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The impact of concurrent HPV infections on the presentation of high grade cervical intraepithelial lesions

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ABSTRACT

Objectives: We investigate how concurrent high-risk (hr) HPV (human papillomavirus) genotypes affect CIN2-3 risk and evaluate the relationship of different genotype combinations with cervical epithelial lesions.

Material and methods: This study included HPV positive patients between the ages of 30 and 60 who underwent liquid-based cervical smears and HPV screening through community-based, cervical cancer screening programs between June 2015 and June 2017. The impact of the increase in hrHPV types was calculated by estimating how it changed the odds ratio of CIN2-3 risk.

Results: The rate of multiple concurrent HPV infections was 48.7% in the CIN2-3 group and 58.4% in the CIN1 group. Among patients in the CIN2-3 and CIN1 groups, the most common HPV coinfection was respectively HPV 16+31 and HPV 16+51. The HPV 51 ratio in CIN1 patients was 28.9% and the HPV 51 ratio in the CIN2-3 patient was 6.6%. With every increase in the number of hrHPV infection types, the frequency of CIN2-3 decreased [OR: 0.72, 95% CI: 0.54-0.95]. For all hrHPV combinations, the addition of HPV 16 was associated with a higher risk of CIN2-3.

Conclusions: An increase in number of hrHPV types is associated with lower CIN2-3 risk. Further cohort studies with larger samples are needed to clarify this relationship. The available evidence suggests that HPV 16 genotype plays an important role in patients with high-grade cervical lesions and has a negative impact on the cervix in concurrent multiple HPV infections.

Key words: Human Papilloma Vırus; coinfection; cervical intraepithelial lesions

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INTRODUCTION

Cervical cancer is the second most common type of cancer among women worldwide and the leading cause of mortality in developing countries. Virtually all cases of cervical cancer are attributable to human papilloma virus (HPV) infection caused by high risk genotypes, with HPV 16 accounting for approximately 50%, HPV 18 for 20%, and HPV 31, 33, 45 and 52 a total of 19% of the cases [1, 2]. In assorted communities, the shares of these different types of HPV vary. As a consequence of the prevalence of HPV, many countries have added HPV genotyping to cervical cytology in the community-based cervical cancer screening programs.

Although screening and treatment management for high-risk HPV (hrHPV) genotypes have well-defined guidelines, the issue of follow-up and treatment strategy in the presence of concurrent multiple HPV genotypes is less established. Co-infections of HPV types are common and have been documented in several epidemiological studies [3–6]. However, the data on the co-infections is limited, and the clinical meaning of the condition and its effect on the risk of cervical cancer and precancerous cervical lesions is not clear.

In this study, patients who were referred to our clinic for colposcopies based on community-based cervical cancer screening program and who were found to have cervical intraepithelial lesion (CIN) 1 and CIN2-3 after cervical biopsy were included. We investigate how an increase in the number of the high-risk HPV genotypes affect CIN2-3 risk and evaluate the relationship of different genotype combinations with cervical epithelial lesions.

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MATERIAL AND METHODS

Within the scope of community-based cervical cancer screening program; we applied colposcopic cervical biopsy (criteria were one of the following *a) HPV 16, 18 positive; b) Cervical cytology normal or abnormal, high-risk HPV positive; c) cervical cytology abnormal*) to 840 patients who underwent fluid-based cervical smear and HPV genotyping between June 2015 and 2017 and referred to our clinic — Bakirkoy Dr. Sadi Konuk Training and Research Hospital, Department of Obstetrics and Gynecology, for colposcopies. Approval was granted for the present study from the Local Ethics Committee.

All cervical cytology samples were obtained through liquid-based Pap tests (Thin Prep Pap Tests). The liquid-based Pap tests were then reported according to the 2001 Bethesda system. In order to identify HPV genotypes, we analyzed cervical specimens using Hybrid Capture 2 for HPV 16, 18 and the other hrHPV (16, 18, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66 and 68) types.

According to the cervical cytology results and HPV genotyping, colposcopies were performed on the patients based on the guidelines of the American Society for Colposcopy and Cervical Pathology (ASCCP). Histological specimens were taken using a colposcopy-guided biopsy. A random biopsy was performed at the squamo-columnar junction of each patient who displayed no lesions caused by the colposcopy. All colposcopic examinations were performed by two gynecological oncology specialist, and the biopsies and final histological excision results were reviewed by one or two experienced gynecological pathologists. For all patients, demographic characteristics and the results of biopsies taken during colposcopies were recorded.

A new classification system, LAST, was used to identify the cervical lesions [7]. In this system, cervical lesions were classified as either high-grade (CIN2 and CIN3) or low-grade (CIN1). Follow-ups and treatments of the patients were managed according to the 2012 ASCCP guidelines.

The present hrHPV genotypes of patients with positive cervical intraepithelial lesions were recorded. All specimens with two or more detected HPV genotypes were considered as concurrent HPV infections.

The primary outcome measure is CIN2-3 risk compared to CIN1 group. The impact of the increase in hrHPV types was calculated by estimating how an increase in the number of concurrent hrHPV types changed the odds ratio of CIN2-3 risk.

Statistical analysis

Statistical Package for the Social Sciences, Version 23.0 (SPSS Inc., Chicago, IL) was used for the statistical analysis. Kolmogorov Smirnov and Shapiro–Wilks tests were conducted to check the distribution of the data. Levene's test was used to assess the homogeneity of variances. For comparison of demographic characteristics, Mann-Whitney U test and Pearson Chi-Square Test were performed as appropriate. Bivariate logistic regressions were conducted for assessing CIN2-3 risk. CIN1 group was accepted as the reference group. Due to the limited number of patients included in the study, the model was adjusted for only demographic characteristics having p-value lower than 10% in the logistic regression model. Parity and the number of hrHPV types were the only variables that satisfied these criteria. Pearson Chi-Square Test or Fisher's Exact Test were used to compare the distribution of hrHPV types among different types of cervical lesions. 2-tailed p-values below 5% were assumed to be statistically significant. Data were presented as Mean ± SD, Median [Minimum-Maximum] or number (percentage).

RESULTS

Colposcopic cervical biopsy revealed no dysplasia in 591 patients. We found cervical intraepithelial lesions in 249 patients. Of these 249 patients, 76 (30.5%) had CIN2-3 and 173 (69.5%) had CIN1. The distribution of single and concurrent hrHPV infections due to various hrHPV genotypes is summarized in Figure 1.

As Table 1 makes clear, there was no significant difference between the CIN groups in terms of demographic characteristics (age, obstetric histories, smoking status, contraception methods and age of marriage).

Table 2 summarizes how carrying HPV16 and HPV18 and increasing the number of hrHPV types affected the CIN2-3 risk compared to CIN1.

The relationships between the number of concurrent hrHPV types and CIN2-3 risk is presented in Table 3. None of the relationships is statistically significant. In particular, having 4 or more concurrent hrHPV infections has very low odds ratio for CIN2-3 risk, but is not significant [OR: 0.13 (0.02–1.07), p-value: 0.058].

Finally, the distribution of hrHPV types among CIN1 and CIN2-3 groups were summarized and compared in Table 4. HPV51 is significantly more common in patients with CIN1 compared to CIN2-3 group.

DISCUSSION

In this cross-sectional study, we evaluate the relationship between multiple concurrent HPV infections and precancerous cervical lesions. The number of hrHPV genotypes is significantly lower in CIN2-3 patients compared to CIN1 patients. Hence, a higher number of hrHPV types is associated with lower CIN2-3 risk. The relationship gets stronger with concurrent phylogenetically independent HPV genotypes and with HPV infection with four or more concurrent hrHPV genotypes, but both of these relationships are statistically insignificant arguably due to the small sample sizes of the

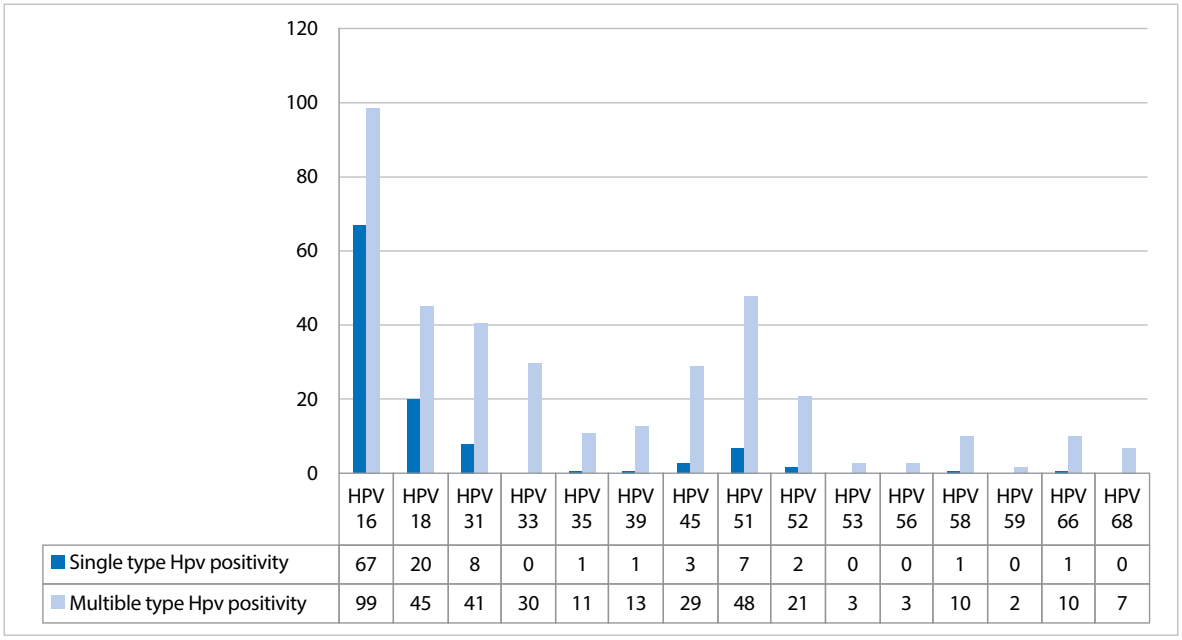

Figure 1. The distribution of single or multiple hrHPV infections related to various hrHPV genotypes

Table 1. Demographic characteristics of cervical intraepithelial lesion groups

	CIN1 (n: 173)	CIN2-3 (n: 76)	p-value
Age (mean ± SD)	39.3 ± 6.6	39.2 ± 6.5	0.850[a]
	39 [34;44]	39 [33; 44]	
Gravidy (mean ± SD)	3.2 ± 1.6	2.9 ± 1.4	0.352[a]
	3 [2; 4]	3 [2; 3.5]	
Parity(mean ± SD)	2.4 ± 1.1	2.2 ± 1.2	0.164[a]
	2 [2; 3]	2 [2; 3]	
Education			0.458[b]
No school	15 (8.7%)	7 (9.2%)	
Elementary school	32 (18.5%)	11 (14.5%)	
Middle school	31 (17.9%)	8 (10.5%)	
High school	71 (41.0%)	39 (51.3%)	
University	24 (13.9%)	11 (14.5%)	
Contraception			0.750[b]
No contraception	93 (53.8%)	36 (47.4%)	
Oral contraceptives	35 (20.2%)	19 (25.0%)	
Preservatives	24 (13.9%)	10 (13.2%)	
Intrauterin devices	21 (12.1%)	11 (14.5%)	
Tubal ligation	0 (0.0%)	0 (0.0%)	
Smoker			0,447[b]
No	124 (71.7%)	58 (76.3%)	
Yes	49 (28.3%)	18 (23.7%)	
Age of marriage (mean ± SD)	22.6 ± 3.9	23.3 ± 4.6	0.401[a]
	22 [20; 25]	22 [20; 26]	
Number of HR-HPV genotypes	2.1 ± 1.2	1.7 ± 0.8	0.047[a,*]
	2 [1; 3]	1 [1; 2]	

CIN — cervical intraepithelial neoplasia; HR — high risk, HPV — Human Papilloma Virus;
Data are presented as mean ± SD; median (interquartile range) or number (percentage)
[a]Mann–Whitney U-Test; [b]Pearson Chi-Square Test; statistically significant comparisons are marked with*

Table 2. The relationship between different concurrent combinations of hrHPV genotypes and CIN2-3 risk in different samples

CIN2-3 risk (reference group: CIN1) (OIITNO: One increase in the number of)	No. of women	OR (% 95 CI)	p-value	Adjusted OR (% 95 CI)[a]	p-value
In the total sample					
OIITNO any HR-HPV type	249	0.72 (0.54–0.95)	0.022*	0.72 (0.54–0.96)[b]	0.025*
adding HPV16	249	1.34 (0.74–2.40)	0.331	1.02 (0.54–1.91)[c]	0.963
adding HPV18	249	0.75 (0.40–1.41)	0.375	0.58 (0.30–1.14)[c]	0.113
adding HPV16 + HPV18	68d	1.09 (0.38–3.14)	0.879	0.42 (0.11–1.64)[c]	0.213
OIITNO α9 species different than HPV16	249	0.95 (0.64–1.43)	0.813	1.02 (0.67–1.57)[c]	0.912
OIITNO α7 species different than HPV18	249	0.78 (0.42–1.43)	0.415	0.79 (0.43–1.45)[c]	0.442
OIITNO HR-HPV types different than HPV16 and 18	249	0.71 (0.54–0.95)	0.018*	0.71 (0.53–0.95)[c]	0.023*
Over the sample with HPV 16;					
OIITNO any HR-HPV type	166	0.75 (0.54–1.03)	0.079	0.76 (0.55–1.05)[c]	0.092
adding HPV18	166	0.97 (0.39–2.42)	0.951	0.90 (0.35–2.28)[c]	0.817
OIITNO α9 species different than HPV16[d]	141[e]	1.15 (0.63–2.10)	0.656	1.78 (0.88–3.60)[c]	0.110
OIITNO α7 species different than HPV18[e]	141[e]	0.69 (0.30–1.62)	0.397	0.68 (0.29–1.59)[c]	0.376
OIITNO HR-HPV types different than HPV16 and 18	141[e]	0.73 (0.50–1.06)	0.096	0.75 (0.51–1.09)[b]	0.126
Over the sample with HPV18					
OIITNO any HR-HPV type	65	0.96 (0.60–1.55)	0.875	0.92 (0.56–1.51)[c]	0.748
adding HPV16	65	1.62 (0.53–4.97)	0.398	1.41 (0.44–4.51)[c]	0.560
OIITNO α9 species different than HPV16	40[f]	1.24 (0.51–3.02)	0.644	1.63 (0.55–4.81)[c]	0.375
OIITNO α7 species different than HPV18	40[f]	0.98 (0.20–4.75)	0.984	1.05 (0.20–5.36)[c]	0.957
OIITNO HR-HPV types different than HPV16 and 18	40[f]	0.95 (0.49–1.87)	0.888	0.94 (0.47–1.88)[b]	0.856
Over the sample with HPV16 and HPV18					
OIITNO α9 species different than HPV16	25	0.78 (0.20–3.09)	0.727	0.81 (0.19–3.56)[c]	0.783
OIITNO α7 species different than HPV18	25	0.67 (0.06–7.64)	0.744	1.99 (0.07–57.19)[c]	0.688
OIITNO HR-HPV types different than HPV16 and 18	25	0.69 (0.26–1.83)	0.453	0.68 (0.25–1.82)[b]	0.444
Over the sample without HPV16 and 18					
OIITNO α9 species different than HPV16	43	0.54 (0.20–1.48)	0.232	0.20 (0.04–1.11)[c]	0.066
OIITNO α7 species different than HPV18	43	0.92 (0.28–3.00)	0.890	0.44 (0.07–2.90)[c]	0.395
Over the sample with only α9 species					
adding HPV 16	102	1.24 (0.40–3.90)	0.713	1.23 (0.39–3.86)[c]	0.728
OIITNO α9 species different than HPV16	102	1.18 (0.61–2.29)	0.629	1.47 (0.67–3.24)[c]	0.342
adding HPV 18	147	0.75 (0.35–1.60)	0.448	0.95 (0.41–2.21)[c]	0.896
OIITNO α7 species different than HPV18	123	0.98 (0.45–2.12)	0.954	0.98 (0.45–2.16)[c]	0.968
Over the sample with only α9 species different than HPV16					
adding HPV18	44	0.60 (0.15–2.41)	0.471	0.54 (0.06–4.86)[c]	0.581
Over the sample with only α7 species					
adding HPV 16	112	1.29 (0.53–3.18)	0.578	1.33 (0.41–4.25)[c]	0.636
OIITNO α9 species different than HPV16	59	0.79 (0.37–1.70)	0.542	0.81 (0.37–1.78)[c]	0.596
adding HPV 18	31	0.13 (0.02–0.89)	0.038*	0.07 (0.002–2.71)[c]	0.156
OIITNO α7 species different than HPV18	31	2.99 (0.70–12.68)	0.139	0.63 (0.04–9.92)[c]	0.743
Over the sample with only α7 species different than HPV18					
adding HPV16	76	0.25 (0.04–1.43)	0.119	0.15 (0.02–1.41)[c]	0.097

CIN – cervical intraepithelial neoplasia; HR – high risk; HPV — Human Papilloma Virus; OR — Odds ratio
[a]Odds ratios were adjusted for all demographic variables having effect on the CIN2-3 risk with p-value lower than 0.100
[b]The logistic regression model was adjusted for only parity according to[a]
[c]The logistic regression model was adjusted for parity and the number of HPV types except the investigated HPV types in each relevant analysis, according to[a]
[d]Women having only one of HPV 16 or HPV 18 excluded from the sample
[e]Patients with HPV 18 were excluded from the sample
[f]Patients with HPV 16 were excluded from the sample
Note: Statistically significant comparisons are marked with*. α9 species include HPV16, 31, 33, 35, 52 and 58. α7 species include HPV18, 39, 45, 59 and 68

Table 3. The relationship between the number of concurrent hrHPV types and CIN2-3 risk

Number of HPV types	CIN1 (n: 173)	CIN2-3 (n: 76)	OR (% 95 CI)	p-value
	n (%)	n (%)		
1	72 (41.6)	39 (51.3)	1.00 (referent)	0.611
2	50 (28.9)	23 (30.3)	0.85 (0.45–1.59)	
2	50 (28.9)	23 (30.3)	1.00 (referent)	0.764
3	32 (18.5)	13 (17.1)	0.88 (0.39–1.99)	
3	32 (18.5)	13 (17.1)	1.00 (referent)	0.058
≥ 4	19 (11.0)	1 (1.3)	0.13 (0.02–1.07)	
Single	72 (41.6)	39 (51.3)	1.00 (referent)	0.157
Multiple	101 (58.4)	37 (48.7)	0.68 (0.39–1.16)	

Data are presented as number (percentage)
*Reference group for calculating odds ratios are women with CIN1

Table 4. Comparison and distribution of hrHPV types for different types of cervical lesions

	CIN1 (n: 173)	CIN2-3 (n: 76)	*p*-value
HPV16	112 (64.7%)	54 (71.1%)	0.331[a]
HPV18	48 (27.7%)	17 (22.4%)	0.374[a]
HPV31	30 (17.3%)	19 (25.0%)	0.162[a]
HPV33	24 (13.9%)	6 (7.9%)	0.182[a]
HPV35	8 (4.6%)	4 (5.3%)	0.760[b]
HPV39	13 (7.5%)	1 (1.3%)	0.070[b]
HPV45	24 (13.9%)	8 (10.5%)	0.467[a]
HPV51	50 (28.9%)	5 (6.6%)	**0,009[a,*]**
HPV52	16 (9.2%)	7 (9.2%)	0.992[a]
HPV53	3 (1.7%)	0 (0.0%)	0.555[b]
HPV56	1 (0.6%)	3 (3.9%)	0.086[b]
HPV58	10 (5.8%)	1 (1.3%)	0.180[b]
HPV59	2 (1.2%)	0 (0.0%)	1.000[b]
HPV66	8 (4.6%)	3 (3.9%)	1.000[b]
HPV68	6 (3.5%)	1 (1.3%)	0.679[b]

Data are presented as number (percentage)
[a]Pearson Chi-Square Test; [b]Fisher's Exact Test; statistically significant comparisons are marked with*
Note: Patients might have more than one HPV genotype

subgroups. The evidence also suggests that the presence of an additional HPV 16 is associated with higher CIN2-3 risk for all different combinations of HPV genotypes.

HPV genotyping is part of the cervical cancer screening programs in many countries [8]. The epidemiological studies show that the prevalence of HPV types in each population is different [9]. Consequently, studies on HPV have limited generalizability except for the pathophysiologic interpretations. However, as most high-grade lesions are associated with HPV 16 and 18 universally, this relationship wastaken into account by diagnostic guidelines.

In this study, HPV 16 was found to be the most frequently genotype in both high-grade and low-grade lesions. In patients with high-grade lesions, HPV 31 and HPV 18 were found to be the second and third most frequent. For low-grade lesions, HPV 51 was the second most common (28.9%) and its frequency was significantly higher compared to patients with high-grade lesions (6.6%). Consistent with our findings, an epidemiologic study of over 1 million women in Turkey found HPV 51 to be the second most common type of HPV in non HPV 16,18 positive women [10]. It can also be conjectured that the HPV 51 genotype might be cleansed by the immune system during the progression of cervical intraepithelial lesion and therefore is not an important threat for precancerous lesions. These patterns should be taken into consideration when developing new and broader spectrum vaccines for immunization in the near future for the Turkish population.

There is a limited number of studies on concurrent HPV infections. A major reason for this was the difficulties associated with detecting other genotypes except HPV 16 and 18. Thanks to the polymerase chain reaction (PCR)-based assays developed especially in the last decade, the rate of detection of multiple HPV infections rose between 24.8% to 52.6% for different kits [11]. The improvements in detection in turn paved the way for investigating the impact of concurrent HPV genotypes on the risk of precancerous lesions and carcinoma of cervix.

Our findings suggest that increases in the number of hrHPV infection types decrease the frequency of CIN2-3. The mean number of hrHPV types are significantly higher in CIN 1 patients. The rate of multiple concurrent HPV infections was 48.7% in the CIN2-3 group and 58.4% in the CIN1 group. The 10% difference between the two groups suggests that some HPV genotypes are cleared by the immune system in the stage of progression of low-grade cervical lesions to high-grade lesion and the women with a lower number of hrHPV types might represent a sample with persistent HPV infection. The frequency of women with short term sexual intercourse is possibly higher in the low-grade lesion group.

The relationships between the number of hrHPV types and precancerous cervical lesions in various subpopulations are presented in Table 2. Arguably due to the small sample sizes, most of the relationships are statistically insignificant. An increase in α7 species of hrHPV types in the sample with α9 species lowers the risk of CIN2-3, probably because they are phylogenetically independent from each other. For all samples and hrHPV combinations, the addition of HPV 16 is associated with a higher risk of CIN2-3.

Because the present study is cross sectional, it does not allow establishing the causation between the number of hrHPV types and CIN2-3 risk. For this purpose, further clinical studies with cohort design are needed. The study, however, provides clues on the interactions between hrHPV types and CIN.

In the literature there are epidemiologic studies investigating multiple HPV infections and cervical carcinogenesis risk based on PAP-smear or colposcopy results. Salazar et al. reports that different combinations of HPV infections are associated with different risk ratios for high grade cervical lesions. The paper conjectures that intergenotypic competition or more effective immune response triggered by multiple infections might be decreasing the precancerous lesions' risk [12]. The limitation of the study was that the risks were not adjusted for demographic characteristics and the PAP-smear test used in study is underpowered to compare cervical lesions with pathological colposcopy evaluations. Dickson et al.'s study which was also based on PAP smear results found that multiple HPV type infections increase abnormal cytology risk relative to single type HPV infections [13]. Morrison et al. [14] and Chaturverdi et al. [3] find that LSIL (low-grade squamous intraepithelial lesion) risk increases substantially when HPV-16 and other HPV types are not present alone. Fife et al. [15] suggests that HPV types 51, 52, 56, and 58 might interact with HPV-16 to cause dysplasia or cancer. Our study also finds that the presence of HPV16 alongside with the other hrHPV types have larger odds ratios than 1 for CIN2-3. However, our other results seem to conflict with them and we can't generalize this situation for other hrHPV infections based on our subgroup analysis (Tab. 2).

Based on colposcopy results, Spinillo et al. in 2014 reports that multiple type HPV infections increases the risk of CIN3+ in both HPV 16 positive and negative women [16]. Recently, Debrot et al. conducted a follow-up study for assessing the CIN2-3 risk, but the study had small sample size and did not adjust for demographic characteristics [17].

The strengths of the present study are that it relies on colposcopy, and assesses the outcome based on the increase in the number of HPV infections while other studies mostly compare cervical lesions based on the presence of single or multiple infections. On the other hand, because the study is cross-sectional and does not track the persistence of HPV infections, it cannot establish causation. As for the sample size, it is large enough to assess the impact of the number of HPV types on CIN2-3 risk, but not large enough to conduct subgroup analysis without type 2 errors.

CONCLUSIONS

All in all, the number of hrHPV types don't have a clear relationship with CIN2-3 risk. Some hrHPVs may increase while others may decrease the risk, and the specific combinations of the types appear to matter.Further cohort studies with larger samples are needed to establish these relationships in a clear way.

IRB status: Bakirkoy Dr. Sadi Konuk Training and Research Hospital, Local Ethics Committee, Project no: 2018/410 Decision no: 2018-19-14

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