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DISTRIBUTION OF HUMAN PAPILLOMAVIRUS GENOTYPES AND CERVICAL CYTOLOGY RESULTS AT A TERTIARY CENTER IN THE EASTERN BLACK SEA REGION OF TURKEY

ABSTRACT

We investigated the genotypes of HPV and the smear results of patients in the Eastern Black Sea region of Turkey. Four hundred four patients who were HPV-positive were analyzed; 278 (68.81%) patients had a single infection, and 126 (31.2%) had multiple infections. Three hundred seventy-eight (93.6%) of patients were HR-HPV positive. There was no significant correlation between multiple HPV infection and HR-HPV frequency with age. The most common HPV genotypes were 16, 18, 31, 51, and 35, respectively. The smear results of 345 patients were obtained and we found no correlation between smear abnormalities and multiple HPV infections. In conclusion, the most common HPV subtypes in the Rize region were HPV type 16, 18, 31, and 51 and regardless of whether HPV 16 and/or 18 were included, multiple HPV infections were not associated with abnormal cytology results.

Keywords: HPV, Cervical Cancer, Cervical Cytology, Cervical Invasive Lesion, Oncology

1. INTRODUCTION

Human papillomavirus (HPV)-related genital infections are the most commonly encountered sexually transmitted viral diseases in the world [1]. Although infection occurs mainly in young women and decreases in rate with the age of 45-50 years, it makes a second peak in the postmenopausal period [2]. There are 200 different HPV serotypes, 49 of which are classified and recognized by the international HPV reference center [3]. Of these, 40 were found in the female genital tract [4]. HPV is considered to be the main factor in cervical cancer. They are classified as low risk (LR-HPV) and high risk (HR-HPV) according to their malignant transformation potential [5]. The International Agency for Research on Cancer has classified and accepted 12 HPV genotypes (16, 18, 33, 35, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59) as high-risk groups [6]. HR-HPVs are a common cause of invasive cervical cancer. LR- HPV groups are the main cause of genital warts; however, there is no consensus in risk scoring categorization for many HPV serotypes. The frequency and type of HPV infections varies by geographic and ethnic populations around the world [2 and 7]. HPV serotype prevalence studies according to countries and regions will probably be the source of vaccination programs to be developed in the future. HPV types 16 and 18 are responsible for approximately 70% of all invasive cervical cancers worldwide [8]. However, HPV 16 is the most common HPV serotype in both healthy patients and those with cervical cancer [4]. HPV 31 is the

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second most common type in Europe, and HPV 52 has gained importance in Africa [9].

2. RESEARCH SIGNIFICANCE

Many studies about the frequency of HPV have been published in Turkey, which is a country that bridges two continents and receives many refugees from neighboring countries. The prevalence of HPV in our country is estimated as 25% [10]. The regional differences in the distribution of HPV types in Turkey is a less known fact. There are no published studies about the distribution of HPV types in Rize, which is located in the Black Sea region at northeastern Turkey. This region received significant immigration from Georgia after visa application restrictions were lifted. The economic difficulties of the immigrants affected the sexual habits of locals and induced multiple sexual partner behavior [11]. Due to this factor, it has been suggested that the distribution of HPV genotypes, which is a sexually transmitted disease, may vary from other regions of Turkey. Also, there are no studies published about the relationship between single or multiple infections of HPV and abnormal cervical cytology in our country. Therefore, in order to point out the need of preventive strategies such as HPV screening programs, public education, and vaccination programs, we aimed to evaluate the distribution of HPV types and the relationship between cervical cytology results and multiple HPV genotypes infections in Rize province.

3. MATERIAL AND METHODS

This is a retrospective review of 404 sexually active patients who were HPV-positive and aged between 23 and 70 years who were consecutively admitted to the outpatient clinics of Recep Tayyip Erdogan University School Hospital between May 2016 and May 2018. Approval was obtained from the ethics committee of the study center. Pregnant or postpartum women (up to the 2nd month), patients with a history of hysterectomy, patients who had undergone conization, and patients diagnosed with cervical, vulva or vaginal cancer were excluded from the study. After the approval of the hospital management, the patient data, HPV status, HPV types, and cervical cytology reports were obtained from the hospital records. Cytological samples taken from our hospital are examined at the National Public Health Laboratory. Two samples were taken from each woman using a National Software Screening System called RUNLEK. The first sample was taken using a cervical sampling brush and spread to a glass slide and evaluated through conventional cytology. The conventional cytology was evaluated by 2 pathologists with a double-blind study and classified according to the Bethesda system [12]. The second sample is taken with a different brush inside of the standard 5 cc transport medium for HPV DNA analysis. HPV DNA positive specimens were detected using a Hybrid Capture 2 (Qiagen), and a CLART kit (Genomica) was used to define the genotype. The data were analyzed using the SPSS 20.0 statistical software package. Number and percentage values are used in the presentation of descriptive data. The Chi-square test was used for the analysis of categorical data. $P<0.05$ was accepted as statistical significance.

4. RESULTS

The mean age of 404 patients who were HPV-positive was 36.9±8.2 (range, 23-70) years. Eighty-eight percent of the women were married, and 12% were nulliparous. Seventy-four percent of the women were in the premenopausal period and 26% were in the postmenopausal period. Of the HPV-positive women, 278 (68.81%) had a single HPV infection, 86

(21.28%) had a double HPV infection, and 40 (9.90%) had more than 3 HPV serotypes. The most common HPVs were HPV 16 (31.7%), HPV 18 (6.9%), HPV 31 (6.6%), HPV 51 (3.6%), HPV 35 (3.0%), HPV 52 (2.8%), HPV 66 (2.5%), and HPV 33 (2.3%), respectively (Figs 1). The great majority (93.6%) of all our patients were HR-HPV-positive.

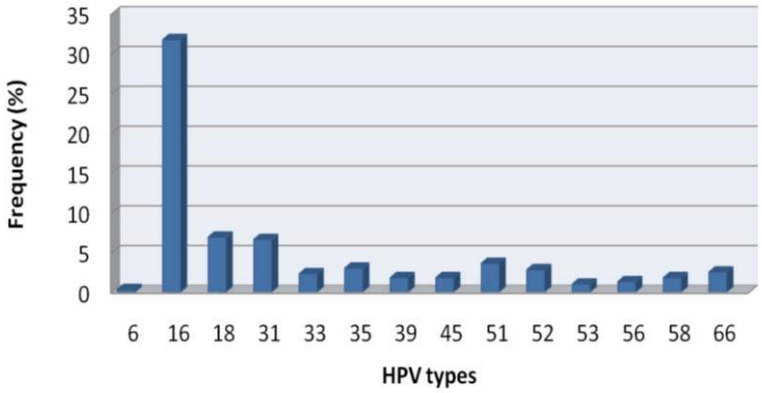

Figure 1. Specific distribution of HPV genotypes

When multiple HPVs were analyzed, it was found that multiple HPVs excluding HPV 16 and 18 were 54.43%, multiple HPVs including HPV 16 were 26.2%, multiple HPVs including HPV 18 were 11.6%, and HPVs including both HPV 16 and 18 were 7.64% (Figure 2).

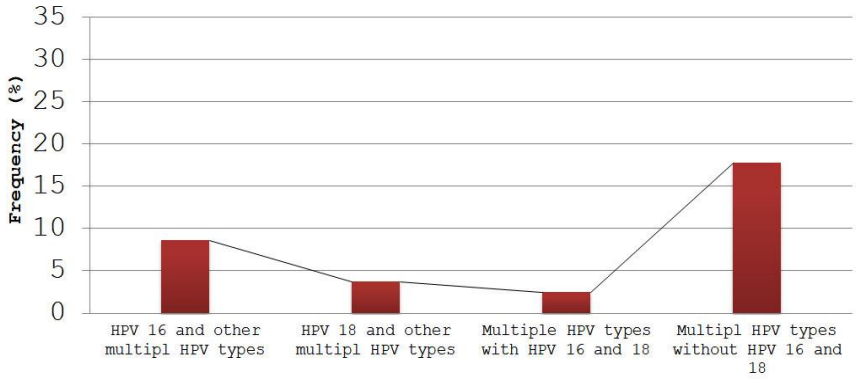

Figure 2. Distribution multiple HPV infections

Table 1 shows the ratios of LR-HPV and HR-HPV according to age groups. Given that most (93.6%) of our patients were HR-HPV-positive, there was no statistically significant difference between the age groups for LR-HPV and HR-HPV carriage (P=0.715).

Table 1. Results of LR-HPV and HR -HPV ratios by age

Age (Years)	LR-HPV	HR-HPV	Total
<30	0(0.0%)	6(100%)	6(100%)
30-39	9(5.6%)	151(94.4%)	160(100%)
40-49	10(7.8%)	118(92.2%)	128(100%)
≥50	7(6.4%)	103(93.6%)	110(100%)
Total	26(6.4%)	378(93.6)	404(100%)

LR-HPV: Low Risk Human Papillomavirus
HR-HPV: High Risk Human Papillomavirus

Table 2 shows the rates of single HPV and multiple-type HPV-infected patients according to age groups. According to Table 2, 31.2% of the patients were found to be infected with a multiple-type of HPV. No statistically significant difference was found between the age groups for single or multiple HPV infections (P=0.206). However, because of the fact that our national screening program does not recommend routine HPV testing under the age of 30 years, we had only 6 patients aged under 30 years.

Table 2. Frequencies of single and multiple type HPV infections by age

Age(Years)	Single Type HPV Infection	Multiple Type HPV Infection	Total
<30	4(66.7)	2(33.3)	6(100.0%)
30-39	101(63.5%)	58(36.5%)	159(100.0%)
40-49	96(75.6%)	31(24.4%)	127(100.0%)
≥50	77(68.8%)	35(31.2%)	112(100.0%)
Total	278(68.8%)	126(31.2%)	404(100.0%)

HPV: Human Papillomavirus

Table 3. Distribution of HPV types and cervical cytological diagnosis

	Total	Insufficient Material (%)	Normal (%)	ASCUS (%)	LGSIL (%)	≥ASC-H and HGSIL (%)
HPV 6	1	0(0.0)	0(0.0)	1(100)	0(0.0)	0(0.0)
HPV16	105	12(11.2)	60(57.1)	20(19)	5(4.8)	8(7.7)
HPV18	24	4(16.7)	14(58.3)	3(12.5)	2(8.3)	1(4.2)
HPV31	26	2(7.7)	19(73.1)	4(15.4)	0(0.0)	1(3.8)
HPV33	9	0(0.0)	3(33.3)	0(0.0)	3(33.3)	3(33.3)
HPV35	11	3(27.3)	6(54.5)	2(18.2)	0(0.0)	0(0.0)
HPV45	7	0(0.0)	4(57.1)	2(28.6)	1(14.3)	0(0.0)
HPV51	13	2(15.4)	6(46.2)	2(15.4)	2(15.4)	1(7.7)
HPV52	8	2(25.0)	6(75.0)	0(0.0)	0(0.0)	0(0.0)
HPV53	4	0(0.0)	3(75.0)	1(25.0)	0(0.0)	0(0.0)
HPV56	5	0(0.0)	3(60.0)	2(40.0)	0(0.0)	0(0.0)
HPV58	7	0(0.0)	5(71.4)	2(28.6)	0(0.0)	0(0.0)
HPV66	9	2(20.0)	5(55.6)	2(22.2)	0(0.0)	0(0.0)
HPV 16 and Other mHPV Types	32	5(15.6)	19(59.4)	4(12.5)	2(6.3)	2(6.3)
HPV 18 and Other mHPV Types	14	0(0.0)	11(78.6)	3(21.4)	0(0.0)	0(0.0)
mHPV Types with HPV 16 and 18	9	1(11.1)	6(66.7)	0(0.0)	2(22.2)	0(0.0)
mHPV Types without HPV 16 and 18	61	5(8.2)	35(57.4)	13(21.3)	6(9.8)	2(3.2)

ASCUS: Atypical Squamous Cells of Undetermined Significance
ASC-H: Atypical Squamous Cells, Cannot Exclude a High-Grade Lesion
HGSIL: high-grade Squamous Intraepithelial Lesion
HPV: Human Papillomavirus
LGSIL: low-grade Squamous Intraepithelial Lesion
m HPV
multipl HPV

Three hundred forty-five of the 404 patients' smear results were successfully obtained. The smear results according to HPV types are given in Table 3. Two hundred five (59.42%) of these had normal cytology, 61 (17.68%) had 'atypical squamous cells of undetermined significance' (ASCUS), 38 (11.01%) had insufficient material, 23 (6.66%) had low-grade squamous intraepithelial lesions (LGSIL), 16

(4.63%) had 'atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesions (HSIL) (ASC-H) or HGSIL, and 2 (0.57%) had 'atypical glandular cells (AGC). Eight of the 16 HGSIL cases were HPV 16. However, 3 of the 9 HPV 33 cases were HGSIL. We found no association between smear abnormalities and multiple HPV serotypes (P=0.242).

5. DISCUSSION

In this study, we investigated the HPV genotype frequency and the significance of these results with cervical cytology in Turkey's Eastern Black Sea region with the given importance of being close to Georgia's border. In our study, the most frequently encountered HPV serotypes were HPV 16, 18, 31, and 51, respectively. Although this result is similar to the results of other studies published in the both Turkish and English literature, the frequency of LR-HPV seems to be lower in our study than in other studies [10, 13 and 14]. Similar results were obtained in a multicenter study involving 6388 women in whom HPV positivity was investigated, where the most common HPV types were found as HPV type 16, 6, 11, 18, 31.51, and 33, respectively [10]. A meta-analysis indicated HPV 52 and 58 as the most common serotypes after HPV 16 and 18 in Asia [15]. Several studies conducted in different regions of China showed that HPV 52 and 58 were the most common serotypes after HPV 16 [16, 17 and 18]. Bruno et al. and Levi et al. demonstrated that HPV 56 was the second most common HPV serotype in Brazil [7 and 19]. After HPV 16, HPV 33 was the second most common HPV type in Balkan countries such as Bulgaria, Serbia, Bosnia, and Romania [20]. HPV 31 is the second most common type in Greece and Croatia [21]. We believe that the different results between the studies may be due to the differences in the population in which the HPV is being investigated and the variety of methods used to identify HPV.

The prevalence of multiple infections may vary between 9% and 50% among European countries [22 and 23]. In the study published by Jeng et al., the rate of multiple infections was reported as 35.8% [24], whereas in our study, it was 31.2%. Although many studies in the literature showed that multiple infection rates increased before the age of 31 years, and this rate decreased with age, reflecting a higher risk in young sexually active women who tended to have multiple partners [25, 26, 27, and 28], Zeng et al. and Ghosh et al. found that HR-HPV was more common in the third decade than in older age groups [29 and 30]. In our study, there was no significant difference in HR-HPV rates or multiple HPV prevalence by decades of life. However, routine HPV screening is not recommended under the age of 30 years in our National HPV Screening Program, so we only had 6 patients in this age group. The reason for obtaining HPV samples from 6 patients under the age of 30 was due to the presence of widespread condyloma acuminata lesions in the genital area.

Although some studies in the literature suggested that multiple HPV infections increase the risk of cervical dysplasia, cancer, and the incidence of cytologic abnormalities [31, 32, 33, and 34], there is no consensus on this issue. In the study by En-Qi et al., it was found that the probability of smear abnormalities was lower in people with multiple infections [35]. In our study, we only evaluated HPV infections and cytologic screening results. We found that there was no difference in ≥ASC-H ratio in single or multiple HPV infections. Although it was shown in literature that HPV 16 was present in 38.1% and 46.5% of HGSIL cases [36 and 37], in our study, 8 of 18 patients with ≥ASC-H and HGSIL (50%) were infected with HPV 16. However, Wright et al. and Wheeler et al. suggested that HPV 31 and 33 increased the

risk for ≥ CIN2 development and might be important in patients who were referred to colposcopy [38 and 39]. Among the patients with HPV 33 who we cytologically analyzed, 33.3% had ASC-H and 33.3% had LG-SIL. ASCUS was reported in 15.4% of the HPV 31 cases and 3.8% had HG-SIL. These results are not sufficiently reliable in aspect of the number of HPV 31 or 33 positive patients in Rize province so that they should be undergo routine colposcopic examination. Therefore, the frequency of high-grade lesions in HPV 33 should be confirmed by large scale studies.

We believe that our study is a remarkable because it is the first to investigate HPV genotypes and to analyze the relationship between multiple HPV infection and cervical cytology results in the northeast region of Turkey but there are some limitations in our study. The relatively small sample size and its retrospective design could be considered as the limitations for our study. Due to the retrospective design of the study, the risk factors for HPV infection could not be investigated, and high HR-HPV rates could not be associated with quality of life and sexual habits of people in the region. In addition, these results were obtained using data of a single hospital and may not be valid across the country. In order to investigate the effects of enhanced human migration and prostitution on HPV types, more multicenter studies conducted in different regions of the country are needed.

6. CONCLUSION

In conclusion, the most common HPV subtypes in the Rize region were HPV types 16,18,31, and 51, with a high risk of cervical cancer. In addition, regardless of whether HPV 16 and/or 18 were included, multiple HPV infections were not associated with abnormal cytology results. The prevalence of sexually transmitted diseases in a society is directly related to the level of education, quality of life, and sexual behavior of the inhabitants of the community. This result is an important data source for epidemiologic studies in our country and the high rates of HPV subtypes in the high-risk group indicate the need for education, screening, and vaccination programs in this region.

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