



Assesment Of Hpv Dna Positive Individuals In Sivas Province In Terms Of Some Variables

Sanem Nemmezi Karaca^{1,a}, Çağlar Yıldız^{2,b*}

¹Sivas Cumhuriyet Üniversitesi, School of Medicine, Department of Family Medicine, Sivas, Turkey, ²Sivas Cumhuriyet Üniversitesi, School of Medicine, Department of Obstetrics and Gynecology, Sivas, Turkey

*Corresponding author

Research Article

History

Received: 17/09/2022

Accepted: 30/09/2022

ABSTRACT

Background: Cervical cancer is one of the most common cancers in women and causes death. Revealing the distribution of HPV prevalence and types in cervical cancer remains important for both treatment and vaccination strategies. The goal of this study is to determine the HPV DNA subtypes of women who are positive for Human Papilloma Virus (HPV) screening, and to evaluate their sociodemographic characteristics and cervical smear results.

Methods: The study was conducted on 215 women who were directed to Sivas Cumhuriyet University Obstetry and Gynecology outpatient clinic by her gynecologists or family physicians between 2015-2018 years. A questionnaire containing datas of patients about age, education levels and jobs of both spouses, smoking status, obstetric history and age of first sexual intercourse was filled out by the researcher. The data were analysed with SPSS (vers 23.0) program and significance level was taken as 0.05.

Results: The most prevalent HPV types were type 16 and category of the others; with the rates of respectively 47% (n: 101), 40% (n: 86). The frequencies of ASCUS (undetermined atypical squamous epithelial cells), LGSIL (low-grade squamous intraepithelial lesion) and HGSIL (high-grade squamous intraepithelial lesion) were respectively found to be 7.9% (n: 17), 23.7% (n: 51) and 1.9% (n: 4). The relationship between HPV types and Pap Smear results was statistically significant (p: 0.011). There was no difference between patients and their spouses about education levels and occupations; and among patients on smoking status, menstrual patterns, age at first sexual intercourse and family planning methods and HPV types (p> 0.05). In women above aged 55, only two types of HPV DNA were observed; which were type 16 and category of the others (p: 0.005). The relationship between abortion history and HPV types was found out to be significant (p: 0.016).

Conclusion: This study has contributed to the literature by revealing the types of HPV which observed in Sivas province over a period of 3 years.

Keywords: Cervical smear, HPV DNA test, HPV types, Pap smear.

Sivas İlinde Hpv Dna Pozitif Bireylerin Bazı Değişkenler Açısından Değerlendirilmesi

Süreç

Geliş: 17/09/2022

Kabul: 30/09/2022

ÖZ

Amaç: Rahim ağzı kanseri kadınlarda en sık görülen kanserlerden biridir ve ölüme neden olur. Rahim ağzı kanserinde HPV prevalansının ve tiplerinin dağılımının ortaya çıkarılması hem tedavi hem de aşılama stratejileri için önemini korumaktadır. Bu çalışmanın amacı, Human Papilloma Virüs (HPV) taraması pozitif olan kadınların HPV DNA alt tiplerini belirlemek, sosyodemografik özelliklerini ve servikal smear sonuçlarını değerlendirmektir.

Yöntem: Araştırma 2015-2018 yılları arasında Sivas Cumhuriyet Üniversitesi Kadın Hastalıkları ve Doğum polikliniğine kadın hastalıkları ve aile hekimleri tarafından yönlendirilen 215 kadın üzerinde yapıldı. Hastaların her iki eşin yaşı, eğitim durumu ve işi, sigara içme durumu, obstetrik öyküsü ve ilk cinsel ilişki yaşı bilgilerini içeren anket araştırmacı tarafından doldurulmuştur. Veriler SPSS (vers 23.0) programı ile analiz edilmiş ve anlamlılık düzeyi 0.05 olarak alınmıştır.

Bulgular: En yaygın HPV tipleri tip 16 ve diğerleri kategorisiydi; sırasıyla %47 (n:101), %40 (n:86) oranlarındadır. ASCUS (belirsiz atipik skuamöz epitel hücreleri), LGSIL (düşük dereceli skuamöz intraepitelial lezyon) ve HGSIL (yüksek dereceli skuamöz intraepitelial lezyon) sıklıkları sırasıyla %7,9 (n:17), %23,7 (n: 51) olarak bulundu.) ve %1,9 (n: 4). HPV tipleri ile Pap Smear sonuçları arasındaki ilişki istatistiksel olarak anlamlıydı (p: 0.011). Hastalar ve eşleri arasında eğitim düzeyleri ve meslekler açısından farklılık yoktu; ve sigara içme durumu, adet düzeni, ilk cinsel ilişki yaşı ve aile planlaması yöntemleri ve HPV tipleri açısından hastalar arasında (p> 0.05). 55 yaş üstü kadınlarda sadece iki tip HPV DNA gözlemlendi; tip 16 ve diğerleri kategorisiydi (p: 0,005). Kürtaj öyküsü ile HPV tipleri arasındaki ilişki anlamlı bulundu (p:0.016).

Sonuç: Bu çalışma Sivas ilinde 3 yıllık bir süreçte gözlenen HPV tiplerini ortaya koyarak literatüre katkı sağlamıştır.

Anahtar sözcükler: Servikal smear, HPV DNA testi, HPV tipleri, Pap smear.

License



This work is licensed under Creative Commons Attribution 4.0 International License

^a drsnemmezi@yahoo.com

^b https://orcid.org/0000-0002-4853-8366

^b dr_caglaryildiz@yahoo.com

^b https://orcid.org/0000-0003-3150-3340

How to Cite: Karaca SN, Yıldız Ç (2022) Assesment Of Hpv Dna Positive Individuals In Sivas Province In Terms Of Some Variables, Cumhuriyet Medical Journal, September 2022, 44 (3): 304-309

Introduction

Despite screening programs around the world, cervical cancer is the fourth most common cancer in women worldwide, causing an estimated 528,000 new cases each year. While almost 12% of all female malignancies occur in the less developed regions, cervical cancer in the developing countries may constitute up to 25% of all female cancer cases. Besides, this malignancy is the second most common cause of cancer deaths in women worldwide after breast cancer. WHO declared that approximative 266,000 deaths in 2012 were due to cervical cancer and almost 90% these deaths occurring in the less developed regions¹. Nearly all cases of cervical cancer (about 99.7%) are owing to persistent or chronic high-risk human papillomavirus (HPV) infections and cervical cancer is by far the most common HPV-related disease². The frequency of HPV infection and its subtypes varies regionally.

HPV is one of deoxyribonucleic acid (DNA) viruses and the most common viral infection of the reproductive tract. It is one of the most common causes of sexually transmitted infection all around the world³. Although it is sexually transmitted, it does not necessary penetrative sexual intercourse for HPV transmission. Skin-to-skin genital contact is a well-known mode of transmission. So, HPV infection has been acquired afterwards becoming sexually active and it should be considered especially in adolescents. Over 70% of sexually active women and men will have been infected at some point of their lives; with some may have even been infected on more than one occasion and most of them clear up spontaneously. If the infection occurs, most of them are asymptomatic or cause benign lesions like cutaneous warts on the hands, feet and anogenital region whereas small proportion of persistent infections with the oncogenic or high-risk types may emerge cancers of the oropharynx and anogenital regions.

For these reasons, HPV testing in the secondary prevention is clinically worthwhile in the early detection of low-grade cytological abnormalities and is also more susceptible than cytology in the primary screening². In a study compared the effectiveness of HPV-DNA and Pap smear test, it was found that HPV-DNA sensitivity and specificity in the high grade lesions were 94.6% and 94.2%, and Pap smear test was 55.4% and 96.8%, respectively. If both of them were combined, sensitivity and specificity were 100% and 92.5%, respectively⁴. High-risk or carcinogenic types of HPV can be tested by looking for pieces of women's DNA in their cervical cells. The HPV gene test can be applied in combination with the Pap test to screen for cervical cancer. The American Cancer Society

recommends this combination for women ages 30 years and above. Besides, in women who have slightly abnormal Pap test results (like ASC-US, LGSIL) can be used HPV DNA to reveal whether they might need more testing and treatment or not. Or the patients, whose Pap smear test results are normal, but their HPV tests are positive, should be recommended to repeat co-testing (with a Pap test and a HPV test) within one year or to analyze in terms of HPV types 16 and 18. If the test is positive for types 16 or 18, colposcopy would be recommended and if does not, repeat of co-testing in one year should be gotten⁵.

The aim of this study was to determine the type distribution of Human Papilloma Virus (HPV) of women who were found positive as a result of cervical cancer screening at the central of Sivas province, to find out their relationship with cervical smear and to evaluate the relation with sociodemographic characteristics.

Material and Methods

In Turkey, The Ministry of Health launched a screening program for five years in 2014 and aimed to screen all women aged 30-65 for cervical cancer. HPV positivity rate was found to be 4.18% with this program. This screening individuals was the population in this study. Firstly, necessity permissions were taken from local health authority and out-patients. Then, between 2015-2018, the data were collected as patients who totally were 333 women came. To the study, 215 women was included whose HPV DNA scans performed at the external centers were positive and who were referred to the Sivas Cumhuriyet University Gynecology outpatient clinic for further investigation and treatment. The individuals were filled out a questionnaire form containing information such as age, educational status and occupation for both of the spouse, smoking status, obstetric history and age of first sexual intercourse. Data on HPV DNA positivity and cervical cytology according to Bethesda 2001 was obtained from the records. All data were loaded into SPSS (vers. 23.0) program. Descriptive statistics and chi-square test were used to evaluate the data. Error level was taken as 0.05.

Results and Discussion

The median age of the women was 40 years old (Min: 25, Max: 66, SD: \pm 7.52). While 92.1% (n: 198) of individuals were not working in any job; most of their spouses (88.4%, n: 190) were employee, official or self-employment. Most of the patients and their spouses were primary school graduates (Table 1). The smoking rate was 30.2% (n: 65).

Table 1. Sociodemographic Characteristics

	Patients n (%)	Their Spouses n (%)
Jobs		
Official	7 (3.3)	17 (7.9)
Employee	7 (3.2)	84 (39.1)
Self-Employment	3 (1.4)	89 (41.4)
Not Working	198 (92.1)	8 (3.7)
Retired	-	17 (7.9)
Educational Level		
Illiterate	17 (7.9)	2 (0.9)
Elementary School	132 (61.4)	89 (41.4)
Secondary School	25 (11.6)	38 (17.7)
High School	34 (15.8)	64 (29.8)
University	7 (3.3)	22 (10.2)

Of 76.7% (n: 165) women stated that their menstrual period was regular, while 11.6% (n: 25) were menopausal. The age of expressed first sexual intercourse was min: 13, max: 40 and mostly (59.5%) between 17-20 years. There were 100 (46.5%) women who expressed their first sexual

experience at age of 18 or younger; it was 158 (73.48%), if the age limit was accepted as 20. It was observed that the number of pregnancies of women ranged from zero to a maximum of 16 (Table 2).

Table 2. Obstetric History

	0 n (%)	1 n (%)	2 n (%)	3 n (%)	4 n (%)	5 n (%)	≥ 6 n (%)
Gravidity	34 (15.8)	10 (4.7)	32 (14.9)	43 (20)	23 (10.7)	26 (12.1)	47 (22.1)
Parity	37 (17.2)	13 (6.0)	59 (27.4)	46 (21.4)	31 (14.4)	16 (7.4)	13 (6.1)
Abortion	149 (69.3)	40 (18.6)	12 (5.6)	10 (4.7)	2 (0.9)	1 (0.5)	1 (0.5)
D&C	165 (76.7)	35 (16.3)	8 (3.7)	5 (2.3)	2 (0.9)	-	-

Which contraceptive methods were used at the time of diagnosis was questioned and it was learned that of 7.4% (n: 16) OCS, 12.1% (n: 26) of condoms, 22.3% (n: 48) of intrauterine devices and 58.1% (n: 125) of other protection methods. Due to variations in the same patient over time, the comparison between contraception methods and HPV DNA types could not be done.

The distribution of HPV DNA were 47% (n: 101) of the patients had type 16, 4.7% (n: 10) of type 18, 2.8% (n: 6) of type 31, 3.3% (n: 7) of type 33, 2.3% (n: 5) type 51 and 40% (n: 86) category of the others (describe other than high-risk HPV types). No individuals who had two or more types together was observed.

In the literature, there have been identified about 30 HPV types that are sexually transmitted and infected primarily the cervix, vagina, vulva, penis, and anus; with of 15 types associated with cervical cancer. This genital HPV types can be classified as high risk (oncogenic) and low-risk (non-oncogenic) according to association with cervical cancer and its precursor lesions. Types 6, 11, 42, 43, and 44 are grouped in low-risk or non-oncogenic HPV types, while the high-risk or oncogenic HPV types include types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82. At least one of these HPV types has been implicated in 99.7% of cases of squamous cell carcinoma of the cervix^{6,7}. If someone were infected with any of types with high-

risk, they might develop cervical intraepithelial neoplasia which may progress to invasive cancer⁷. Type 16 and 18 are the most frequently isolated types in cervical cancer cases and type 16 is seen in more than 50% of patients^{2,8}.

According to the cervical smear, different cytological results are observed in the literature. In a study evaluating HPV frequency and having genotypic analysis made in Turkey in 2018, individuals were evaluated cytologically. Normal and infection related results were observed as 25.18% and 41.34%, respectively. The most common abnormal cytological findings were LGSIL and ASCUS (8.21%, 6.32%)⁹. HPV prevalence has been reported to range from 1.6% to 14.2% in patients without cytological

abnormalities in Asian continents¹⁰. Similarly, in a large series of 961,029 specimens in China, 18% of HPV positive cases had normal cytological results. The detection of HPV positivity rates of 89.74% and 93.43% in LGSIL and HGSIL cases, respectively, reveals the strong causal relationship between HPV infection and cervical neoplasia¹¹.

The rates of ASCUS, LGSIL and HGSIL in this study were 7.9% (n: 17), 23.7% (n: 51) and 1.9% (n: 4), respectively. Normal cervical cytology was observed %28.8 of patients and infection was %37.7. The relationship between HPV types and Pap Smear results was statistically significant (p: 0.011); with mostly type 16 and category of the others (Table 3).

Table 3. The relation between cervical cytology and HPV types

	Normal n (%)	Infection n (%)	ASCUS n (%)	LGSIL n (%)	HGSIL n (%)
HPV Type 16	29 (46.8)	45 (55.6)	6 (35.3)	18 (35.3)	3 (75.0)
HPV Type 18	5 (8.1)	4 (4.9)	0	1 (2.0)	0
HPV Type 31	3 (4.8)	2 (2.5)	0	1 (2.0)	0
HPV Type 33	0	3 (3.7)	1 (5.9)	3 (5.9)	0
HPV Type 51	2 (3.2)	0	3 (17.6)	0	0
Category of the others	23 (37.1)	27 (33.3)	7 (41.2)	28 (54.9)	1 (25)
Totally	62 (100)	81 (100)	17 (100)	51 (100)	4 (100)

The rate of LGSIL have been reported almost by normal cytological signs. Distribution of the HPV types in patients with abnormal cytology were mostly in type 16 and category of the others (p: 0.011), (Table 3).

It was indicated that suppressed primary immune response, long-term use of oral contraceptives, cigarette smoking, multiple sexual partners at any time of life or to have a partner who has had multiple sexual partners, having sexual activity at an early ages, having a history of other sexually transmitted infections, genital warts, or cervical or penile cancer in an individual or her sexual partner and increasing parity posed a risk of acquiring HPV and contributed to the progression of clinical outcomes². In addition, age is an important determinant of the risk of HPV infection. Between the ages of 18 and 30 years, the infection is most common among sexually active young women and after the age of 30 years there was a decline in the prevalence. Because of the slow progression rates to cancer; the infection occurs at younger ages but

cervical cancer is more common in older women of 35 years and above. The high-risk or oncogenic types which play an important role in the development of invasive cancer of the cervix cause more frequently to the persistent HPV infection^{12,13}.

There was no statistically significant difference between first sexual intercourse experience and observed HPV types (p: 0.177). However, it was determined that 42% of the patients under the age of 18 had type 16, 7% had type 18, 3% had type 31, 6% had type 33, 2% had type 51 and 40% had the category of the others (Table 4). Also, between first sexual intercourse experience and cervical cytology was not found significant difference (p: 0.289). Though not statistically significant, infection and LGSIL rates are higher in individuals under 20 years of age. This finding shows the importance of safe sexual intercourse education in adolescents. Especially in women above aged 55, only two types of HPV DNA were observed; which were type 16 and category of the others (p: 0.005).

Table 4. HPV types to the age of first sexual intercourse

	HPV Type 16 n (%)	HPV Type 18 n (%)	HPV Type 31 n (%)	HPV Type 33 n (%)	HPV Type 51 n (%)	Category of the others n (%)
≤ 18 years	42 (42.0)	7 (7.0)	3 (3.0)	6 (6.0)	2 (2.0)	40 (40.0)
≥ 19 years	59 (51.3)	3 (2.6)	3 (2.6)	1 (0.9)	3 (2.6)	46 (40.0)
Totally	101	10	6	7	5	86

Significant difference was not found between the spouses' vocation and HPV types and cervical cytology. (p:0.503).

The relationship between abortion history and HPV types was found to be significant (p: 0.016). 77.2% of those with HPV 16 positivity, 70% of those with 18, 83.3% of those with 31, 85.7% of those with 33, 100% of those with 51, 55.8% of those with other types and 69.3% of women in totally (n: 149) did not have a history of abortion. However, when HPV types of patients who has 3 or more abortion history were examined, it was observed that 57.1% (n: 8) were type 16 and 42.9% (n: 6) were category of the others; none of individuals having type 16, 18, 31, 33 and 51 were abortus history.

It was reported in the previous study that, a two fold increase in the rate of spontaneous abortion occurred in 66 women with current genital HPV infection (12%) compared with 900 HPV-negative women (6%), despite a lower anamnestic rate of pregnancies in HPV-positive women ¹⁴. Besides, it has been shown that HPV infection was three times more prevalent in spontaneous abortion specimens compared with specimens from elective abortions (60% vs. 20%, respectively) ¹⁵. However, according to our results, there seems probable to be a difference between HPV types for the risk of abortion.

Conclusion

It is known that the most important risk factor for the development of cervical cancer is HPV. The distribution of HPV subtypes varies by region and country, so it is important to know the more common HPV types. It is thought that the inclusion of HPV vaccines in vaccination programs will have an important role in the elimination of cervical cancer.

In the study conducted for this purpose; HPV type 16 and category of the others were observed more frequently. It was shown that category of the others were more common in women with a history of abortion. The most frequent types in abnormal cervical smear results was type 16 and category of the others.

The data of this study was presented as an oral presentation at "I International cancer days" on 19 - 21 September 2019.

References

1. WHO: International Agency for Research on Cancer. Cervical cancer: Estimated incidence, mortality and prevalence worldwide in 2012. In: The GLOBOCAN 2012 Database. Lyon, France: International Agency for Research on Cancer.
2. Okunade KS. Human Papillomavirus and Cervical Cancer. Current Perspectives in Human Papillomavirus. Shailendra K. Saxena, IntechOpen, DOI: 10.5772/intechopen.81581.
3. Burd EM. Human papillomavirus and cervical cancer. Clinical Microbiology Reviews. 2003;16(1):1-17.
4. Koliopoulos G, Arbyn M, Martin-Hirsch P, Kyrgiou M, Prendiville W, Paraskevidis E. Diagnostic accuracy of human papillomavirus testing in primary cervical screening: A systematic review and meta-analysis of non-randomized studies. Gynecol Oncol, 2007;104: 232-46.
5. Cervical Cancer Prevention and Early Detection. The American Cancer Society (AAC). <https://www.cancer.org/cancer/cervical-cancer/prevention-and-early-detection/hpv-test.html>
6. 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. The Journal of Pathology. 1999;189:12-19.
7. Munoz N, Bosch FX, de Sanjose S, Herrero R, Castellsague X, Shah KV, et al. Epidemiologic classification of human papillomavirustypes associated with cervical cancer. N Engl J Med, 2003;348:518-27.
8. de Sanjose S, Quint WG, Alemany L, Geraets DT, Klaustermeier JE, Lloveras B, et al. Human papillomavirus genotype attribution in invasive cervical cancer: a retrospective cross-sectional worldwide study. Lancet Oncol, 2010;11(11):1048-56.
9. Kan Ö, Görkem Ü, Barış A, Koçak Ö, Toğrul C, Yıldırım E. Kanser erken teşhis ve tarama eğitim merkezleri (KETEM)'ne başvuran kadınlarda human papillomavirüs (HPV) sıklığının değerlendirilmesi ve genotiplerin analizi. Turk Hij Den Biyol Derg, 2019;76(2):163-68.

10. Clifford GM, Gallus S, Herrero R, Munoz N, Snijders PJ, Vaccarella S, et al. HPV prevalence surveys: a pooled analysis, *Lancet*, 2005;366(9490):991-98.
11. Chen X, Xu H, Xu W, Zeng W, Liu J, Wu Q, et al. Prevalence and genotype distribution of human papillomavirus in 961,029 screening tests in southeastern China (Zhejiang Province) between 2011 and 2015. *Sci Rep*, 2017;7(1):14813.
12. Adam E, Berkova Z, Daxnerova Z, Icenogle J, Reeves WC, Kaufman RH. Papillomavirus detection: Demographic and behavioral characteristics influencing the identification of cervical disease. *American Journal of Obstetrics and Gynecology*. 2000;182:257-64.
13. Burk RD, Kelly P, Feldman J, Bromberg J, Vermund SH, Deltovitz JA, et al. Declining presence of cervicovaginal human papillomavirus infection with age is independent of other risk factors. *Sexually Transmitted Diseases*. 1996;23:333-41.
14. Hellberg D, Nilsson S. IVF and HPV. *Fertility and Sterility*. 2007;87(6):1498 (Author Reply).
15. Perino A, Giovannelli L, Schillaci R, Ruvolo G, Fiorentino FP, Alimondi P, Cefalù E, Ammatuna P. Human papillomavirus infection in couples undergoing in vitro fertilization procedures: impact on reproductive outcomes. *Fertil Steril*. 2011;95(5):1845-48.