ORIGINAL ARTICLE

Evaluation of cervical smear screening and colposcopy assessments at a tertiary obstetrics and gynecology center in the blacksea region of Turkey: Retrospective chart-review of the last 5 years

Mesut Onal[1], Yunus Katirci[1], Adem Kocaman[2], Caglanur Yildiz[1]

¹Ondokuz Mayıs University, Facult of Medicine, Department of Gynecology and Obstetrics, Samsun, Türkiye
²Ondokuz Mayıs University, Facult of Medicine, Department of Histology and Embryology, Samsun, Türkiye

Abstract

Cervical cancer is the fourth most common cancer worldwide. Furthermore, it is the 9thmost common cancer in all ages and the 4thmost common in the 25-49 age group of women in Turkey. Given these significantly high figures, it is a significant public health problem. Therefore, this study aimed to evaluate the epidemiological characteristics of patients screened for Human papillomavirus (HPV) in a tertiary-care setting in Turkey. This is a retrospective chart review of patients admitted for clinical examinations and who underwent cervical cancer screening between 1 January 2017 and 1 March 2022. The data analyses included HPV positivity, genotype distribution, cytology analyses, colposcopy results, pathological diagnoses, and follow-up methods. A total of 529 cases were included, of whom 41.6% were HPV positive. The most frequent HPV types were HPV-16 (16.6%) and HPV-high risk (HR) (12.1%). Cytology analyses revealed atypical squamous cells of undetermined significance (ASC-US) in 17.8% and low-grade squamous intraepithelial lesions (LSIL) in 12.7%. The most common pathological finding was cervicitis in 23.1% (n=122), cervical intraepithelial neoplasia (CIN)-1 in 9.3% (n=49), CIN-3 in 4% (n=21), and CIN-2 in 3.8% (n=20) of patients. HPV-59 (p=0.027) and HPV-HR (p=0.003) genotypes were determined in higher proportions in patients with ≥ASC-US cytology, and HPV-16 was significantly higher among patients with ≥CIN-1 lesions. The HPV positivity rate was 41.6% among women admitted to our tertiary-care university hospital for gynecological assessments. Distribution differences in HPV genotypes, cytology assessments, and pathological diagnoses might reflect the population characteristics in different geographical regions from previous studies. Our results provide current data for HPV surveillance in the Turkish population.

Keywords: Cervical cancer, colposcopy, genotype, human papilloma virus, pathological diagnoses, screening

Introduction

The World Health Organization (WHO) reported that cervical cancer was the fourth most common cancer worldwide, which was responsible for 6.5% of female cancers diagnosed, and 7.7% of all cancer mortality in 2020 [1]. The most recent national cancer statistics of Turkey reported that cervical cancers were the 9th most common cancer in all ages in females, with an age-standardized incidence rate of 4.3 per 100.000 population in 2017, which increased to the 4th most common cancer rank in 25-49 age group [2]. Given these significantly high figures, cervical cancer causesa significant disease burden and a striking public health problem.

The persistent Human Papilloma Virus (HPV) infection is the most prominent risk factor for cervical cancer progression, accounting for more than 90% of all cases [3]. Relatively lower cancer incidencerates in Turkey compared to the developing countries are associated with the lower prevalence of HPV infections, which was reported to be about 3.5% in the population [4]. However, this low HPV prevalence does not exclude the importance of screening programs,mainly when other lifestyle-associated risk factors are considered, and routine gynecological screening is the critical element of successful cervical cancer control among women.

Turkey'spopulation-based cervical cancer screening programcurrently includes a cervical smear and HPV-DNA testing every five years for women between 30 and 65 years [5]. Nevertheless, it was reported that the coverage is lower than desired, and the acceptance rate for HPV-based cancer screening was reported at about 36.5% after the first invitation [4]. Thus,

*Corresponding Author: Mesut Onal, Ondokuz Mayıs University, Facult of Medicine, Department of, Gynecology and Obstetrics, Samsun, Türkiye
E-mail: mesut.onal@omu.edu.tr

screening patients in clinical settings is still essential for an effective battle against cervical cancer. Based on this necessity, screening of women with cervical smear and HPV typing is continued at our tertiary obstetrics and gynecology outpatient clinic, and this study aimed to report our results from the last five years to provide current data on our screening outcomes to provide data on the epidemiology of HPV in Turkey.

Material and Methods

This retrospective study was conducted in the Obstetrics and Gynecology Department of the OndokuzMayis University Faculty of Medicine in Samsun, Turkey. Records of patients admitted for clinical examinations and who underwent cervical cancer screening between 1 January 2017 and1 March 2022 were included in the analyses.

Demographic and clinical data were collected from the hospital data management system and patients' archival records. Study endpoints were the HPV genotypes and initial cytological diagnoses determined in pap smear analyses and the final pathological diagnoses based on assessing biopsy specimens from colposcopic examinations. The HPV genotypes analyzed were HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68, and high-risk (HR). The diagnoses in cervical cytology assessments were atypical squamous cells of undetermined significance (ASC-US), atypical squamous cells cannot rule out high-grade squamous intraepithelial lesions (ASC-H), low-grade squamous intraepithelial lesions (LSIL), high-grade squamous intraepithelial lesions (HSIL), atypical glandular cells (AGC), and adenocarcinoma in-situ (AIS). The diagnoses referred to as malignant lesions were cervical intraepithelial neoplasias (CIN-1, 2, 3), adenocarcinoma, squamous carcinoma, and adenosquamous carcinoma.

The study protocol was reviewed and approved by the local ethical committee of the Ondokuz Mayis University Faculty of Medicine in 2022 with an approval number of 273.

Statistical Analyses

The descriptive statistics were presented using frequency and percent for categorical variables and median and interquartile range (25th-75th percentiles –IQR) values for continuous variables. The categorical variables were compared between independent groups using the Chi-square test. When the assumptions of the Chi-square test (at least 80% of the cells in crosstable should have countshigher than 5, and the minimum expected count in any cell should be 2) were not met, Fisher's exact test was used instead. A type-I error level of 5% was considered the threshold for statistical significance ($p<0.05$). All hypotheses were tested in a two-tailed design using the SPSS 25 software (IBM Inc., Armonk, NY, USA).

Results

Data from 529 caseswere analyzed (Figure 1). The median age was 32 years (IQR: 26-36), the median body-mass index was 24.9kg/m2 (IQR: 21.9-29.1), the smoking rate was 40.6%, and 3.4% of cases had multiple sexual partners. Among these 529 cases, 309 (58.4%) cases were HPV negative. Genotyping was performed in 220 (41.6%) patients who were HPV positive, and the most frequent isolated type was HPV-16 (n=88, 16.6%), followed by HR types (n=64, 12.1%). Cytological analyses were present for

461 cases (87.1%), 37.1% of patients had normal cytology, and the most frequent pathological finding was ASC-US in 17.8% (n=94), followed by LSIL in 12.7% (n=67) of samples (Table 1).

Table 1. HPV genotypes and cytology assessments in cervical smear analyses

	n (%)
Genotype	
HPV-16	88 (16.6)
HPV-18	29 (5.5)
HPV-31	15 (2.8)
HPV-33	9 (1.7)
HPV-35	15 (2.8)
HPV-39	16 (3.0)
HPV-45	7 (1.3)
HPV-51	10 (1.9)
HPV-52	11 (2.1)
HPV-56	16 (3.0)
HPV-58	11 (2.1)
HPV-59	15 (2.8)
HPV-66	11 (2.1)
HPV-68	11 (2.1)
HPV-HR	64 (12.1)
None	309 (58.4)
Cytology	
Normal	196 (37.1)
ASC-US	94 (17.8)
LSIL	67 (12.7)
HSIL	29 (5.5)
Infection	26 (4.9)
Other	21 (4.0)
ASC-H	10 (1.9)
Inadequatesample	9 (1.7)
AGC	8 (1.5)
AIS	1 (0.2)

HPV: Human papillomavirus
ASC-US: Atypical squamous cells of undetermined significance
ASC-H: Atypical squamous cells cannot rule out high-grade squamous intraepithelial lesions
LSIL: Low-grade squamous intraepithelial lesions
HSIL: High-grade squamous intraepithelial lesions
AGC: Atypical glandular cells
AIS: Adenocarcinoma in-situ

All patients underwent a colposcopy assessment, and the highest number of applications were performed in 2021 (n=164, 31%). A complete assessment was achieved in all patients, and the transformation zone was visualized in 97.7% of all applications. Based on the analyses of punch biopsies, 64.1% of patients (n=339) were called for routine follow-up, cold knife cone was applied in 14% (n=74), Loopelectrosurgicalexcisionprocedure (LEEP) in 3.8% (n=20), hysterectomy in 3.6% (n=19), and other management procedures in 2% (n=16).

The final pathological assessments revealed that 34.2% of cases had normal findings. The most common pathological finding was cervicitis in 23.1% (n=122), CIN-1 in 9.3% (n=49), CIN-3 in 4% (n=21), and CIN-2 in 3.8% (n=20) of patients. Malignant lesions were determined in 3.4%, distributed as squamous carcinoma

(2.8%, n=15), adenocarcinoma (0.4%, n=2), and adenosquamous carcinoma (0.2%, n=1). Based on these results, 35.7% (n=189) of patients were enrolled to follow-up with smear and HPV screening, 24% (n=127) to smear follow-up, 10.4% (n=55) to smear+HPV+colposcopy screening, and 10% (n=53) to only colposcopy follow-up (Table 2).

Table 2. Treatments, pathologies, and follow-up methods after colposcopy assessments

	n (%)
Treatment	
Follow-up	229 (64.1)
Coldcone	74 (14.0)
LEEP	20 (3.8)
Hysterectomy	19 (3.6)
Other	16 (3.0)
Final pathology	
CIN-1	54 (10.3)
CIN-2	20 (3.8)
CIN-3	21 (4.0)
Adenocarcinoma	2 (0.4)
Squamouscarcinoma	15 (2.8)
Adenosquamouscarcinoma	1 (0.2)
Cervisitis	128 (24.2)
Endocervicalpolyp	11 (2.1)
Normal	181 (34.2)
Other	31 (5.9)
Follow-up	
Smear+HPV	189 (35.7)
Smear	127 (24.0)
Smear+HPV+Colposcopy	55 (10.4)
Colposcopy	53 (10.0)
Other	42 (7.9)

LEEP: Loopelectrosurgicalexcisionprocedure
CIN: Cervical intraepithelial neoplasia
HPV: Human papillomavirus

The comparisons of HPV genotypes between cases with normal and abnormal results in cervical smear analyses revealed that HPV-59 (p=0.027) and HPV-HR (p=0.003) genotypes were determined in higher proportions of patients with ≥ASC-US cytologyresults. And comparisons between patients with and without high-risk pathological diagnoses in biopsies at colposcopy assessments showed that the HPV-16 genotype was significantly higher among patients with ≥CIN-1 lesions (Table 3). When the final pathological diagnoses were evaluated according to the HPV positivity, 5.3% and 4.9% of HPV-positive cases were found to have CIN-2 and CIN-3, respectively. In contrast, these were 3.5% and 4.3% among HPV negative cases. However, cervix cancer diagnoses were more frequent in the HPV negative group (5.1%) than positive cases (2.4%) (Table 4).

Table 3. Distribution of HPV genotypes between cases with and without pathological findings in cervical smear and colposcopy assessments

	<ASC-US	≥ASC-US	p	<CIN-1	≥CIN-1	p
Genotypes						
HPV-16	46 (18.3)	39 (18.7)	0.91	53 (14.9)	30 (27.8)	0.002
HPV-18	19 (7.5)	9 (4.3)	0.15	20 (5.6)	8 (7.4)	0.49
HPV-31	8 (3.2)	6 (2.9)	0.85	8 (2.2)	3 (2.8)	0.72
HPV-33	4 (1.6)	5 (2.4)	0.53	4 (1.1)	3 (2.8)	0.21
HPV-35	9 (3.6)	6 (2.9)	0.67	9 (2.5)	2 (1.9)	1.0
HPV-39	10 (4)	6 (2.9)	0.52	8 (2.2)	4 (3.7)	0.49
HPV-45	5 (2)	2 (1)	0.46	5 (1.4)	1 (0.9)	1.0
HPV-51	7 (2.8)	3 (1.4)	0.36	7 (2)	1 (0.9)	0.69
HPV-52	8 (3.2)	3 (1.4)	0.36	5 (1.4)	4 (3.7)	0.22
HPV-56	6 (2.4)	10 (4.8)	0.16	12 (3.4)	2 (1.9)	0.54
HPV-58	7 (2.8)	4 (1.9)	0.76	6 (1.7)	3 (2.8)	0.44
HPV-59	4 (1.6)	11 (5.3)	0.027	10 (2.8)	3 (2.8)	1.0
HPV-66	4 (1.6)	7 (3.3)	0.24	9 (2.5)	1 (0.9)	0.47
HPV-68	4 (1.6)	7 (3.3)	0.24	5 (1.4)	3 (2.8)	0.40
HPV-HR	23 (9.1)	39 (18.7)	0.003	50 (14)	10 (9.3)	0.19

ASC-US: Atypical squamous cells of undetermined significance
CIN: Cervical intraepithelial neoplasia
HPV: Human papillomavirus

Table 4. Distribution of final diagnoses in HPV negative and positive patients

	HPV negativen (%)	HPV positiven (%)
CIN-1	22 (8.6)	32 (15.5)
CIN-2	9 (3.5)	11(5.3)
CIN-3	11 (4.3)	10 (4.9)
Adenocarcinoma	2 (0.8)	-
Squamouscarcinoma	10 (3.9)	5 (2.4)
Adenosquamouscarcinoma	1 (0.4)	-
Cervicitis	66 (25.6)	62 (30.1)
Endocervicalpolyp	7 (2.7)	4 (1.9)
Normal	109 (42.2)	72 (35)
Other	21 (8.1)	10 (4.9)

HPV: Human papillomavirus
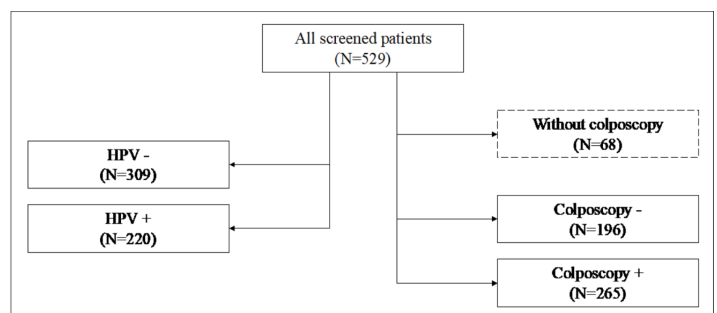CIN: Cervical intraepithelial neoplasia

Figure 1. Study flowchart

Discussion

In this study, we reported our results of cervical smear and HPV screening in the last five years. Our results showed that about 42% of patients admitted were HPV positive, HPV-16, HPV-HR, and HPV-18 were the most commonly reported genotypes, ASC-US and LSIL were the most common pathologies detected in cervical smear analyses, and the CIN-1 was the most common pathological diagnosis in specimens from colposcopy assessments. Also, HPV-59 and HPV-HR were associated with higher grade cytology, whereas HPV-16 was associated with more severe pathological diagnoses in colposcopy assessments.

Cervical cancer screening is one of the priorities for women's health worldwide. The World Health Assembly set targets for countries to be met by 2030 as reaching an HPV vaccination rate of 90% of girls by 15 years of age, screening with a high-performance test of 70% of women by 35 years and 45 years of age, and treatment of 90% of women identified with cervical disease [6]. In a previous report on the results of the population-based cervical cancer screening program using HPV testing in Turkey, the acceptance rate for screening was reported as 36.5%, which was also said to have increased considerably over the years [4]. Nevertheless, opportunistic or planned screening in clinical settings is essential to reach the desired levels of screening in the population.

Professional organizations recommend cervical cancer screening with HPV DNA [7], and Turkey is conducting a national screening program following the current recommendations. Nevertheless, the coverage is not adequate yet, and screenings in clinical settings still have importance to increase the reachability of the prevention interventions for women with a high risk of cervical cancer. Our clinic serves as a central tertiary health center, and our results may represent the population in the northern region.

A previous national report on the outcomes of the cervical cancer screening program in our country reported that the most common HPV genotypes were 16, 51, 31, 52, and 18, which is similar to our results [4], but we also found that HPV-59 was also associated with advanced cytology in the pap smear. This might be related to geographical differences, but the population characteristics might also play a role, mainly when advanced cases are considered to apply to clinical settings.Our study's relatively higher HPV positivity rate compared to previous hospital-based reports also suggests the admission of advanced patients to our center. Astudy by Dursun et al. evaluated the prevalence of HPV DNA and cervical cytological abnormalities in twelve centers and reported that 25% of 6388 women were HPV positive [8]. Another study by Kaleli et al. evaluated HPV positivity in a tertiary healthcare setting in the Aegean region of Turkey and reported a positivity rate of 37.2% [9]. A more recent study by Alacam and Bakir evaluated the HPV prevalence and genotype distribution in Istanbul, Turkey, and reported that 36.3% of 2285 women were positive for HPV [10]. As can be seen from other reports on the Turkish population, our HPV positivity rate of 41.6% was slightly higher, which might reflect the admission of advanced cases or the local population characteristics in the Black Sea region of Turkey. However, also a higher prevalence of HPV was reported in other reports, which still suggests the importance of populations assessed, like a previous study by Akyar et al., which reported a positivity rate of 69.6% in

a clinical sample of women [11].

Other than HPV positivity rates, the distribution of genotypes we found was partly similar but partly different from other reports from our country.In our study, the most frequent genotype was also HPV-16, followed by HPV-18, 39, and 56. Themost extensive study by Gultekin et al. that evaluated the results of the national cervical cancer screening program that included one million women reported the most common genotypes were HPV-16, 51, 31, 52, and 18 [4]. Another study by Yuce et al. evaluated the HPV positivity among Turkish women in a hospital-based study and reported that the prevalence of any HPV was 25.7%, while high-risk HPV was positive at 23.0%, and the genotype distribution showed that the most common single type was HPV-16, followed by HPV-31 and HPV-51 [12]. The HPV genotypes 16 and 18 were common in almost all studies in the literature, but the HPV-39 and HPV-56 found in our study were not commonly or frequently reported in other studies [8,9,13]. To our knowledge, only Alacam and Bakir reported that HPV-39 was one of the most common genotypes found in women with cervical dysplasias [10]. The differences between genotype distributions strongly suggest the role of the geographical distribution of HPV.

The most common cytological pathologies were ASC-US in 18%, LSIL in 13%, and HSIL in 6% of cases. This was slightly different from the national figures, reported as the most common cytological abnormalities wereLSIL, ASC-US,HSIL, and ASC-H[4].Nevertheless, studies conducted with clinical samples reported similar results to ours [13], suggesting the importance of continuous screening to detect earlier lesions for timely and accurate clinical interventions. This was also consistent with the distribution of final pathologies in colposcopy assessments, which showed that early-stage lesions constituted the most common diagnoses.

Besides providing recent and representative data, this study also has some limitations. First, the sample was restricted to the population admitted to a tertiary care center, which might encounter a selection bias. Second, a limited sample might be considered a source of bias, particularly for the distributions of genotypes or pathological diagnoses. Third, the period included in the study was contaminated by the COVID-19 pandemic, which affected the number of admissions, patient characteristics, and clinical severities at admissions. However, despite these limitations, the results reported in this study provide current and robust data on HPV epidemiology in the Turkish population. Nevertheless, more robust surveillance systems, standardized data collection methods, and continuous reports to follow upon the recent trends in HPV epidemiology are needed in Turkey.

Conclusion

The HPV positivity rate was 41.6% among women admitted to our tertiary-care university hospital for gynecological assessments. Pap smear analyses showed that the most common pathologies in cytology assessments were ASC-US and LSIL, and the most common genotypes were HPV-16, HPV-HR, and HPV-18. Moreover, HPV-59 and HPV-HR were associated with higher grade cytology, whereas HPV-16 was associated with more severe pathological diagnoses in colposcopy assessments. These results provide current data for HPV surveillance in the Turkish

population. However, accumulating data from multiple clinical centers should considerably contribute to HPV epidemiology in Turkey.

References

1. The Global Cancer Observatory (GLOBOCAN) of the International Agency for Research on Cancer (IARC) of the World Health Organization (WHO). Cancer Today -GLOBOCAN. 2022 https://gco.iarc.fr/today/online analysispie ?v=2020&mode=cancer&mode_population=continents&population=900&populations=900&key=total&sex=2&cancer=39&type=1&statistic=5&prevalence=0&population_group=0&ages_group%5B%5D=0&ages_group%5B%5D=17&nb_items=7&group_cancer=1&include_nmsc=1&include_nmsc_other=1&half_pie=0&donut=0 access date 05.06.2022

2. Ministry of Health of Turkey. National Cancer Statistics Report. https://hsgm.saglik.gov.tr/depo/birimler/kanser-db/istatistik/Turkiye_Kanser_Istatistikleri_2017.pdf access date 05.06.2022

3. Okunade KS. Human papillomavirus and cervical cancer. J Obstet Gynaecol. 2020;40:602-8.

4. Gultekin M, Zayifoglu Karaca M, Kucukyildiz I, et al. Initial results of population based cervical cancer screening program using HPV testing in one million Turkish women. Int J Cancer. 2018;142:1952-58.

5. Ministry of Health of Turkey. Cancer Screening. https://hsgm.saglik.gov.tr/tr/kanser-taramalari. access date 05.06.2022

6. World Health Organization (WHO). Meeting of WHO Director-General's Expert Group on Cervical Cancer Elimination, 19 April 2022. https://www.who.int/news/item/12-04-2022-meeting-of-who-director-general-s-expert-group-on-cervical-cancer-elimination--19-april-2022. access date 05.06.2022.

7. Huh WK, Ault KA, Chelmow D, et al. Use of primary high-risk human papillomavirus testing for cervical cancer screening: interim clinical guidance. Gynecol Oncol. 2015;136:178-82.

8. 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.

9. Kaleli İ, Aksoy L, Demir M, et al. Jinekoloji polikliniğine başvuran hastalarda insan papillomavirüs prevalansı ve genotip dağılımı [Prevalence and genotype distribution of human papillomavirus in patients attending to gynecology polyclinics]. Mikrobiyol Bul. 2019;53:170-8.

10. Alacam S, Bakir A. Human Papillomavirus Prevalence and Genotype Distribution in Cervical Swab Samples in Istanbul, Turkey. J Infect Dev Ctries. 2021;15(8):1190-1196. Published 2021 Aug 31.

11. 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. Turkish Journal of Medical Sciences. 2013;43:963-70.

12. Yuce 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.

13. Altay-Kocak A, Kazanci F, Dogu-Tok C, et al. The prevalence and distribution of human papillomavirus in 4267 Turkish women with or without cervical lesions: A hospital-based study. J Med Virol. 2022;94:5026-32.