RESEARCH ARTICLE

Distribution of High Risk Human Papillomavirus Types in Western Kazakhstan - Retrospective Analysis of PCR Data

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Abstract

Background: Virtually all cases of cervical cancer are caused by persistent infections with a restricted set of human papillomaviruses (HPV). Cancer of the cervix is the third or even the second most common cancer in women worldwide, more than 85% of the cases occurring in developing countries, such as China and India, including the Republic of Kazakhstan. The purpose was to determine the HPV type distribution to evaluate efficacy of vaccination and adjust cancer prevention strategy in Western Kazakhstan in the future. Materials and Methods: A retrospective analysis was conducted of data obtained from PCR laboratories in 4 regional centers for the time period covering 12 months, 2013-2014, using AmpliSens® Real-Time PCR kits for HPV testing of 12 genotypes (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59). Results: A total of 1,661 persons were HPV tested within 2013-14, but a proprotion examined for 16 and 18 genotypes only (563) was not been included for statistic analysis of distribution and ratio of the most common genotypes. Males accounted for only a small number (N=90 in total). Conclusions: Total number of the HPV-positive appeared to be 26.0%, or 286 of N=1098. Types distribution was as follows: type 16 (10.7%), 39 (5.83%), 51 (5.27%), 31 (4.85%), 56 (4.58%), 18 (3.61%), 59 (2.64%), 58 (2.22%), 35 (1.94%), 33 (1.25%). Overall the HPV infection was highest in 16-29 years old (62.4%) and decreased with age. Total prevalence of the HR-HPVs amongst male population was 21.4% with top five types 16, 18, 39, 51, 31. Trends forcorrelations between Aktau site and type 33 (Cramer's V 0.2029), between Caucasian ethnicity and type 33 (Cramer's V .1716), and between European ethnicities in Uralsk and type 45 (Cramer's V .1752) were found. Of N 563 tested separately for 16 or 18 types, 13.6% were positive. As a whole, the distribution of 16/18 types had a ratio of 3.53:1. Given the vaccine-targeted type 16 is widely spread amongst this regional population, HPV immunization program of adolescent girls 10-13 years should be implemented appropriately.

Keywords: Human papillomavirus - high risk group - PCR typing - western Kazakhstan - prevalence

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Introduction

Cancer has become a priority public health challenge in the Member States of the World Health Organization's (WHO) Western Pacific Region, and in Asia in whole. According to up-to-date point of view, "rapid and unplanned urbanization, demographic transition, and lifestyle changes are driving the increase in noncommunicable diseases (NCDs), which include cancer". The WHO Global Action Plan for the Prevention and Control of Noncommunicable Diseases 2013-2020, targets a reduction in premature mortality from NCDs by 25% by 2025 (Varghese et al., 2014). Cancer of the cervix is the third or even the second most common cancer in women worldwide, more than 85% of the cases occurring in developing countries, such as China and India (Senapathy et al., 2011; Li et al., 2013). The Republic of Kazakhstan is not an exclusion in this range, given the length of the border between Kazakhstan and China up to 1460 km.

Virtually all cases of cervical cancer are caused by persistent infections with a restricted set of human papillomaviruses (HPV) (Schiffman et al., 2009). HPVs are a large and diverse group of viruses with 189 completely characterized types, with new HPV types being continuously found (Feoli et al., 1998; Bernard et al., 2010). HPVs infect epithelial cells in genital mucosa (alpha papilloma viruses only), oral mucosa or skin (representatives of all five genera) (Bzhalava et al., 2013). HPVs cause a wide range of diseases from benign lesions to invasive tumors. In 2009, an International Agency for Research on Cancer (IARC) working group classified

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12 mucosal HPV types (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59) as carcinogenic to humans (Group 1) for their association with cervical cancer, hereafter also referred to as high-risk (HR) HPV types. These 12 types cluster together in the same evolutionary branch or "high-risk clade" that includes Alphapapillomavirus species groups 5, 6, 7, 9 and 11 (IARC, Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 100B, 2012). But the need to re-assess the carcinogenicity of different HPV types, especially other clades, now is embodied in an approach recently taken by a World Health Organization International Agency for Research on Cancer (IARC) Monographs Working Group (Schiffman et al., 2009).

Human papillomavirus (HPV) infection is very common in young women after the onset of sexual activity and, when it persists, the viral oncoproteins produce perturbation of the cell-cycle controls resulting in cervical intraepithelial neoplasia (CIN), up to cervical cancer (Cuzick et al., 2008).

According to Kazakh Statistics, annually in our country fall ill more than 1200 and die more than 600 women for cervical cancer (CC), of them 20% - during the first year after diagnostics (National Statistical Compendium, Astana, Kazakhstan, 2012). Researchers reported that annual incidence rate of cervical cancer for Kazakhstan was 14.5±0.3 for the period 1999-2008 and mortality was 8.0±0.1 (Igissinov et al., 2012). Despite some progress achieved, situation with cervical cancer prevention still remains tense in the country. According to the data of ICO HPV-center updated 23.12.2015, there are 6.72 million women aged 15 years and older who are at risk of developing cervical cancer, moreover mortality in Kazakhstan in the age group 15-44, being 5.8 per 100000 as of 2014, still is on top, leading to 982 deaths annually (Bruni et al., 2015). And meanwhile, cervical cancer is quite easy for early detection due to its belonging to visual forms, so it can be prevented through screening.

However, still limited data are available on the burden of human papillomavirus (HPV) and its associated diseases in the Russian Federation, the Western Countries of the former Soviet Union, the Caucasus region and Central Asia including Kazakhstan (Rogovskaya et al., 2013). Therefore, reviewing data on HR-HPV prevalence in different coutries is important in the context of better understanding the cervical cancer burden and for evaluation of the potential impact of HPV vaccination in the country (Li et al., 2013).

The purpose of the work is collection initial data on HPV types distribution to evaluate efficacy of vaccination and adjust cancer prevention strategy in Western Kazakhstan in future. Research has the following objectives: to identify the most common HPV genotypes in the region; to identify the most important possible correlations between age, ethnicities, gender and HPV types at infected population.

Materials and Methods

The study constitutes a retrospective analysis of data obtained from PCR laboratories of the region for the time period covering 12 months 2013-2014. Use of AmpliSens® Real-Time PCR kits for HPV testing, which detect 12 different HR-HPV genotypes (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59) is common practice in the region. Assays have been processed with PCR-analyser Rotor-Gene 6000 (Germany). All four involved PCR-laboratories of the Russian-Kazakh joint venture "Olympus" laboratories network" are equipped with the mentioned kind of kits and analysers and accredited by ISO 15189.

Permission to use PCR data has been received from the "Olympus" network authorities according to the Agreement of scientific cooperation. The method of the HPV testing was recently compared with nested GP5+/6+ and MY09/11-PCR and HC2. AmpliSens® was found to be more sensitive (analytic sensitivity 1-5 × 103 GE/ml) and specific than the two other methods tested (Rogovskaya et al., 2013).

Moreover, this method is inherent to all post-soviet countries, and allows comparison of regional data within at least mentioned ones.

Analysis has been done in general non-randomized population suspected in relation HPV infection. PCR swabs have been taken by sentinel specialists or gynecologists from private clinics without an intention to explore the data. Cytological status before PCR or other information relatively health status of patients is unknown. Population presented is urban entirely and only in main characteristics: age, gender, ethnicity. Rural population practically is not included because the PCR laboratories are present only in large regional centers. Consequently, the study has no specific inclusion or exclusion criteria and represents population of 4 regional centers of Western Kazakhstan: Aktobe, Mangystau, Atyrau, West Kazakhstan. Regional population density is the lowest in Kazakhstan, as of 3.4 person per square kilometer*.

Statistical processing has been performed in Statistica.10. (USA).

Results

General data

Total 1661 persons of two genders have been HPV tested within 2013-14, but a part of them examined for 16 and 18 genotypes only (563), and this part of patients has not been included for statistic analysis of distribution and ratio of the most common genotypes. These two groups (16 and 18 types only (N 563) and all HPV types, (N 1098)) have been statistically processed separately. Besides, there was a little part of tested men (N=90 totally).

The largest ethnic groups in the region are Kazakhs and Russians, they account 74.3 and 21% respectively, and the rest 4.7% are of other ethnicities, mostly Caucasians (the region's border runs along the Caspian Sea). Except Kazakhs, there is a little part of other Turkic people living in the region, such as Bashkirs and Tatars, they are all united by the term "Turkic ethnicities". The same with the "European ethnicities", where except Russians, a little part of other European nationalities, such as Germans, Belarussians, Ukrainians has been united under the term. Caucasians living in the region mostly are Azerbajanians

Table 1. Main Characteristics of Examined Population

City (province):	Aktobe (Aktobe)	Aktau (Mangystau)	Uralsk (West Kazakhstan)	Atyrau (Atyrau)	Total	%
Number of urban population*	421101	181905	278096	217312	1098414	
Ethnicities:						
Turkic	684	158	253	249	1344	80.9
European		20	95	23	288	17.3
Caucasian	6	10	5	8	29	1.8
Gender:						
Men	15	26	18	31	90	5.4
Women	825	162	335	249	1571	94.6
Age:						
16-18	2	3	0	0	5	0.3
19-39	664	138	275	229	1306	78.6
40-59	163	45	76	48	332	20.0
60 and >	11	2	2	3	18	1.1
Total:	840	188	353	280	1661	

*Information on density and number of urban population has been extracted from the data of the National Statistics Agency "Population of the Republic of Kazakhstan by individual ethnic groups at the beginning of 2014"

because of territorial neigbourhood. All available features of the tested population are summarized in Table 1.

For all HR-HPV types (N 1098)

Age of population tested was from 16 to 66 years, mean age 32.3 ± 9.75 years (CI 95%). Total number of men tested was 56 (5.4%) and the rest 1042 were women, gender ratio appeared to be 1:19.8. Distribution of the most common genotypes in the region has been carried out for N 1098, and data are summarized in Figure 1 (CI 95%). Top five genotypes in the region belong to the following Alphapapillomavirus species groups: A9 (types 16, 31), A7 (39) and A5-A6 (types 51, 56) (IARC, 2012). The division into groups is important, as different groups of HPV have different ability to persist (Bernard et al, 2010; Chen et al, 2014).

Total number of the HPV-positive appeared to be 26.0%, or 286 of N=1098 (CI 95%, p=0.0043). Combination of the HPV genotypes (co-infection), up to 6 types per sample, has been revealed in 21.6% of all cases. Distribution and% of the HPV-positive results by each site is summarized in Table 2. The overwhelming majority (62.4%) of all HPV-positive appeared to be in the age category 16-29 years and decreased with age. Distribution of the HPV-positive results by age/types is summarized in Table 3 (HPV types are listed according to its significance in the region).

Total prevalence of the HR-HPV infection amongst men (N=56) was 21.4% (CI 95%) and the most common genotypes were: 16, 18, 39, 51, 31 (in order of significance).

Contingency analysis of the available variables (age, gender, ethnicity, site) revealed the following: *i*). sites are heterogeneous by ethnicity (Cramer's V = .121, p=0.004): Europeans in Uralsk (N 95) are much more than expected; *ii*). sites are heterogeneous by 33 genotype: the most common prevalence has been observed in Aktau (Cramer's V .203, p=0.0082); *iii*). a trend to relationship between Caucasian ethnicity and 33 HPV type (in Aktau) has been found (Cramer's V .172, p=0.0324); *iv*). a trend to relationship between 45 genotype and European ethnicity (in Uralsk) has been found (Cramer's V .175, p=0.028).

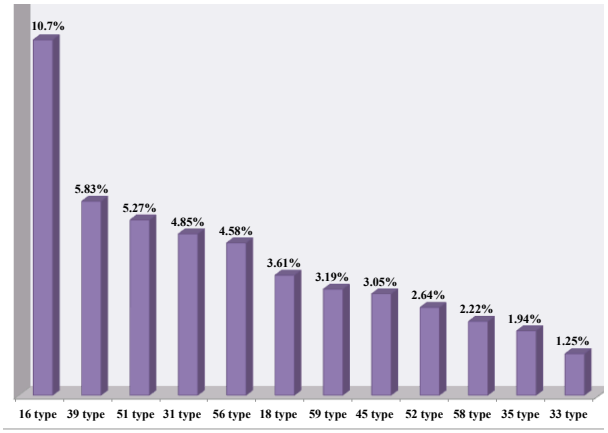

Figure 1. Prevalence of High Risk HPV Types

Table 2. HPV-Positive Population by Sites and Types

HPV types	Aktau, %	Atyrau, %	Uralsk, %	Aktobe, %
16	17.0	17.10	9.62	8.71
39	2.13	6.31	4.81	6.32
51	6.38	1.80	5.77	5.88
31	0.69	6.31	5.77	3.70
56	4.26	3.60	3.85	5.01
18	2.13	0.90	2.88	4.58
59	2.13	0.00	3.85	3.92
45	2.13	4.50	2.88	2.83
52	0.00	3.60	3.85	2.40
58	0.00	0.90	2.88	2.61
35	2.13	0.90	2.88	1.96
33	6.38	0.00	0.96	1.09

Table 3. HPV-% Positive Results by Age and Types

HPV types	16-29	30-39	40-49	50-66
16	59.7	19.5	14.3	6.5
39	76.2	16.7	4.8	2.4
51	71.0	18.4	10.5	0.0
31	68.6	17.4	8.6	5.7
56	48.5	27.3	15.2	9.1
18	69.2	23.1	7.7	0.0
59	65.2	21.7	8.7	4.4
45	50.0	18.2	27.3	4.5
52	73.7	15.8	10.5	0.0
58	68.8	12.5	18.8	0.0
35	42.9	21.4	35.7	0.0
33	55.6	33.3	11.1	0.0

No correlation between ethnicity and genotype 16 (most prevailing) has been found.

And meanwhile, analysis of multipositive assays with number of genotypes up to 6 (21.6% of all results), has shown the following: *i*). between 16 and 18 genotypes - 2 times more frequent (p <.0001, Cramer's V .686); *ii*). between 16 and 31 - 2 times (p .0141, Cramer's V .191); *iii*). between 16 and 35 - 3 times (p <.0001, Cramer's V .297); *iv*). between 35 and 39 - (p .0063, Cramer's V .209); *v*). between 18 and 59 - (p .0062, Cramer's V .187); *vi*). between 51 and 59 - (p .0012, Cramer's V 0.24).

As to the group tested for 16/18 only (N 563), results are the following: mean age is 31.21±8.77 (CI 95%).

Distribution by ethnicity: Turkics are 82.4% (16-positive 10.2%, 18-positive 3.3%), Europeans are 16.5% (12.3% 16-positive, 2.0% 18-positive), and Caucasians 1% (HPV 16 - 9.1% positive, 18 - .5%) respectively. No correlations between ethnicity and 16/18 types have not been found (for type 16 p=0.728, for type 18 p=0.584 respectively).

Distribution by gender: total men tested are 7.2% and 92.8% of women respectively; of whom men type 16 positive appeared to be in 16.42%, type 18 positive 5.6%, and women 16 type positive 10.1%, 18 type positive 2.75% respectively. No correlations between gender and 16/18 types have not been found (for type 16 p=0.066, for type 18 p=0.989 respectively).

In whole, distribution of 16 /18 types is presented as ratio 3.53:1. In this group 13.6% of population tested has been found 16 or 18 type positive, among them 17.1% (N 96) appeared to be positive both for 16 and 18 types. Comparatively low share of positive assays in this group might be explained by the tactics of local specialists: in case of low probability of positive results they commonly did not administer relatively expensive HPV genotyping.

Discussion

As it is known, many researches are dedicated to the HPV prevalence and type distribution in world scientific periodicals. The purpose of these studies is the evaluation of local data related to vaccine-targeted genotypes, since to date there is no another way to prevent cervical cancer except primary prophylaxis, or vaccination. The greatest and the earliest health gains will be ensured by high vaccine coverage among all susceptible people (Orlando et al., 2014; Van Kriekinge et al., 2014).

Our study is not an exclusion. We identified top five most common HR-HPV types inherent to the western territories of the country as 16 (10.7%), 39 (5.83%), 51 (5.27%), 31 (4.85%) and 56 (4.58%). We identified type 16 as dominating and widely spread in the region. Such figures might evidence about low efficacy of planned vaccination program supported by state in the countries where it had been introduced. Started in the Republic of Kazakhstan within 2011-2013 prophylactic vaccination of adolescent girls 10-13 years has not found proper scope, and now almost fully discontinued. For instance, data from Australia demonstrate efficacy of the vaccination strategies - researchers reported that only 1.6% samples were vaccine-targeted, all of type 16, whereas type 18 was not identified (Osborne et al., 2015). The same situation is observed in other developed countries with high coverage by HPV immunization program: the prevalence of HPV 16/18 infection in the post-immunization survey in England was 6.5% amongst 16-18 year olds, compared to 19.1% in the similar survey conducted prior (Mesher et al., 2013).

Researchers from oriental Asian countries where HPV immunization program has not been introduced yet, report different state of the HPV prevalence and type distribution. Despite low prevalence of the HPV itself (6.5%), researchers from Tunis identified as most frequent 16 and 11, or vaccine-targeted types (Guettiti H, Ennaifer E et al., 2014). Human papillomavirus infections have been found in 43% of the specimens with the most prevalent genotypes HPV 16 (30%) and HPV 18 (8.0%), according to the Saudi Arabian report (Turki et al., 2013). According to Iranian researchers, overall HPV infection was highest in women aged 18 - 25 years and decreased with age. 19 different HPV types were detected (31.1%). Type-specific prevalence of HPV-16 and 18 was 7.3% and 2.8% respectively and the prevalence of the HPV co-infection was 29.1% (Yousefzadeh et al., 2014).

Starting since this decade, Chinese researchers have been actively publishing reports on the current situation with the HPV infection prevalence and type-distribution in different provinces. For instance, the most commonly detected hr-HPV types in cervical specimens were HPV-52 (4.0%) and HPV-16 (3.7%) with total prevalence 15.3% in Jiangsu province (Zhao et al., 2014); the prevalence of HPV infection in Shenzhen city was 13.8% with the five most commonly types 16 (3.47%), 58 (1.68%), 33 (1.38%), 43 (1.36%) and 18 (1.27%). Besides, authors emphasize that the prevalence of HPV 18 infection is increasing faster than any others, which will lead it to be one of the main subtypes in this city in the future (Wang et al., 2013). However, according to Chinese authors, in cases of cervical cancer HPV 16 (calculated as 73.8%) and HPV 18 (calculated as 16.4%) still remain the most prevalent infection types among patients (Yang et al., 2014).

But the current worldwide trends mostly consist in careful exploration of the types other than 16 and 18, whose role is known well enough. In our research we established a trend to correlation between Aktau population (Caspian Sea shore, the most large percent of the Caucasian diaspora in all over the republic) and type 33, and between European ethnicity (maximally represented in Uralsk, borderline with Russia) and type 45. As it is known, type 33, a member of the HPV16-related alpha-9 species group, is found in approximately 5% of cervical cancers worldwide. It was supposed the genetic diversity of HPV 33 and eventually identified 28 HPV 33 variants. One of them, the A1 sublineage was strongly over-represented in cervical cases (Chen et al., 2014). The same with the type 45: HPV 45 is a member of the HPV18-related alpha-7 species and accounts for approximately 5% of all cervical cancer cases worldwide. A total of 43 HPV 45 sequence variants were identified, the distribution of which varied by geographical region. The B2 sublineage was significantly overrepresented in cervical cancer (Chen et al., 2014). As long as we revealed a trend to such a

bond, further we should determine whether correlation between regional ethnicities and genetic variants of the HPV 33 and 45 exists.

Albeit HPV infection results in much more sad outcomes for women than for men, researchers worldwide currently study the issues of the HPV prevalence and type distribution amongst men, because infected men constitute a viral reservoir, contributing to transmission of HR-HPV to women. Chinese researchers did not reveal high prevalence of the HR-HPV in sexual partners of positive women, moreover, they determined low concordance of viral type between couples (Huang et al., 2013). On the contrary, Brazilian authors demonstrated very high prevalence and the level of HPV co-infection at men: the most frequent HPV types were 6, 16, 42 and 51. Co-infection was found in 59% with a number of types up to 9 (Freire et al., 2014). In our research total prevalence of the HR-HPV infection amongst men was 21.4% and the most common genotypes were: 16,18, 39, 51, 31 (in order of significance). Given N=56, our data concerning men should not be quite robust, and the next research of the issue is required. However, indirect signs concerning relatively high prevalence of the HPV infection amongst male population exist in the region. According to the data of the retrospective analysis of Kazakh researchers covering time period 1999-2009 relatively incidence of laryngeal cancer, a gender ratio of 10.5:1 was inherent to all cases of the laryngeal cancer in the republic (Igissinov et al., 2013).

Analyzing the data obtained, one should realize that this study has a lot of limitations, which might seriously impact on findings. The study which might provide robust information on the true prevalence of the HR-HPV infection amongst population, should have definite exclusion and inclusion criteria (for instance, vaccination history, cytological data and etc), or in other words, population presented should be selected. In our case, we just analyzed PCR data of the patients mostly suspected in relation the HPV infection. Perhaps, because of these limitations our data on the prevalence (26.0%) has not coincided with findings of the other researchers from post-soviet countries. According to Lithuanian and Belarusian authors, prevalence of the HPV infection in their countries were 20.0% and 18.3% respectively, though dominating type was the same, 16 (Gudleviciene et al., 2014). We suppose our rate is slightly higher than it should be. But type distribution has been shown upon relatively large statistic material (N 1098), and judgement on the distribution of HR-HPV types in the region should be considered true enough.

In conclusion, according to the retrospective analysis of PCR assays collected within 12 months of the period 2013-2014 in four regional PCR laboratories in Western Kazakhstan, 26.0% of samples appeared to be HPV positive (p=0.0043). Due to numerous limitations of the study this index should not be considered robust, and true prevalence of the HR-HPV infection expected to be slightly lower. Given the vaccine-targeted type 16 is widely spread amongst regional population, HPV immunization program of adolescent girls 10-13 years should be implemented appropriately.

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