TÜRK JİNEKOLOJİK ONKOLOJİ DERGİSİ
2021-1, Sayfa 19-26
Araştırma

Comparison of Cervical Pathologies in Presence of High-Risk HPV Positivity in Women with Normal Cytology

Sitolojileri Normal Kadınlarda Yüksek Riskli Hpv Pozitifliği Varlığında Servikal Patolojilerin Karşılaştırılması

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ÖZET

Amaç: Servıks kanseri tarama programında Hpv 16-18 tipi pozitif hastalara kolposkopi yapılmaktadır. Smear negatif olan, Tip 16-18 dışı yüksek riskli Hpv pozitifliği olan hastalar 1 yıl sonra kotest ile değerlendirilmektedir. Biz çalışmamız ile kolposkopi yapılan; tip 16-18 Hpv pozitifliği ve tip 16-18 dışı yüksek riskli Hpv pozitifliği olan hastaların sonuçlarını karşılaştırmayı hedefledik.

Gereç ve Yöntemler: Sitolojileri normal olan; tip 16-18 dışı HR-HPV tip pozitifliği olan 192 hastanın, kolposkopiye bağlı çıkan histopatolojik bulguları, tip 16-18 HR-HPV pozitifliği olan 217 hastanın kolposkopiye bağlı çıkan histopatolojik bulguları ile karşılaştırdı. Demografik veriler, body mass indeksi (BMI) ve histolojik sınıflandırma ile ilgili veriler kaydedildi.

Bulgular: Yaş ortalaması 41.6± 8.5, BMI ları 29.2±4.4 idi. Değerlendirilen 409 kadından 217'si HPV tip 16/18 (% 53), 192'si non-16/18 tip (%47) için pozitifti. Tip 16-18 HR-HPV pozitifliği olan kadınlarda yapılan kolposkopik biyopsi sonuçları; normal biyopsi sonucu 147(%67.7), invaziv serviks karsinomu 2(%0.9) olarak saptandı. Tip non-16-18 HR-HPV pozitifliği olan kadınlarda ise normal biyopsi sonucu 159(%83), invaziv serviks karsinomu 1(%0.5) olarak saptandı. Grup 1'de anormal biyopsi sonuçları anlamlı olarak daha fazla idi (p=0.003).

Sonuç: HPV 16 ve 18 ile oluşan enfeksiyonlar, CIN 2 veya daha ileri (≥CIN 2) lezyonlar için en yüksek risk ile ilişkilidir. Kolposkopik muayene yaptığımız tip 16/18 HR-HPV hastalarından 2 tanesinde ve non-tip 16/18 HR-HPV hastalarının 1 tanesinde invaziv serviks kanseri saptadık. Bu durum invazive servikal kanseri saptamada kolposkopik yönetim sonuçlarının her iki grupta da farklı olmadığını ve bu şekilde invaziv serviks kanserini erken yakalayabileceğimizi düşündürüyor. Çalışmamızda hasta sayısının az olması nedeniyle bu konuda gelecekte daha kapsamlı çalışmaların yapılması ve kolposkopinin yüksek riskli HPV'nin tüm tiplerinde uygulanabilirliğinin araştırılması gerektiğini düşünmekteyiz.

Anahtar sözcükler: Human Papillomavirus, Yüksek Riskli HPV, Servical İntraepitelyal Neoplazi, Servical Neoplasm, Kolposkopi.

ABSTRACT

Aim: The primary objective was to determine cases of premalignant cervical lesions and possible cervical carcinomas at an early stage with colposcopy in women with non-16/18 high-risk human papilloma virus (HR-HPV) positivity (31, 33, 35, 45, 5 etc.), instead of waiting 12 months for the follow-up cotest. Our secondary objective was to compare the results of women with type 16-18 HR-HPV and non-16/18 HR-HPV positivity, who underwent colposcopy, to find out whether there were any differences between these two groups.

Material and Methods: In this retrospective study, 409 patients who visited the outpatient gynecological oncology clinic of our tertiary center between December 2016 and December 2018 were included. Patients were divided into two groups. Groups 1 (n=217) consisted of patients with high-risk HPV (HR-HPV) positivity for 16 and 18 and in group 2 (n=192) patients with HR-HPV positive results for other HPV strains were included. Each patient's demographic data, body mass index (BMI) and histology result obtained from cervical biopsy were recorded from the patient files and the hospital's database. Histopathological findings were compared between the two groups.

Results: 217 (53%) patients were evaluated in group 1 and 192 (47%) were in group 2. The mean age and BMI were calculated to be 41.6±8.5 years and 29.2±4.4, respectively. The following cervical biopsy results were reported for patients in group 1: 147 (67.7%) patients had normal biopsy results; 68(31.4%) patients had premalignant cervical lesions and 2 (0.9%) patients had invasive cervix carcinoma. In group 2, 159 (83%) patients had normal biopsy results, 32(16.6%) patients had premalignant cervical lesions and 1 (0.5%) patient had invasive cervix carcinoma. The rate of abnormal biopsy results was significantly higher in group 1 (p=0.003).

Conclusions: Infections caused by HPV16/18 are considered high risk for ≥CIN2 lesions. We determined invasive cervix carcinoma in 2 patients with type 16-18 HR-HPV positivity and in 1 patient with non-16/18 HR-HPV positivity. Due to the small number of patients in our study, we believe that there is a need for more comprehensive studies and for the investigation of the benefits of the colposcopy in all types of HR-HPV infections.

Keywords: Human Papillomavirus, High-Risk HPV, Cervical Intraepithelial Neoplasia, Cervical Neoplasm, Colposcopy

Geliş Tarihi: 13/10/2020 Kabul Tarihi: 13/02/2021

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Introduction

Cervical cancer is the third most common malignant gynecological cancer worldwide. It is well known that the persistent infection with high-risk human papillomavirus (HR-HPV) is a required etiological factor for the premalignant cervical lesions and cervical cancer (1). Infections caused by HPV-16 and HPV-18 are considered high risk for the development of cervical intraepithelial neoplasia (CIN2) and more progressed lesions (≥CIN2) [2]. HPV-16 and HPV-18 are responsible for 70% of all invasive cervical carcinomas, which is followed by HPV-45/31/33 (2,3,4). Following the implementation of a screening test using cytology incidence and mortality rate of cervical cancer has declined. On the other hand, new guidelines have included HPV-DNA test in addition to the cytology test, which are together referred to as cotesting (4). HPV-DNA is included in the cervical cancer screening programs in many countries and thus significant improvements in screening results are achieved (1,5,6). Moreover, the addition of HPV-DNA to the screening has enabled a prolonged screening interval of 5 years, which was previously 3 years with the availability of the cytology test only. On the other hand, this practice may lead to the excessive perfomance of colposcopy and the risk of overtreatment in women, who have transient HPV infection, which may regress spontaneously in 1-2 years (7,8). Therefore, the best method of triage with the secondary screening in order to determine the actual precancerous lesions in women with HPV positivity is still unclear (9).

The updated guidelines published by the American Society for Colposcopy and Cervical Pathology (ASCCP) recommend the cytological examination for the follow-up of women with non-16/18 HR-HPV positivity (4). There is no dispute over the specificity of the cytology screening (10), but its application in the low-income countries can be difficult, because of the limited availability of high-quality cytology screening programs and experienced cytopathologists, limited health sources and poor infrastructure.

The accumulated evidence shows that HPV-DNA test, which is used for screening, has high sensitivity, reproducibility, and reliability in determination of the high-grade CIN, but has a lower specificity compared to the cytology test (11). Following a series of clinical trials, the HPV-DNA test has been introduced as the primary screening method for cervical cancer in Europe (11,12,13). In 2015, HR-HPV testing was recommended as a test for detection of cervical cancer by Society of Gynecologic Oncology (SGO) / (ASCCP) interim clinical guideline (4). According to this guideline, HPV test is recommended to women older than 25 years as the primary screening method. A follow-up test is recommended for HR-HPV negative women 3 years after the initial test. A direct colposcopy examination is recommended to HPV 16/18 positive women and cytological examination is recommended to non-16/18 HR-HPV positive women. If the cytology test is negative, a follow-up with both cytology and HR-HPV tests is recommended in 12 months. If the cytology result has an undetermined significance (ASCUS) or shows atypical squamous cells, colposcopy examination is recommended (4).

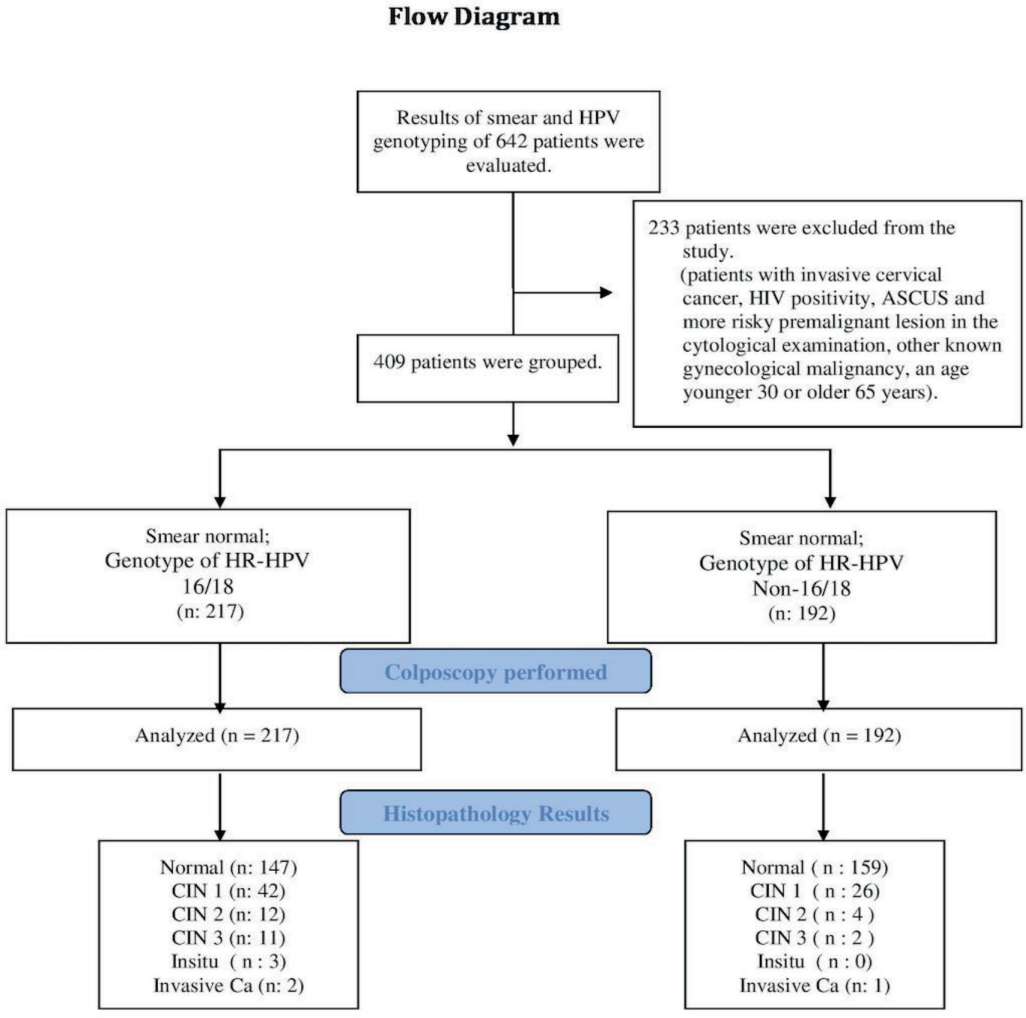
Nationwide data on to the prevalence of the cervical pathology among non-16/18 HR-HPV positive Turkish women is limited. In our study, the primary objective was to determine cases of premalignant cervical lesions and possible cervical carcinomas at an early stage with the colposcopy in women with non-16/18 HR-HPV positivity (31, 33, 35, 45, 5 etc.), instead of waiting 12 months for the follow-up cotest. In addition, our secondary objective was to compare the results of women with type 16-18 HR-HPV and non-16/18 HR-HPV positivity, who underwent colposcopy, to find out whether there were any differences between these two groups.

Material and Methods

This retrospective sectional study was planned in the Istanbul Kanuni Sultan Suleyman Health Practices and Research Central Clinic of gynecology and obstetrics at Health Sciences University. The study was initiated following the approval of the Istanbul Kanuni Sultan Suleyman Health Practices and Research Central Ethics Committee of Health Sciences University in 2018 (approval no: KAEK/2018.7.03) and registered to ClinicalTrials.gov (NCT03895905). Our study was carried out according to the principles of the Helsinki Declaration.

A total of 642 patients, who applied to the outpatient gynaecologic oncology clinic between December 2016 and December 2018, were evaluated. Patients, who had invasive cervical carcinoma, HIV positivity, ASCUS and/or riskier premalignant lesions according to the cytological examination, patients who were older than 65 years and younger than 30 years, had been diagnosed with another malignancy, were excluded from the study. A total of 409 patients were included in the study. All patients underwent colposcopy examination by the experienced gynaecologic oncologist team of our clinic. For colposcopy examination, the patient was placed in a relaxed modified lithotomy position and the external genitalia was examined. Then the speculum was inserted into the vagina for a complete visualization of the cervix. After the insertion of the speculum, the upper vagina and cervix were examined under increased magnification. Following the cleaning of the cervical epithelium with a saline solution, 3-5% acetic acid solution was applied on the cervix. After 60-90 seconds, the cervix was re-

Figure 1. Flowchart of the study population



examined for lesions and vascular pattern. After the application of Schiller solution (a mixture of %1 Lugol, 3% potassium iodine) onto the upper vagina, suspected areas were biopsied. The results of the pathological examinations were recorded. The pathology results were classified as normal, CIN1, CIN2, CIN3, in-situ carcinoma, and invasive cancer. Age, body mass index (BMI), and smoking habits of all patients were obtained from patients' files.

Statistical Analysis

Data were analysed with IBM Statistical Package for the Social Sciences version 20 (SPSS Inc., Chicago, IL, USA). The mean and standard deviation values were used for the continuous variables and percentage and numeric values for the categorical variables. The normal distribution in the groups was checked with the Kolmogorov-Smirnov test. According to the results of the distribution assessment, Mann-Whitney U test, or Student's T-test was used for the comparison of the mean values. The Chi-square test and Fisher's Exact test were used for the comparison of the categorical variables. Age adjusted odds ratio for ≥CIN 2 of each HR-HPV group with the respective 95% CIs were determined by binary logistic regression analysis. Regarding the results, a p-value smaller than 0.05 ($p<0.05$) was considered statistically significant.

Results

The smear and HPV typology results of 642 patients were evaluated. 233 patients were excluded because they did not meet the inclusion criteria of the study (Figure 1). A total of 409 female patients were included in the study. Patients tested negative for intraepithelial lesions or neoplasia. 217 patients out of 409 were

Table 1. Characteristics of Women Stratified by Types of HR-HPV

Characteristics	All patients (n: 409)	Genotype of HR-HPV 16/18 (n: 217)	Genotype of HR-HPV Non-16/18 (n: 192)	***p* value**
Mean age, SD (years)	41.6 ± 8.5	41.58 ± 9.01	41.74 ± 8.06	0.856*
Body mass index (BMI)	29.2 ± 4.4	28.83 ± 4.27	29.62 ± 4.54	0.765*
Smoking	47.9%	52.5%	42.7%	0.549**
Nulliparous	16.7%	5%	11.7%	0.236**
Multiparous	83.3%	48.1%	35.2%	

HR-HPV**, high-risk Human Papillomavirus; **BMI**: Body Mass Index; **P<0.05
**** Independent Sample t test ** Chi-square test***

positive for HPV-16, HPV-18 or both, and 192 had non-16/18 HPV positivity.

The mean age and BMI of the women were 41.6±8.5 and 29.2±4.4, respectively (Table 1). A total of 217 patients (53.0%) were HR-HPV 16/18 positive (100 patients were HPV-16 positive (24.4%); 72 patients were HPV-18 positive (17.6%) and 45 patients were HPV-16/18 positive). 196 patients (47%) were non-16/18 HPV positive. None of the patients had a pre-invasive lesion in the smear test or positivity for malignancy.

The patients were divided into two groups: Group 1 and Group 2 constituted of the patients with HPV 16/18 positivity and non-16/18 HPV positivity, respectively. The mean age in Group 1 was 41.58±9.01 and in Group 2 was 41.74±8.06 years. The mean BMI were 28.83±4.27 and BMI 29.62±4.54, respectively. There was no significant difference between the groups for age and BMI (p>0.05). No significant differences were observed between the groups regarding smoking habits (p>0.05). The smoking rate was 52.5% in Group 1 and 42.7% in Group 2 (Table 1).

The comparison of two groups for the colposcopy findings revealed the following results: Group 1: 95 patients had normal colposcopy findings (43.8%); 105 patients had acetowhite epithelium (48.4%) and 17 patients had Lugol solution negativity (7.8%). Group 2: 108 patients had normal colposcopy findings (56.2%); 63 patients had acetowhite epithelium (32.8%) and 21 patients had Lugol solution negativity (11%). There was a statistically significant difference between the groups based on the colposcopy findings (p=0.002) (Table 2)

Table 2. Comparison of colposcopy findings

Colposcopy	Genotype of HR-HPV 16/18 (n: 217)		Genotype of HR-HPV Non-16/18 (n: 192)		**p value**
	n	%	n	%	
Normal	95	43.8	108	56.2	
Acetowhite	105	48.4	63	32.8	**0.002**
Lugol	17	7.8	21	11	

***HR-HPV**, high-risk Human Papillomavirus; Chi-square test*

Table 3. Final Pathology Results Cross - tabulated with Genotypes of HR-HPV

Pathology	All patients (n : 409)	Genotype of HR-HPV 16/18 (n: 217)	Genotype ofHR-HPV Non-16/18 (n: 192)	***p* value**
Normal colposcopy	306	67.7%	83%	
CIN 1	68	19.4%	13.5%	
CIN 2	16	5.5%	2.1%	
CIN 3	13	5.1%	1.0%	0.003
In-situ	3	1.4%	0%	
Invasive	3	0.9%	0.5%	

HR-HPV, *high-risk Human Papillomavirus;* ***CIN****, cervical intraepithelial neoplasia; Chi-square test*

The comparison of Group 1 and 2 for the biopsy results after the colposcopy revealed the following results: Group 1: 147 patients had normal biopsy results (67.7%); 42 patients had CIN1 (19.4%), 12 patients had CIN2 (5.5%), 11 patients had CIN3 (1.4%), 3 patients had in-situ lesion (1.4%), 2 patients had invasive cervical carcinoma (0.9%). Group 2: 159 patients had normal biopsy results (83%); 26 patients had CIN1 (13.5%), 4 patients had CIN2 (2.1%), 2 patients had CIN3 (1.0%), none of the patients had in-situ lesion (0%), 1 patient had invasive cervical carcinoma (0.5%). The statistical comparison of the groups showed that there was a significant difference between the groups for the abnormal biopsy results (p=0.003) (Table 3).

The pathological evaluation of CIN2 and >CIN2 lesions revealed the following results in patients with ≥CIN2 lesion: OR=1.62; CI=0.78-2.65 and HR-HPV rate=83.3%. 51.3% of them were HPV 16/18 positive and the remaining 48.7% were non-HPV 16/18 positive (Table 4). There was no significant difference between the groups for invasive cervical cancer, which indicated that the rate of invasive cervical cancer was comparable in both groups.

Table 4. Age adjusted odds ratio for ≥CIN 2 of each HR-HPV group: HPV 16/18 (+) and non-16/18 HR-HPV (+)

Variable	Total	≥CIN 2	OR† (95% CI)	***p* value**
HPV-16/18 (+)	217	51.3%	1.53 (0.89-2.61)	
Non-16/18 HR-HPV (+); HPV; 31/33/35/39/45/51/52/56/58/59/66/68 (+)	192	48.7%	1.49 (0.91-2.39)	0.024
Total	409	341	1.62 (0.78-2.65)	

CIN*, cervical intraepithelial neoplasia;* ***HR-HPV,*** *high-risk human papillomavirus , Values are presented as number (%)., Odds ratio, age-adjusted odds ratio for ≥CIN 2. Binary logistic regression analysis*

Discussion

The cause-and-effect relationship between the HR-HPV and cervical carcinoma is well established. HPV worldwide prevalence is 11.7% (14). In the classification based on the L1 gene sequences, which code the capsid proteins, it was determined that there are at least 200 different HPV types (15,16). These types can be also classified as mucosal and dermal types according to their tissue affinity (17). Although some of the HPV types are low-risk and non-oncogenic agents and cause benign lesions, some of them are highly oncogenic and cause several malignant lesions. The most important one among these malignancies is cervical cancer, which is rather common in women starting from the age of 30 and exhibits a progressive character if the diagnosis is delayed. Cervical cancer takes place near the top among the cancer types and its incidence can be decreased with the screening programs. Although screening programs are implemented worldwide with the help of awareness campaigns, cervical cancer is still an important cancer type in daily practice (18).

Currently, the PCR method is used for the HPV typology, as HPV cannot be cultured in the known culture media and the cytological test has diagnostic limitations (19). The amount of sampling necessary for the HPV typology done with PCR method is smaller than the amount necessary for the cytology. Therefore, self-sampling is considered as an alternative for the patients, who cannot access the screening centers or hesitate to visit these centers. The aim of this approach is to access a relatively larger female population. Thus, only the HPV positive patients among the women, whose results have been delivered to the screening centers, can be invited for the cytology testing and women, who have a negative cytology result, can repeat the self-sampling procedure 5 years later. There are studies demonstrating that more women can be accessed with this screening method (20,21). However, the disadvantage of this approach is that ¼ of women, who receive this kit, send the kit back without taking any action (22).

The investigation of women with HR-HPV infection showed that the most common types are 16, 18, 33, 45, 31, 58, 52 and 35 (23). The results of our study were consistent with the literature. HPV-16, which is one of the HR-HPV, was placed on the top with a rate of 24.4%, which was followed by HPV-18 with 17.6%. The rate of the mixed infections with HPV-16 and HPV-18 was 11%. 47% of women were non-16/18 HR-HPV positive.

In several countries including Turkey, the cervical cancer screening and management of the patients are based on the algorithms of the ASCCP. According to these algorithms, direct colposcopy is recommended in women with type 16-18 HPV positivity, even if the cytology is normal. In patients with non-16/18 HR-HPV positivity, cotesting is recommended after one year if the cytology is normal (24). However, at this step, differences of opinion exist between the gynaecologists. Some of them recommend cotesting in a year in accordance with the algorithms, while some gynaecologists recommend direct colposcopy in patients with non-16/18 HR-HPV positivity and normal cytology.

In a meta-analysis published by Arbyn et al., it was demonstrated that the addition of the cytology to the HPV genotyping did not provide any additional benefits (25). In this context, if each patient, who is at high-risk according to the results of HPV genotyping, is referred to colposcopy, the rate of colposcopic biopsy and pathology increases parallel to an increase in referrals.Thus, the cost per patient increases during the cervical cancer screening.

Moreover, a non-16/18 HR-HPV positivity includes 10 HR-HPV strains without clearly pointing out which strains are positive. It is clear that there can be types with a relatively aggressive progress among these no specified HR-HPV strains, even though they are not HPV-16 and HPV-18. In related studies conducted in the Scandinavian countries, it was found out that the progress rate to HSIL in patients with HPV-31 and 33 infections was similar to HPV-16 and HPV-18 (11,26,27). In a study, which was conducted by Matsumoto et al., it was determined that the progress from LSIL to HSIL in women with 16, 18, 31, 35, 35, 52 and 58 HPV positivity was 3.5 times faster compared to other high-risk HPV types (28). Therefore, it seems that the recommendation of colposcopy to HR-HPV positive patients is not so much inappropriate, even though it increases the cost. In a recent study conducted in Turkey, relatively high positive predictive values (PPV) were shown for CIN2+ lesions in non-16/18 HR-HPV patients with negative cytology. Furthermore, similar PPV values were determined for HPV strains 33, 51, 58, 59 and 18 (29).

In our study, the comparison of the colposcopy results between the groups showed that there was a significant difference between the patients with type 16-18 HR-HPV positivity and non-16/18 HR-HPV positivity. We observed more abnormal appearances under colposcopy in patients with type 16-18 HR-HPV positivity.

In our study, the examination of the colposcopic biopsy results revealed that there was also a statistically

significant difference between the patients with type 16-18 HR-HPV positivity and non-16/18 HR-HPV positivity. The rate of abnormal biopsy results was significantly higher in patients with type 16-18 HR-HPV positivity. Although this was an expected outcome, after the examination of the results in patients with non-16/18 HR-HPV positivity, we believe that abnormal biopsy results should not be ignored. For example, we detected invasive cervical cancer in 1 of 192 patients (approx. 0.5%) and CIN3 in 2 patients (approx. 1%). Due to this early diagnosis the patients were managed timely. In this group, preinvasive lesions were found to be lower (CIN2, 2.1%; CIN1, 13.5%), and these values were significantly lower than that of the HPV type 16-18 positive group. If these patients were scheduled for cotesting one year later instead of direct colposcopy, they could have been lost to follow-up or the disease could have progressed to a more advanced stage. Furthermore, there can be also a difference in progression to invasive cancer in patients, who are positive for only HPV-16 or HPV-18 and for multiple non-16/18 HR-HPV types. In patients, who are infected simultaneously with multiple non-16/18 HR-HPV types, the progression to invasive cancer may be faster due to the cumulative effects of the high-risk strains. However, this rate is very low according to related studies. In a study conducted by Hwang et al., the rate of persisting infection was 3% for the non-16/18 HR-HPV types, although the same rate was approximately 15% for HPV-16 and HPV-18 (30).

Infections with HPV-16 and 18 are considered high risk for ≥CIN2 lesions. As the result of a study conducted with over 4 million women in Turkey, genotyping of 31, 33, 35 and 45 HPV strains in addition to 16 and 18 is also recommended. Comparison of different triage methods for detection of ≥CIN2+ lesions with regard to different HPV genotypes revealed a PPV of 32.6% for HPV 16; 15.3% for HPV 18 and for HPV 33, 31, 45 and 35 the values were 34.4%, 19.3%, 15.3% and 14.0%, respectively. These results indicate that the rate of preinvasive cancerous lesions in non-16/18 HR-HPV positive patients is not negligible. Therefore, colposcopy evaluation of these patients can be useful in early detection (31). The comparison with patients, who had non-16/18 HPV infection, confirmed this suggestion. In patients who underwent colposcopy, we diagnosed invasive cervical cancer in 2 patients with type 16-18 HR-HPV positivity and in 1 patient with non-16/18 HR-HPV positivity. As there was no statistically significant difference between the groups, we believe that invasive cervical cancer can be diagnosed early in both groups. However, as the sample size was rather small in our study, we believe that there is a need for more comprehensive studies for the investigation of the benefits of the colposcopy in all types of HR-HPV infections.

Compliance with ethical standards

Disclosures all authors have no conflicts of interest or financial ties to disclose.

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