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Prevalence of high-risk human papillomavirus infection among Kazakhstani women attending gynecological outpatient clinics

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ABSTRACT

Objectives: To conduct a nationwide high-risk human papillomavirus (HR-HPV) infection genotyping analysis of women attending gynecological clinics and identify factors associated with HR-HPV infection.
Methods: A cross-sectional survey-based study with 759 participants. Demographics, lifestyle, and medical history data were collected by questionnaire completed by gynecologists during patients' visits. Cervical swabs were used for HPV genotyping using AmpliSens kit. Data analysis included descriptive statistics consisting of mean values, standard deviations, and frequencies, where applicable. Ordinal logistic regression was performed to identify factors associated with HPV infection status.
Results: The mean age of participants was 36.51 ± 10.09 years. The majority of participants were aged 26–35 years. Less than half of the women (39%) were HPV positive; 26% had single HR-HPV, and 13% had multiple HR-HPV infection. The most prevalent HR-HPV genotypes were HPV-16 (54%), HPV-51 (7%), HPV-68 (7%), and HPV-18 (6%). Ordinal logistic regression demonstrated that older age, not being single, and having a history of sexually transmitted infections, decrease the odds of HPV infection.
Conclusion: This study identified high prevalence of HR-HPV among Kazakhstani women. Our results showed that adding HPV testing to compulsory cervical cancer screening in Kazakhstan could improve the screening program and decrease cervical cancer rates.

Introduction

During 2010 to 2019, cervical cancer is estimated to be the fourth most common cancer in women worldwide and the leading cause of cancer death among women in developing countries (Arbyn et al., 2020; Canfell, 2019). According to GLOBACAN data, the absolute number of cervical cancer cases worldwide has increased over time (471 000 in 2000, 529 000 in 2008, and 570 000 in 2018) (Arbyn et al., 2011; Arbyn et al., 2020), and it continues to be a significant public health issue with almost 0.6 million cases and 0.3 million deaths per year (Arbyn et al., 2020; Bruni et al., 2019a; Serrano et al., 2018). Kazakhstan has a high

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incidence of cervical cancer in women of all ages, with a crude incidence rate of 18.2 per 100 000 women (Aimagambetova et al., 2021; Balmagambetova et al., 2020; Bruni et al., 2019b). Cervical cancer ranks as the second leading cause of female cancer and cancer-related death in Kazakhstani women, with over 1700 new cervical cancer cases diagnosed annually (Aimagambetova et al., 2021; Balmagambetova et al., 2020; Bruni et al., 2019a).

According to several sources, approximately 80%–99% of all cervical cancer cases have been linked to human papillomavirus (HPV) infection (Bosch et al., 2016; Bruni et al., 2019a; Burd and Dean, 2016; de Martel et al., 2017; Serrano et al., 2018;). HPV is a small non-enveloped, double-stranded DNA virus of the Papillomaviridae family (Burd and Dean, 2016; zur Hausen, 2002). Out of more than 200 HPV types, due to their strong correlation to anogenital cancers, 15 are identified as high-risk HPV (HR-HPV): HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82 (Adcock et al., 2019; Burd and Dean, 2016; Chan et al., 2019; Paavonen, 2007). HR-HPV types 16 and 18 are responsible for approximately 70% of all cervical cancer cases worldwide, while the other high-risk types (31, 33, 35, 45, 52 and 58) are responsible for 20% of cervical cancer cases (Bruni et al., 2019a; Clifford et al., 2006; Serrano et al., 2018).

The prevalence of HPV infection varies among countries in the world. According to Vinodhini et al. (2012), a high prevalence of HR-HPV infection (54.4%) among women aged <20 was identified in China. Significant prevalence of HPV infection was observed among the less developed regions of South (44.4%) and Eastern Asia (36.3%). The most recent report from the HPV Information Centre shows prevalence of HR-HPV in women with normal cervical cytology of approximately 30%, with the highest in Africa and Oceania (~50%) and lowest in Asia (~20%) (Bruni et al., 2019a).

While HR-HPV distribution has been reported from most countries in the world, there is a lack of sufficient information about the prevalence of HR-HPV types in Kazakhstani women. A handful of reports have been published from the western part of the country (Bekmukhambetov et al., 2016) and the capital city (Niyazmetova et al., 2017). More information about the types of prevalent HPV strains, especially in patients with abnormal cytology, could help in cervical cancer prevention and the introduction of a vaccination program. Therefore, our study aimed to conduct a nationwide HR-HPV genotyping analysis of women attending gynecological clinics. In addition, we aimed to identify risk factors for HR-HPV infection using a 30-item questionnaire.

Methods

A prospective cross-sectional study among women from 5 cities of central (Nur-Sultan, the capital city), southern (Almaty), western (Aktobe), northern (Pavlodar), and eastern (Oskemen) parts of Kazakhstan was conducted from 25 May 2019 to 30 December 2020. Women aged between 18 and 70 attending gynecological outpatient clinics were recruited to the study by convenience sampling. The participant recruitment process for the study is presented in Figure 1.

Study instrument

The study employed a 30-item questionnaire covering the following patient information: socio-demographic characteristics, gynecological characteristics and history of gynecological diseases. After obtaining informed consent from patients, data were collected via patient interviews and patients' medical records.

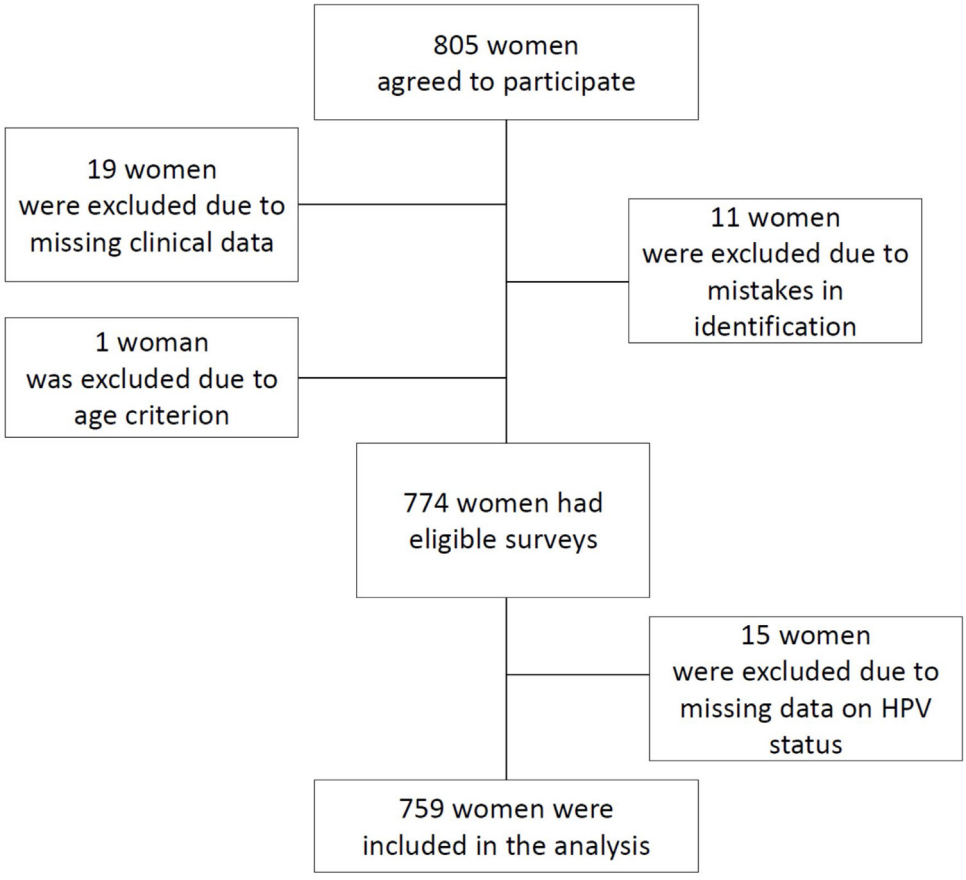

Figure 1. Exclusion and inclusion flow chart of the study.

The questionnaire was completed by gynecologists during patients' visits.

Sample collection

All study participants had Pap smear testing. The cervical swabs were used as a source for HPV genotyping using AmpliSens kit that identifies 14 high-risk HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68). The swab samples were collected into 1.5-mL Eppendorf tubes by gynecologists using a cytobrush, and the samples were transported and stored in a frozen state (−20 °C) until needed for DNA extraction.

DNA extraction and genotyping

DNA extraction from the samples was performed using Wizard Genomic DNA Purification Kit (Promega) according to the manufacturer's manual. Purity and quantity of the DNA were checked and recorded on Nanodrop 2000, Thermo Scientific. Purified DNA was stored at −80 °C until it was used for HPV DNA genotyping. HPV genotyping was performed by the method of real-time multiplex polymerase chain reaction (PCR) using AmpliSens® HPV HCR genotype-titre-FRT kit according to the manufacturer's instructions. The kit can detect and differentiate 14 high-risk HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68). The instrument used for real-time PCR was the CFX 96 RealTime PCR, Bio-Rad Laboratories. For each PCR reaction, positive and negative controls were used. DNA concentration of samples used was 3.75 ng/uL, resulting in 37.5 ng per well. The generated data were transferred into the manufacturer's software. The positivity or negativity of the samples for HPV type was determined according to the manufacturer's thresholds.

Study variables

To determine the factors that increase risk of HR-HPV, the following independent variables were analyzed: social and demographic characteristics (age, ethnicity [Kazakh, Russian and other ethnicities] and city of residence) of participants; marital status (not single – married, in a committed relationship; single – single, widowed, divorced) and family history (number of children, history of delivery, history of abortion etc); and data on gynecological health (age at the start of sexual life, menarche, gynecological operations, gynecological diseases, history of sexually transmitted infections (STIs), result of Pap test).

Data analysis

Statistical analysis was performed using STATA 16 (StataCorp, 2019). Data analysis included descriptive statistics consisting of mean values, standard deviations, and frequencies, where applicable. Independent variables were further tested using one-way analysis of variance, Chi-square test or Fisher's exact test, where appropriate. Ordinal logistic regression was performed to identify factors associated with HPV infection status. Assumptions for ordinal logistic regression, such as parallel lines and proportional odds, were checked. A *P*-value of <0.05 was considered significant for all analyses.

Ethical considerations

The study was approved by the Institutional Research Ethics Committee of Nazarbayev University (NU IREC) on 23 April 2019 (IREC number: 146/4042019). All participants were informed of the risks, benefits, goals, and methods of the study. Verbal consent was received from participants after being made aware of the volunteer and anonymous nature of the study. No personal information related to any of the patients was made available to the investigators at any time before, during or after the study.

Results

Participant characteristics

In total, 759 women from all regions of Kazakhstan participated in the study. A summary of their social and demographic

Table 1
Social and demographic characteristics of study participants classified by high-risk human papillomavirus infection (n = 759).

Characteristics	Values	No HR-HPV infection	Single HR-HPV infection	Multiple HR-HPV infection	*P*-value
Age cont.					
Range	18–69 years				0.002*
Mean (SD)	36.51 ± 10.09	37.30 ± 10.34	36.22 ± 9.90	33.32 ± 5.59	
Median (IQR)	35 (29–42) years				
18–25 y	87 (11.46%)	45 (51.72%)	24 (27.59%)	18 (20.69%)	0.042*
26–35 y	310 (40.84%)	190 (61.29%)	76 (24.52%)	44 (14.19%)	
36–45 y	235 (30.96%)	141 (60%)	68 (28.94%)	26 (11.06%)	
46> y	127 (16.73%)	90 (70.87%)	27 (21.26%)	10 (7.87%)	
Ethnicity					
Kazakh	547 (72.07%)	334 (61.06%)	141 (25.78%)	72 (13.16%)	0.701
Russian	164 (21.61%)	99 (60.37%)	42 (25.61%)	23 (14.02%)	
Other	48 (6.32%)	33 (68.75%)	12 (25%)	3 (6.25%)	
City					
Nur-Sultan	133 (17.52%)	104 (78.20%)	20 (15.04%)	9 (6.77%)	0.00*
Almaty	165 (21.74%)	86 (52.12%)	44 (26.67%)	35 (21.21%)	
Aktobe	126 (16.60%)	67 (53.17%)	41 (26.67%)	18 (14.29%)	
Oskemen	212 (27.93%)	136 (64.15%)	52 (24.53%)	24 (11.32%)	
Pavlodar	123 (16.21%)	73 (59.35%)	38 (30.89%)	12 (9.76%)	
Education					
School	127 (16.73%)	80 (62.99%)	34 (26.77%)	13 (10.24%)	0.391
College	208 (27.40%)	131 (62.98%)	56 (26.92%)	21 (10.10%)	
University	424 (55.86%)	255 (60.14%)	105 (24.76%)	64 (15.09%)	
Family					
Single	156 (20.55%)	81 (51.92%)	46 (29.49%)	29 (18.59%)	0.012*
Married/in relationship	603 (79.45%)	385 (63.85%)	149 (24.71%)	69 (11.44%)	

HR-HPV: high-risk human papillomavirus; IQR: interquartile range; SD: standard deviation.
* *P* value < 0.05.

characteristics is provided in Table 1. The mean age of participants was 36.51 ± 10.09 years, with the majority of women (40.84%) aged between 26 and 35 years. Almost three-quarters of women (72.07%) were of Kazakh ethnicity. The distribution of women recruited from the 5 cities (namely Nur-Sultan, Almaty, Pavlodar, Aktobe and Oskemen) was almost equal, but the largest number of women were from Oskemen (27.93%) and Almaty (21.74%). More than half of the participants were educated to graduate level (55.86%), and almost a quarter had undergraduate-level education (27.40%). The majority of participants (79.45%) were either married or in a committed relationship.

Social and demographic characteristics statistically significantly associated with HR-HPV infection were age, city, and family status. The majority of women with no HPV infection were older than 45 years. The majority of women with no HR-HPV infection were from Nur-Sultan (78.20%). Among those with single HPV infection, 30.89% were from Pavlodar and among those with multiple HR-HPV infection, 21.21% were from Almaty. More than one-quarter from each level of education had single HR-HPV infection. More than one quarter (29.49%) had single infection, and their marital status was single (Table 1).

Regarding gynecological and clinical characteristics of women, the mean age of their menarche was 13.65 ± 1.65 years and 85.64% of women had a normal menstrual cycle. The mean age at the start of sexual life was 20.42 ± 3.05. Almost one quarter (24.64%) had pelvic inflammatory disease. More than 70% of women had never had gynecological surgery. More than three-quarters of study participants (80.76%) had a history of one or more labors. The rest of the women had one or more pregnancies and labors. More than half of the participants had no history of abortion (56.13%). Almost 20.16% of women did not have children, the rest (79.84%) had either one or more children. In terms of Pap smear, 672 (88.54%) had a normal result (Table 2).

HPV prevalence: distribution of HR-HPV in single and multiple infection

In the sample population, 61% had no HR-HPV infection (Figure 2); 26% had single HR-HPV infection (only one type of HPV detected), and 13% had multiple infection (2 or more HR-HPV types detected). Out of all cases of single infection, HPV-16 had a 54% prevalence, followed by HPV-68 and HPV-51, both 7%, and

Table 2
Gynecological and clinical characteristics of study participants classified by high-risk human papillomavirus infection (n = 759).

Characteristics	Values (%) N	No HR-HPV infection	Single HR-HPV infection	Multiple HR-HPV infection	*P*-value
Age of menarche					
<13 y	89 (11.73%)	58 (65.17%)	20 (22.47%)	11 (12.36%)	
13–15 y	502 (66.14%)	300 (59.76%)	135 (26.89%)	67 (13.35%)	
>15 y	171 (22.13%)	108 (64.29%)	40 (23.81%)	20 (11.90%)	0.781
Menstrual function					
Abnormal	109 (14.36%)	67 (61.47%)	32 (29.36%)	10 (9.17%)	0.360
Normal	650 (85.64%)	399 (61.38%)	163 (25.08%)	88 (13.54%)	
Age of first intercourse categorical					
<18 y	84 (11.07%)	49 (58.33%)	22 (26.19%)	13 (15.48%)	0.728
≥18 y	675 (88.93%)	417 (61.78%)	173 (25.63%)	85 (12.59%)	
Polycystic ovary syndrome					0.932
Yes	16 (2.11%)	11 (68.75%)	3 (18.75%)	2 (12.50%)	
No	743 (97.89%)	455 (61.24%)	192 (25.84%)	96 (12.92%)	
Endometriosis					
Yes	52 (6.85%)	34 (65.38%)	16 (30.77%)	2 (3.85%)	0.099
No	707 (93.15%)	432 (61.10%)	179 (25.32%)	96 (13.58%)	
Pelvic inflammatory disease					0.095
Yes	187 (24.64%)	126 (67.38%)	44 (23.53%)	17 (9.09%)	
No	572 (75.36%)	340 (59.44%)	151 (26.40%)	81 (14.16%)	
Myoma					0.155
Yes	118 (15.55%)	79 (66.95%)	30 (25.42%)	9 (7.63%)	
No	641 (84.45%)	387 (60.37%)	165 (25.75%)	89 (13.88%)	
Ovarian cyst					0.737
Yes	70 (9.22%)	45 (64.29%)	18 (25.71%)	7 (10%)	
No	689 (90.78%)	421 (61.10%)	177 (25.69%)	91 (13.21%)	
History of STIs					
Yes	30 (3.95%)	23 (76.67%)	5 (16.67%)	2 (6.67%)	0.269
No	729 (96.05%)	443 (60.77%)	190 (26.06%)	96 (13.17%)	
Gynecological surgery					
Yes	224 (29.51%)	138 (61.61%)	58 (25.89%)	28 (12.50%)	0.976
No	535 (70.49%)	328 (61.31%)	137 (25.61%)	70 (13.08%)	
Number of labors					
0	146 (19.24%)	69 (47.26%)	47 (32.19%)	30 (20.55%)	0.000*
1 or more	613 (80.76%)	397 (64.76%)	148 (24.14%)	68 (11.09%)	
Number of abortions					
0	333 (43.87%)	204 (61.26%)	84 (25.23%)	45 (13.51%)	0.897
1 or more	426 (56.13%)	262 (61.50%)	111 (26.06%)	53 (12.44%)	
Number of children					
0	153 (20.16%)	72 (47.06%)	51 (33.33%)	30 (19.61%)	0.000*
1 or more	606 (79.84%)	394 (65.02%)	144 (23.76%)	68 (11.22%)	
Pap smear test					
Normal	672 (88.54%)	419 (62.35%)	171 (25.45%)	82 (12.20%)	0.488
Squamous atypia	29 (3.82%)	16 (55.17%)	7 (24.14%)	6 (20.69%)	
CIN1	13 (1.71%)	7 (53.85%)	3 (23.08%)	3 (23.08%)	
CIN2	1 (0.13%)	1 (100%)	–	–	
CIN3	14 (1.84%)	6 (42.86%)	6 (42.86%)	2 (14.29%)	
No data	30 (3.96%)	–	–	–	

CIN: cervical intraepithelial neoplasia; HR-HPV: high-risk human papillomavirus; STI: sexually transmitted infections.
* *P* value < 0.05.

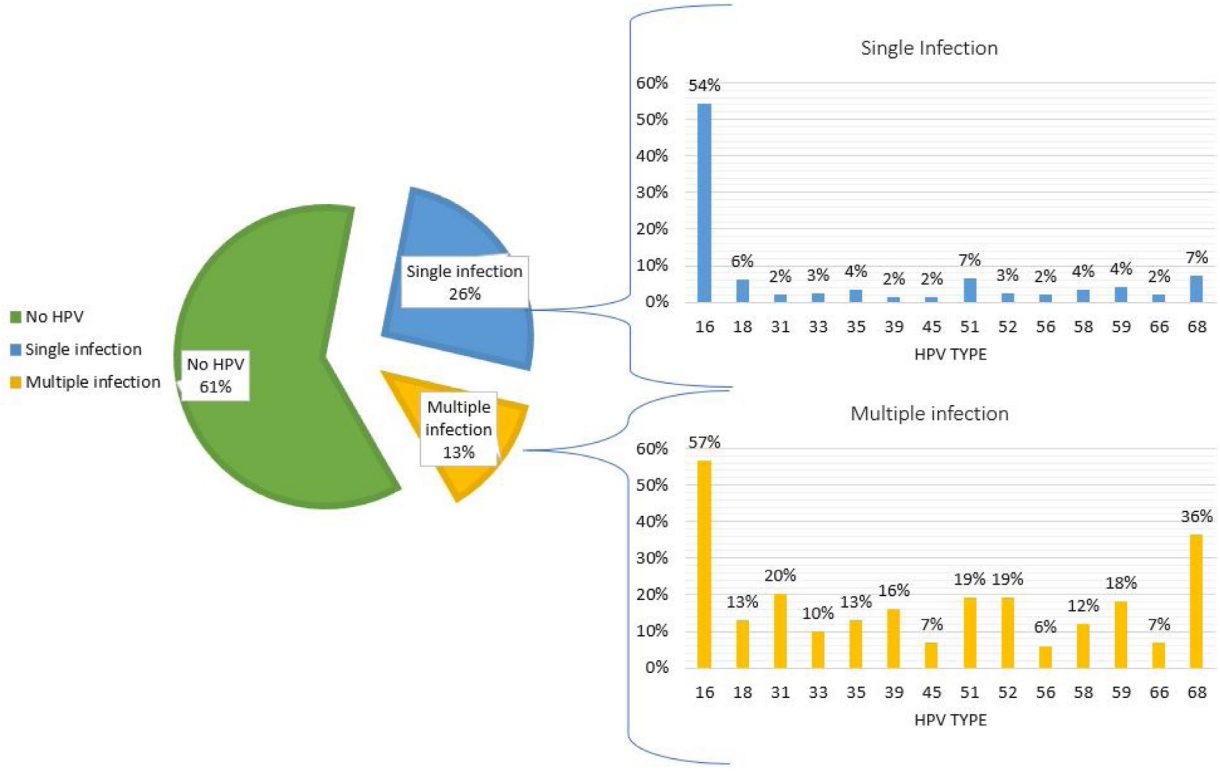

Figure 2. Distribution of high-risk human papillomavirus in single and multiple infection.

HPV-18 at 6%. Out of all cases with multiple infection, 57% had HPV-16, 36% had HPV-68, 20% had HPV-31, and 19% had HPV-51 and HPV-52.

Distribution of HR-HPV by age

Cases of women with HPV infection were the highest in the 26–35 age group, followed by those 36–45 years old (Figure 3). Prevalence was lowest in the age group ≥46. In all groups, HPV-16 was the most common HPV type. The second most common type was HPV-68 in all age groups, except 18–25, where HPV-51 took second place. Prevalence of HPV-18 decreased with older age, being highest among the 18–25-year-olds and lowest in the age group 46 and above.

Distribution of HR-HPV among the cities

The most prevalent type of HR-HPV varied among cities in Kazakhstan (Figure 4). The highest prevalence of HPV-16 was in Almaty (24%) and Oskemen (26%). The highest prevalence of HPV-18 was in Almaty (46%) and Aktobe (24%).

Correlation between HPV-HR and CIN in positive samples

The proportion of patients who were positive for both HR-HPV and cervical intraepithelial neoplasia (CIN) was 1.72% (Figure 5). More than 2% of women were HPV-negative but CIN positive. More than half of women were both CIN and HR-HPV negative (59.02%). More than 30% of women were positive for HR-HPV.

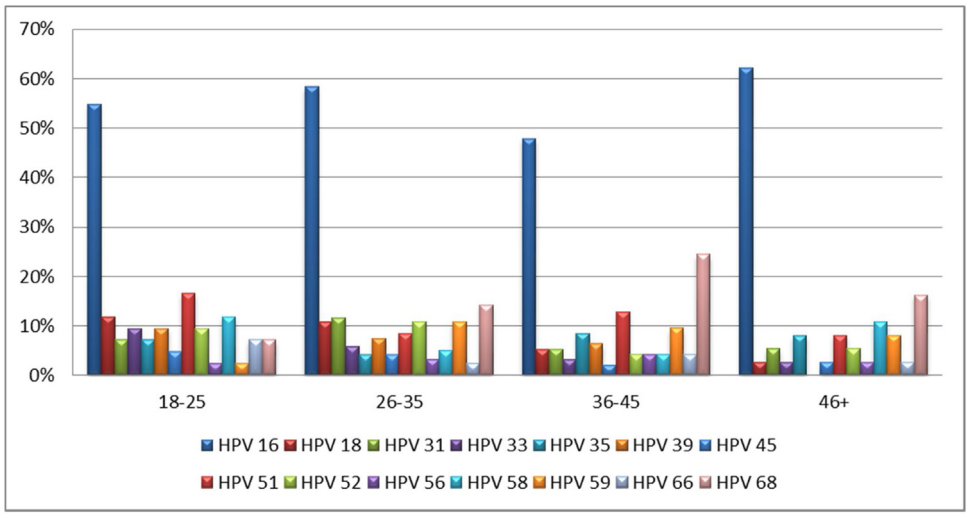

Figure 3. Distribution of high-risk human papillomavirus types by age groups.

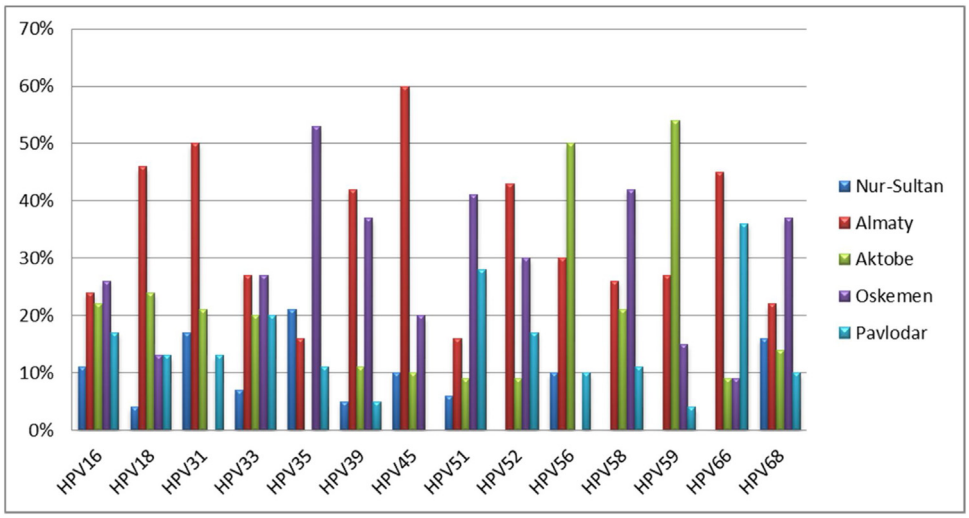

Figure 4. Distribution of high-risk human papillomavirus types by cities.

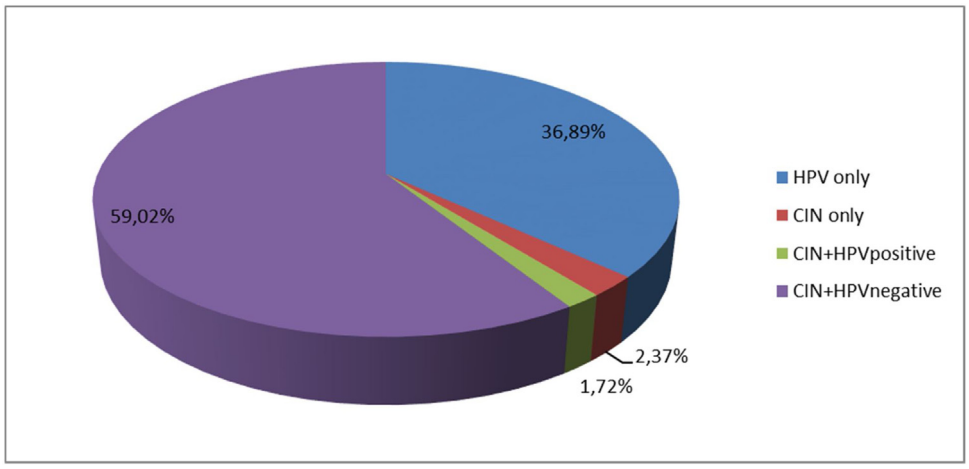

Figure 5. Predominance of high-risk human papillomavirus infection and cervical intraepithelial neoplasia results of the Pap test.

Table 3
Bivariable and multivariable ordinal logistic regression modeling examining factors associated with single or multiple high-risk human papillomavirus infection.

Variable	COR (95% CI)	*P*-value	AOR (95% CI)	*P*-value
Age	0.98 (0.96–0.99)	0.002*	0.98 (0.97–1)	0.020*
City				
Nur-Sultan	Reference	Reference	Reference	Reference
Almaty	3.5 (2.11–5.8)	<0.001*	2.84 (1.66–4.85)	<0.001*
Aktobe	3 (1.77–5.09)	<0.001*	2.63 (1.52–4.55)	0.001*
Oskemen	1.99 (1.21–3.25)	0.006*	1.74 (1.03–2.94)	0.038*
Pavlodar	2.3 (1.34–1.93)	0.002*	1.8 (1.02–3.17)	0.041*
Smoking				
No	Reference	Reference	Reference	Reference
Yes	1.93 (1.07–3.49)	0.03*	1.55 (0.83–2.88)	0.168
Family status				
Single	Reference	Reference	Reference	Reference
Not single	0.6 (0.43–0.85)	0.003*	0.61 (0.43–0.88)	0.008*
History of STI				
No	Reference	Reference	Reference	Reference
Yes	0.46 (0.19–1.09)	0.076	0.43 (0.18–1.03)	0.059
Age of first intercourse	0.98 (0.93–1.03)	0.384	1 (0.95–1.05)	0.891

COR: crude odds ratio; AOR: adjusted odds ratio; HPV: human papillomavirus; STI: sexually transmitted infection.
* *P*-value < 0.05.

Multivariable analysis

To determine factors associated with HR-HPV infection, an ordinal logistic regression was performed based on the variables that showed significance in bivariable analysis and fitted with the epidemiological picture. Therefore, participants' age, city of residence, smoking status, family status, history of STI, and age at first sexual contact were considered (Table 3).

With an increase in age by 1 year the likelihood of having an HR-HPV infection decreased by 2%, adjusting for other variables. Compared with participants living in Nur-Sultan, the likelihood of having an HPV infection for those in Almaty is 2.84-fold, Aktobe 2.63-fold, Oskemen 1.74-fold, and Pavlodar 1.8-fold higher, after adjusting for other variables. Smoking increased the odds of having infection by 1.55-fold compared with those who do not smoke, holding other variables constant. Not being single decreased the odds of having infection by 0.61-fold compared with those who are single, after adjusting for other variables. History of STI decreased the odds of having HPV infection 0.43-fold compared with those who did not have STI history, after adjusting for other variables. Age at first intercourse did not influence the likelihood of having an HR-HPV infection (Table 3).

Discussion

To our knowledge, this is the first study to explore the prevalence of HR-HPV genotypes in 5 major cities encompassing all regions of Kazakhstan. Previous studies have been limited to the western region and the capital city (Bekmukhambetov et al., 2016; Niyazmetova et al., 2017). However, high incidence and mortality rates from cervical cancer in the country mean our investigation of HR-HPV infection prevalence is important and apropos (Aimagambetova et al., 2021; Bruni et al., 2019a).

Our study found high prevalence of HR-HPV (39%), 26% of participants had single HR-HPV type infection and 13% had multiple HR-HPV infection. Most prevalent HR-HPV genotypes among single HPV infection were HPV-16 (54%), HPV-51 (7%), HPV-68 (7%), and HPV-18 (6%). HPV-16 (57%), HPV-68 (36%), HPV-31 (20%), HPV-51 (19%), and HPV-52 (19%) were the most prevalent in multiple HR-HPV infection. The distinction between single and multiple infection is important in understanding the carcinogenic role of HPV in cervical cancer. Previous studies have shown that HR-HPV infection with more than one genotype can increase the risk of cervical cancer and cervical precancerous lesions (Lee et al., 2003; Schmitt et al., 2013). Compared with studies conducted in other countries, the prevalence of multiple HPV infection in our study is low (Bruni et al., 2010; Jiang et al., 2019).

Previous studies on the prevalence of HR-HPV genotypes in Kazakhstan were conducted only in the western and central regions. The study by Bekmukhambetov et al. (2016) in Western Kazakhstan found that 26% of respondents were HPV positive, including both men and women. The most prevalent genotypes of HR-HPV were HPV-16 (10.7%), HPV-39 (5.8%), HPV-51 (5.3%), HPV-31 (4.9%) and HPV-18 (3.6%). In the second study conducted in Western Kazakhstan, the prevalence of HPV was found to be 25%, and the most common HPV genotypes were HPV-16 (26.4%), HPV-31 (10.1%), HPV-51 (9.4%), HPV-52 (9%), and HPV-6 (7.9) (Balmagambetova et al., 2020). In our pilot study conducted in Nur-Sultan in 2016, HR-HPV prevalence was 43.6%, and the most prevalent genotypes were HPV-16 (18.4%), HPV-18 (9.2%) followed by HPV-33 (4.9%), HPV-51 (4.9%), and HPV-52 (4.9%), (Niyazmetova et al., 2017).

There are similarities and differences when the results of this study are compared with those from other countries. Similar to the results of this study, HPV-16 is the most common HR-HPV genotype in other countries (Stamataki et al., 2010). The second most common HR-HPV genotype reported in other countries is HPV-18 which is different from our findings (Forman et al., 2012; de Sanjosé et al., 2007). Similar to our study, HPV-51 was found to be the dominant HR-HPV genotype in China, although the prevalence was only 2.6% (Jiang et al., 2019). No studies showed a high prevalence of HPV-68. It is important to mention that although HPV infections are widespread in many countries, prevalence and distribution are heterogeneous (Chan et al., 2019).

In terms of age distribution, HPV-16, HPV-68, and HPV-51 were most prevalent in all age groups. This study found a statistically significant association (P = 0.042) between age group and HPV infection. The highest prevalence of HR-HPV infection was in the age groups of 26–35 and 36–45 years old, and the lowest prevalence was in the age group ≥46. This finding is similar to the study conducted by Hermansson et al., where they found that HPV prevalence is lower among women aged >60 (Hermansson et al., 2018). In addition, in a Greek study, the highest prevalence of HPV was also found among the youngest age group of 16–20- year-olds (Stamataki et al., 2010). However, in the study conducted in Saudi Arabia, the peak of HPV prevalence among women was at age 60 (Bondagji et al., 2013).

Our study showed that HPV genotype distribution varies geographically. This study found a statistically significant (P < 0.001) correlation between cities and HPV infection. Among the most prevalent genotypes found in this study in Almaty (southern region of Kazakhstan) were HPV-31 (50%), HPV-18 (46%), HPV-52 (43%), and HPV-16 (24%). In Aktobe (western region of Kazakhstan), there was a high prevalence of HPV-18 (24%) and HPV-51(41%). In Oskemen (eastern region of Kazakhstan), there was a high prevalence of HPV-68 (37%) and HPV-16 (26%). These differences in HPV genotype prevalence between regions could be explained by the fact that Kazakhstan has a large territory and large uninhabited areas between regions. A study conducted in China showed that HPV prevalence could vary significantly within regions of one province (Jiang et al., 2019).

Although in this study CIN was not identified as a statistically significant risk factor, many other studies show that having HR-HPV infection was a high risk for developing precancerous conditions (Mirabello et al., 2018; Skinner et al., 2016; Stanley, 2010). The results of the questionnaire analysis showed that 20% of tested women had CIN of grades 1 (1.71%), 2 (0.13%), and 3 (1.84%), and squamous atypia (3.82%). After comparing HPV genotyping data, we found that only 1.71% of women had both CIN and HR-HPV. However, it is worth mentioning that studies show that the results of Pap smear tests have high false-negative rates (Consul et al., 2012). Therefore, to see relevant association between CIN and HPV, HPV-positive patients with normal cytology should be observed for some period.

To determine factors associated with HPV infection, participants' HR-HPV genotyping results were divided into 3 groups: no infection, single infection and multiple infection. The results of ordinal logistic regression demonstrated that older age decreases the odds of having HPV infection, which is in line with the results of other studies (Smith et al., 2008), where those from a younger age range have a higher prevalence of the infection. Being in a committed relationship also decreased the odds of having an HR-HPV infection when compared with being single. This finding could be related to having a constant sexual partner when in a committed relationship, which reduces risk of infection as the number of sexual partners has been found to be one of the risk factors for developing an HPV infection (Chan et al., 2003). Smoking is another risk factor in our model that demonstrated increased odds of having an HPV infection. The results are in line with conclusions of other studies that indicate increased risks of having an HPV infection were associated with increased smoking (Vaccarella et al., 2008). Compared with all other cities, living in

the capital city of Kazakhstan (Nur-Sultan) decreased the likelihood of a participant being HPV positive. This decreased likelihood may be explained by better access to healthcare and more comprehensive patient education. Although HPV is often reported as a co-infection with other STIs and having a history of STI is one of the risk factors (Kops et al., 2019), it had only marginal association with the outcome variable in our model. Moreover, in our study, it decreased the odds of a woman having an HPV infection. This finding could be due to reporting bias, where women did not fully disclose their STI status. Another risk factor included in our model, age at first intercourse, had no effect on the likelihood of women having an HPV infection; again, this could also be related to reporting bias, as women may be uncomfortable disclosing sensitive information.

Strengths and limitations

Ours is the first study with such a wide geographical reach in Kazakhstan. A major city from the northern, southern, eastern, western, and central regions of the country was included. Moreover, the information collected with the help of practicing gynecologists included not only clinical data but also socio-demographic characteristics provided by the patients themselves. This data allowed us to build an ordinal logistic model that identified predicting factors on the presence or absence of HPV infection in our study participants. However, this was an observational cross-sectional study, the factors identified through statistical modeling are not causal.

Moreover, the convenience sampling method introduces selection bias. Because information on women who did not participate in the study was not collected, we cannot identify if a significant difference between respondents and non-respondents was present. Also, despite the broad outreach to different parts of the country, our findings might not be generalizable to all women in Kazakhstan. For example, women from rural areas and other demographic groups could have been excluded through convenience sampling. In addition, the self-reporting nature of the participants' answers could result in recall bias, underreporting or exaggeration of the responses.

Conclusion

Beyond confirming and adding to the results of previous studies conducted in Kazakhstan on the prevalence of HPV infection, this study expanded the geographical scale and identified socio-demographic characteristics associated with the presence of HR-HPV infection. It identified that younger, single, smoking women, who do not live in the capital city, Nur-Sultan, have increased likelihood of having an HR-HPV infection. HPV-16, HPV-68 and HPV-51 were found to be the most common genotypes in the sample population. Information collected through this study can provide a basis for future research and policy changes in the methods used in Kazakhstan to manage and prevent cervical cancer.

Authors' contribution

GA, CKC, AzAz, SAK were involved in creating the study protocol; TU, BI, ZhD were involved in the process of the samples collection. TI, AB, AA, KN and ZA performed PCR sample analysis; AI, TI, AB, performed statistical analysis and data interpretation; SK, AA and involved in preliminary data design and assessment, literature review. GA, AB, TI drafted the manuscript. CKC, SAK, AzAz and GA provided a critical revision and regular feedback of the manuscript. All authors contributed to refinement of the study protocol. All authors have read and approved the final manuscript.

Data availability statement

The study questionnaires and raw data are available via the link: https://zenodo.org/record/4600664#.YEsv6WgzbIU (accessed on 21 April 2021).

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ijid.2021.06.006.

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