TITLE:

Prevalence of high-risk human papillomavirus infection among Kazakhstani women with abnormal cervical cytology

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Abstract

Aim: This study aims to determine prevalence of HR-HPV in Kazakhstani women with abnormal cervical cytology results. The hypothesis is that HR-HPV prevalence will be high among these women.

Methods: An anonymous patient database (de-identified patient records) will be used for data analysis. Statistical analysis will be carried out with STATA 16.

Results: Women with abnormal cytology were slightly older (mean age: 36.8) than those with no abnormal cytology (mean age: 36.0). The most prevalent age group in both categories was 25-34. Overall frequency of HPV was higher among women with abnormal cytology (81.6%) compared to those with no abnormal cytology (39.5%). HPV16 was the most frequent type, observed in 28.4% of women with abnormal cytology and 9.2% of women with no abnormal cytology. Multiple HPV infections were more frequent in women with abnormal cytology, particularly co-infections of HPV16 and HPV18.

Conclusion: This study highlights the high prevalence of HPV infection in Kazakhstani women with abnormal cervical cytology, with HPV 16 and HPV 18 being the most prevalent types. The findings support the need for targeted HPV vaccination and enhanced screening programs to prevent cervical cancer in Kazakhstan.

Introduction

Cervical cancer (CC) is a malignant disease of the uterine cervix that develops due to the uncontrollable growth of epithelial cells that line the cervix (National Cancer Institute, n.d.). It is the fourth most widespread cancer and also the most prevalent reason for deaths related to cancer amidst women, especially in low- and middle-income countries (LMICs), where CC accounts for nearly 85% (Sung et al., 2021; Serrano et al., 2018). About 604,000 new cases and 324,000 deaths of CC were found in 2020, with incidence rates varying significantly by country (Arbyn et al., 2020; Sung et al., 2021).

Human papillomavirus (HPV) was shown to be linked to CC development, predominantly transmitted through genital skin-to-skin contact, though other transmission routes exist (Zur Hausen, 2002; Okunade, 2020; Petca et al., 2020). Seventy percent and more of sexually active people will become infected sometime during their lives (Bruni et al., 2010; Chan et al., 2019). High-risk HPV (HR-HPV) types, particularly HPV16 and 18, are strongly correlated with CC, while most HPV infections are transitory and rarely advance to cancer (Okunade 2020). Persistent HR-HPV infections, however, may give rise to cervical intraepithelial neoplasia (CIN), a premalignant condition with a potential to progress to CC (Crosbie et al., 2013; Stanley et al., 2007; Woodman et al., 2007).

The natural history of CC is long (up to 20 years), and there are stages of neoplastic premalignant lesions called cervical intraepithelial neoplasia (CIN) preceding the CC (Crosbie et al., 2013; Stanley et al., 2007; Woodman et al., 2007). CIN lesions are categorized into CIN1, CIN2, and CIN3, with varying risks of progression to CC. CIN1 typically regresses spontaneously, while CIN3 is a true precancerous lesion with a significant risk of developing into CC if left untreated (Chan et al., 2019; Moscicki et al., 2010).

In Kazakhstan, CC incidence is high, with rates increasing between 2009 and 2018 (Igissinov et al., 2021). Contributing factors include the high prevalence of HPV, lack of vaccination against HPV, and low coverage of CC screening (Aimagambetova et al., 2021; Bekmukhambetov et al., 2016; Niyazmetova et al., 2017). Improving screening program accuracy and coverage is essential. This research project aims to determine the prevalence of HR-HPV in Kazakhstani women with abnormal cervical cytology, hypothesizing that it will be higher in women who attend gynecological clinics than in the overall population.

Methods

Study design and study subjects

The project's design was a cross-sectional study. The data was collected between May 2019 and June 2020, and then anonymized. Data analysis and subsequent report generation were done using de-identified records of patients (an anonymous patient database). The database included patients' dates of birth, results of their Papanicolaou test, and their HPV status. Women aged 18 to 70 who visited gyneacological clinics were recruited using convenience sampling.

Study settings

The study included women from five cities different regions of Kazakhstan: central (Astana), western (Aktobe), southern (Almaty), eastern (Oskemen), and northern (Pavlodar). Cervical samples for HPV genotyping were collected during routine cervical screening with the Papanicolaou test (Pap test) and analyzed in the NUSOM laboratory by PCR. In this study the analysis of anonymized patients' data was performed.

Ethical considerations

Initial data collection was approved by the Institutional Research Ethics Committee of Nazarbayev University on 23 April 2019 (IREC number: 146/4042019). Every participant was made aware of the study's objectives, methodology, risks and benefits. After being informed that the study was anonymous and voluntary, verbal consent was received from each participant. In this study, only an anonymous dataset was analyzed. Anonymous dataset analyses were approved by the Nazarbayev University School of Medicine Institutional Research Ethics Committee (NU IREC), which granted this project an exemption.

Statistical Analysis

STATA 16 was used for the statistical analysis. When appropriate, descriptive statistics from mean values, standard deviations, and frequencies will be used in data analysis. Continuous independent variables were examined using the Kruskal-Wallis test and student t-test. Categorical independent variables will be analyzed using Fischer's exact tests as well as Chi-square tests. All analyzes were regarded as significant if the P-value is less than 0.05.

Results

Table 1 describes the mean ages of women with “no abnormal cytology and a "positive HPV test” and “abnormal cytology and a "positive HPV test”. Overall, women with no abnormal cytology were slightly younger (36.02±10.9) than women with abnormal cytology (36.8±11.3) (Table 1). Women were also divided into age categories. The most prevalent category in both was women aged 25-34 (Table 1). The least prevalent age category in women with no abnormal cytology was 55-70 (11.1%), while in women with abnormal cytology, the least prevalent was the 45-54 age group (10.1%).

The mean ages of the two groups were analyzed using a student’s t-test, indicating no statistically significant difference ($p = 0.331$), suggesting that in this dataset, age was not a determining factor for abnormal cytology. Age categories were compared using a chi-square test, which produced p-value of 0.496, further indicating that there was no significant difference in the age distribution between the two groups.

Table 1. Data on participants’ HPV status.

Variables	No abnormal cytology and a "+" HPV test	Abnormal cytology and a ‘+’ HPV test	p-value
Age	36.02±10.9	36.8±11.3	0.331 (student t-test)
Age categories:			0.496 (Chi-square)
<25	31 (14.9%)	12 (11.0%)	
25-34	83 (39.9%)	46 (42.2%)	
35-44	40 (19.2%)	23 (21.1%)	
45-54	31 (14.9%)	11 (10.1%)	

55-70	23 (11.1%)	17 (15.6%)	
Single HPV infection:	No abnormal cytology and a "+" HPV test		
HPV16	19 (9.2%)	31 (28.4%)	0.968 (Chi-square)
HPV18	9 (4.3%)	17 (15.6%)	0.728 (Chi-square)
HPV31	4 (1.9%)	2 (1.8%)	1.0 (Fischer's exact)
HPV33	10 (4.8%)	10 (9.2%)	0.400 (Fischer's exact)
HPV35	2 (0.9%)	1 (0.9%)	1.0 (Fischer's exact)
HPV39	7 (3.4%)	4 (3.7%)	1.0 (Fischer's exact)
HPV45	6 (2.9%)	2 (1.8%)	1.0 (Fischer's exact)
HPV51	8 (3.8%)	5 (4.6%)	0.248 (Fischer's exact)
HPV52	7 (3.4%)	6 (5.5%)	0.628 (Fischer's exact)
HPV56	1 (0.5%)	3 (2.8%)	0.400 (Fischer's exact)
HPV58	2 (1.0%)	6 (5.5%)	1.0 (Fischer's exact)
HPV59	7 (3.4%)	2 (1.8%)	0.109 (Fischer's exact)
Total:	39.5%	81.6%	
Multiple HPV infections:			0.083 (Chi-square)
HPV 16 & HPV 18	2 (14.3%)	6 (31.2%)	
HPV16 & HPV58	0	2 (10.5%)	
HPV52 & HPV56	0	2 (10.5%)	
HPV16 & HPV51	3 (21.4%)	2 (10.5%)	
HPV16 & HPV59 & HPV33	0	2 (10.5%)	

HPV58 & HPV33	0	2 (10.5%)	
HPV16 & HPV39	2 (14.3%)	1 (5.3%)	
HPV18&31	0	2 (10.5%)	
HPV18 & HPV45	1 (7.1%)	0	
HPV18 & HPV56	1 (7.1%)	0	
HPV18& HPV45 & HPV51	2 (14.3%)	0	
HPV31 & HPV51	2 (14.3%)	0	
HPV31& HPV52 & HPV33	1 (7.1%)	0	

These women, with or without abnormal cytology, were also tested for the HPV infection prevalence and its different types. The overall prevalence of HPV among women with abnormal cytology was 81.6%, while in women with normal cytology, it was 39.5% (Table 1). Thus, the total prevalence of HPV was two times higher in women with abnormal cytology. Among women with normal cytology, the highly prevalent HPV types were HPV16 (9.2%), HPV18 (4.3%), and HPV33 (4.8%). The same can be said about women with abnormal cytology since the highest prevalence was seen with HPV 16 (28.4%), 18 (15.6%), and 33 (9.2%). The percentages of all other types can be seen in Table 1.

Chi-square tests were used for HPV16 and HPV18 to check for statistical difference in HPV prevalence between women with normal and abnormal cytology. The results showed no significant difference with p-values of 0.968 and 0.728, respectively. Low sample size HPV types, such as HPV31, HPV33 and others, were subjected to Fisher's exact test. These types were also not statistically associated with abnormal cytology (p-values> 0.05).

There were also multiple infections with different types of HPV. Women with normal cytology mostly had HPV16 and HPV51 co-infections (21.4%), while those with abnormal cytology mostly had HPV16 and HPV18 (31.2%). To boost statistical power and account for the small sample sizes of individual multiple HPV infection types, multiple HPV infections were combined into a contingency table. To determine if these infections were to linked to abnormal cytology, a chi-square test was conducted. The test's p-value of 0.083 indicated that there was no significant correlation between abnormal cytology and multiple infections.

Women with abnormal cytology were further divided into women with CIN1, 2, and 3 lesions. Figure 1 describes the prevalence of these different CIN lesions in women with abnormal cytology and a positive HPV test. As one can see, the highest prevalence, more than half, is attributed to CIN1, with 61% (Figure 1). CIN2 and CIN3 are roughly similar, with 22% and 17%, respectively.

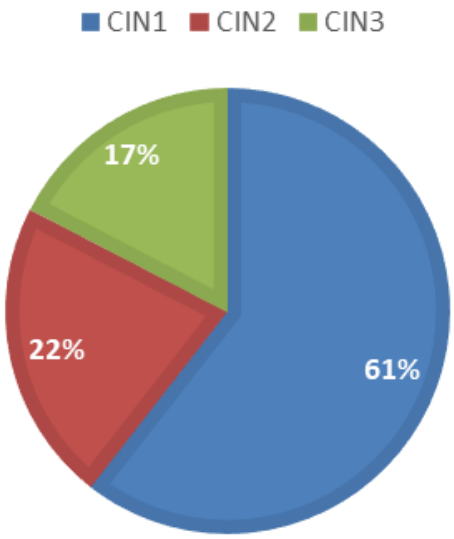

Figure 1. Prevalence of CIN lesions in women with abnormal cytology and a positive HPV test

Table 2 illustrates data for women with CIN1, 2, and 3 lesions. The lowest mean age among these women was CIN3 (35.6±9.7), and the highest was CIN1 (37.3±11.4). The age category with the highest prevalence was again 25-34 with around 40% (Table 2). In women with CIN1 lesions, the lowest prevalence was in age categories "<25" and "45-54" with 10.%. Similarly, women in the "45-54" age group are the least prevalent (8.3%) in CIN2 lesions. The lowest prevalence among women with CIN3 lesions was 10.5%, which was seen in the "<25", "45-54" and "55-70" age categories. Age differences between the CIN1, CIN2, and CIN3 groups were assessed using the Kruskal-Wallis test. Since the data was not regularly distributed, this test was selected. The test's p-value of 0.396 indicated that there was not significant variation in the age distribution of the three CIN groups.

Table 2. Data on participants with CIN 1, 2, and 3 lesions

	CIN1	CIN2	CIN3	p-value
Age	37.3±11.4	36.5±12.7	35.6±9.7	0.396 (Kruskal-Wallis)
Age categories:				0.999 (Chi-square)
<25	7 (10.6%)	3 (12.5%)	2 (10.5%)	
25-34	28 (42.4%)	10 (41.7%)	8 (42.1%)	
35-44	13 (19.7%)	5 (20.8%)	5 (26.3%)	
45-54	7 (10.6%)	2 (8.3%)	2 (10.5%)	

55-70	11 (16.7%)	4 (16.7%)	2 (10.5%)	
Single HPV infection:				
HPV16	13 (19.7%)	9 (37.5%)	9 (47.4%)	1.0 (Chi-square)
HPV18	5 (7.6%)	5 (20.8%)	7 (36.8%)	1.0 (Chi-square)
HPV31	0	0	2 (10.5%)	N/A
HPV33	2 (3.0%)	6 (25.0%)	2 (10.5%)	N/A
HPV35	1 (1.5%)	0	0	N/A
HPV39	3 (4.5%)	1 (4.2%)	0	N/A
HPV45	2 (3.0%)	0	0	N/A
HPV51	5 (7.6%)	0	0	N/A
HPV52	2 (3.0%)	0	4 (21.1%)	N/A
HPV56	1 (1.5%)	0	2 (10.5%)	N/A
HPV58	2 (3.0%)	4 (16.7%)	0	N/A
HPV59	0	2 (8.3%)		N/A
Total HR-HPV	36	27	26	1.0 (Chi-square)
Multiple HPV infections:				0.008 (Chi-square, χ^2 = 29.77)
HPV16 & HPV18	2 (40%)	0	4 (50%)	
HPV16 & HPV58	0	2 (33.3%)	0	
HPV52 & HPV56	0	0	2 (25%)	
HPV16 & HPV51	2 (40%)	0	0	
HPV16 & HPV59 & HPV33	0	2 (33.3%)	0	
HPV58 & HPV33	0	2 (33.3%)	0	
HPV16 & HPV39	1 (20%)	0	0	

HPV18& HPV31	0	0	2 (25%)	

Figure 2 portrays the frequency of single HPV infections among women with CIN1, 2, and 3 lesions. These are visual representations of the data in Table 2. As one can see in Figure 2, women with CIN1 lesions had 10 different single HPV infections. The most predominant HPV types were HPV16 (19.7%), HPV18 (7.6%), and HPV51 (7.6%). Women with CIN2 lesions mostly had six different single HPV infections, with the most prevalent being HPV 16, 18, and 33 with 37.5, 20.8, and 25 percent, respectively (Figure 2). There were also six types of HPV in women with CIN3 lesions (Figure 2). The most common among them was HPV16 with almost half (47.4%), HPV18 with 36.8%, and HPV52 with 21.1%.

The results of a chi-square test for HR-HPV presence across CIN1, CIN2 and CIN3 showed a p-value of 1.0, showing that there was no statistically significant difference in high-risk HPV infections across CIN severity levels. Because of their greater sample numbers, HPV16 and HPV18 were examined independently, whereas other HPV types, along with HPV16 and HPV18, were grouped together into a single high-risk HPV category. This approach was necessary because the small sample for individual HPV types made separate statistical tests infeasible.

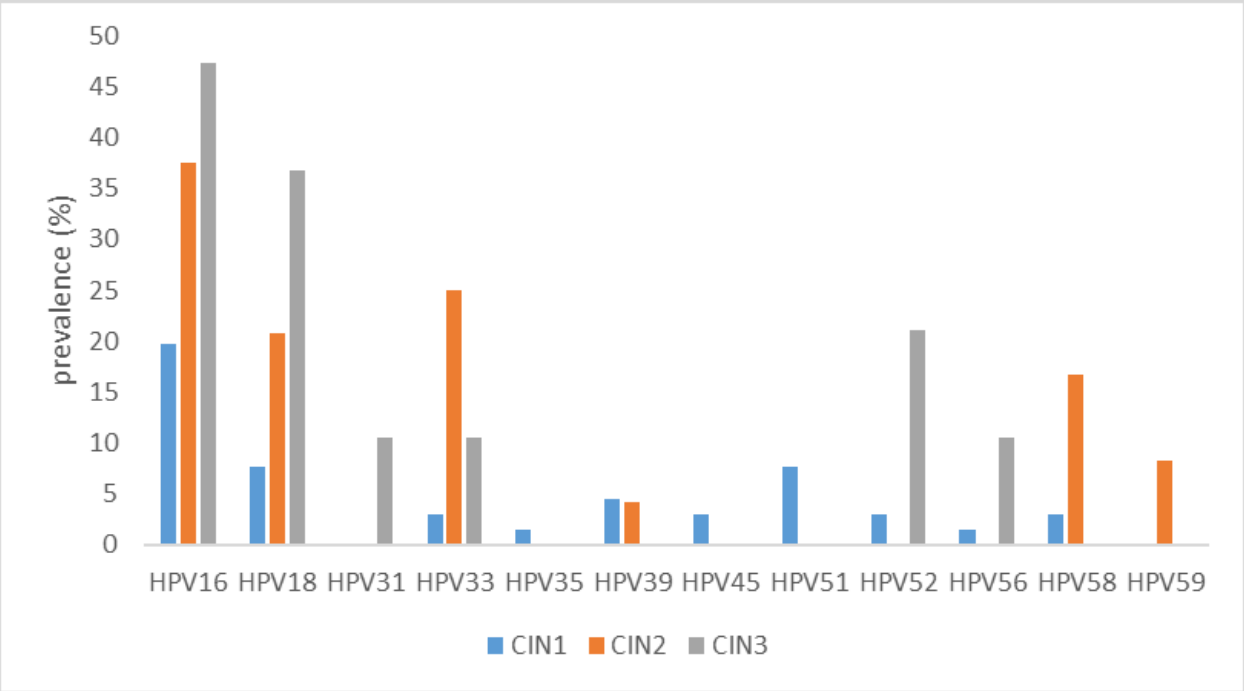

Figure 2. Prevalence of different HPV types in women with CIN1, CIN2 and CIN3

Multiple infections are also visualized in Figure 3. CIN lesions were used to categorize women with abnormal cytology. Overall, more than half of women with multiple HPV infections had abnormal cytology. Co-infections with HPV16 & HPV51 and HPV16 & HPV18 were most common (40%) in women with CIN1 lesions. Among women with CIN2, co-infections with

HPV58 & HPV33, HPV16 & HPV18, and a triple infection with HPV16 & HPV33 & HPV59 had equal prevalences (33%). Half of the women with CIN3 had an HPV16 & HPV18 co-infection.

Multiple HPV infections were put into a contingency table and evaluated using a chi-square test in order to further examine the connection between the severity of CIN and multiple HPV infections. This test produced a statistically significant p-value of 0.008, which is different from the case of abnormal cytology. This indicates that the severity of CIN increased with the number of HPV infections. This finding suggest that the severity of CIN increased with the number of HPV infections.

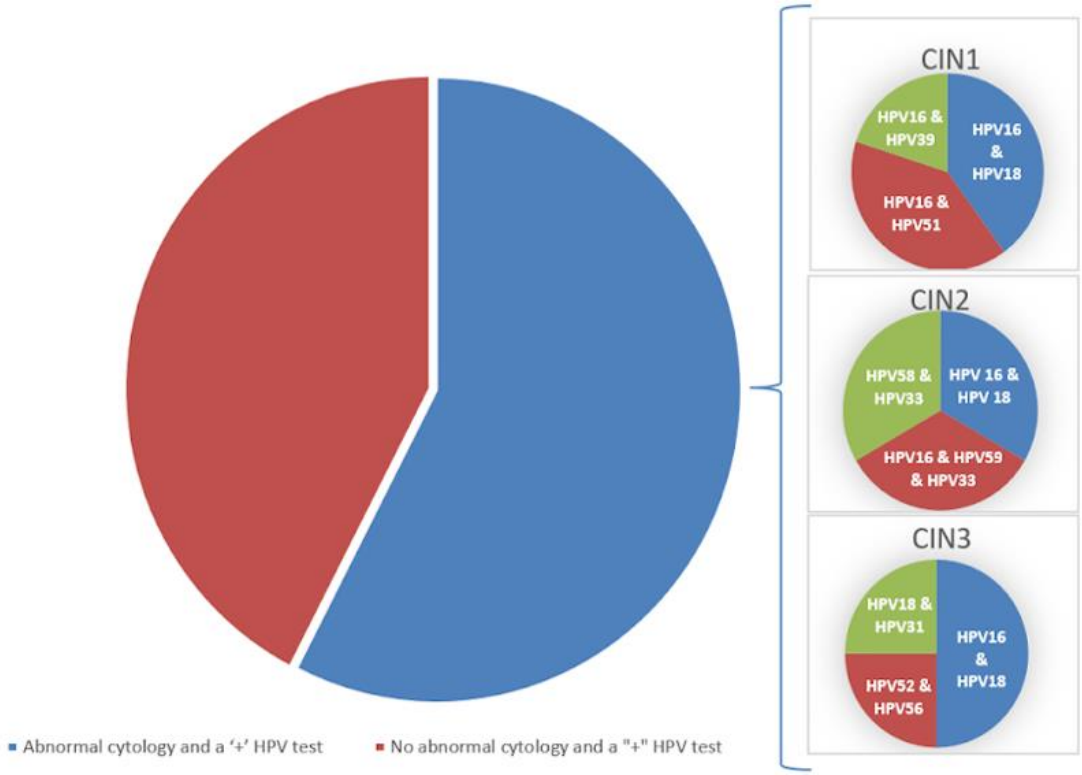

Figure 3. Multiple HPV infections in women with abnormal cytology, categorized by CIN1, CIN2, and CIN3 lesions.

Discussion

Cervical cancer (CC) remains to be a significant problem for medicine and public health globally (Arbyn et al., 2018), even though the World Health Organization is heavily integrating HPV vaccination and screening programs into local healthcare systems (Aimagambetova et al., 2022). Cervical cancer development has been directly correlated with persistent HR-HPV infection (zur Hausen, 2002; Serrano et al., 2018), with more than 95% of CC cases being attributed to HR-HPV infection (Okunade, 2020; Castellsagué, 2008). In a study done in various Kazakhstani regions, the prevalence of HR-HPV was around 39–43%, which is relatively high (Babi et al., 2021; Niyazmetova et al., 2017). Fortunately, CC has a long progression span of around 20 years (Rodriguez et al., 2008; Chan et al., 2019), which means that precancerous lesions are treatable when detected early. When it comes to Kazakhstan, incidence of CC has risen over the past ten years (Igissinov et al., 2021), despite the presence of a national cervical cancer screening program in the country (Aimagambetova et al., 2021). Although there is some understanding about prevalence of high-risk HPV in women attending gynecological clinics, no studies on the frequency of high-risk HPV types amidst Kazakhstani women with precancerous cervical lesions have been conducted. Thus, objective of this research project was to assess the prevalence of high-risk HPV types in women who have abnormal cervical cytology.

One of the main findings of this study is that 81.6% of women with abnormal cytology had HR-HPV infection, while the prevalence in women with normal cytology was 39.5%. This outcome is comparable to another study in Ethiopia, where the prevalence of HR-HPV in women with abnormal cytology was 83.2% (Wolday et al., 2018). Similarly, an Israeli study found that HPV was identified in 85% of the samples with CIN3 lesions (Bassal et al., 2015).

Another finding was that among women with abnormal cytology, the most prevalent HPV types were HPV16 (28.4%), HPV18 (15.6%), HPV33 (9.2%), HPV52 (5.5%), and HPV58 (5.5%). This is similar to other studies in countries like Russia (Shipitsina et al., 2011), Cyprus (Krashias et al., 2017), Ethiopia (Wolday et al., 2018), Mongolia (Tsedenbal., 2018), and Turkiye (Beyazit et al., 2018; Muderries et al., 2019). Especially, in studies from Japan (Zhang et al., 2019) and China (Xu et al., 2023), one can see similarities in HR-HPV types with the highest prevalence. Xu et al. (2023) claim that this might be because some genotypes of HPV are more common among various races or regions.

This study also stratified abnormal cytology by CIN lesions and identified the HPV prevalence for each. For CIN1 lesions, the top three most common HPV types were HPV16 (19.7%), HPV18 (7.6%), and HPV51 (7.6%). In a study done in Northern China, the results were quite different, with the three most frequent HR-HPV types for CIN1 being HPV16 (36.7%), HPV58 (20.4%), and HPV56 (15.3%) (Zhao et al., 2019). In a different study done also in China, the HPV types with the highest prevalence for CIN1 were 16, 52, 33, 58, 56, 66, and 68 (Ma and Yang, 2021). In Iran, despite common high-risk types like HPV types 16 (32%) and 18 (12%), other low-risk types like 6 (15%), 42 (8%), and 53 (6%) were found for CIN1 (Salavatiha et al., 2021). The authors suggest that these low-risk types might be more aggressive in Iran, which is why they are found in CIN1 lesions. When it comes to more developed countries, in a study done on Portuguese women, the top three HPV types detected for CIN1 were HPV 16, HPV31,

and HPV66 (Pista et al., 2010). HPV 16 and HPV18 were the most common HPV types in another Israeli study, with HPV51, HPV 58, HPV59, and HPV66 sharing third place (Siegler et al., 2017). One can see that the most common HPV genotype for the CIN1 lesion is HPV16, with other types being more common depending on different regions.

The prevalence of different HPV types within high-grade cervical lesions like CIN2 and CIN3 was also identified in this study. The most predominant HPV types among women with CIN2 were HPV 16 (37.5%), 18 (20.8%), and 33 (25%). Around half (47.4%) of the women with CIN3 had HPV 16. HPV18 and HPV52 were also common, with 36.8% and 21.1%, respectively. In many studies, CIN2 and CIN3 were combined and considered together as high-grade cervical intraepithelial neoplasias. In an EDITH study in France, HPV16, HPV31, and HPV33 were, in descending order, the three most prevalent HPV genotypes in both CIN2 and CIN3 lesions (Pretet et al., 2007). Similarly, in an Israeli study, HPV16 and HPV31 had the highest prevalence among CIN 2-3 lesions, with HPV18 being the third (Siegler et al., 2017). According to Pista et al. (2010), HPV16 and HPV31 infections were again the most prevalent in Portuguese women's CIN2+ lesions, with HPV51 and HPV53 sharing the third place. In Iran, CIN2-3 cases frequently exhibited the presence of HPV types 16, 18, and 31 (Salavatiha et al., 2021). In two studies from China (Zhao et al., 2019; Ma and Yang, 2021), CIN2+ lesions were mostly infected with HPV16, 52, 58, and HPV16, 18, 58, respectively. All studies discussed, including our own, had HPV16 as the most predominant genotype, just like CIN1 lesions do.

In this study, abnormal cytology was present in more than half of the women with multiple HPV infections. A co-infection present in all three CIN lesions was HPV16 and HPV18. In an EDITH study (Pretet et al., 2007), HPV16 and HPV18 co-infection was infrequent, however, HPV16 with other high-risk HPVs, excluding HPV18, was the most common co-infection. An important statistical finding of this study is that while multiple HPV infections were not significantly associated with abnormal cytology, they were significantly associated with CIN severity ($p = 0.008$). The strong correlation implies that having several HPV infections could be a factor in the development of more severe lesions after CIN1. The study by Jaisamrarn et al. (2013), which analyzed the development of HPV infection in the PATRICIA study's control arm, supports this conclusion. Their findings suggest that numerous HPV infections may enhance the probability of cervical lesion progression, emphasizing the potential significance of co-infections in CIN severity.

This is the first study in Kazakhstan that we are aware of that looks into the frequency of high-risk HPV in women with abnormal cervical cytology. In contrast to earlier research from Kazakhstan (Balmagambetova et al., 2020; Imankulova et al., 2018), which only reported the prevalence of cervical lesions, this study connected the participants' HPV with abnormal cervical cytology. Another strength of this study is that because the participants came from a variety of regions of the country, the study's conclusions are probably applicable to women in Kazakhstan. Moreover, finding out how common high-risk HPV infection is in women with abnormal cervical cytology will aid in both choosing the best HPV vaccine and advancing the HPV vaccination cause. Still, there are some limitations to this study. The sample size of the study was comparatively small, which could have led to a reduction in the precision of the estimates. Some other limitations include incomplete information regarding the participants' past medical and

parity histories, as well as the lack of information regarding Pap test results following proper treatment of cervical lesions. A larger sample size with more participant information should be used in future research on the prevalence of HR-HPV and abnormal cervical cytology to enhance the validity of the results.

Cervical cancer is among the cancers that can be prevented. Thus, one crucial public health strategy for women with abnormal cervical cytology is screening for HR-HPV because it has been established that HPV infection and CC are connected. The introduction of an HPV vaccination program is essential given the high frequency of high-risk HPV types, especially types 16, 18, 31, 33, and 52, among Kazakhstani women who have abnormal cervical cytology. Gardasil-9 would be the most suitable vaccination for immunizing women in Kazakhstan for that reason. Vaccination could help prevent most cases of cervical lesions if it were put into practice.

In conclusion, this study shows a high rate of high-risk HPV (HR-HPV) amidst women with abnormal cervical cytology in Kazakhstan, with 81.6% of these women carrying HPV types like 16, 18, 33, 52, and 58. These findings match global data, highlighting the important role of HR-HPV in the development of cervical cancer. Even though Kazakhstan has a national screening program, the rising number of CC cases over the past decade suggests that stronger public health efforts are needed. In addition to that, introducing an HPV vaccination program, especially with Gardasil-9, could help lower CC cases. However, the study's small sample size and incomplete data suggest that more research is necessary to confirm these results. Overall, the study emphasizes the need for widespread HPV vaccination and screening to prevent cervical cancer and improve women's health in Kazakhstan.

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