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Original Research

The effect of other high-risk HPV types on cervical intraepithelial neoplasia and cancer

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Abstract

Objective: Cervical cancer is an serious healthcare problem with a high mortality rate. High-risk Human papillomavirus (HPV) genotypes, especially HPV 16, 31, 33, and 18, are the leading cause of cervical cancer and cervical intraepithelial neoplasia. Cervical cancer screening programs, especially ones that are HPV-based, have gained prominence in many countries. Herein, we evaluated the effect of other high-risk (hr) HPV types (HPV 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) with normal cytology on cervical intraepithelial neoplasia and cancer. **Methods**: 9015 patients were screened via HPV typing and cytology. 520 patients with high-risk HPV positivity, aged 25–65, and unvaccinated for HPV were included in the study. Patients with high-risk HPV DNA positivity and cytologic abnormality, HPV 16–18 positivity, or with high-risk HPV DNA positivity and normal cytology or with postcoital bleeding and/or suspicious appearance of the cervix underwent colposcopy and colposcopic-directed biopsy. **Results**: Of the 520 women included in the study, the prevalence of the hr-HPV types is as follows: HPV 16 (29%), HPV 18 (13.7%), other high-risk HPV (43.8%), and HPV 16 or 18 plus other hr-HPV (13.5%). Among patients diagnosed with $\geq$ CIN2, 36.3% had HPV 16 positivity, 21.8% had HPV 18, 24.2% had other hr-HPV and 17.7% had co-infection with HPV type 16 and 18 and other hr-HPV types. HPV 16 (Odds Ratio (OR) = 3.099, 95% Confidence Interval (CI) = 1.933–4.968), HPV 18 (OR = 4.834, 95% CI = 2.715–8.608), and co-infection with HPV 16 or 18 with other hr-HPV types (OR = 3.324, 95% CI = 1.851–5.969) were statistically significantly associated $\geq$ CIN2 on biopsy. Among patietns with normal cytology and positive for other hr-HPV types CIN2+ was detected in 10.3% of patients who underwent biopsy, but only 1.5% had CIN3 and no cancers were detected. **Conclusion**: Consistent with our national screening guidelines, the risk for CIN3+ for women with normal cytology but positive for hr-HPV types other than 16 and 18 is low. Re-testing these patients in one year appears acceptable.

Keywords: Cervical intraepithelial neoplasia; Cervical cancer; High-risk HPV; Cytological abnormalities; Colposcopy

1. Introduction

Cervical carcinoma is a common gynecological cancer worldwide, with 604,127 new cases per year and a 50% mortality rate [1]. The main cause of cervical cancer is Human Papilloma Virus (HPV); HPV infection is the most common sexually transmitted disease. Over 40 anogenital HPV types have been isolated, 12 of which are associated with human carcinogenesis [2]. Cervical cancer and cervical intraepithelial lesions are the most frequent diseases caused by HPV 16, HPV 31, HPV 33 and HPV 18. While HPV vaccines and HPV-based screening have gained prominence in the detection and elimination of cervical cancer, cervical cancer screening remains the cornerstone of cervical cancer prevention.

The most effective prevention of cervical cancer is achieved via a proper national screening and vaccination program. In Turkey, a national screening program with HPV genotyping and cervical cytology has been active since 2014 [3]. According to the screening program, women with high-risk HPV positivity and abnormal cytology or only HPV 16 or 18 positivity are referred for colposcopy.

The effect of other high risk (hr) HPV types (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68) and co-infections on cervical dysplasia and carcinogenesis is in some debate. Certain studies have shown that these other high-risk HPV types have a significant effect on cervical carcinogenesis, while others detect no significant effects [4–8].

This study aims to examine the effects of non-16/18 hr-HPVs with normal cytology on the development of cervical cancer; according to the national Turkish screening program, such cases are not generally referred for colposcopy.

2. Materials and methods

2.1 Study design and enrollment procedure

A total of 9015 patients who were referred to Ankara University Faculty of Medicine and submitted to Pap smear and HPV DNA tests between January 2016 and May 2020 were retrospectively analyzed via the hospital's records.

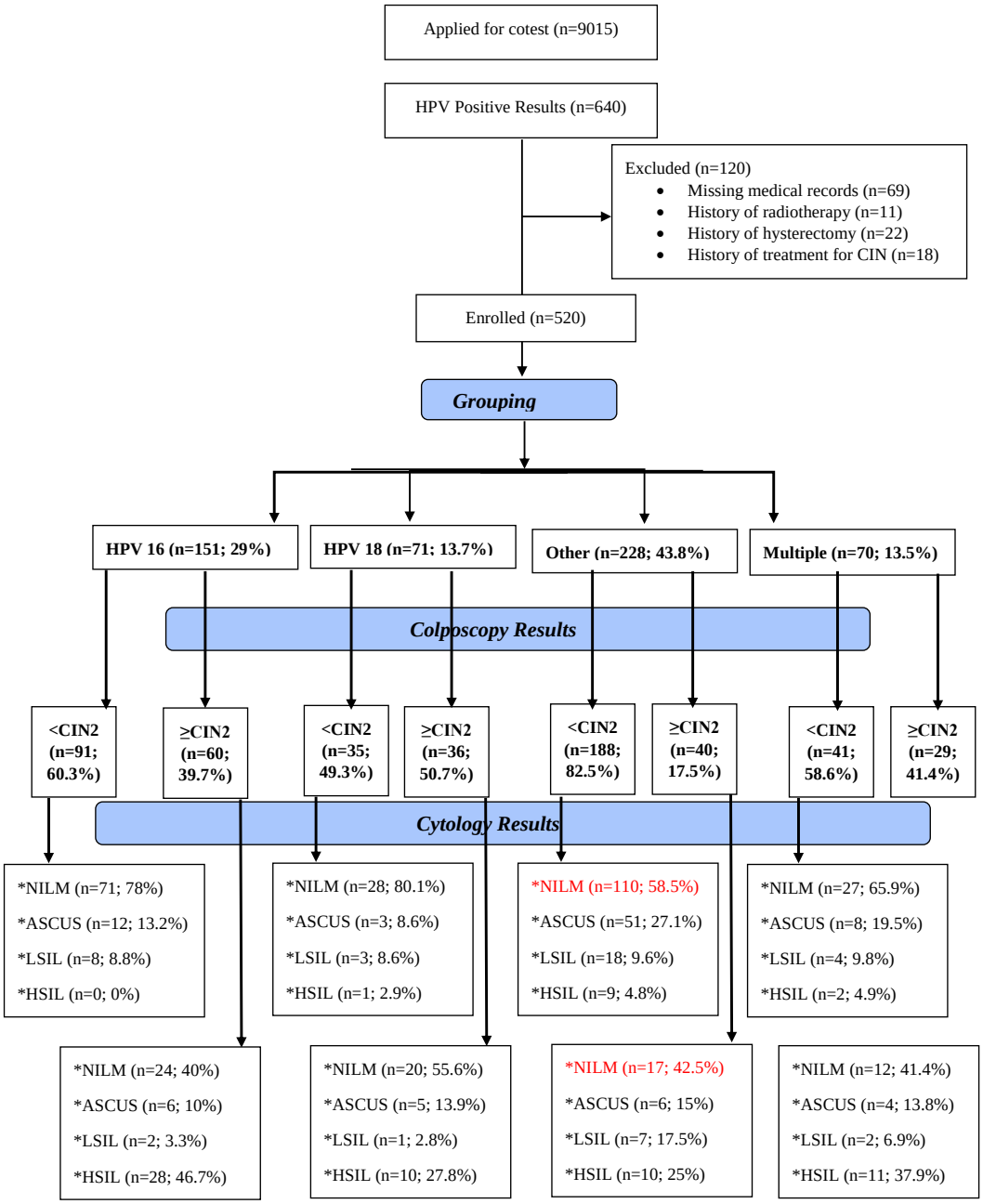

Fig. 1. Diagram showing data on colposcopic biopsy and cytology results according to the groups.

Age, menopausal status, gravidity, smoking status, contraception usage, presence of genital condyloma, cervical cytology results, HPV types, and histopathology results of the colposcopic biopsy were evaluated by patients' medical records.

Inclusion criteria were the following: patients with high-risk HPV positivity, aged 25–65 and unvaccinated for HPV were included in the study. Patients were excluded according to the following criteria: younger than 25 years old, older than 65 years, previously treated for cervical intraepithelial neoplasia (CIN), incomplete medical records, history of radiation therapy and/or total hysterectomy, and pregnancy.

For high-risk HPV genotyping, the Cobas 4800 system was used according to the manufacturer's instructions (Roche Molecular Systems, Alameda, CA). Positive test results were classified as HPV 16, HPV 18 and "other hr-HPVs", namely, HPV 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68.

Liquid-based cytology was used. The Bethesda system was used for cytology evaluations and the results reported as negative for intraepithelial lesions or malignancy (NILM), atypical squamous cells of undetermined significance (ASC-US), low grade squamous intraepithelial lesion (LSIL), high grade squamous intraepithelial lesion (HSIL).

Table 1. Demographic data of the patients.

Variables		Mean ± SD	
Age		41.93 ± 9.63	
Gravidity		1.93 ± 1.33	
		n	%
Menopausal Status	Reproductive age	388	74.6
	Postmenopausal	132	25.4
Smoking	No	349	67.1
	Yes	171	32.9
Contraception Method	No method usage	334	64.2
	Condom	73	14.0
	Oral contraceptives	29	5.6
	Tubal ligation	19	3.7
	Other	11	2.1
Condyloma	Negative	459	88.3
	Positive	61	11.7
HPV Genotype	Other hr-HPV	228	43.8
	16	151	29.0
	18	71	13.7
	16 or 18 and other hr-HPV	70	13.5
Cytology results	NILM	309	59.4
	ASCUS	95	18.3
	HSIL	71	13.7
	LSIL	45	8.6
Endocervical Curettage	No	360	69.2
	Yes	160	30.8
ECC results	Normal	123	76.9
	Carcinoma	14	8.8
	CIN3	11	6.9
	CIN2	9	5.6
	CIN1	3	1.8
Colposcopic Biopsy Results	Normal	196	37.8
	CIN1	159	30.6
	CIN2	93	17.7
	CIN3	58	11.2
	Carcinoma	14	2.7

Patients with high-risk HPV DNA positivity and cytologic abnormality, HPV 16–18 positivity regardless of cytologic diagnosis, and those with high-risk HPV DNA positivity and normal cytology but with postcoital bleeding or suspicious appearance of the cervix underwent colposcopy and colposcopic-directed biopsies. Patients were evaluated by a gynecologic oncologist or a trained fellow of gynecologic oncology at the Department of Gynecologic Oncology of Ankara University Faculty of Medicine.

Colposcopic biopsy results were classified as normal, CIN1, CIN2, CIN3 and cervical carcinoma. Biopsies were taken from all suspicious areas at colposcopy. Endocervical curettage (ECC) was performed when cervical squamocolumnar junction was unable to be visualized. Biopsies were evaluated by a single, experienced gynecopathologist. The study was conducted in accordance with the Declaration of Helsinki, the protocol was approved by the ethics committee of Ankara University, and all procedures were performed as per the ethical standards specified by the institution.

2.2 Statistical analysis

Statistical analyses were performed using WEKA 3.7 and Statistical Package for the Social Sciences (SPSS) 11.5 programs (IBM Corp, Armonk, NY, USA). Descriptive data were presented as mean ± standard deviation (SD) and median (min–max) for quantitative variables and as frequency (percentage) for categorical variables. A statistically significant difference between the categories of the qualitative variable that has two categories in terms

of quantitative variable, Mann-Whitney U test was used, since normal distribution assumptions were not provided. The relationship between the two qualitative variables, the Chi-square test, was used. The statistical significance level was taken as 0.05. In the WEKA program, Naive Bayes, Logistic Regression, Support Vector Machine and J48 were used in Classification methods. The data set was evaluated using the 10-fold Cross-Validation test option. Accuracy, F-Measure, Matthews Correlation Coefficient (MCC), Precision-Recall Curve (PRC Area) and ROC Area were used as data mining performance criteria.

2.2 Study groups

In our study, we divided the patients into four groups according to the HPV DNA results: (1) HPV 16 group, (2) HPV 18 group, (3) other hr-HPV group (HPV 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68), and (4) multiple hr-HPV group (the combination of other hr-HPV plus HPV 16 and/or HPV 18).

3. Results

In the 9015 screened patients by co-tests, the HPV positivity rate was 7.1%. A colposcopic biopsy was performed on 640 patients with high-risk HPV positivity. 120 patients were excluded from the study because of missing medical records (n = 69), history of radiotherapy (n = 11), history of total hysterectomy (n = 22), and history of treatment for CIN (n = 18). The remaining 520 patients who were evaluated in the study (Fig. 1) had a mean age of 41.93 $\pm$ 9.63 and a median gravidity value of 2. The majority of the patients were of reproductive age (74.6%, n = 388) and were non-smokers (n = 349, 67.1%). Condyloma was present in 11.7% of patients (n = 61) and contraception method usage was present in 34.8% (n = 186). Demographic data of the patients are shown in Table 1.

Pap smear results of all patients in the sample were examined; the majority of the patients (59.4%) fell into the NILM group (n = 309), 95 in the ASCUS group (18.3%), 71 in the HSIL group (13.7%) and 45 in the LSIL group (8.6%). Likewise, when colposcopic biopsy results were evaluated, 355 patients had a diagnosis $<$ CIN2 (68.3%) and 165 of the patients had a diagnosis $\geq$ CIN2 after colposcopic biopsy results (31.7%). When we examined patients with $<$ CIN 2, 25.63% had HPV 16, 9.85% HPV 18, 52.95% other hr-HPV types, and 11.54% co-infection with HPV 16 or 18 and other hr-HPV types. When we examined $\geq$ CIN2 patients, 36.36% had HPV 16, 21.81% HPV 18, 24.24% other hr-HPV types, and 17.57% co-infection with HPV 16 or 18 and other hr-HPV types. Only 160 patients had an endocervical curettage (30.8%), of whom 123 had a normal result (76.9%), 3 had CIN1 (1.8%), 9 had CIN2 (5.6%), 11 had CIN3 (6.9%), and 14 patients had carcinoma (8.8%). Statistical results of the whole sample without grouping are shown in Table 1. The rate of carcinoma in the entire study group was 2.7% (n = 14) while the CIN3 rate was 11.2% (n = 58). In the carcinoma group, 35.7% of the patients had HPV 16, 35.7% had HPV 18, 21.4% had other hr-HPV, and 7.2 had co-infection with HPV 16 or 18 and other hr-HPV. In the CIN3 group, the HPV 16 rate was 44.8%, HPV 18 rate was 20.6%, other hr-HPV was 15.5%, and co-infection with HPV 16 and 18 and other hr-HPV was 19.1%. Table 2 shows univariate logistic regression results for colposcopic biopsy results.

Smoking and contraceptive system use showed no relevant statistical impact on $\geq$ CIN2 pathology findings (p = 0.25 and p = 0.79), according to univariate analyses. Patients of reproductive age showed a substantial difference (OR = 2.688, 95% CI = 1.494–4.836) as compared to postmenopausal patients. Gravidity had a statistically important association on patients affected by $\geq$ CIN2 (OR = 1.155, 95% CI = 1.006–1.326). HPV 16 (OR = 3.099, 95% CI = 1.933–4.968), HPV 18 (OR = 4.834, 95% CI = 2.715–8.608), and multiple hr-HPV (OR = 3.324, 95% CI = 1.851–5.969) had a statistically significant impact on $\geq$ CIN2 results, respectively. NILM and LSIL results had no important association (p = 0.759 and p = 0.553, respectively) on the effect of cytology findings, with ASCUS used as a reference value. The effects of HSIL were statistically significant (OR = 17.325, 95% CI = 7.883–38.077).

Finally, 520 patients were divided into four groups, mainly based on the presence of HPV 16, HPV 18 and other hr-HPV. According to this subdivision, 228 patients were in the other hr-HPV group (43.8%), 151 patients were in HPV 16 group (29%), 71 patients were in HPV 18 group (13.7%) and 70 patients in HPV 16 and/or 18 plus other hr-HPV group (13.5%). Fig. 1 (Diagram) shows data on colposcopic biopsy and cytology results according to the groups.

There were 228 patients in the other hr-HPV group. When Pap smear results were analyzed in these patients, 127 resulted in normal cytology. As a result of colposcopic biopsy performed on these 127 patients, 67 (52.7%) were reported as normal, 43 had CIN1 (33.8%), 15 had CIN2 (11.8%), and 2 had CIN3 (1.5%). 101 patients fell into the other hr-HPV with abnormal cytology group. As for colposcopic biopsy results, 45 were normal (44.5%), 33 had CIN1 (32.6%), 13 had CIN2 (12.8%), 7 had CIN3 (6.9%), and 3 showed a diagnosis of carcinoma (2.9%).

4. Discussion

In Turkey, the HPV-based national screening system has been in use since 2014 for cervical cancer screening [4]. The incidence of hr-HPV for four million screened women is 4.39% [5], whereas it was 7.2% in our study. Our center is a tertiary health center located in a low-income region, which may explain the higher rate.

Table 2. Univariate logistic regression results for colposcopic biopsy results.

Variables (Reference)		*p*-value	OR	95% CI	
				Lower limit	Upper limit
Gravidity		**0.041***	1.155	1.006	1.326
Menopausal Status (Postmenopause)	Reproductive Age	**0.001***	2.688	1.494	4.836
Smoking (No)	Yes	0.250	1.256	0.852	1.853
Contraception Method (No)	Yes	0.798	1.051	0.716	1.545
HPV Genotype (Non16-18 hr-HPV)	16	<**0.001***	3.099	1.933	4.968
	18	<**0.001***	4.834	2.715	8.608
	Multiple hr-HPV	<**0.001***	3.324	1.851	5.969
Cytology results (ASC-US)	HSIL	<**0.001***	17.325	7.883	38.077
	LSIL	0.553	1.281	0.565	2.908
	NILM	0.759	1.090	0.628	1.891

β, Beta coefficient; S.E., Standard error of mean; OR, Odds Ratio; CI, Confidence interval.

*Statistically significant values are marked in bold.

In the ATHENA study, the overall prevalence of high-risk HPV, HPV 16 and HPV 18 was 12.6%, 2.8%, and 1.0%, respectively [6]. In the NHANES survey, the overall prevalence of high-risk HPV, HPV 16 and HPV 18 was 15.2%, 1.5% and 0.8% [9]. In our study, the prevalence of high-risk HPV, HPV 16, and HPV 18 was 7.2%, 2.1% and 1%.

In this study, there was no significance between the $<$ CIN2 and $\geq$ CIN2 groups on demographic characteristics, menopausal and smoking status, or contraception methods. For high-grade lesions, we detected a statistically significant difference in premenopausal patients compared to postmenopausal patients (OR = 2.688, 95% CI = 1.494–4.836).

Adela et al found multiple types of HPV: 47.12% for high-grade lesions and 40.17% for low-grade lesions [10]. We found that co-infection with HPV 16 or 18 and other hr-HPV types hr-HPV types rate was 11.54% for the $<$ CIN2 group and 17.57% for the $\geq$ CIN2 group.

The effect of smoking on HPV infections and cervical dysplasia is still controversial. Some studies found that smoking is associated with HPV positivity and cervical dysplasia [11–13], while others found no correlation between smoking, HPV positivity and cervical dysplasia [14]. We did not find association of smoking with cervical high-grade/low-grade intraepithelial lesions.

Castle *et al*. [15] found that 40% of cervical cancer patients have HPV18. In our study, the cervical cancer rate was 2.7% (n = 14) of the colposcopic biopsy results, wherein 35.7% of patients had HPV 18 genotype. Of the 9015 patients we screened, 14 (0.15%) had cervical cancer diagnoses. This can be attributed to the fact that 66% of the patients (n = 5950) had not been screened before, as well as our hospital location and the low-income population. The prevalence of HPV 16 increases with high-grade lesions [15,16]. Castle *et al*. [15] found the rate of HPV 16 was 57.28%, and that the prevalence of other hr-HPV types was 30.09% in patients with $\geq$ CIN2. In our study, HPV 16 was found in 36.36% of patients with $\geq$ CIN2 while hr-HPV types other than HPV 16 or 18 was detected in 24.24%.

The effect of multiple hr-HPV types on cervical neoplasia and cancer is controversial. Several studies found that multiple hr-HPV types have an effect on cervical carcinogenesis and high-grade cervical lesions [4,5]. Other studies, conversely, found no effect on cervical carcinogenesis or high-grade lesions [6]. By molecular effects, HPV types can synergistically induce lesion progression [17]. According to our findings, co-infection with HPV 16 or 18 and other hr-HPV had a statistically important impact on $\geq$ CIN2 lesions (OR = 3.324, 95% CI = 1.851–5.969). HPV genotyping with the Cobas 4800 system classifies high-risk HPV groups as HPV 16, HPV 18 and "other hr-HPVs". In addition, long-term follow-up results demonstrate the importance of identifying other hr-HPV types, especially types 31, 33, 45, 52 and 58. Poveda *et al*. and Gilham *et al*. [13,18] showed that these genotypes can be useful for triage.

According to Clifford *et al*. [19], HPV 16 is the most common genotype observed worldwide. This is followed by HPV 42, 58, 31, 18 and 56. In the study of prevalence in Turkey conducted by Gultekin *et al*. [20], only high-risk HPV types were investigated; HPV 16 was found to be the most common type, followed by 51, 31, 52, 56 and 18.

In our study, we found that the most common types were other hr-HPV types, followed by HPV 16, HPV 18 and co-infection with HPV 16 or 18 and other hr-HPV types. This is because the HPV genotyping test we performed detects HPV 16 and HPV 18 and classifies the remaining high-risk types as other hr-HPV types. If we had used a test that identifies the types classified as "other hr-HPV types" separately, HPV 16 would most likel had been the most frequent type observed.

Turkey's national cervical screening program is based on HPV genotyping and liquid-based cytology. The screening profile includes women aged 30–65 and recommends screening every five years. Colposcopy referral indications are HPV 16 positivity, HPV 18 positivity and other hr-HPV with cytological abnormalities. In the national program, other hr-HPV with normal cytology re-screens after one year [4].

We focused on the association of other hr-HPV with cervical lesions. Among patients with biopsy-proven $\geq$ CIN2 10.3% had other hr-HPV and normal cytology and and 7.27% co-infection with HPV 16 or 18 and other hr-HPV. One hundred and twenty seven patients with hr-HPV other than type 16 or 18 and normal cytology underwent colposcopic procedures to diagnose 17 (13.3%) CIN2+ and 2 (1.5%) CIN3. The guidelines put forth by the American Society of Colposocpy and Crevical Pathology (ASCCP) for the management of abnormal cervical screening tests proposes surveillance rather than colposcopy if the calculated immediate risk of the patient harboring CIN3+ is $<$4%. In our study only 1.5% of patietns with normal cytology and positive HPV other than 16 and 18 were found to have CIN3 on biopsy. However, these patients underwent colpsocopic evaluation because of postcoital bleeding or abnormal appearance of the cervix.

One limitation of our study is that it does not address cost-effectiveness. While our findings do not challenge the national screening program, further studies are needed to analyze the cost-effectiveness. Other limitations concerned the small sample size; the number of "other hr-HPV with normal cytology" was not representative of the entire population; and the kits used for HPV genotype analyses do not give the results of other hr-HPV types, meaning we could not evaluate the effect of other hr-HPV types with their genotype. Moreover, most of the patients did not answer either on the sexual partner numbers or on first intercourse age because of religious beliefs, thus we could not evaluate the impact of these parameters.

Among strengths of the study, all patients were evaluated by a gynecologic oncologist and the study group was on unvaccinated women. The study group included a large distribution of socioeconomically different classes of our country.

5. Conclusions

HPV screening programs remain a vital resource in the monitoring and prevention of cervical cancer; each country should manage screening programs according to the results of community HPV genotypes distribution. The present study provides information about the effect of non-16/18 hr-HPV genotypes and co-infection with type 16 or 18 and other hr-HPV types on cervical carcinogenesis. Other hr-HPV types with normal cytology were present in almost half of recorded cases, and 14.8% were found to harbor CIN2+, but only 1.5% had CIN3. In line with the recommendations of our national screening program, re-testing in one year when "other hr-HPV types with normal cytology" is reported is consistent with ASCCP risk-based scoring system. In the future, data derived from large studies that identify other hr-HPV types individually may be incorporated into national screening programs to improve risk stratification. However, the cost-effectiveness of this approach also needs to be analyzed.

Abbreviations

HPV, Human papillomavirus; CIN, Cervical intraepithelial neoplasia; NILM, Negative for intraepithelial lesions or malignancy; ASC-US, Atypical squamous cells of undetermined significance; LSIL, low grade squamous intraepithelial lesion; HSIL, high grade squamous intraepithelial lesion; SD, Standard deviation; MCC, Matthews Correlation Coefficient; PRC, Precision-Recall Curve; hr-HPV, high risk HPV; ECC, endocervical curettage.

Author contributions

SSA conceived, designed, performed the research and wrote the paper; BB analyzed the data and made statistics; FO designed the research and edited the manuscript; AT edited and revised the manuscript.

Ethics approval and consent to participate

The Ethics Committee Board of Ankara Faculty of Medicine, Ankara University approved this retrospective study (Approbation number: İ5-298-20, Approbation date: 01.06.2020).

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Conflict of interest

The authors declare no conflict of interest. AT is serving as one of the Editorial Board members of this journal. We declare that AT had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Prof. Enrique Hernandez.

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