blood and Tissue Kit (QIAGEN Inc., Hilden, Germany) according to the manufacturer's protocol (28). The target HPV genotyping was done after total genomic DNA isolation from cervicovaginal smear samples for each patient. Briefly, HPV genotyping was performed by the F-HPV typing™ multiplex PCR (Molgentix SL, Barcelona, Spain). The assay uses 16 specific primers amplifying within E6 and E7 regions of the HPV genome and permits the detection of 13 high-risk genotypes (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68) and 12 low-risk genotypes (6, 11, 34, 40, 42, 43, 44, 53, 54, 66, 70, and 74). The presence of DNA of these HPV subtypes was detected by multiplex PCR amplification using type-specific primers. For the multiplex PCR, a total of 25 µL reagent mixtures contained 5 µL f-HPV PCR master mix that contained 5 U hot start Taq DNA polymerase enzyme, 15 µL primers mix, and 5 µL target DNA were used for the amplification of target genes. The amplification conditions were; 96°C for 2 min for initial denaturation and holding phase cycles and in a total of thirty-five amplification cycles (ten and twenty-five tandem repeated sequences) were performed in the current genotyping procedure. Ten cycles included denaturation at 94°C for 30 s, annealing at 64°C for 40 s, and extension at 70°C for 30 s tandemly followed by twenty-five cycles included denaturation at 90°C for 30 s, annealing at 60°C for 40 s and extension at 70°C for 30 min. In the final phase, the temperature was maintained at 60°C for 30 min for polymerization of incomplete fragments. The PCR amplicons were separated and detected in terms of their size by using capillary electrophoresis

Statistical Analysis

Statistical analyses were done with SPSS software windows version 18.0. Descriptive statistics were used for persistence and clearance analysis of type-specific infection. Pearson chi-square test was used for verification of the association between all dependent and independent variables. A p level of <0.05 was accepted as statistically significant.

Results

The mean age of 115 patients who met inclusion criteria was 40.1 years (range 23-70). While single HPV infection was detected in 82 (71.3%) patients, multiple HPV infection (two or more lesions) was detected in 33 (28.7%). While 81.5% (128/157) of the infections were HR-HPV infections, 18.5% were LR-HPV. The most frequent genotype of HR-HPV was HPV 16 (27.3%).

Consecutive control HPV tests of 115 patients were obtained at mean 20th month (95% CI, 18-24). The same HPV genotype had persisted in 23 patients (14.6%), clearance was detected in 94 patients (85.4%). A significant difference was not found between persistence rates with regard to the infection's being single/multiple or HPV genotype's being HR/LR (p=0.113, p=0.191) (Table I). The most persisted genotypes were 31, 52, 68, 16, and 35, respectively (Table II) HPV 11 persistence was the most common in LR-HPV (Table II). A

Table I: *Clearance and persistence of human papillomavirus infection according to the oncogenic risk and being single/multiple*

	Total n (%)	Clearance n (%)	Persistence n (%)	p
Infection				
Single	82 (71.3)	70 (85.3)	12 (14.7)	0.113
Multiple	33 (28.6)	24 (72.7)	9 (27.3)	
Oncogenic risk				
LR-HPV	29	27 (93.1)	2 (6.9)	0.191
HR-HPV	128	107 (83.5)	21 (16.5)	

LR-HPV: Low risk human papillomavirus, HR-HPV: High risk human papillomavirus. p<0.05 was accepted to be statistically significant.

significant difference was not found between age groups and persistence (Table III).

Table II: *Clearance and persistence results in high risk human papillomavirus and low risk human papilloma virus infection*

HPV type	Clearance n (%)	Persistence n (%)	Total (n)
16	27 (77.1)	8 (22.9)	35
18	8 (88.8)	1 (11.2)	9
31	9 (64.2)	5 (35.8)	14
33	2 (100)	0 (0)	2
35	7 (77.7)	2 (22.3)	9
39	11 (91.6)	1 (8.4)	12
45	6 (100)	0 (0)	6
51	12 (100)	0 (0)	12
52	6 (75)	2 (25)	8
56	7 (87.5)	1 (12.5)	8
58	4 (100)	0 (0)	4
59	5 (100)	0 (0)	5
68	3 (75)	1 (25)	4
HR-HPV	**107 (83.5)**	**21 (16.5)**	**128**
6	16 (94.1)	1 (5.9)	17
11	3 (75)	1 (25)	4
61	1 (100)	0 (0)	1
66	7 (100)	0 (0)	7
LR-HPV	**27 (93.1)**	**2 (6.9)**	**29**

HR-HPV: High risk human papillomavirus, LR-HPV: Low risk human papillomavirus

Table III: *Comparison of clearance/persistence of human papillomavirus infection among different age groups*

Age group	Total n	Clearance n (%)	Persistence n (%)	*p*
<30	18	15 (83.3)	3 (16.7)	
30-49	74	60 (81.0)	14 (19.0)	0.969
≥50	23	19 (82.6)	4 (17.4)	

p<0.05 was accepted to be statistically significant.

Discussion

In our study which was aimed to investigate HPV persistence and clearance rates in Turkish women, persistence rates of HPV infections during the first two years were 14.6%, and HPV types with the highest rate of HPV persistence were found to be 31, 53, 68, 16, 35, respectively. It has been indicated that the HPV persistence rate is not affected by the presence of multiple or single HPV types of infection. Also, the persistence rates of low-grade and high-grade HPV types were detected to be similar. In the comparison of HPV persistence among women under 30, between 30-49, and 50+, there was no difference in persistence rates.

The estimated half-life of HR-HPV infections is 8-10 months (29). More than 90% of the infections are cleared within two years (8,11). However, this ratio differs among countries. While HPV persistence was found to be 12.4% in South Korea (30), this ratio was 19.2% in Brazil (22), 49.1% in Italy (26), 31.4% in Denmark (31), and 44.1% in the Netherlands (32). The persistence rate was quite lower (18.2%) in our study as compared to European countries. However, this difference may emerge from the variability of the target population and test intervals. Though, a meta-analysis showed that HPV persistence decreased with time following the first infection (33).

While many studies report the most persistent types like HPV 16 and 18 (22,24,26,32-35), Ingabire et al. reported that the most persisted genotypes as HPV 33, 45, 16, and 35, respectively; and Sammarco et al reported as 31, 39, and 73 (26,30). In our study, the most persisted genotype was found to be HPV 31 followed by 52, 68, and 16.

The relationship between age and HPV persistence is of debate. While studies are available reporting that persistence increases in younger ages (21,22,32,36), studies are available reporting that persistence increases directly proportionally with age (8). Similar to some studies in the literature, an association between age and persistence have not been detected in this study (25,30,31,37-39).

Unlike the low LR-HPV persistence in our study, Miranda et al (25) found a high ratio of persistence in LR-HPV (70.6%); however, he did not find a significant relationship between persistence rates of LR-HPV and HR-HPV, as in our study. Other data also support these results (34,27).

Although multiple HPV infections were reported to persist in higher ratios as compared to single HPV infections at the end of 24 months of follow up (25,24,37,8), a statistically significant difference was not found in some studies, as in our study (26,31).

In literature, although smoking was reported to increase HPV persistence (27), the relationship between persistence and these cofactors could not be clearly shown (30,26,24,21). The clearance of HPV was reported to be related to intrinsic host-related factors, not with behavioral factors (27). Persistence was associated with high viral load (40,41). Stensen et al reported that HPV persistence risk was higher only in patients with genital condyloma (31).

The limitation of the present study does not include persistence-related potential risk factors due to the small sample size and the retrospective design of the study.

In conclusion, it is valuable that the results of the study reflect the Turkish population-specific data. Being aware of the natural course of type-specific HPV infections are of importance for developing strategies for screening and screening interval, detection of the population-based type-specific HPV infection prevalence, and the potential benefits of the targeted vaccination schedules.

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