ORIGINAL RESEARCH

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The Distribution of Oncogenic HPV Types Between CIN 2 and 3: A Retrospective Study

Cemre ALAN[a], Beyza GÜZELKARA ERGENE[a], Ali ACAR[a]

[a]Necmettin Erbakan University Meram Faculty of Medicine, Department of Gynecology and Obstetrics, Konya, Türkiye

ABSTRACT Objective: Cervical cancer is a major public health problem worldwide. The most important risk factor is persistent infection with oncogenic human papillomavirus (HPV) types. The distribution of HPV genotypes varies geographically. There are differences in HPV types depending on the degree of cervical intraepithelial neoplasia (CIN). This study aimed to compare patients diagnosed with CIN 2 or 3 by colposcopic biopsy about the high-risk HPV types they carry. **Material and Methods:** Between January 2013 and September 2024, 229 patients diagnosed with CIN 2 or 3 and attending the gynecological oncology outpatient clinic of the university hospital were included in the study. The distribution of high-risk HPV types according to age and pathological diagnosis was investigated. **Results:** HPV 16 positivity was significantly higher in patients diagnosed with CIN 3 than CIN 2 (p=0.003). The prevalence of HPV 16 and 39 was significantly higher in patients aged 40 and older compared to those under 40 (p=0.003, p=0.018, respectively). **Conclusion:** In conclusion, HPV 16 positivity was significantly higher in patients diagnosed with CIN 3 than with CIN 2 (p=0.003). The most common HPV types in patients with CIN 2/3 in this study were 16, 18, 31, 35, 39, and 51 (the last three were equally frequent). In addition, more than half of the patients diagnosed with CIN 2/3 are positive for high-risk HPV types other than HPV 16-18.

Keywords: Cervical intraepithelial neoplasia (CIN); human papillomavirus (HPV)

Cervical cancer is a major health problem worldwide, particularly in low- and middle-income countries.[1] The main risk factor for developing cervical cancer and precancerous lesions of the cervix is persistent infection with oncogenic human papillomavirus (HPV) types.[2] It is recognized that one in every ten women globally has tested positive for HPV.[3] Oncogenic HPV types causing cervical cancer are 16 and 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68.[4,5] The prevalence of different HPV genotypes varies in different parts of the world.[6] Cervical cancer screening guidelines recommend that women aged 25-65 years are screened with an HPV test every 5 years.[7] The ASSCP (American Society for Colposcopy and Cervical Pathology) advises colposcopy for individuals who test positive for HPV types 16 and/or 18. If other oncogenic HPV types show positive results, it is advised to retest after one year.[5] According to the National Cervical Cancer Screening Standards in our country, screening with HPV test is recommended every 5 years for women between the ages of 30-65.[8] Screening utilizing HPV is proficient in identifying cervical intraepithelial neoplasia (CIN).[9,10] The majority of research available examines chronic cervicitis/CIN 1 alongside CIN 2/3 regarding HPV types.[5,11-13] This study aims to compare patients diagnosed with CIN 2 or 3 in colposcopic biopsy in terms of the high-risk HPV types they carry.

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Correspondence: Cemre ALAN
Necmettin Erbakan University Meram Faculty of Medicine, Department of Gynecology and Obstetrics, Konya, Türkiye
E-mail: drcemrealan@gmail.com

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MATERIAL AND METHODS

Approval from the ethics committee for this retrospective analysis was secured (Decision no: 2024/5204). The investigation was conducted following the ethical guidelines of the Declaration of Helsinki. As this was a retrospective analysis, obtaining informed consent from the patients was unnecessary. Participants included in this research were women who visited the gynecologic oncology outpatient clinic at our institution from January 2013 to September 2024. Eligible candidates were women aged 25 to 65, non-smokers, and without systemic illnesses. Smokers were excluded from the study due to the effect of smoking on HPV persistence. Those with any form of cancer diagnosis, users of combined oral contraceptives, grand multiparous women, hysterectomized individuals, and those who were pregnant were excluded from this research. The study focused on patients exhibiting negative cervical cytology, positive HPV 16/18, or those with persistent test results for other high-risk HPV types lasting for one year. HPV DNA typing was conducted using TÜSEB-DiaVTM® viral medium at Cancer Early Screening Diagnosis, Screening, and Education Centers [Kanser Erken Teşhis Tarama ve Eğitim Merkezi (KETEM)]. The HPV tests utilized in our nation are well-suited for community-centered screening, carry international credibility, and are FDA-approved. In this study, patients diagnosed with CIN 2 or 3 based on cervical biopsy results following a colposcopic examination were compared based on the variety and quantity of high-risk HPV they possessed. The co-infection status was assessed for patients whose types were explicitly detailed in the HPV test results. Patients with a positive high-risk HPV test that did not specify the type were classified as 'other'. A colposcopic assessment was carried out following the 2011 guidelines established by the International Federation for Cervical Pathology and Colposcopy for colposcopic terminology.[14] If abnormal colposcopy findings (minor or major) were present, a punch biopsy was conducted on the visible lesion. Endocervical curettage was performed on patients where the squamocolumnar junction was not visible (type 3 transformation zone), when feasible.

Statistical analysis was executed using the SPSS software (Version 22.0 for Windows; SPSS, Inc, Chicago, IL). The Chi-square test was applied to determine the distribution of HPV types in the group comparisons.

RESULTS

A total of 245 patients with HPV test results participated in the study. Among them, 229 patients were diagnosed with CIN 2 or CIN 3, and statistical analyses of HPV distribution were conducted within this group. The Shapiro-Wilk test indicated a significant non-normal distribution of age among the patients ($p<0.001$). The median age of the patients was 44 years, with a range from 25 to 65 years. Among the patients, 65.1% were aged 40 years or older. There were 113 patients (49.3%) diagnosed with CIN 2 and 116 patients (50.7%) diagnosed with CIN 3. The prevalence of HPV 16 and 39 was significantly higher in patients aged 40 and older compared to those under 40 ($p=0.003$, $p=0.018$, respectively). Conversely, HPV 59 was found to be significantly more prevalent in patients under 40 years of age than in those aged 40 and older ($p<0.001$). Additionally, other high-risk HPV types were more frequently seen in patients 40 years and older compared to those under 40 ($p=0.048$).

Table 1 illustrates the distribution of HPV types across different age groups. A comparison of patients' pathology diagnoses by age groups revealed no significant differences ($p=0.492$). Among the patients, HPV 16 and/or 18 were found to be positive in 107 individuals (46.7%), while other HPV types were positive in 122 patients (53.3%). Of those who tested positive for HPV 16, 61.3% had a single infection, and 38.7% had multiple infections. In contrast, among HPV 18-positive patients, 43.5% had a single infection, whereas 56.5% had multiple infections. Figure 1 presents the distribution of HPV positivity status regarding uni- and multi-infections. There was no statistically significant difference between patients' pathological diagnosis and whether they had single or multiple infections ($p=0.574$).

The HPV type distribution among patients according to their pathology diagnoses is presented in

TABLE 1: The distribution of human papillomavirus types according to age groups.

HPV	Patient age <40	Patient age ≥40	p value *
16	43	50	**0.003**
18	11	12	0.172
31	8	8	0.190
33	2	2	0.524
35	3	9	0.458
39	4	8	**0.018**
45	1	6	0.245
51	7	5	0.081
52	5	2	0.720
53	3	6	0.918
54	1	1	0.654
56	2	2	0.524
59	10	1	**<0.001**
61	1	2	0.953
66	6	2	0.016
68	3	4	0.655
70	0	2	0.298
82	1	1	0.654
Other	32	80	**0.048**

HPV: Human papillomavirus; CIN: Cervical intraepithelial neoplasia;
*p value for chi-square test.

Table 2. The positivity rate for HPV 16 was considerably higher in patients diagnosed with CIN 3 compared to those diagnosed with CIN 2 (p=0.003). No statistically significant differences were observed between patients with CIN 2 and CIN 3 for other HPV types. However, while the positivity for HPV 52 in patients with CIN 2 was not statistically significant, it was greater than that in patients with CIN 3 (p=0.051). Additionally, HPV types 54, 56, and 82 were detected exclusively in patients with CIN 2.

Upon examining all patients diagnosed with CIN 2/3, the predominant HPV types identified in our study were HPV 16, 18, 31, 35, 39, and 51, with the latter three types occurring at the same frequency. The dominant types in the CIN 2 cohort were HPV 16, 18, 31, and 35. In contrast, the most common types among patients with CIN 3 were HPV 16, 18, 31, 51 (with types 31 and 51 having equal frequencies), and 68.

During the archival review period, 11 patients were diagnosed with carcinoma in situ, and 1 patient was diagnosed with invasive cervical cancer. The HPV type was undetermined for 3 of the patients with carcinoma in situ, while 5 tested positive for other HPV types. Specifically, one patient had HPV types 16 and 51, another had HPV types 16, 51, 66, 68, and 70, and one patient was positive for HPV 18. The sole

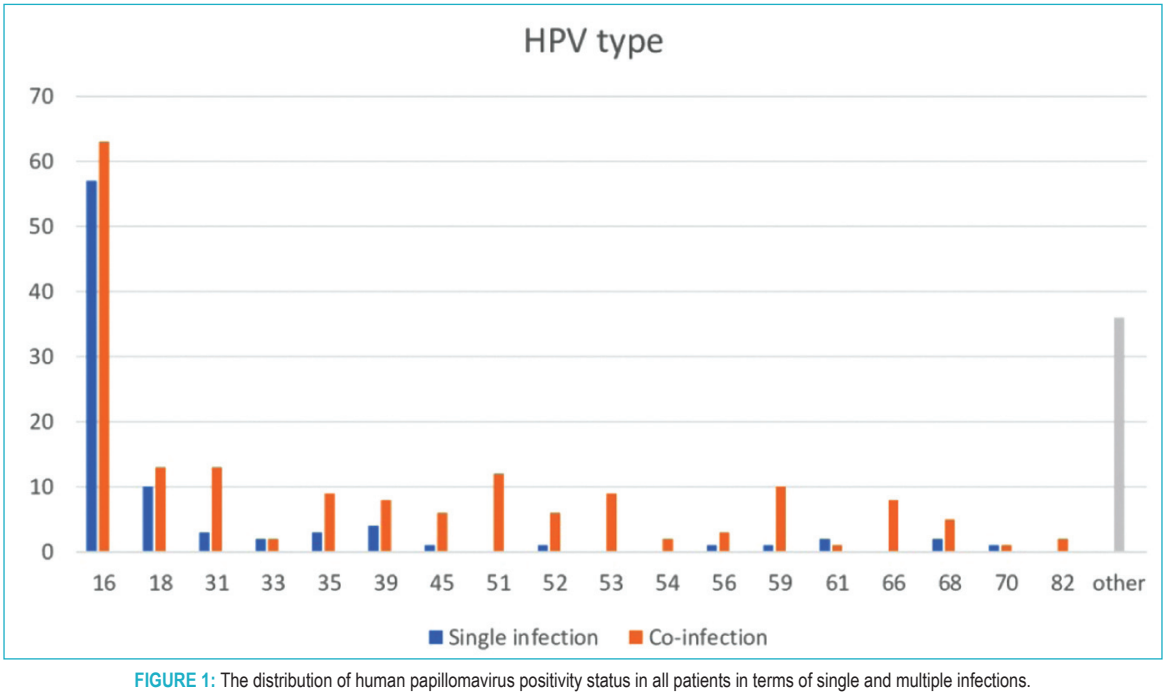

FIGURE 1: The distribution of human papillomavirus positivity status in all patients in terms of single and multiple infections.

TABLE 2: The human papillomavirus type distribution of the patients according to their pathology diagnoses.

HPV type		CIN 2 n=113%		CIN 3 n=116%		Total count (n=229)	p value*
HPV 16	positive	35	30.9%	58	50%	93	**0.003**
	negative	78	69.1%	58	50%	136	
HPV 18	positive	14	12.4%	9	7.8%	23	0.244
	negative	99	87.6%	107	92.2%	206	
HPV 31	positive	10	8.9%	6	5.2%	16	0.275
	negative	103	91.1%	110	94.8%	213	
HPV 33	positive	3	2.7%	1	0.9%	4	0.300
	negative	110	97.3%	115	99.1%	225	
HPV 35	positive	8	7.1%	4	3.5%	12	0.218
	negative	105	92.9%	112	96.5%	217	
HPV 39	positive	9	8%	3	2.6%	12	0.068
	negative	104	92%	113	97.4%	217	
HPV 45	positive	5	4.4%	2	1.7%	7	0.235
	negative	108	95.6%	114	98.3%	222	
HPV 51	positive	6	5.3%	6	5.2%	12	0.963
	negative	107	94.7%	110	94.8%	217	
HPV 52	positive	6	5.3%	1	0.9%	7	0.051
	negative	107	94.7%	115	99.1%	222	
HPV 53	positive	7	6.2%	2	1.7%	9	0.082
	negative	106	93.8%	114	98.3%	220	
HPV 54	positive	2	1.8%	0	0%	2	0.150
	negative	111	98.2%	116	100%	227	
HPV 56	positive	4	3.6%	0	0%	4	0.058
	negative	109	96.4%	116	100%	225	
HPV 59	positive	7	6.2%	4	3.5%	11	0.331
	negative	106	93.8%	112	96.5%	218	
HPV 61	positive	1	0.9%	2	1.7%	3	0.577
	negative	112	99.1%	114	98.3%	226	
HPV 66	positive	6	5.3%	2	1.7%	8	0.140
	negative	107	94.7%	114	98.3%	221	
HPV 68	positive	2	1.8%	5	4.3%	7	0.264
	negative	111	98.2%	111	95.7%	222	
HPV 70	positive	1	0.9%	1	0.9%	2	0.985
	negative	112	99.1%	115	99.1%	227	
HPV 82	positive	2	1.8%	0	0%	2	0.150
	negative	111	98.2%	116	100%	227	

HPV: Human papillomavirus; CIN: Cervical intraepithelial neoplasia; *p value for chi-square test; Percentages given are for each HPV type.

patient with invasive cancer tested positive for HPV 45. The average age of patients diagnosed with cervical carcinoma was 48.75±11.5 years, with 25% being under 40 years of age. The patient with invasive cervical cancer was 45 years old.

DISCUSSION

In this retrospective single-center study, we analyzed colposcopic biopsy results from women with HPV types 16/18 or persistent high-risk HPV positivity, aiming to compare HPV types based on their diagnosis of CIN 2 or CIN 3. HPV 16 was identified in 30.9% of patients with CIN 2 and in 50% of patients with CIN 3, making it the most prevalent type. Following HPV 16, HPV 18 was present in 12.4% of CIN 2 cases and 7.8% of CIN 3 cases. HPV 31 ranked third, found in 8.9% of CIN 2 cases, while both HPV 31 and HPV 51 were observed in 5.2% of CIN 3 cases. The distribution of HPV types shows

geographic variation.[15] According to a European investigation, the predominant HPV strains identified in individuals with CIN 2/3 were HPV16 (48.1%), HPV31 (13.9%), and HPV33 (9.9%), respectively.[16] A meta-analysis conducted in China reported that the most common HPV types in patients diagnosed with CIN 2/3 were HPV 16, 58, and 52, respectively.[11] When all patients diagnosed with CIN 2/3 were examined, the most common types in our study were HPV 16, 18, 31, 35, 39, and 51 (the last three types were equal in frequency). In our study, HPV 16 positivity was significantly higher in patients diagnosed with CIN 3 than CIN 2 (p=0.003). Although HPV 52 positivity was not statistically significant in patients with CIN 2, it was higher than in patients with CIN 3 (p=0.051). This may be because of the small sample size. In the study by Zhang et al. in which 1,916 women were examined at colposcopy, the distribution of HPV types was found to be different in patients diagnosed with CIN 2 and 3. HPV16, HPV18, HPV58, HPV52, and HPV33 were the main types in women with CIN 2; HPV16, HPV18, HPV58, HPV52, and HPV31 were the main types in women with CIN 3. In the same study, HPV 16 and 18 were positive in 82.68% of CIN 2 cases and 92.11% of CIN 3 cases.[17] A study conducted in Thailand found that 50% of women with CIN 2+ lesions were associated with HPV 16 and 18 13.[13] In our study, 46.7% of CIN 2/3 cases were HPV 16 and/or 18 positive.

In a study conducted in Türkiye by Gültekin et al., 3.8 million women were screened and the HPV positivity rate was 4.29%. In the same study, the most common HPV types were HPV 16, HPV 51, and HPV 31 (20.7%, 10.8%, and 8.7%, respectively).[18] In another study conducted in Türkiye, the most common high-risk HPV types besides HPV16/18 were HPV31 (11.9%) and HPV51 (10.5%).[19]

Some CIN 2 lesions may regress spontaneously.[20] If colposcopy is performed without waiting 1 year for high-risk HPV type positivity other than HPV 16/18, more CIN 2 cases will be diagnosed, the risk of missed detection and the development of a higher-grade lesion will be avoided.[21-23]

In our study, high-risk HPV types, grouped as HPV 16, 39 and other, were more frequently positive in those aged 40 years and older than in those under 40 years (p=0.003, p=0.018, and p=0.048, respectively). HPV 59 was statistically significantly more positive in patients under 40 years of age than in those over 40 years of age (p<0.001). Several hypotheses have been proposed to explain the age-related distribution of HPV types in cervical intraepithelial neoplasia.[24] Evidence suggests that HPV infections that persist with age are caused by increased viral reactivation and not because of new sexual partners.[25] Age-related immunosenescence may have an impact on both the development and the reactivation of HPV infection.[26] It is possible that HPV types that are rapidly cleared by the immune system in young adulthood may persist into old age and lead to progression of cervical lesions.[27]

A recent review found that the average age of diagnosis of HPV-related cervical cancer was 51 years, but 30% of cases were diagnosed before the age of 30 years.[28]

This study has several limitations. These include being a retrospective, single-centre study with a limited sample size. The positive predictive value could not be calculated because the data of HPV-positive patients without CIN diagnosis were not accessible. However, as this is a cross-sectional study, we believe it provides information on the frequency of high-risk HPV types in women diagnosed as having CIN 2/3.

CONCLUSION

In conclusion, the most common HPV types in patients with CIN2/3 in this study were 16, 18, 31, 35, 39, and 51 (the last three types were equal in frequency). We found that HPV 16 positivity was higher in patients diagnosed with CIN 3 than CIN 2. Although HPV 52 was not statistically significant, it tended to be more common in patients diagnosed with CIN 2. HPV 16 and 39 are more common over the age of 40; this may indicate that these types are more likely to persist. In addition, it is noteworthy that more than half of the patients diagnosed with CIN 2/3 are positive for high-risk HPV types other than HPV 16-18. However, multicentre studies with larger samples are needed to clarify these issues.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Cemre Alan;* ***Design:*** *Cemre Alan;* ***Control/Supervision:*** *Ali Acar;* ***Data Collection and/or Processing:*** *Beyza Güzelkara Ergene;* ***Analysis and/or Interpretation:*** *Cemre Alan;* ***Literature Review:*** *Cemre Alan;* ***Writing the Article:*** *Cemre Alan;* ***Critical Review:*** *Ali Acar.*

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