ISSN 2458-8865 E-ISSN 2459-1505
www.fppc.com.tr
Family Practice & Palliative Care

Research Article

Age distribution of patients with multiple High-Risk Human Papilloma Virus (HR-HPV) genotypes and HPV vaccine recommendations by age

Çok sayıda yüksek riskli Human Papilloma Virüs (HR-HPV) genotipi saptanan hastalarda yaş dağılımı ve HPV aşılama yaş önerileri

Gülçin Çetin Uysal[a], Nil Tekin[b]

[a] Department of Gynecology and Obstetrics, Izmir Tinaztepe University, İzmir, Türkiye

[b] Department of Family Medicine, Home Health Care Unit, University of Health Sciences İzmir Tepecik Training and Research Hospital, İzmir, Türkiye

Abstract

Introduction: The aim of this study to identify the age distribution of patients with multiple high risk Human Papilloma Virus (HR-HPV) genotypes and to evaluate HPV vaccination programs through age distribution.

Methods: Patients between the ages of 20-70, who had cervical screening (cervical smear) and HPV genotype tests between January 2017 and December 2021 in Gynecology and Obstetrics Department in Tınaztepe University Hospital, were included in this study. HR-HPV genotype tests and age information which were performed evaluated retrospectively.

Results: The study consisted of 66 patients analysis with multiple HR-HPV genotypes. The median age of the patients with multiple HR- HPV was found to be 32.6 years old. The most frequent combination of multiple HR-HPV was found two sub-types of HR-HPV (66.7%), median age was found as 36.6 years old. In this study the frequency for three sub-types of HR-HPV was found 24.2% and median age for this group was found to be 34.7

years old. We found frequency in patients with four or more sub-types of HR-HPV as 9.1%, and the median age for this group as 33.1 years old was found.

Conclusion: The most common cause of cervical cancer is HPV infection. Multiple HR-HPV infection progression may promote high risk cervical lesions and neoplasia. HPV genotype testing results considering combination of subtypes may direct individual treatment, follow-up protocols for patients. HPV vaccination research may comprise multiple HR-HPV subtypes relations and age distribution for optimal immunization.

Keywords: Human Papillomavirus, Papillomavirus Vaccines, Genotype

Öz

Giriş: Bu çalışmanın amacı, birden fazla yüksek riskli Human Papilloma Virüsü (HR-HPV) genotipine sahip hastaların yaş dağılımını belirlemek ve yaş dağılımları üzerinden HPV aşılama programlarını değerlendirmektir.

Yöntem: Bu çalışmaya Tınaztepe Üniversitesi Hastanesi Kadın Hastalıkları ve Doğum Kliniğinde Ocak 2017 ile Aralık 2021 tarihleri arasında servikal smear ve HPV genotip testleri yapılan 20-70 arası hastalar dahil edildi. HR-HPV genotiplendirme test sonuçları ve hastaların yaş dağılımları geriye dönük olarak değerlendirildi.

Bulgular: Çalışma birden fazla HR-HPV genotipine sahip 66 hastanın analizini içermektedir. Çoklu HR-HPV tanısı alan hastaların ortalama yaşı 32,6 olarak belirlendi. Çoklu HR-HPV saptanan hastalarda en sık kombinasyon iki alt tip birlikteliği (%66,7) olarak saptandı, ortalama yaş 36,6 olarak belirlendi. Bu çalışmada HR-HPV üç alt tip birlikteliği %24,2 ve ortalama yaş 34,7 olarak saptandı. HR-HPV dört veya daha fazla alt tip birlikteliği olan hastaların sıklığı %9,1 ve ortalama yaş 33,1 olarak bulundu.

Sonuç: Serviks kanserinin en sık nedeni HPV enfeksiyonudur. Çoklu HR-HPV enfeksiyonu varlığı, yüksek riskli servikal lezyonlara ve neoplaziye ilerlemeye yol açabilir. Hastalar, çoklu HR-HPV genotip test sonuçları göz önüne alınarak bireysel tedavi ve takip protokollerine yönlendirilebilir. HPV aşılama araştırmaları, en uygun bağışıklama sağlamak için serviks kanseri ile birden fazla HR-HPV alt tipi ilişkisini ve yaş dağılımlarını içerebilir.

Anahtar kelimeler: Human Papilloma virüs, Papilloma aşıları, Genotip

Received	Accepted	Published Online	Corresponding Author	E-mail
May 22, 2024	August 20, 2024	October 25, 2024	Gülçin Çetin Uysal	gcetinuysal@gmail.com
Correspondence	Dr. Gülçin Çetin Uysal. Tınaztepe Üniversitesi Hastanesi, Ahmet Piriştina Bulvarı, Buca/İzmir, Türkiye			
doi	https://doi.org/10.22391/fppc.1487298			

Key Points

1. Human Papilloma Virus (HPV) screening is essential for public health.
2. Patients with multiple high risk HPV should be followed closely for cervical intraepithelial neoplasia progression.
3. Studies on HPV vaccines schedules should take age distributions of multiple high risk HPV (HR-HPV) into consideration.

Introduction

Globally, cervical cancer is the fourth most common cancer in women, with 660,000 new cases and 35,000 deaths reported in 2022 [1]. The most common cause of cervical cancer is Human Papilloma Virus (HPV) infection. HPV genotypes are classified as low-risk HPV (LR- HPV), intermediate-risk HPV(IR-HPV), a high- risk HPV (HR-HPV). LR-HPV types are; 6, 11, 42, 43, 44, and 81 and one intermediate risk HPV (IR-HPV) is type 53. HR-HPV types, which are HPV- 16, - 18, -31, -33, -35, -39, -45, -51, -52, -56, -58, -59, -66, -68, are responsible for 99% of cervical cancer cases [2,3]. Especially HPV- 16 and HPV- 18 are responsible for 71% of cervical cancer [4]. Persistent infection with HR-HPV is associated with the progression of cervical intraepithelial lesions (LSILs) and cervical cancer. Progression of SILs and cervical cancer may depend on high viral load. Some studies have reported that multiple concomitant infections of HR-HPV due to high viral load increase the progression of lesions [5,6,7]. HR-HPV genotyping can conduct the treatment regimen of HPV-positive women and detect co-infections multiple HR-HPV infections as co-infections that have been related to the high-risk cervical lesions and progression of neoplasia. Multiple HR-HPV infections have been demonstrated to have more E6/E7 HPV mRNA expressions conducing precancerous lesions. Determining multiple HR-HPV viral loads could predict diagnosis and be useful for follow-up protocol [8].

Multiple HR-HPV infection rates vary from 24.3% to 38.1%, with age-related distribution for multiple HR-HPV infections similar to single-type HR-HPV infection. Multiple HR-HPV infections occur more frequently in younger women than in older women. Multiple HR- HPV prevalence lowers with age due to infection-clearing duration and developed immune response [9]. Identifying multiple HR-HPV infected patients was reported as a valuable tool for screening for higher risk of progression to High-Grade Squamous Intraepithelial Lesions (HSIL) and Cervical Squamous Cell cancer (SCC). The finding that 40% of women with HSIL were related to HPV co- infection and high viral load and persistence may be reason for progression [10]. Also, many risk factors, such as smoking, sexual history, and economic status, can increase the odds of developing progression to cervical cancer [11]. Smoking promotes both the progression and persistence of LSILs and cervical cancer. Impairing cellular activity and destroying natural antibody production could lead to persistent infection [12]. Smoking also affects HPV replication, HPV E6, and E7 expression, suggesting a synergy between HR-HPV infection and smoking. HR- HPV infections and smoking increase both persistence and progression with interaction [13]. This study aimed to research the multiple HR-HPV genotypes and age distributions. Risk assessment of HPV infections may include genotyping, genotype count, viral load and age.

Methods

Patients aged 20-50 who underwent cervical screening and HPV genotype analysis at Tınaztepe University Hospital Gynecology and Obstetrics Clinics between January 2017 and December 2021 were included. Cervical smear and HPV genotype tests evaluated retrospectively. This study included 66 patients who had undergone cervical screening and HPV genotype tests. Patients cervical screening and HPV genotype tests results were obtained from electronic and written patient files, which were obtained during routine gynecological examinations. Those with a previous history of hysterectomy or for whom cervical cytological or histopathological missing findings were excluded.

HPV genotype analyzes were performed together with cervical cytological examinations in all participants. HPV DNA was detected as previously described by Polymerase Chain Reaction (PCR). Recordings and expositions were automated with the Seegene Viewer software as per the manufacturer's instructions.
The analyzes results were classified as HR-HPV positive, including HPV- 16, - 18, -31, -33, -35, -39, -45, -51, -52, -56, -58, -59, -66, -68. We analyzed the age distribution of multiple HR-HPV infections and correlation with age recommendations of HPV vaccination programs.

Ethical approval

The research was approved by İzmir Tınaztepe University (İZTÜ) Ethics Committee (İZTÜ - Non-Invasive Clinical Research Ethics Committee Decision Form: (770/02- 15.01.2021).

Statical analysis

The data collected were analyzed using the SPSS (SPSS Inc., Chicago, USA) 23.0 Package program and Excel (Microsoft Corporation, USA) 2016 versions. The data were summarized with descriptive statistics and visualized with various graphs.

Results

The median age of patients with multiple HR-HPV was 36. 1 year (range= min 20- max 70). The study group comprises 66 patients evaluated with multiple HR-HPV genotypes (Figure 1) .

The median age for two types of HR-HPV was 32.6 years old; for three types of HR-HPV analyzed, 34.7 years old; for four types of HR-HPV analyzed, 26.1 years old; for four or more types of HR-HPV types analyzed,
33.1 years old (Figure 1) .

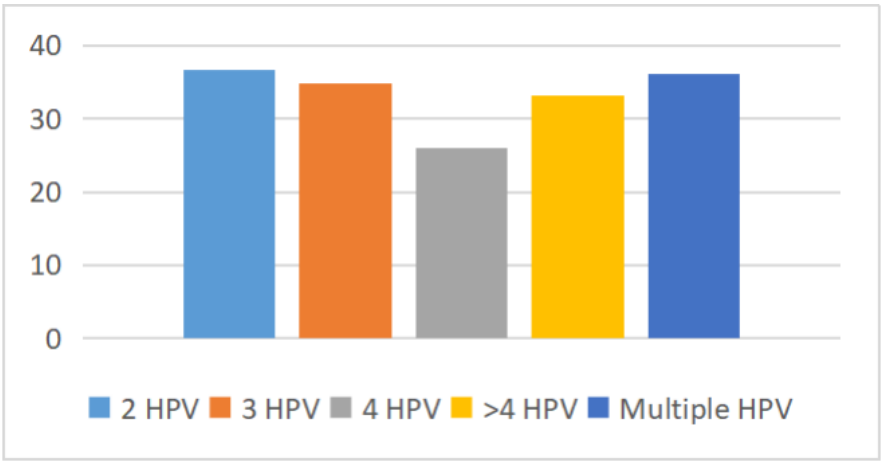

Figure 1. Median ages of the patients

The frequency for two types of HR-HPV was 66.6%; for three types of HR-HPV, 24.2%; and for four and more than four types 9.2% (Figure 2).

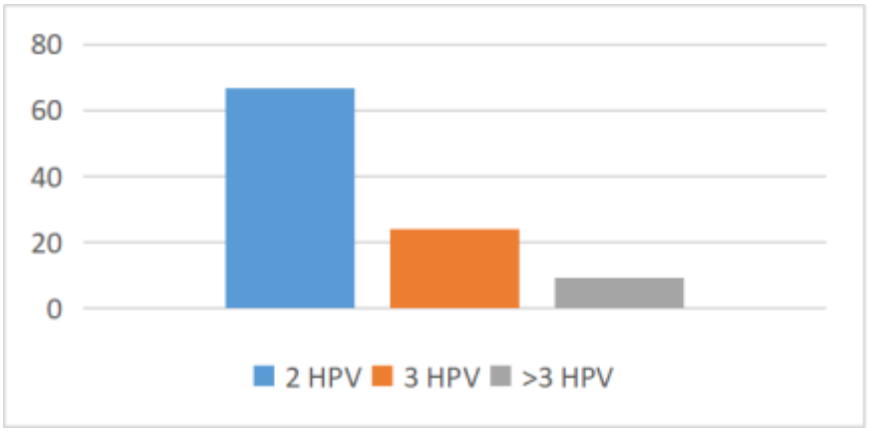

Figure 2. Frequencies of HR-HPV types

Distribution of HR-HPV: HPV 16 rate was detected 33.9%, HPV 18/31/39/56 rate 16.9%, HPV 51 rate 15.0%, HPV 68 rate 11.3%, HPV 52/66 rate 9.4%, HPV 53/58 rate 3.7%, HPV 66 rate 1.8%.

Discussion

As the role of HR-HPV co-infections remains unclear, recent studies suggested an association with a higher risk of cytological abnormalities [14, 15]. The risk of cervical cancer and high-grade cervical lesions are more related to multiple type HR-HPV infections compared with single type HPV infections. Multiple HR-HPV genotype also excluded HPV genotype- 16 and - 18, finding a significant association with High-Grade Cervical Intraepithelial Lesions (HSIL). Co-infection with multiple HR-HPV genotypes might cooperate and promote cervical carcinogenesis [16]. Multiple HR-HPV infections have been documented in some studies as the reason for viral persistence, and the result may be dedicated to an increased risk of HSIL [17].

We analyzed age distribution of patients with multiple High-Risk Human Papillomavirus (HR-HPV) genotypes. In our study, the median age for all groups of multiple HR-HPV infections is 32.6. Median age correlated with multiple HR-HPV infections, especially for two types of HR-HPV, was found to be 36.6 years old, and the most frequent combination of multiple HR-HPV was two sub-types (66.7%). In this study, the median age for three sub-types of HR-HPV was found to be 34.7 years, and 24.2% frequency was found. We found frequency in patients with four or more sub-types of HR-HPV as 9.1%, and the median age for this group 33.1 years old was found. In our study, multiple HR-HPV sub-types were more frequent before 40 years old. Limited studies are available on multiple HR-HPV infections, and retrospective study analyzed the correlation between age and multiple HR-HPV distributions. Two sub-types of HR-HPV are mostly frequent between ages 51-60 (28.6%), and four or more types of HR-HPV were found mostly again at 51-60 (7.1%). This study found multiple HR- HPV infections at older ages more frequently. The proportion of double HR-HPV types (65%) was the highest group, similar to our study (66.6%) [18]. Another study investigated frequencies of multiple HR-HPV across age groups and found the highest incidence occurring double or more co-infections detected younger than 35 years old (58%), like our study [19].

HPV 16 (33.9%) was the most accompanied subtype with multiple HR-HPV in our study, similar to the World Health Organization reported that the most prevalent type is HPV 16 (5%) worldwide [20]. On the point of co-infections become meaningful for HPV genotype interactions. Search for HR-HPV genotype combinations and incidence rate of co-infections maybe significant for vaccine trials and vaccination programs. WHO (World Health Organization) updated vaccination recommendations indicated to use in females aged 9 to 26 and enlarged the age range to 45 [21]. Age-related HPV vaccine updated limitations may be due to the more frequent progression of multiple HR-HPV to cervical premalignant lesions, which means the interval time to progression maybe shorter.

Limitations

The sample size of this study was limited, especially the amount of age distribution of multiple HR-HPV subtype combinations and increasing the sample size remarkable increase the strength of the study.

Conclusion

In summary, multiple HR-HPV infections are detected primarily in younger ages, emphasizing the importance of optimal vaccination age. The effect of vaccination programs on the incidence of HPV genotypes other than co-infections needs to be evaluated in more clinical trials. Nearly 5- 10% of all infected women develop a persistent infection, which may progress to premalignant or malignant cervical lesions. Persistency of HPV infections may be correlated with multiple HR-HPV and viral load and HPV genotype combinations. Vaccination and national immunization programs may update genotypes and age-related immunization with large-scale analyses.

Conflict of interest: The authors declared no conflict of interest regarding this article.

Author Contributions	Author Initials
SCD (Study Conception and Design)	GCU, NT
AD (Acquisition of Data)	GCU, NT
AID (Analysis and Interpretation of Data)	GCU, NT
DM (Drafting of Manuscript)	GCU
CR (Critical Revision)	GCU, NT

Financial support: The author declares that no financial support was received from any institution or individual for this study.

Acknowledgments: The authors would like to thank all the participants in the study.

Prior publication: The author declares that this study was not presented as a paper or published in another journal beforehand.

References

1. World Health Organization. Global Strategy to Accelerate the Elimination of Cervical Cancer as a Public Health Problem. Geneva: World Health Organization; 2020. License: CC BY-NC-SA 3.0 IGO.
2. Doorbar J, Egawa N, Griffin H, Kranjec C, Murakami I. Human papillomavirus molecular biology and disease association. Rev Med Virol. 2015;25(suppl 1):2-23. https://doi.org/10.1002/rmv.1822
3. Bouvard V, BaanR, StraifK, Grosse Y, Secretan B, El Ghissassi F et al. A review of human carcinogens -part b: biological agents. Lancet Oncol. 2009;10(4):321-322. https://doi.org/10.1016/S1470-2045(09)70096- 8
4. Pandey S, Chandravati C. Human papillomavirus-mediated cervical cancer awareness and gardasil vaccination: a pilot survey among north Indian women. J Community Health. 2013;38:907- 10. https://doi.org/10.1007/s10900-013-9697-6
5. Dalstein V, Riethmuller D, Prétet JL, Le Bail CK, Sautière JL, Carbillet JP, et al. Persistence and load of high-risk HPV are predictors for development of high-grade cervical lesions: a longitudinal French cohort study. Int J Cancer. 2003;106(3):396-403. https://doi.org/10.1002/ijc.11222
6. Dong L, Wang MZ, Zhao XL, Feng RM, Hu SY, Zhang Q, et al. Human papillomavirus viral load as a useful triage tool for non- 16/18 high-risk human papillomavirus positive women: a prospective screening cohort study. Gynecol Oncol. 2018;148(1):103- 110. https://doi.org/10.1016/j.ygyno.2017.11.016
7. Luo H, Belinson JL, Du H, Liu Z, Zhang L, Wang C, et al. Evaluation of viral load as a triage strategy with primary high-risk human papillomavirus cervical cancer screening. J Low Genit Tract Dis. 2017;21(1):12- 16. https://doi.org/10.1097/LGT.0000000000000277
8. Li Y, Wang H, Zhang Y, Jing X, Wu N, Hou Y, Hao C. Correlation between Multi-type human papillomavirus infections and viral loads and the cervical pathological grade. Int J Gynecol Obstet. 2021;152(1):96- 102. https://doi.org/10.1002/ijgo.13406
9. Zeng Z, Austin RM, Wang L, Guo X, Zeng Q, Zheng B, Zhao C. Nationwide prevalence and genotype distribution of high-risk human papillomavirus infection in China. Am J Clin Pathol. 2022;157(5):718-23. https://doi.org/10.1093/ajcp/aqab181
10. De Brot L, Pellegrini B, Moretti ST, Carraro DM, Soares FA, Rocha RM, et al. Infections with multiple high-risk HPV types are associated with high-grade and persistent low-grade intraepithelial lesions of the cervix. Cancer Cytopathol. 2017;125(2):138- 143. https://doi.org/10.1002/cncy.21789
11. American Cancer Society, Risk Factors for Cervical Cancer. Available at: https://www.cancer.org/cancer/types/cervical-cancer/causes-risks-prevention/risk-factors.html (Access Date: June 10, 2024).
12. Simen-Kapeu A, KatajaV, YliskoskiM, Syrjänen K, Dillner J, Koskela P, et al. Smoking impairs human papillomavirus (HPV) type 16 and 18 capsid antibody response following natural HPV infection. Scand J Infect Dis. 2008;40(9):745-75. https://doi.org/10.1080/00365540801995360
13. AguayoF, Muñoz JP, Perez-Dominguez F, Carrillo-Beltrán D, Oliva C, CalafGM, et al. High-risk human papillomavirus and tobacco smoke interactions in epithelial carcinogenesis. Cancers. 2020;12(8):2201. https://doi.org/10.3390/cancers12082201
14. Schmitt M, Depuydt C, Benoy I, Bogers J, Antoine J, Arbyn M, Pawlita M. Multiple human papillomavirus infections with high viral loads are associated with cervical lesions but do not differentiate grades of cervical abnormalities. J Clin Microbiol. 2013;51(5):1458-64. https://doi.org/10.1128/JCM.00087- 13

15. Saslow D, Solomon D, Lawson HW, Killackey M, Kulasingam SL, Cain J, et al. American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. Am J Clin Pathol. 2012;137(4):516-42. https://doi.org/10.1309/AJCPTGD94EVRSJCG
16. Kim J, Kim M, Park JY. Evaluation of the characteristics of multiple human papillomavirus (HPV) infections identified using the BD Onclarity HPV assay and comparison with those of single HPV infection. J Pathol Transl Med. 2022;56(5):289-93. https://doi.org/10.4132/jptm.2022.08.02
17. Trottier H, Mahmud S, Costa MC, Sobrinho JP, Duarte-Franco E, Rohan TE, et al. Human papillomavirus infections with multiple types and risk of cervical neoplasia. Cancer Epidemiol Biomarkers Prev. 2006;15(7):1274-80. https://doi.org/10.1158/1055-9965.EPI-06-0129
18. Na J, Li Y, Wang J, Wang X, Lu J, Han S. The correlation between multiple HPV infections and the occurrence, development, and prognosis of cervical cancer. Front Microbiol. 2023;14:1220522. https://doi.org/10.3389/fmicb.2023.1220522
19. De Brot L, Pellegrini B, Moretti ST, Carraro DM, Soares FA, Rocha RM, et al. Infections with multiple high-risk HPV types are associated with high-grade and persistent low-grade intraepithelial lesions of the cervix. Cancer Cytopathol. 2017;125(2):138-43. https://doi.org/10.1002/cncy.21789
20. World Health Organization, One in Three Men Worldwide Are Infected with Genital Human Papillomavirus. Available at:https://www.who.int/news/item/01-09-2023-one-in-three-men-worldwide- are-infected-with-genital-human-papillomavirus (Access Date: June 10, 2024).
21. World Health Organization, Human papillomavirus vaccines: WHO position paper, December 2022. Available at: https://www.who.int/publications/i/item/who-wer9750-645-672 (Access Date: June 10, 2024).