

# Concordance of the frequency, typing, and results of high risk human papilloma virus in cervical cytology materials with biopsy: Retrospective analysis of 5604 patients

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## Abstract

**Aim:** The aim of the study is to evaluate retrospectively the results of human papilloma virüs (HPV) screening test started at our center, to identify the rates of high risk HPV (hrHPV) causing /not causing cellular anomalies and HPV16, 18/45 genotypes, to review the concordance of smear results and biopsy, and to compare our results with the similar studies conducted in different parts of the world and our country.

**Material and Methods:** Five thousand six hundred four cases in Hospital, between 2016 and 2017, with transcription-mediated amplification and hybridization protection method, 14 hrHPV types including HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68 were investigated with presence of HPV E6/E7 mRNA. HPV(+) cases were reevaluated with the genotyping study for detection of HPV16, 18/45.

**Results:** When the hrHPV results of 5604 patients were evaluated, 421 cases (7.5%) were hrHPV positive and 5183 cases (92.5%) were hrHPV negative. In the genotyping study of hrHPV positive cases, it was found that HPV16 was present in 97 cases (23%), HPV18/45 was present in 40 cases (9.5%) and other hrHPVs were found in 282 cases (67%). HPV16 and HPV 18/45 coexisted in 2 cases (0.5%).

Biopsy results of hrHPV positive cases were 56 cases (32.7%), 40 cases (23.4%) and 5 cases (2.9%) for low grade squamous intraepithelial lesion (LGSIL), high grade squamous intraepithelial lesion (HGSIL) and Squamous Cell Carcinoma (SCC), respectively.

**Conclusion:** In our study, prevalence of hrHPV is 1.2% in cases with normal cytology results and 7.5% in general population. In the majority of studies conducted in our country, HPV positivity is very high because HPV is studied in smear and cervical anomaly cases instead of general population.

We believe that this study contributes to determine the frequency and genotype distribution in normal/ abnormal cytology of HPV in our country.

**Keywords:** HPV; Cervix; Pap Smear; Cervical Intraepithelial Neoplasia.

## INTRODUCTION

Cervical cancer is the second or third most common cancer in women worldwide. Although there are differences in developed and undeveloped countries, approximately 0.5 million new cases are reported each year (1). Persistent infection of uterine cervix with hrHPV is well known in its etiology (2). The identification and treatment of asymptomatic precursor lesions has become very important since the invasive cancer progression of precancerous lesions takes much time as long as 15-20 years (3). Among the hrHPV types, type 16 and 18 have been shown to be the most associated genotypes with

invasive cancers and to be more than 70% in cervical cancers worldwide (1,3,4). Therefore, the investigation of the presence of hrHPV and the detection of genotypes which are the most common causes of cancer are very important in terms of follow-up and treatment of the cases.

The results of the HPV screening test started to be applied in our clinic have been evaluated retrospectively. hrHPV frequency and HPV 16, 18/45 genotype ratios have been determined. Pap smear data obtained have been reviewed for concordance with biopsy. Our results have been compared with similar studies conducted in different regions of the world and throughout our country.

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## MATERIAL and METHODS

A retrospective study was conducted in the Department of Pathology. This work has been approved by the Institutional Review Board. Five thousand six hundred four cases in Hospital Pathology Training Clinic between September 2016 and August 2017, with transcription-mediated amplification and hybridization protection method (Optima-Panther system), 14 hrHPV types including HPV 16,18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68 have been investigated with presence of HPV E6 / E7 mRNA. hrHPV (+) cases have been re-evaluated with the genotyping study (Aptima HPV16, 18 / 45 Genotype Assay-Panther System) for detection of HPV16, HPV18/45.

## RESULTS

The mean age of 5604 patients was 42.5 (18-87). The distribution of hrHPV according to ages is shown in Table 1.

Age	Negative for hrHPV	Positive for hrHPV	Percentage of hrHPV positivity in age groups	Percentage distribution of hrHPV (+) cases by age groups
under 20 years	25	1	3.8%	0.2%
20-29	426	59	12.2%	14%
30-39	1617	166	9.9%	39.4%
40-49	1891	112	5.6%	26.7%
50-59	895	53	5.6%	12.6%
Over 60 years	329	30	8.4%	7.1%
<b>TOTAL</b>	<b>5183</b>	<b>421</b>	<b>7.5%</b>	<b>100%</b>

When the hrHPV results of 5604 patients were evaluated, 421 cases (7.5%) were hrHPV positive and 5183 cases (92.5%) were hrHPV negative. In the genotyping study of hrHPV positive cases, it was found that HPV 16 was present in 97 cases (23%), HPV 18/45 was present in 40 cases (9.5%) and other hrHPVs (HPV 31,33,35,39,51,52,56,58,59,66,68) were found in 282 cases (67%). HPV 16 and HPV 18/45 coexisted in 2 cases (0.5%) (Figure 1).

There were 573 (10.2%) cases with abnormal cervical cytology. Of the 5031 patients with normal cytology, 61 (1.2%) were found to be hrHPV positive. Of 573 patients with abnormal cytology, 360 (62.8 %) were found to be positive for hrHPV (Table 2).

Papsmear results of all hrHPV positive cases were 61 (14.5%), 188 (44.7%), 10 (2.4%), 135 (32.1%) and 27 (6.4%) for reactive changes, atypical squamous cells of undetermined significance (ASCUS), atypical squamous cells-which cannot exclude high-grade squamous intraepithelial lesion (ASC-H), LGSIL and HGSIL, respectively (Table 2).

Smear results according to distribution of hrHPV genotypes are shown in Table 3.

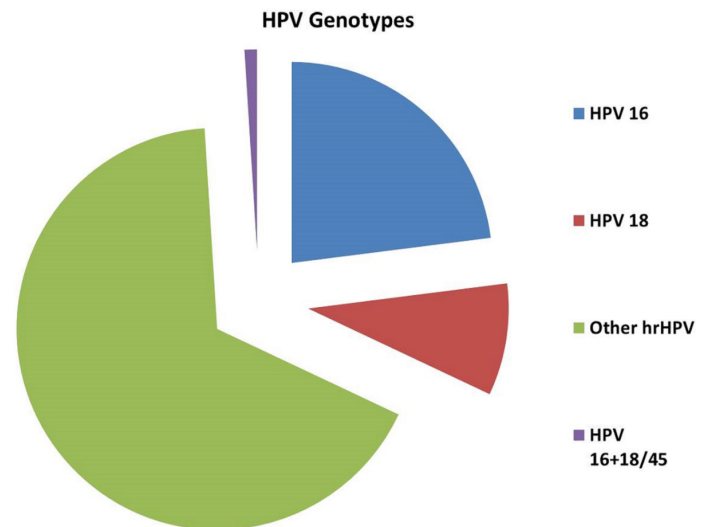


Figure 1. Graph of genotype distribution of hrHPV (+) cases

Cervical cytology	Negative for hrHPV	Positive for hrHPV	Total
<b>Normal/ Reactive Changes</b>	4970	61	5031
ASCUS	204	188	392
ASCH	3	10	13
LSIL	4	135	139
HGSIL	1	27	28
AGUS	1	-	1
<b>Total</b>	<b>5183</b>	<b>421</b>	<b>5604</b>

hrHPV genotype/smear result	Normal/ Reactive Changes	ASCUS	ASC-H	LGSIL	HGSIL	Total
HPV 16	5	32	3	40	17	97
HPV 18/45	2	15	1	19	3	40
Other hrHPV	54	141	6	74	7	282
HPV 16 and 18/45 coexisted	-	-	-	2	-	2
<b>Total</b>	<b>61</b>	<b>188</b>	<b>10</b>	<b>135</b>	<b>27</b>	<b>421</b>

Of the patients whose biopsies were obtained after smear, squamous intraepithelial lesion was detected in 28 of 74 ASCUS-diagnosed cases (37.8%), 10 of ASC-H-diagnosed 12 cases (83.3%), 42 of 60 LGSIL-diagnosed patients (70%) and all of 21 HGSIL-diagnosed patients (100%) (Table 4).

Of the HPV 16 positive cases, biopsies of 52 cases are available. Biopsy results were 3 SCC, 24 HGSIL, 14 LGSIL and 11 normal/reactive changes (Table 4).

Of the HPV 18/45 positive cases, biopsies of 22 cases are available. Biopsy results were 1 SCC, 4 HGSIL, 12 LGSIL and 5 normal/reactive changes (Table 4).

Of the 2 cases in which HPV 16 and HPV 18/45 coexisted, biopsy of 1 case is available. The biopsy result was LGSIL (Table 4).

Of the other hrHPV positive cases, biopsies of 96 cases

are available. Biopsy results were 1 SCC, 12 HGSIL, 29 LGSIL, 54 reactive changes (Table 4).

In 168 cases diagnosed as positive for intraepithelial lesion with pap smear, the false positive rate was 39.2% (66 cases), and the false negative rate was 0.5% (1 case). Biopsy results of false positive cases were reactive changes, 46 were diagnosed for ASCUS, 2 were diagnosed for ASC-H, and 18 were diagnosed for LGSIL with pap smear (Table 4).

**Table 4. The distribution of biopsy results and cervical cytology results according to hrHPV genotypes**

	Cervical cytology Result		Biopsy Results				Total
		Normal/Reactive changes	LGSIL	HGSIL	SCC	Adenocarcinoma	
<b>Positive for hrHPV type 16</b>	ASCUS	9	5	3	-	-	17
	ASC-H	-	2	1	-	-	3
	LGSIL	2	6	10	1	-	19
	HGSIL	-	1	9	2	-	12
	Nondiagnostic	-	-	1	-	-	1
<b>Positive for hrHPV type 18/45</b>	ASCUS	2	4	1	1	-	8
	ASC-H	-	1	-	-	-	1
	LGSIL	3	5	2	-	-	10
	HGSIL	-	2	1	-	-	3
	Nondiagnostic	-	-	-	-	-	-
<b>Positive for Other hrHPV</b>	ASCUS	35	11	2	1	-	49
	ASC-H	1	3	2	-	-	6
	LGSIL	12	13	3	-	-	28
	HGSIL	-	1	4	-	-	5
	Nondiagnostic	-	1	-	-	-	1
	N/R changes	6	-	1	-	-	7
<b>Positive for hrHPV Type 16 and 18/45 coexisted</b>	ASCUS	-	-	-	-	-	-
	ASC-H	-	-	-	-	-	-
	LGSIL	-	1	-	-	-	1
	HGSIL	-	-	-	-	-	-
	Nondiagnostic	-	-	-	-	-	-
<b>Negative for hrHPV</b>	ASCUS	-	-	-	-	-	-
	ASC-H	1	1	-	-	-	2
	LGSIL	1	-	1	-	-	2
	HGSIL	-	-	1	-	-	1
	AGUS	-	-	-	-	1	1
<b>Total</b>		72	57	42	5	1	177

## DISCUSSION

Despite the widespread presence of HPV infection in sexually active young women, most of them regress spontaneously without causing clinical symptoms. However, some women develop permanent HPV infections. Detection of HPV for longer than 12 months is a sign of persistent infection. These individuals are under the risk of cervical cancer and its precursors (2,5,6).

The incidence of cervical cancer with the use of pap smear test, a cervical screening method, has been reduced by

70% over the last 50 years, but no eradication has been achieved. Concomitant hrHPV testing in the presence of abnormal cytology instead of using pap smear test alone for women aged 30-65 years increases the rate of detection of precancerous lesions and reduces the incidence of invasive cancer (5,7).

The prevalence of HPV varies significantly from country to country, with a frequency ranging from 2 to 44% (8). In our country, this rate was reported as 2.1% and 24.8% for the lowest and highest values in general population,

respectively (9,10). HPV strains causing precancerous lesions (HGSIL and LGSIL) and cervical cancer are called hrHPV. In our study, hrHPV prevalence was found to be 1.2% in cases with normal cytology results and 7.5% in general population and 73.4% in cases with abnormal cytology. In other studies in which hrHPV subtypes were evaluated in our country, this rate ranges between 3.4% and 33.7% (5,11-15). The reason for this wide range is that instead of general population, HPV was studied in cases in which the cervical anomaly is detected with smear in the majority of the studies.

HPV 16, 18 and 45 are known to be present in about 75% of cervical cancers (1). The incidence of hrHPV genotypes varies according to the countries. The most common genotypes in Venezuela are HPV 16 and HPV 18, HPV 16 and HPV 58 in China, HPV 16 and HPV 53 in Italy and Spain (8). With the exception of three of the studies in our country, including our study, the most common type was found to be HPV 16. This is followed by HPV 18, 31, and 51 (5,6,12-21). Of the three studies with different findings, the most common HPV type was found to be HPV 18 in two studies and HPV 66 in one study (4,22,23). Among the HrHPV positive cases in our study, HPV 16 rate was 23% and HPV 18/45 rate was 9.5%. All of our cases with cervical cancer are positive for hrHPV. In these cases, the most common genotype is HPV 16 with 60%, followed by HPV 18/45 with 20% and other hrHPV with 20% (Table 3., Figure 1.). These results are compatible with the results of the World Health Organization.

In cervical cancer screening and management guidelines of American Society of Colposcopy and Cervical Pathology (ASCCP), concurrent hrHPV screening with pap smear and HPV 16/18 genotyping in hrHPV positive cases are recommended for the women between the ages of 30-65 in every 5 years (7). In our study, hrHPV positivity was found to be at most between 30-39 years old (39.4%). In the age group of 30-60 years, this rate increases to 78.7%. Although different socio-cultural environments show changes in HPV frequency and type, the types of hrHPV causing cancer are outnumbered between 30-60 years. Our results also support the need for follow-up for this age range.

## CONCLUSION

With biopsies after pap smear, squamous intraepithelial lesions were detected in 83.3% of ASC-H-diagnosed cases, in 70% of LGSIL-diagnosed patients and in all of HGSIL-diagnosed patients. Cervical cytology and hrHPV tests are used simultaneously in our clinic. Our biopsy and pap smear results are coherent to a great extent. For this reason, we do support and recommend the approach performing cervical cancer screening together with the investigation of the presence of HPV and determination of type.

The data we have obtained in this study are not specific to a particular group, but reflect the general population. More and comprehensive data on hrHPV are needed in

order to determine the prevalence of hrHPV in our country. We believe that this study contributes to determine the frequency and genotype distribution of normal / abnormal cytology of HPV in our country.

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## REFERENCES

1. Kurman RJ, Carcangiu ML, Herrington CS, Young RH. World Health Organization classification of Tumors of Female Reproductive Organs. Lyon: IARC Press; 2014. p. 172-81.
2. Huh WK, Ault KA, Chelmow D, et al. Use of primary high-risk human papillomavirus testing for cervical cancer screening: interim clinical guidance. *Obstet Gynecol* 2015;125:330-7.
3. Akcali S, Goker A, Ecemis T, et al. Human papilloma virus frequency and genotype distribution in a Turkish population. *Asian Pac J Cancer Prev* 2013;14:503-6.
4. Tezcan S, Ozgur D, Ulger M, et al. Human papillomavirus genotype distribution and E6/E7 oncogene expression in Turkish women with cervical cytological findings. *Asian Pac J Cancer Prev* 2014;15:3997-4003.
5. Altun Z, Yarkin F, Vardar MA, et al. The Prevalence of human papilloma virus infection among women who admitted to çukurova university faculty of medicine hospital. *Turkiye Klinikleri J Med Sci* 2011;31:307-14.
6. Ergünay K, Mısırlıoğlu M, Fırat P, et al. Sitolojik olarak anomalis aptanan serviks örneklerinde insan papilloma virus DNA'sının araştırılması ve virusun tiplendirilmesi. *Mikrobiyol Bül* 2007;41:219-26.
7. Massad LS, Einstein MH, Huh WK, et al. 2012 updated consensus guidelines for the management of abnormal cervical cancer screening tests and cancer precursors. *J Low Genit Tract Dis* 2013;17:1-27.
8. Akyar I, Aydın Ö, Yakıcıer MC, et al. Human papillomavirus prevalence and type in liquid-based cervical samples from Turkish women in a selected risk group. *Turk J Med Sci* 2013;43:963-70.
9. Inal MM, Köse S, Yildirim Y, et al. The relationship between human papillomavirus infection and cervical intraepithelial neoplasia in Turkish women. *Int J Gynecol Cancer* 2007;17:1266-70.
10. Dursun P, Ayhan A, Mutlu L, et al. HPV types in Turkey: multicenter hospital based evaluation of 6388 patients in Turkish gynecologic oncology group centers. *Turk Patoloji Derg* 2013;29:210-6.
11. Taskin MI, Adali E, Yavuz T, et al. Identification and Genotyping of HighRisk HPV in Cervical Swaps with Real-Time PCR in Women Attending Balıkesir University Hospital. *J Clin Anal Med* 2015.
12. Fındık D, Türk Dağı H, Arslan U, et al. Servikal örneklerde human papillomavirus sıklığı ve genotip dağılımı. *Genel Tıp Derg* 2012;22:116-20.
13. Bayram A, Derici YK, Yılmaz NO, et al. Prevalence of high-risk human papillomavirus in women from Turkey. *Clin Obstet Gynecol Reprod Med* 2015;1:84-6.
14. Yuçe K, Pinar A, Salman MC, et al. Detection and genotyping

- of cervical HPV with simultaneous cervical cytology in Turkish women: a hospital-based study. Arch Gynecol Obstet 2012;286:203-8.
15. Barışık NÖ, Keser SH, Gül AE, et al. Prevalence of high-risk human papilloma virus and identification of type using real-time polymerase chain reaction analysis and liquid-based cytology south. Clin Ist Euras 2017;28:175-80.
  16. Yıldırım D, Yıldırım ME, Bakici MZ. Human papillomavirus positivity and frequency of genotypes in servical samples of women living in Sivas Region. Fırat Med J 2013;18:94-7.
  17. Şahiner F, Gümral R, Şener K, et al. A. Servikal Sürüntü Örneklerinde İki Farklı Yöntemle HPV-DNA Varlığının Araştırılması: MY09/11 Konsensus PCR ve Tipe Özgül Gerçek Zamanlı PCR. Mikrobiyol Bul 2012;46:624-36.
  18. Güçkan R, Kiliç Ç, Gözdemir E, et al. Prevalence and distribution of high-risk human papillomavirus in amasya region, Turkey. Biomedical Research 2016;27:3.
  19. Ozalp SS, Us T, Arslan E, et al. HPV DNA and Pap smear test results in cases with and without cervical pathology. J Turk Ger Gynecol Assoc 2012;13:8-14.
  20. Dursun P, Senger SS, Arslan H, et al. Human papillomavirus (HPV) prevalence and types among Turkish women at a gynecology outpatient unit. BMC Infect Dis 2009;30;9:191.
  21. Sapmaz E, Şimşek M, Çelik H, et al. Bölgemizdeki Servikal intraepitelyal neoplazi vakalarında HPV 16 ve 18 genomlarının PCR Yöntemi İle Araştırılması. Türkiye Klinikleri J Gynecol Obst 2003;13:58-61.
  22. Eroglu C, Kesli R, Eryılmaz MA, et al. Serviks kanseri için riski olan kadınlarda HPV tiplendirmesi HPV sıklığının risk faktörleri ve servikal smearla ilişkisi Nobel Med 2011;7:72-7.
  23. Abike F, Bingol B, Yılmaz A. et al. HPV Infection and HPV Subtypes in Normal and Abnormal Cervical Cytology in Turkish Women. J Virol Microbiol Article 2013.