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Genotype Distribution and Prevalence of Human Papillomavirus Among Russian Women in Rostov, Southern Federal District of Russia

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Abstract

HPV burden is a marker for cervical neoplasms and cancer. Prevalence of HPV infection and HPV genotypes varies amongst different regions. This research was aimed to investigate the age distribution patterns and prevalence of high-risk HPV genotypes among Rostov-on-Don women. Scrapings of epithelial cells obtained from the urogenital tract of 5655 women. Total DNA was extracted by the sorbent method; Real-Time PCR was used to investigate the HPV load and HPV genotyping. HPV was found in 40% of the DNA samples. The HPV infection was most prevalent among women age ≤ 20 years (55,26%) compared to 27,34% of women older than 40 years (p = 0,001). The prevalence of HPV 16/18 types was almost the same in all age groups. More 50% of women with a high HPV load were women at age group 20-30 years old. Among 254 women, 79,13% had single HPV type infection, and 20,86% had multiple HPV infection. The most frequent of high-risk HPV types were 16, 51 and 31 types. The most common variant of genotypes co-exist for multiple HPV infections were genotypes of A7 + A9 phylogenetic groups (30,18 %). Multiple HPV infections were the most prevalent (67,92%) in women at age group 20-30 years old. We concluded the prevalence of HPV infection among younger women was the highest and declined gradually with age among Rostov-on-Don women.

Keywords: Human Papillomavirus, HPV Genotypes, Multiple HPV Infections, Rostov-on-Don, Russia.

1. Introduction

Human papillomavirus (HPV) is one of the most common sexually transmitted viruses in the world. Anogenital HPV is the most predominant infection (Suligoi et al., 2017). Genital HPV types were subdivided into high-risk and low-risk types, based on the risk of infection-induced malignant neoplasms. The high-risk HPV genotypes identified to date (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73 and 82) are the main causative agents for various cancers types, most oropharyngeal and anal cancers, some cancers of the vagina and vulva. Also, low-risk types (HPV 6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81, and 89) cause different clinical symptoms of lesions of the skin and mucous membranes, including anogenital warts (Muñoz et al., 2003; Bihl et al., 2017). Other types of HPV are under review and may be categorized in the near future as high-risk or low-risk types (Chan et al., 2019). HPV 16 is the most prevalent and carcinogenic type worldwide, followed by HPV 18. In many regions, the HPV 16 and HPV 18 contribute to more than 70% of all cervical cancer cases (Li et al., 2011). The distribution of HPV genotypes varies geographically around the world. HPV 31 and 33 are predominant in Brazil. HPV 16 and HPV 52 are the most common types in Africa (Silva et al., 2009; Omar et al., 2017). The most common three HPV genotypes in Asian are 52, 58 and 16 (Vinodhini et al., 2012; Nah et al., 2017; Niyazmetova et al., 2017; Aimagambetova and Azizan, 2018; Wang et al., 2019a). The HPV 16 type prevails in the population of Russia, while the HPV genotypes 31, 39, 52 and 18 are less frequent (Sirotkina and Smith, 2012). In addition, the distribution of different HPV genotypes changes significantly according to age, race, economic situation, and sexual behaviors (Mitchell et al., 2014). The probability infection with HPV rises shortly after teenagers beginning sexual activity, but in most instances, the infection has a transient character and does not contribute to pathological changes (Boda et al., 2018). The frequencies of HPV-infection reach the maximum level among females between 20 to 25 years old, after which it decreases in the third decade of life (Gravitt and Winer, 2017). The HPV disappears in most cases during 1-2 years after infected. Nonetheless, the persistent infection with specific HPV genotypes can cause cellular changes and induce cervical intraepithelial neoplasia and cervical cancer (Radley et al., 2016). Several studies have demonstrated that mixed HPV infection and high viral load were associated with persistent HPV infection. They are regarded as critical risk factors for developing cervical lesions and predicting the progress of the HPV infection

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(Sun et al., 2001; Bello et al., 2009). Over the past years, in many countries, the incidence of cervical cancer has decreased. At the same time, Russia has a high incidence of cervical cancer per 100,000 people. In 2018, about 18,164 new cervical cancer cases were diagnosed in the Russian Federation. Cervical cancer is the fourth-largest cause of women's cancer and the second-most common cause of women's cancer in aged between 15 and 44 years in Russian Federation (ICO/IARC Information Centre on HPV and Cancer, 2019). The studies about HPV distribution and prevalence provide important information on the epidemiology of HPV infection and as basic data for determining the changes in the prevalence of specific HPV genotypes that may direct potential screening applications in different regions to the identification and prevention of the predominant HPV genotypes related-cervical carcinogenesis; consequently reducing the health burdens and helping assess the possible benefits of immunization against HPV types. In Rostov-on-Don, by the beginning of 2018, more than half of the region's population was women - 53.6%. The proportion of women in the total population by age group were 48,5% for (10-19) years old, 49,7% for (20-34) years old, 50,9% for (35-44) years old and 68,6% for (45 – 70) years old (Federal State Statistics Service, 2018). The high level of the cervical cancer occurrence, high prevalence of HPV infection and the differences of HPV genotypes prevalence across geographical. So, our study aimed to analyze data for HPV virus load, genotypes and to assess rates of co-infection among women in Rostov-on-Don (Russia, Southern Federal District of Russia).

2. Material and methods

2.1. Materials study

The materials used in our study were DNA samples collected from epithelial cells of the urogenital tract of women. A total number was 5655 DNA samples from women who underwent a screening examination at the “Nauka” clinical diagnostic laboratory (Rostov-on-Don, Russia) during the period: September 2016 to November 2019. All individuals had previously signed forms of informed consent and the laboratory questionnaire. The study was approved by the Bioethics Committee of the Academy of Biology and Biotechnology of the Southern Federal University (Protocol No. 2 of March 29, 2016) according to the standards and ethical guidelines of the World Medical Association (Declaration of Helsinki) for human experiments.

2.2. DNA extraction from epithelial cells

The total DNA was extracted from epithelial cells of cervical canal scrapings according to the protocol of DNA-sorb-AM kit (NextBio, Russia).

2.3. HPV Genotyping analysis

High carcinogenic risk HPV genotypes were analyzed according to the AmpliSense HPV HCR genotype-FL reagent kit (Interlabservice, Russia) protocol by polymerase chain reaction (PCR) with hybridization-fluorescence detection. The method relies on the simultaneous amplification (multiplex-PCR) of HPV DNA regions and the β-globin gene region used as an endogenous internal control. PCR analyses were conducted in real-time in a single tube on a 4-channel RotorGene amplifier. The four major phylogenetic groups were analyzed: A9 group (16, 31, 33, 35, 52 and 58 types), A7 group (18, 39, 45 and 59), as well as HPV DNA 51 (group A5) and HPV DNA 56 (group A6) types.

2.4. HPV Quantitative analysis

DNA quantification of high carcinogenic risk HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59) in biological materials was analyzed according to the protocol of the AmpliSense HPV HCR screen-titer-FL reagent kit (Interlabservice, Russia). It should be mentioned that the risk of developing epithelial cells dysplasia depends on the concentration of HPV. The viral load of less than 3 lg of HPV genomes per 100 thousand human cells has low clinical significance because the probability of virus elimination from the human organism is high. A viral load, more than 3 lg of HPV genomes per 100 thousand human cells, is a clinically significant threshold where the risk of cell dysplasia and the probability of malignant cell transformation is increased (Federal Budget Institute of Science, 2018).

2.5. Statistical analysis

The percentages and standard deviation were determined. Comparison of frequencies of discrete variables was performed using Student's t-test. P values of <0,05 were assumed as statistically significant. All the statistical calculations were performed using Excel (version 2016) and SPSS software (version 25,0).

3. Results

A total of 5655 DNA samples were examined to detect the presence of human papillomavirus. (Table 1) shows the distribution of women according to the age groups. The majority of the women belong to the age groups from 20 to over 40 years old. Our analysis revealed the frequency of HPV-positive women was 40% (95% CI 38,72-41,27) (2262 from 5655 women). The frequencies of HPV-positive samples, depending on age, are shown in (Table 2). The maximum frequency of HPV-positive samples was observed among women under 20 years old. In this age group, more than half of the individuals were carriers of the human papillomavirus (55,26%). The lowest frequency of HPV positive samples (27,34%) was found in the women group for over 40 years. Analysis of the HPV 16/18 types was conducted for 2262 women among different age groups. The identification frequency of the most carcinogenic dangerous types HPV was almost the same in all age groups. It showed that 57 women from 215 HPV-positive in the age group less 20 years old were diagnosed with 16/18 HPV types; 404 women from 1446 with HPV16/18 were revealed at the age group 20-30 years old, 141 women from 534 at the age group 31-40 years old were found with HPV 16/18 and revealed 13 women infected with HPV16/18 types from 67 in the age group over 40 years old. The frequency of the detected HPV 16 /18 types in women from the Rostov region is shown in (Table 3). We conducted a quantitative analysis of the HPV DNA level for 2262 HPV-positive women. According to the HPV DNA content, 3 groups were identified. The first group included women with less than 3 lg of HPV genomes per 100 thousand human cells

(clinically insignificant). The second group included DNA samples with HPV load 3 - 5 lg, and the third group included women with HPV level more than 5 lg of HPV genomes per 100 thousand human cells which is a clinically significant threshold where a high probability of cell dysplasia and development to cervix cancer can arise. 42,79% of HPV-positive women had a viral load between 3 to 5 lg. The lowest percentage of women was (26,55%) infected by HPV in the viral load above 5 lg. Viral load distributions among HPV-positive women groups are shown in (Table 4). Among women with a high concentration of human papillomavirus (more than 5 lg HPV per 100 thousand cells) above 50% were women at age group 20-30 years old. The lowest quantity (4,64 %) women with high HPV load observed at the age group over 40 years old (Table 5). Our genotype analysis for 12 different types of high carcinogenic risk HPV types was performed for 254 women. Single HPV type infection was observed in 201 samples (79,13%), and co-infection with two or more types of HPV was observed in 53 samples (20,86%). The most common types of HPV were 16 and 51 (Table 6). 31 and 56 types of HPV were detected with a frequency of about 10%. 58 and 59 types of HPV were detected less often. We have analyzed 53 samples with co-infection and determined HPV genotypes depending on the four main phylogenetic groups A9, A7, A5 and A6. Two women had more than one HPV type from A7 phylogenetic group 3,77% (95% CI -1,35-8,90). The simultaneous presence of HPV types of A7 and A5/6 phylogenetic groups was detected in 11,32 % cases (95% CI 2,79-19,85). 13,20 % (95% CI 4,09-22,32) of women carrying HPV types from the A9 phylogenetic group. However, in 30,18 % (95% CI 17,82-42,54) of cases, virus types from A7 and A9 phylogenetic groups were detected. Co-infection of HPV types from A9 and A5/6 phylogenetic groups was detected in 26,41% (95% CI 14,5-38,28). Eight women have HPV types from all phylogenetic groups A7, A9 and A5/6 (15,09 %, 95% CI 5,45-24,73). Among women infected with several types of human papillomavirus, 15,09% (95% CI 5,45- 24,73) was from group less 20 years old. 67,92%, (95% CI 55,35-80,49) are young women at age group 20-30 years old. This age group is characterized by high sexual activity, possibly a frequent change of sexual partners, which contributes to HPV infection. Women with mixed HPV infection between the 30 and 40 account for only 11,32% (95% CI 2,79-19,85). 5,66 % of women (95% CI -0,56-11,88) were in the age group of over 40 years old.

4. Discussion

In this study of Rostov-on-Don women, the frequency of HPV-positive samples among residents of the Rostov region was 40,0%. According to the literature, infection of the population in the world with human papillomavirus is from 40 to 80% (Forman et al., 2012; Guan et al., 2012; Bruni et al., 2019). In Western European countries, Russian Federation, the Western countries of the former Soviet Union(Republic of Moldova, Belarus, Ukraine), the Central Asia and Caucasus region, high-risk HPV prevalence ranged to 48.4% (Rogovskaya et al., 2013; Belyaeva et al., 2018; Zykova et al., 2018). Several studies were conducted around the world and in different regions in Russia, but prevalence ratios were always different (Clifford et al., 2005; Sanjosé et al., 2007; Kulmala et al., 2007; Shipitsyna et al., 2011). The estimates of hr-HPV prevalence vary across regions, partially due to the different demographics and ages groups included in studies, utilization various methods for HPV identification, different screening programs implemented, or variability in test and study designs. We observed a significant association between age and HPV prevalence. In women under 20 to 30 years old, the prevalence was greater than in women over 40 years. Younger women had an HPV infection most frequently. Our data correspond to the results of other studies, according to which the peak of HPV detection occurs in age groups of women younger than 30 years old who have the highest sexual activity and change of sexual partners (Zeng et al., 2016; Roik et al., 2018). In the United States population, the prevalence range of HPV positive was in young women under 30 years old, between 41-51%(Karuri et al., 2017). Among women of the Rostov region in the older age groups, the proportion of HPV-positive people is steadily decreasing. But our analysis for 2262 women demonstrated that the frequency of the most carcinogenic dangerous high-risk HPV 16/18 prevailed almost all age groups. About a third of people over 30 years are carriers of the high-risk HPV, which increases the risk of malignant neoplasms development. HPV 16/18 types are associated with the largest contribution to the incidence of precancerous and cancerous lesions (Ahmed et al., 2017). Risk degree is higher among high carcinogenic HPV types 16/18 carriers. Our analysis for determining the viral load among HPV-positive women of the Rostov region demonstrated that about a third of HPV-positive individuals have a low viral load (less 3lg). That level of HPV is associated with a high probability of spontaneous disappearance of the human papillomavirus. More than 40% of the HPV-positive women demonstrate HPV load of 3 - 5 lg, at which cell dysplasia is possible. In 26,55% of cases, a high HPV load of the virus is observed, which is associated with a high risk of developing a malignant process. Certain studies showed that cells of HPV-positive women with higher viral load are more likely to progress to high-grade cervical intraepithelial neoplasia (Moberg et al., 2005; Cricca et al., 2007; Xi et al., 2011). Their own study showed that among women with a high human papillomavirus viral load (above 5 lg HPV per 100 thousand cells), young women under 30 years are 66 %. However, women older than 30 years (33% from total women with high HPV level) should thoroughly require constant medical monitoring. Most likely, in this case, the virus persists for a long time in the body; that is, the virus has not been eliminated, and a high viral load indicates active reproduction of the virus (Rodríguez et al., 2008, 2010). Long-term persistence of the virus leads to the integration of virus DNA into the human genome, expression of oncogenic proteins E6 and E7, and the development of cancer(Gupta and Mania-Pramanik, 2019). At the next stage of our work, using the AmpliSense HPV HCR genotype FRT test system, we analyzed the frequency of 12 different types of HPV with high carcinogenic risk (the test system uses type-specific primers located in the E6-E7 region of HPV genes). Genotyping of HPV was performed for 254 women. 79,13% HPV positive of women in Rostov Region population are carriers one of high carcinogenic risk HPV

type. Our findings indicate that 16, 51 and 31 (15,42%, 11,94% and 9,95% respectively) are the most common HPV genotypes in women in Rostov region. The HPV 18, 58 and 59 genotypes were less frequent. Our data are consistent with literature data on the dominance of 16, 39, 31 HPV genotypes in Russia (Marochko and Artymuk, 2017; Mkrtchyan et al., 2018). In the Russian Federation, HPV 16 had been confirmed as the most common type with a prevalence range of (2.7–14.1%) and Belarus, (4.0–7.1%), while in Georgia, (16.1%) (Samoylova et al., 1995; Kleter et al., 1999; Zumbach et al., 2000; Alibegashvili et al., 2011). In 20,86% of cases, co-infection with two or more types of HPV was observed. The most prevalent variant of genotypes co-existing for multiple HPV infections were genotypes of A7 + A9 phylogenetic groups (30,18 %) and A9 and A5/6 phylogenetic groups (26,41%). Our data are consistent with other studies, the most of high-risk HPV genotypes appear in the Co-infection infections (Oliveira et al., 2008; Conesa-Zamora et al., 2009; Wang et al., 2019b). Among women infected with several types of human papillomavirus, nearly 83% are young women at age 20 to 30 years. This age group is characterized by high sexual activity, possibly a frequent change of sexual partners, which contributes to mixed HPV infection. The prevalence of multiple infections among women with various lifetime sex partners was significantly higher, consistent with the sexual transmission of genital HPV infections (Widdice et al., 2010). Immunological mechanisms can also determine multiple infection prevalence. The prevalence of mixed infections among immunosuppressed women infected with HIV is still high(Massad et al., 2016). Women with HPV Co-infection between the ages of 30 to 40 account for only 11,32%. About 5,66 % are in the age group over 40 years old. However, people over 30 years infected with multiple types of HPV high oncogenic risk are highly likely to develop malignant neoplasms(Brot et al., 2017). Determining the epidemiology of mono and co-infections of HPV is essential to develop suitable preventive strategies according to each population. For some countries, co-infection with HPV is less frequent than mono-infection (Li et al., 2016), but in others, co-infection incidence is higher (Gallegos-Bolaños et al., 2017). In this analysis, there are many limitations. First, our analysis may not reflect the whole population. Our study represents only the women infected with high-risk HPV without men, HPV DNA tests unable to determine if the HPV detected was for a participant or a partner, Demographic nature of the population from either urban or rural areas is not specified. Our data reflected only three years of data for a particular subset of the population, and over the years, the distribution of HPV types may change. Second, we did not study the possible effect of social and sexual behaviors on the infection. Third, the absence of follow-up data for each patient in this study is a limitation. Finally, we recommend further studies among women and male populations in Rostov-on-Don. These studies are of considerable significance in terms of the effects of the vaccine program and in determining the transmission rate of the most prevalent of HPV types.

Table 1. The distribution of women among the age groups.

Age groups	≤ 20 years	20-30 years	31-40 years	> 40 years
Frequency, abs. (%) (95% CI)	389 (6,87%) (6,21-7,53)	3236 (57,22%) (55,93-58,51)	1785 (31,56%) (30,35-32,77)	245 (4,33%) (3,80-4,86)

Table 2. The frequency of HPV-positive women among the age groups.

Age groups	**≤ 20 years**	**20-30 years**	**31-40 years**	**> 40 years**
Cases / Total	215/389	1446/3236	534/1785	67/245
Frequency, %	55,26%	44,68% ***	29,91% ***	27,34% ***
(95% CI)	(50,32-60,21)	(42,97-46,39)	(27,79-32,04)	(21,76-32,92)

Note: ***-Significant differences compared with the first age group at P<0,001

Table 3. The frequency of HPV 16 / 18 types among HPV-positive women depending on the age.

Age groups	**≤ 20 years**	**20-30 years**	**31-40 years**	**> 40 years**
Frequency, abs. (%) (95% CI)	57 (26,51%) (20,61-32,41)	404 (27,55%) (25,27-29,84)	141 (26,40 %) (22,66-30,14)	13 (19,40 %) (9,93-28,87)

Table 4. Quantitative level of human papillomavirus among HPV-positive individuals.

Viral loads groups	**HPV level (lg HPV per 100 thousand cells)**		
	≤3 lg	**3 - 5 lg**	**> 5 lg**
Frequency, abs. (%)	691 (30,54 %)	968 (42,79 %)	603 (26,65 %)
(95% CI)	(28,64-32,44)	(40,75-44,83)	(24,83-28,48)
Average concentration of DNA HPV lg	1,89	4,17	5,98

Table 5. The frequency of women with high HPV load (≥5 lg HPV per 100 thousand cells) depending on the age groups.

Age groups	**≤ 20 years**	**20-30 years**	**31-40 years**	**> 40 years**
Cases/Total	86/603	313/603	176/603	28/603
Frequency, %	14,26 %	51,90 %	29,18 %	4,64 %
(95% CI)	(11,47-17,05)	(47,91-55,89)	(25,55-32,81)	(2,96-6,32)

Table 6. Prevalence (%) of HPV genotype distribution in HPV-infected women.

HPV types	Abs. cases / Total	% (95% CI)
HPV 16	31/201	15,42 % (10,42-20,41)
HPV 18	10/201	4,97 % (1,96-7,98)
HPV 31	20/201	9.95 % (5,81-14,08)
HPV 33	16/201	7,96 % (4,21-11,70)
HPV 35	17/201	8,45% (4,61-12,30)
HPV 39	16/201	7,96 % (4,21-11,70)
HPV 45	17/201	8,45% (4,61-12,30)
HPV 51	24/201	11,94 % (7,45-16,42)
HPV 52	17/201	8,45% (4,61-12,30)
HPV 56	19/201	9,45 % (5,40-13,49)
HPV 58	5/201	2,48 % (0,33-4,64)
HPV 59	9/201	4,47 % (1,61-7,33)

5. Conclusions

Based on these study results, we hypothesized that besides HPV 16, the genotypes 51 and 31 are of public health issues and could contribute to cervical carcinogenesis in Rostov-on-Don population due to their high frequency. Moreover, the correlation of various HPV genotypes, especially high-risk HPV genotypes, most likely represents a synergistic interaction in the development of certain carcinogenesis. These results call for our research efforts to focus on the clinical effects of interaction between the different HPV genotypes, and to establish new preventive and therapeutic approaches based on HPV types-prevalence trends in Russia.

Conflict of interest:

None.

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