International Journal of Tokat Medical Sciences

Research Article / Araştırma Makalesi

Int J Tokat Med Sci
2024;16(3):91-96

Evaluation of HPV 16 positive cases

HPV16 pozitif vakaların değerlendirilmesi

Yiğit YÜKSEL[1], Yasemin ALAN[2], Mücahit Furkan BALCI[1], Murat ALAN[1,*]

[1]Tepecik Education and Research Hospital
[2] İzmir Metropolitan Municipality Eşrefpaşa Hospital

Abstract

Objective: The most significant risk factor for cervical cancer is a positive HPV test. Among the types of HPV, types 16 and 18 pose the highest risk. In cases where HPV is found to be positive, particularly in high-risk HPV types, colposcopy and cervical biopsy examination are recommended. Our study will evaluate the smear results of patients who are positive for HPV type 16.
Material and Methods: We evaluated the correlation between age and cervical biopsy results in 1062 patients who tested positive for HPV type 16. The age, smear, and colposcopic biopsy results of the cases were recorded. Every woman participating in the screening gave two samples, one for the traditional cytology test and the other for the HPV DNA test. Tissue sampling was performed within a month, including colposcopic biopsy, Loop Electrosurgical Excision Procedure (LEEP), conization, and hysterectomy of 1062 patients. Diagnoses obtained from histological samples were taken as the gold standard.
Results: The study included 1062 female patients who tested positive for isolated HPV type 16. The average age of the patients was determined to be 42.02±8.81 (min:21, max:77). When smoking usage was examined, it was found that 482 (45.4%) were smokers, while 580 (54.6%) were non-smokers. 284 (26.7%) of the patients were menopausal. The relationship between age, menopausal status, and smoking usage with smear and colposcopy results in women positive for HPV type 16 was examined. No statistically significant result was found.
Conclusion: There is no correlation between age, menopausal status, and smoking usage with smear and colposcopy results in women positive for HPV type 16. The most significant risk factor for abnormal smear and colposcopy results, in line with the literature, is HPV type 16 itself.

Keywords: Hpv 16, smear, colposcopy, biopsy.

Öz

Amaç: Serviks kanseri için gösterilmiş en önemli risk faktörü HPV pozitifliğidir. HPV tipleri arasında ise en yüksek riske sahip olan tipler ise 16 ve 18'dir. HPV incelemesi sonucunda yüksek riskli HPV tiplerinde kolposkopi ve serviks biyopsisi incelemesi önerilmektedir. Biz bu çalışmada HPV tip 16 pozitif hastaların smear sonuçları değerlendirilmiştir.
Gereç ve yöntem: 1062 adet HPV tip 16 pozitif hastanın yaş ile korelasyonunu ve servikal biyopsi sonuçlarını değerlendirdik. Olguların yaş, smear ve kolposkopik biyopsi sonuçları kaydedildi. Taramaya katılan her kadın, biri geleneksel sitoloji testi ve diğeri HPV DNA testi olmak üzere iki örnek alındı. Test sonuçları, hastanemiz Patoloji laboratuvarında 2001 Bethesda sınıflandırması esas alınarak yorumlanmasıyla elde edilmiştir. 1062 hastanın kolposkopik biyopsi, Loop Electrosurgical Excision Procedure (LEEP), konizasyon ve histerektomi dahil olmak üzere bir ay içinde takip doku örneklemesi yapıldı. Histolojik örneklerden elde edilen tanılar altın standart olarak alındı.
Bulgular: Çalışmaya izole HPV tip 16 pozitif 1062 kadın hasta dahil edildi. Hastaların ortalama yaşı 42,02±8,81 (min:21, max:77) olarak tespit edildi. Sigara kullanımı incelendiğinde 482 (%45,4)'si sigara kullanmakta olduğu görüldü. Hastaların 284 (%26,7)'ü menopozda idi. HPV tip 16 pozitif kadınlarda smear ve kolposkopi sonuçlarının yaş, menopozla durum, sigara kullanımı ile ilişkisi incelendi. İstatistiksel olarak anlamlı sonuç saptanmadı.
Sonuç: HPV tip 16 pozitif kadınlarda smear ve kolposkopi sonuçlarının yaş, menopozla durum ve sigara kullanımı ile ilişkisi yoktur. Anormal smear ve kolposkopi sonucu için en önemli risk faktörü, literatür ile uyumlu olarak, HPV tip 16'nın kendisidir.

Anahtar Kelimeler: Hpv 16, smear, kolposkopi, biyopsi.

Geliş Tarihi: 28.03.2024 • **Kabul Tarihi:** 31.07.2024 • **Sorumlu Yazar:** gozdealan@hotmail.com

Introduction

Cervical cancer is the 3rd most common cancer in women in the world. In women, 1.6% of cancer-related deaths and 15% of deaths related to gynecological tumors are caused by cervical cancer (1). The PAP smear test and cervical cytology screening have significantly reduced the mortality rate associated with cervical cancer and are now considered the most cost-effective cancer screening test today (2). However, cervical cytology has its drawbacks, including false positive and false negative results. Cervical cancer screening can be performed either with a PAP smear test alone or in conjunction with an HPV DNA test (3).

Following the realization that cytology-based screenings are not adequate due to high rates of false negatives, the need for expertise, and the lack of objective criteria, the use of molecular tests has been initiated to enhance the effectiveness of screenings. Some types of HPV cause anogenital warts, while HPV type 16 and Type 18 are considered carcinogenic. Type 16 is the most common HPV virus type in cervical cancers and is found in 53.5% of all cervical cancers (4).

HPV type 18 is the second most commonly seen type with a rate of 17.2%. The responsibility for more than 70% of all cervical cancers can be attributed to HPV type 16 and 18. Screening programs should be included in the services offered to groups at risk for certain diseases. Determining the prevalence of HPV is a crucial factor for the planning of health services. It is especially important to meticulously examine the key elements that affect public health. Information dissemination is essential to ease the integration of these topics in service provision (5,6). In this article, we focused on HPV type 16, a sexually transmitted disease that is one of the health issues.

Material and Methods

The research took place in an institution providing tertiary health services at Tepecik Training and Research Hospital, which is affiliated with the Health Sciences University. In this study, we analyzed the relationship between age and cervical biopsy results of 1062 HPV type 16 positive patients who applied between January 2023 and December 2023. From the patient's initial consultation to the treatment is meticulously carried out in our health center, and all information related to the service provided is recorded in a regular and detailed manner in the computer database.

Age, smear, and colposcopic biopsy results were documented within the dataset. Participants who were pregnant, had a history of hysterectomy surgery, or had uncertain obstetric history and medical condition were not included in the study Cases in which satisfactory colposcopic examination could not be performed, biopsy was found to be inadequate, or not obtained at all were excluded from the study. Every female participant in the study submitted two samples, one for the conventional cytology test and the other for the HPV DNA test. The smears were dispatched to the pathology laboratory of our hospital. The cytology test results were interpreted based on the 2001 Bethesda classification in our hospital's Pathology laboratory. The HPV-DNA test was performed using the real-time polymerase chain reaction method by 'Roche, USA'.

Samples testing positive included HPV type 16,18, and other high-risk HPV types (such as 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68) were classified as HPV. In our center, procedures and operations were performed for patients with pathological colposcopic findings requiring treatment and/or advanced treatment. The cervical biopsy samples were dispatched in formaldehyde for examination at the pathology unit.

Throughout the duration of the study, the cytopathologist examined the biopsies at our center. Within a month, tissue sampling procedures such as colposcopic biopsy, Loop Electrosurgical Excision Procedure (LEEP), conization, and hysterectomy were performed on 1062 patients The diagnoses obtained from histological samples were considered as the gold standard. When cases subjected to

histological examination contain more 'serious' findings, a definitive diagnosis is made for further procedures. Conversely, negative results were obtained in cases with normal histological samples.

Statistical analyses

Statistical analyses of the data were conducted using the SPSS software package (Version 22.0, SPSS Inc., Chicago, IL, USA .Descriptive statistics are presented as mean ± standard deviation along with median (min-max) values for continuous variables, and in terms of count and percentage for categorical data. Kolmogorov-Smirnov and Shapiro-Wilk tests were utilized to assess the normality distribution of the data for selecting the appropriate statistical test. In comparing the ages of patients across different HPV groups, a t-test was conducted. Research on the relationship between categorical variables and comparisons of proportions were carried out using either the Chi-square test or Fisher's exact test. The statistical significance level was determined as '$p < 0.05$'.

Results

Our study was conducted on 1062 women who tested positive for HPV type 16. The average age and age distribution of the women are presented in Table 1. The rate of HPV type 16 positivity was determined to be 64.9% in cases with normal cervical cytology. Among 1062 patients with cervical cytology, 23.8% were diagnosed with ASCUS, 11.62% with LSIL, while no cases of ASCH and HSIL were detected. In accordance with the smear test results, 35.1% of patients exhibited positive results for both smear and HPV. Furthermore, among patients with HPV type 16 positivity, 16.8% had normal cervical biopsies. LSIL was present in 46.9% of the patients, while HSIL was present in 36.1% of them. Biopsy results did not reveal any signs of cervical cancer. In the evaluation conducted taking into account the ages of the patients,it was noted that there were 6 patients under the age of 25 who tested positive for HPV type 16. The reason for this low rate could stem from the higher age at which sexual intercourse occurs or the less frequent HPV sampling in this age group (Table 1).

The reason for the higher HPV type 16 positivity in other age groups may be attributed to more regular attendance in screenings and enhanced public awareness. Despite the higher incidence of HPV between the ages of 35-45, no statistically significant correlation has been established when considering various age ranges. The relationship between cervical smear results, colposcopic biopsy results, age ranges, and HPV positivity of the cases was examined in Table 1, and no statistically significant difference was found ($p>0.05$) (Table 1).

Table 1. Comparison of the smear and cervikal biopsy characteristics of the subjects

		Age(year)					**Total(n)**	**P value**
		<25	25-35	35-45	45-54	≥55		
Smear(n)	Normal	2(%33.3/%0.2)	137(%62).2/%19.8)	301(%66.5/%43.6)	181(%65.3/%26.2)	69(%64.4/%10)	690(%100)	0.507
	ASCUS	3(%50/%1.1)	57(%25.9/%22.5)	95(%21/%37.5)	70(%25.2/%27.6)	28(%26.1/%11)	253(%100)	
	LSIL	1(%16.6/%0.8)	26(%11.8/%21.8)	56(%12.3/%47)	26(%9.3/%21.8)	10(%9.3/%8.4)	119(%100)	
	HSIL	0	0	0	0	0	0	
Cervical Biopsy(n)	Normal	1(%16.6/%0.5)	36(%16/%20.1)	74(%16.3/%41.3)	48(%17.3/%26.8)	20(%18.6/%11.1)	179(%100)	0.331
	LSIL	2(%33.3/%0.4)	99(%45/%19.8)	208(%46/%41.6)	138(%49.8/%27.6)	52(%48.5/%10.4)	499(%100)	
	HSIL	3(%50/%0.7)	85(%38.6/%22.1)	170(%37.6/%44.2)	91(%32.8/%23.6)	35(%32.7/%9.1)	384(%100)	
Total(n)		6(%100/%)	220(%100)	452(%100)	277(%100)	107(%100)	1062(%100)	

Abbreviation: ASCUS: Atypical squamous cells of undetermined significance LSIL: Low-grade squamous intraepithelial lesion HSIL: High-grade squamous intraepithelial lesion

Results are given in mean ± SD.

aIndependent samples t-test was used.

A p value of <0.05 was considered significant

Discussion

Globally, cervical cancer ranks as the second most prevalent form of cancer among women and is the second leading cause of cancer-related mortality in the female population. It is known to be responsible for approximately 10% of all cancer deaths. In today's conditions, molecular technology-supported epidemiological research has confirmed the key role of HPV infections in the development of cervical cancer. HPV type 16 is the carcinogenic HPV genotype accountable for 55-60% of all cervical cancers. Numerous investigations have been undertaken to gather data on HPV prevalence, vaccination, treatment strategies, and HPV genotype distribution in Turkey in order to shed light on the prevalence of HPV within a particular population (7-15). The data available to us originates from hospitals, underscoring the necessity for studies carried out in community health centers to gain accurate understanding of the prevalence of HPV strains in Turkey.

The findings of our research demonstrate a significant prevalence rate of 64.9% for HPV type 16 among those with normal cervical cytology. In the majority of cervical cancer cases, HPV type 16 is detected, while it is also frequently found in cytologically normal women. Our research revealed an abnormality rate of 83.2% in cervical biopsies conducted on individuals with normal or abnormal cervical cytology who were HPV type 16 positive (14,15).

In our study, we investigated HPV infection across five different age groups. The regional prevalence of HPV was determined to be 4.2%, with HPV infection being most commonly detected in women aged 35-34 years (34.5%). Among women under the age of 35, the prevalence of HPV is at its peak and tends to decrease in the elderly population across various populations (16,17). However, we did not find a significant difference between age and HPV prevalence in our study. Similarly, similar results have been obtained in several other studies. In Turkey, the rates of HPV infection decrease as age advances (10,11). Our study revealed that only 107 (10.1%) cases were detected in individuals aged 55 and above. In various studies, researchers have found that the frequency of HPV is highest in individuals under the age of 30 and lowest in those over the age of 54 (13,14).

Upon analyzing the age distribution in our research, it is hypothesized that HPV infection is acquired after a woman becomes sexually active, a notion which is further supported by other studies. An increase in HPV prevalence may be associated with the reactivation of latent infection at an advanced age. Taking into account all of these factors, cervical screening programs are crucial for perimenopausal women in terms of HPV control (17,18). According to a study, the most common age group for HPV in South Africa is women aged 18-25, with a prevalence rate of 74%. This finding differs from the results of our research. Also, in some studies, it is mentioned that HPV infection is more frequent in elderly women after menopause (19,20).

A study revealed that the prevalence of HPV among Turkish women is 45.2% (21). The findings of this research indicate that there is a higher incidence of cervical dysplasia linked to the cervicovaginal transmission of high-risk HPV types, with 32.5% of women positive for high-risk HPV having normal PAP test results. (21). In our study, 64.9% of women who tested positive for HPV type 16 had normal PAP smear test results. Therefore, it is essential to regularly monitor patients who have normal PAP smear test results but are positive for high-risk HPV types. The reason for this is that women who are hrHPV positive and have negative PAP smear test results for intraepithelial lesions are at a high risk of developing serious HPV-related lesions in the future. Patients at risk of epithelial changes may face serious danger due to delayed follow-up. Hence, it is usually advised to monitor women with mild cell changes (such as ASCUS and LSIL) when HPV type 16 positivity is detected. In women diagnosed with HSIL, particularly, the most effective management strategy involves performing colposcopy with endocervical sampling (22).

Inadequate information and guidance on cervical cancer, HPV vaccines, and cervical cytology screenings may lead to public health issues in the future, even if not for the present day. When women are faced with health risks, it is essential for health and social workers to provide preventive and curative health services, as well as education, screening, and treatment projects for sexually transmitted diseases. This will reduce the financial burden on the state. Despite the limitation in the scope of our study due to being conducted in a single center, the similarity of healthcare services in the region to those in other parts of the country highlights the significance of the findings as an important source of information.

In conclusion, it is important to consider the prevalence of HPV in women when making decisions about participation in vaccination and screening programs, just like other individuals in the community. For this purpose, comprehensive involvement-centered activities ought to be conducted in Turkey. Even though HPV type 16 is recognized as the most prevalent globally, studies have revealed that genotypes other than type 16 are also commonly detected in women who undergo routine cervical cancer screening. Additionally, it is essential to conduct multicenter studies for the detection of HPV types and determination of genotype prevalence in women, irrespective of age, and these studies hold significant importance for monitoring purposes.

Conflict of interest: There is no conflict of interest in this work.

Funding: This study received no funding.

Ethical approval: The ethical appropriateness of the study was ensured in accordance with the local ethics committee decision numbered 21.12.2023-3 of SBU Tepecik Education Research Hospital. The universal principles of the Helsinki Declaration were applied.

Author contribution: Research Idea: Y.Y., M.A.; Study Design: M.F.B.; Data Collection: Y.A., Data Analysis: M.F.B.; Data Interpretation: Y.A.; Drafting the Manuscript: Y.Y., M.F.B.; Critical Review of the Manuscript: Y.Y., M.A.; Approval of the Final Manuscript: M.A.

References

1. Sezgin B, Kinci MF, Pirinççi F, Camuzcuoğlu A, Erel Ö, Neşelioğlu S, et al. Thiol-disulfide status of patients with cervical cancer. J Obstet Gynaecol Res. 2020; 46(11):2423-2429.

2. Shingleton HM, Patrick RL, Johnston WW, Smith RA. The current status of the Papanicolaou smear. CA Cancer J Clin. 1995; 45(5):305-320.

3. Wright TC Jr, Schiffman M. Adding a test for human papillomavirus DNA to cervical-cancer screening. N Engl J Med. 2003;348(6):489-90.

4. Akpak YK, Savasci U, Ören C, Coskun O, Yıldız H, Karagöz E, et al. Health Care Professionals' Knowledge and Attitudes About Sexually Transmitted Diseases and Legal Aspects of Medical Services. CJMB. 2026; 3(1): 14-18.

5. Walboomers JM, Jacobs MV, Manos MM, Bosch FX, Kummer JA, Shah KV, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. J Pathol. 1999; 189(1):12-19.

6. Stănculescu RV, Brătilă E, Bauşic V, Vlădescu TC, Vasilescu F, Bauşic A, et al. Review of the biotechnologies and tests used for precancerous cervical lesions diagnosis. Rom J Morphol Embryol. 2017;58(1):7-14.

7. Kan Ö, Gorkem U, Barış A, Kocak Ö, Togrul C, Yıldırım E. Kanser erken teşhis ve tarama eğitim merkezleri'ne KETEM başvuran kadınlarda Human Papillomavirüs HPV sıklığının değerlendirilmesi ve genotiplerin analizi. Türk Hijyen ve Deneysel Biyoloji Derg. 2019; 76(2): 163–168.

8. Sankaranarayanan R, Basu P, Wesley RS, Mahe C, Keita N, Mbalawa CC, et al. IARC Multicentre Study Group on Cervical Cancer Early Detection. Accuracy of visual screening for cervical neoplasia: Results from an IARC multicentre study in India and Africa. Int J Cancer. 2004;110(6):907-913.

9. Beutner KR, Tyring S. Human papillomavirus and human disease. Am J Med. 1997;102(5):9-15.

10. Muderris T, Afsar I, Yıldız A, Akpınar Varer C. HPV genotype distribution among women with normal and abnormal cervical cytology in Turkey. Rev Esp Quimioter. 2019;32(6):516-524.

11. Taskin MH, Nursal AF, Oruc MA, Kariptas E. Genotype Distribution and Prevalence of High-Risk Human Papillomavirus Infection among Women in Samsun Province of Turkey. Asian Pac J Cancer Prev. 2022;23(7):2477-2482.

12. Dursun P, Senger SS, Arslan H, Kuşçu E, Ayhan A. Human papillomavirus (HPV) prevalence and types among Turkish women at a gynecology outpatient unit. BMC Infect Dis. 2009;30;9:191.

13. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021;71(3):209-249.

14. Lăără E, Day NE, Hakama M. Trends in mortality from cervical cancer in the Nordic countries: association with organised screening programmes. Lancet. 1987;30(1):1247-1249.

15. Paraskevaidis E, Arbyn M, Sotiriadis A, Diakomanolis E, Martin-Hirsch P, Koliopoulos G, et al. The role of HPV DNA testing in the follow-up period after treatment for CIN: a systematic review of the literature. Cancer Treat Rev. 2004; 30(2):205-11.

16. Zito Marino F, Ronchi A, Stilo M, Cozzolino I, La Mantia E, Colacurci N, et al. Multiplex HPV RNA in situ hybridization/p16 immunohistochemistry: a novel approach to detect papillomavirus in HPV-related cancers. A novel multiplex ISH/IHC assay to detect HPV. Infect Agent Cancer. 2020;15(1): 46.

17. Boccardo E, Lepique AP, Villa LL. The role of inflammation in HPV carcinogenesis. Carcinogenesis. 2010; 31(11):1905-12.

18. Koutsky LA, Ault KA, Wheeler CM, Brown DR, Barr E, Alvarez FB, et al. Proof of Principle Study Investigators. A controlled trial of a human papillomavirus type 16 vaccine. N Engl J Med. 2002; 347(21):1645-1651.

19. Mbulawa ZZ, Coetzee D, Williamson AL. Human papillomavirus prevalence in South African women and men according to age and human immunodeficiency virus status. BMC Infect Dis. 2015;26:459.

20. Alotaibi HJ, Almajhdi FN, Alsaleh AN, Obeid DA, Khayat HH, Al-Muammer TA, et al. Association of sexually transmitted infections and human papillomavirus co-infection with abnormal cervical cytology among women in Saudi Arabia. Saudi J Biol Sci. 2020; 27(6):1587-1595.

21. Findik S, Findik S, Abuoğlu S, Cihan FG, Ilter H, Iyisoy MS. Human papillomavirus (HPV) subtypes and their relationships with cervical smear results in cervical cancer screening: a community-based study from the central Anatolia region of Turkey. Int J Clin Exp Pathol. 2019;12(4):1391-1398.

22. Jans L, Zetterström K, Bergengren L, Helenius G. The value of adding a single co-test in HPV primary screening. Prev Med. 2021; 149:106617.