

# Prevalence and Correlation between High-Risk HPV Genotypes and Pap Smear Findings in Bahrain: A Retrospective Approach

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## Abstract

**Background:** Human papillomavirus (HPV) is currently the most common pathogen responsible for cervical cancer (CC), a major cause of cancer-related deaths in women. This study aimed to estimate the current HPV prevalence in Bahrain and to determine the association of high-risk HPV (HR-HPV) genotypes with cytological findings, age, and clinical history of the patients.

**Methods and Results:** Our study used a retrospective approach. Convenience sampling was used to gather 100 cases of HPV-positive women with abnormal and normal Pap smear findings from January 2017 to April 2023 in the Cytology Department at King Hamad University Hospital. Out of 100 HR-HPV positive cases, non-16/18/45 HR-HPV was found in 62%, and 73% had abnormal Pap smear findings. Among Pap smear findings, ASC-US/ASC-H ( $P=0.038$ ) and LSIL/HSIL ( $P=0.017$ ) were significantly associated with HR-HPV genotypes. ASC-US was found to be more frequently associated with HPV16+non-16/18/45 HR-HPV and LSIL with HPV18/45+non-16/18/45 HR-HPV. Most HR-HPV cases (59%) were aged  $\leq 40$  years, 25% - from 41 to 50 years old, while only 16% were  $>50$ . The age group  $\leq 40$  had the highest peak with non-16/18/45 HR-HPV genotype (35%) and HPV16 (19%). The predominant genotypes for age groups 41-50 and  $>50$  were non-16/18/45 HR-HPV types (19% and 8%, respectively).

**Conclusion:** In Bahrain, non-16/18/45 HR-HPV infection is becoming more prevalent, with ASC-US being the most common abnormal Pap finding and the highest HPV infection in women aged 40 years or younger. Based on our findings, we recommend effective screening and vaccine programs for women aged 40 years and younger, as early detection can lower infection rates and improve recovery. (International Journal of Biomedicine. 2024;14(1):52-58.)

**Keywords:** HR-HPV • cervical cancer • Pap smear • ASC-US

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## Abbreviations

ASC-US, atypical squamous cells of undetermined significance; ASC-H, atypical squamous cells, HSIL cannot be excluded; CC, cervical cancer; DI, double infection; HPV, human papillomavirus; HR-HPV, high-risk HPV; HSIL, high-grade SIL; LR-HPV, low-risk HPV; LSIL, low-grade SIL; NILM, negative for intraepithelial lesion or malignancy; SIL, squamous intraepithelial lesion; SQC, squamous cell carcinoma.

## Introduction

Human papillomavirus (HPV) is currently the most common pathogen responsible for cervical cancer (CC), a major cause of cancer-related deaths in women. Globally, CC is the fourth most common type of cancer among women worldwide,

with over 600,000 new cases and over 300,000 deaths.<sup>(1)</sup> The rate at which CC has affected young women has increased dramatically from 10% to 40% over the past 30 years.<sup>(2)</sup> In the Kingdom of Bahrain, the estimated incidence rate of CC is 4.3 per 100,000 people per year, making it the fourth most prevalent cancer in the country and the second-highest incidence rate of

CC among the Cooperation Council for the Arab States of the Gulf countries (GCC).<sup>(3)</sup> Unfortunately, CC is difficult to detect early because it typically has no symptoms.<sup>(4)</sup>

The introduction of the Papanicolaou (Pap) test led to a notable decrease in CC mortality in developed countries during the 20th century. Pap test results are classified as negative for intraepithelial lesion or malignancy (NILM) or positive (ASC-US, LSIL, ASC-H, HSIL or SQC) based on altered squamous cells, severity of abnormalities, preservation of specimens, and clinical setting (Table 1).<sup>(5)</sup>

Human papillomavirus (HPV) is considered the most common cause of CC in women. HPV is a small, non-enveloped, circular, double-stranded DNA virus belonging to the Papillomaviridae family. Many HPV infections that result in warts or subclinical infections are spread through personal, non-sexual contact. However, there are more than 40 types that can spread through sexual contact and are classified into two categories according to their risk of causing CC.<sup>(6)</sup> These categories include LR-HPVs and HR-HPVs. LR-HPV is responsible for anogenital and cutaneous warts, while HR-HPV is responsible for oropharyngeal cancers and anogenital cancers, including cervical, anal, vulvar, vaginal, and penile cancers.<sup>(7)</sup> There are over 150 different HPV genotypes, out of which 14 HR-HPV genotypes are known to be carcinogenic. The most frequently detected are HPV types 16, 18, 52, 31, and 58.<sup>(8)</sup> Several studies suggested that the prevalence of HPV genotypes varies geographically based on the incidence and genotypic distribution of HPV infections across nations (Table 2). Moreover, there is a relationship between HR-HPV genotypes and cytology results.<sup>(8-10)</sup>

This research will be the first study in Bahrain to correlate the HR-HPV genotypes with patients' cytological findings, demographics, and clinical profiles. This study aimed to estimate the current HPV prevalence in Bahrain and to determine the association of HR-HPV genotypes with cytological findings, age, and clinical history of the patients.

**Table 1.**

**Squamous abnormalities in Pap Smears.**<sup>(5, 25)</sup>

Squamous Abnormality	Definition	Cytomorphology
Atypical Squamous Cells (ASC)	ASC is cytologic changes indicating SIL and is divided into ASC-US and ASC-H. ASC-US is atypical mature squamous cells with SIL features, accounting for 4.3% of all pap smear diagnoses. ASC-H is immature squamous cells with HSIL-like cytologic changes, accounting for 0.3% of all pap smear diagnoses.	ASC-US has nuclei 2.5-3 times larger than normal intermediate squamous cells or twice the size of squamous metaplastic cells. It has a slightly increased nuclear-to-cytoplasmic ratio (N:C) and minimal nuclear hyperchromasia. ASC-H has a few immature squamous cells with high N:C and mild-to-moderate nuclear atypia. Clustered squamous cells show atypical nuclear features, with nuclei 1.5-2 times larger than normal and significant nuclear membrane irregularity. The N:C is markedly increased, similar to HSIL.
Squamous Intraepithelial Lesion (SIL)	Squamous intraepithelial lesion (SIL) refers to precursors to invasive squamous cell carcinoma, previously known as dysplasia, carcinoma in situ, borderline lesion, and CIN. SIL can be categorized into mature cell lesion (LSIL) and immature cell lesion (HSIL) types, with both highly associated with HR-HPV 97%. Both types account for 3% of pap smear findings.	LSIL cells are intermediate-sized squamous cells with abundant cytoplasm and a low but slightly increased N:C. They are hyperchromatic with variable size and uniformly distributed chromatin. HSIL are smaller and show less cytoplasmic maturity than LSIL cells. They occur singly, in sheets, or in syncytial-like aggregates. The N:C is higher compared to LSIL, and the degree of nuclear enlargement is more variable. Hyperchromatic nuclei with coarse granular or fine chromatin are common.
Squamous Cell Carcinoma (SQC)	SQCs are invasive epithelial tumors with varying degrees of differentiation. They can be well-differentiated, keratinizing or poorly differentiated, non-keratinizing. SQC accounts for 75% of cervical cancer cases, with HPV-16 in 50-60% and HPV-18 in 10-15%.	Keratinizing SQC cells are isolated, single cells with marked pleomorphic cells, dense orangeophilic cytoplasm, and variable nuclei, irregular nuclear membranes, and coarsely granular chromatin. Non-keratinizing SQC cells are smaller, occur singly or in syncytial aggregates, have poorly defined cell borders, and have variable nuclei size, irregular nuclear membranes, and coarsely clumped chromatin with chromatin clearing. Tumor diathesis is often present.

**Table 2.**

**Global findings on HR-HPV genotypes based on recent articles.**

Location	HPV Genotype Prevalence
Saudi Arabia (Kussaibi et al., 2021) <sup>(8)</sup>	HPV16 (5%), HPV16+18/45 (1%), Other HR-HPV (9%)
Oman (Al-Lawati et al., 2020) <sup>(21)</sup>	HPV82 (10.77%), HPV68 (7.69%)
Latin America (Correa et al., 2022) <sup>(13)</sup>	HPV16/18 (71.1%)
Africa (Seyoum et al., 2022) <sup>(14)</sup>	HPV16 (42.1%), HPV52 (30.3%), HPV18 (27.7%)
China (Yu et al., 2022) <sup>(15)</sup>	HPV16 was the most common in all regions except southern and eastern China, where HPV52 was predominant.

## Materials and Methods

Our study used a retrospective approach. Convenience sampling was used to gather 100 cases of HPV-positive women with abnormal and normal Pap smear findings from January 2017 to April 2023 in the Cytology Department at King Hamad University Hospital.

### Cytology Procedures

#### Thin-Prep

Thin-Prep collects cervical specimens using a cervix brush, which is rinsed in a vial with preservative fluid based on methanol. By pushing the brush to the bottom, forcing the bristles apart, and swirling it in the fluid, cells are released. The brush is then discarded.

#### Sure-Path

Sure-Path collects cervical specimens with a broom-like device with a detachable head. The practitioner must snip off the tip (detachable head) of the collection device and place it in a sample vial that contains an ethanol-based preservative fluid.

**HR-HPV Detection**

All cervical samples with ASC-US features must comply with CAP (College of American Pathologists) standards and be sent for HR-HPV testing. Patients at risk must undergo HR-HPV testing and Pap smears. The Cepheid Xpert HPV Assay is a fully automated, qualitative in vitro test for detecting the E6/E7 region of the viral DNA genome from HR-HPV in patient specimens. The test performs multiplexed amplification of target DNA by RT-PCR of 14 HR-HPV types in a single analysis. Xpert HPV specifically identifies HPV16 and HPV18/45 types in two distinct detection channels. It reports 11 non-16/18/45 HR-HPV types (31, 33, 35, 39, 51, 52, 56, 58, 59, 66 and 68) in a pooled result. Specimens are limited to cervical cells collected in PreservCyt® Solution (Hologic Corp.). Cervical samples collected in PreservCyt Solution pretreated with glacial acetic acid to lyse excess red blood cells for cytology review have also been validated with the Xpert HPV Assay.

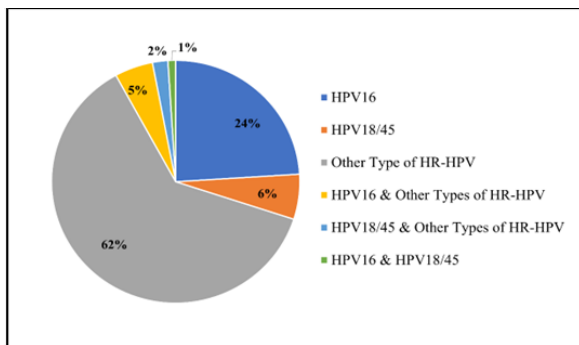
Statistical analysis was performed using the statistical software package SPSS version 21.0 (SPSS Inc, Armonk, NY: IBM Corp). Baseline characteristics were summarized as frequencies and percentages for categorical variables. Group comparisons concerning categorical variables were performed using Fisher’s exact test. A probability value of  $P < 0.05$  was considered statistically significant.

**Ethical Statements**

The Institutional Review Board of King Hamad University Hospital (KHUH) approved this research study in March 2023 (Ref. #: 23-590).

**Results**

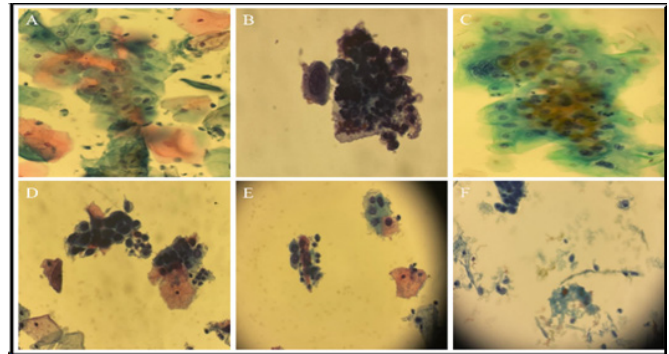
Over the specified period, 100 cases were positive for the HR-HPV test; HPV16 was detected in 24%, HPV18/45 in 6%, and non-16/18/45 HR-HPV in 62%. The remaining 8% revealed double HR-HPV genotypes, which was distributed among the cases (5% with HPV16 & non-16/18/45 HR-HPV, 2% with HPV18/45 and non-16/18/45 HR-HPV and 1% with HPV16 & HPV18/45) (Figure 1).



**Fig. 1.** Frequency of positive HR-HPV cases between Jan 2017 and April 2023 (n=100).

Among 100 positive HR-HPV cases, 73% had abnormal Pap smear findings (50% ASC-US - 50%, 1% ASC-H - 1%,

13% LSIL - 13%, 7% HSIL - 7%, and SQC - 2%), while 27% had negative Pap smear. Figure 2 shows the abnormal Pap smear findings retrieved from the cases (Figure 2)



**Fig. 2.** Abnormal Pap smear findings in patients. A: ASC-US, B: ASC-H, C: LSIL, D: HSIL, E: Keratinizing SQC, F: Non-keratinizing SQC.

**Correlation between HR-HPV and Pap smear findings**

This study has found a significant correlation between HR-HPV and Pap smear findings ( $P=0.003$ ). Among Pap smear findings, ASC-US/ASC-H ( $P=0.038$ ) and LSIL/HSIL ( $P=0.017$ ) were significantly associated with HR-HPV genotypes. However, no significant relationship was determined regarding SQC and negative Pap smear results with HR-HPV genotypes.

Out of the 24% of the total HPV16-positive cases, 8% showed negative Pap smear while 16% had an abnormal Pap smear result (ASCUS - 9%, ASC-H - 1%, LSIL - 3%, HSIL - 2%, SQC - 1%). Six percent of the total cases were positive for HPV18/45; 2% had negative Pap smear, and 4% had abnormal Pap smear (ASC-US - 1%, LSIL - 3%). Among 62% of non-16/18/45 HR-HPV genotypes, 16% of the cases had negative Pap smear results, while 46% had abnormal Pap smear findings (ASC-US - 38%, LSIL - 6%, HSIL - 2%). Among the 8% of total DI-HR-HPV, 1% had negative Pap smear (HPV16 & non-16/18/45 HR-HPV), and 7% had abnormal Pap smear (ASC-US - 2%, LSIL - 1%, HSIL - 3%, and SQC - 1%). In other words, ASC-US was found to be more frequently associated with HPV16+non-16/18/45 HR-HPV and LSIL with HPV18/45+non-16/18/45 HR-HPV. HSIL was detected in 2% of the cases with HPV16+non-16/18/45 HR-HPV genotype and in 1% of the cases with HPV18/45+non-16/18/45 HR-HPV, whereas only one case of SQC was found with DI (HPV16 + HPV18/45) (Table 3).

**Table 3.**

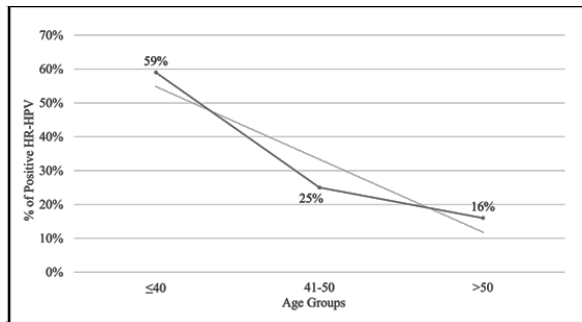
**Correlation between HR-HPV and Pap smear findings.**

	HPV16	HPV18/45	Non-16/18/45 HR-HPV	DI-HR-HPV	Total	P-value
Negative	8%	2%	16%	1%	27%	0.680
ASC-US	9%	1%	38%	2%	50%	0.038*
ASC-H	1%	0%	0%	0%	1%	
LSIL	3%	3%	6%	1%	13%	0.017*
HSIL	2%	0%	2%	3%	7%	
SQC	1%	0%	0%	1%	2%	0.086
Total	24%	6%	62%	8%	100%	0.003*

\* A significant correlation between HPV types and Pap smear findings.

**Correlation between HR-HPV and age**

Patients' ages ranged from 23 to 67 years. All patients were grouped into three categories ( $\leq 40$ , 41-50, and  $>50$ ). Most cases (59%) were aged  $\leq 40$  years, 25% - from 41 to 50 years old, while only 16% were  $>50$  years old (Figure 3).



**Fig. 3.** Overall age-related percentage for positive HR-HPV cases between Jan 2017 and April 2023 (n=100).

Considering the relationship between HR-HPV genotype and age, this study has found a significant correlation between HPV16 and HPV18/45 with all age categories ( $P=0.022$  and  $P=0.035$ , respectively). On the other hand, DI-HR-HPV and non-16/18/45 HR-HPV genotypes showed no significant correlation with the age groups (Table 4).

**Table 4.**

**Correlation between HR-HPV and age.**

HR-HPV genotypes	40	41-50	50	P-value
HPV16	19%	1%	4%	0.022*
HPV18/45	1%	2%	3%	0.035*
DI-HR-HPV	4%	3%	1%	0.694
Non-16/18/45 HR-HRV	35%	19%	8%	0.198
Total	59%	25%	16%	0.012*

\*A significant correlation between HR-HPV type and age.

The relation between the age and HR-HPV genotype was further analyzed, and it was found that the age group  $\leq 40$  had the highest peak with non-16/18/45 HR-HPV genotype (35%) and HPV16 (19%). The predominant genotypes for age groups 41-50 and  $>50$  were non-16/18/45 HR-HPV types (19% and 8%, respectively) (Table 4).

**Patient history in relation to HR-HPV**

Based on the available patients' history, data was collected only from 39 out of 100 cases. The genital wart was the most common diagnosis, with 23.1% infected with non-16/18/45 HR-HPV, 5.1% (2/39) with HPV16, and 2.6% (1/39) with DI (HPV16 and non-16/18/45 HR-HRV). The frequency of the patients with other symptoms was shown in Table 5.

**Discussion**

When discussing the results obtained, it should be noted that 62% of the patients with a single infection were positive with non-16/18/45 HR-HPV. This coincides with

**Table 5.**

**Review of patient history with HR-HPV genotypes.**

HPV Genotype	Number of cases (n=39)
<b>HPV16</b>	
Abnormal vaginal bleeding	1
Cervicitis	1
Fungal infection	1
Genital warts	2
Nulligravida & Nullipara	1
Postmenopause	1
Postcoital bleeding	1
Vaginal discharge	1
<b>HPV16 &amp; HPV18-45</b>	
Perimenopausal Bleeding	1
<b>HPV16 &amp; non-16/18/45 HR-HRV</b>	
Vaginal discharge	1
Genital warts	1
<b>HPV18-45</b>	
History of chronic cervicitis	1
<b>HPV18-45 &amp; non-16/18/45 HR-HRV</b>	
History of irregular periods	1
Vaginal discharge	1
History of HPV-18	1
<b>non-16/18/45 HR-HRV</b>	
Abdominal pain	2
Bacterial vaginosis	1
Genital warts	9
Irregular periods	1
Nulligravida & Nullipara	3
Pelvic inflammatory disease	1
Postmenopause	2
Postcoital Bleeding	2
History of HPV	2

the results reported by Kussaibi et al.,<sup>(8)</sup> revealing that non-16/18/45 HR-HPV caused most HR-HPV-positive cases. The last study, conducted in Bahrain in 2014, found HPV52 to be the most frequent genotype (1.4%), which agrees with the current findings.<sup>(11)</sup> A recent study reflecting the HPV prevalence in the GCC region also exhibited similar results, whereas non-HPV16/18 were mainly responsible for HR-HPV-positive cases.<sup>(12)</sup> On the contrary, a study conducted by Correa et al.<sup>(18)</sup> found that HPV16 is the most common HR-HPV genotype, while non-16/18/45 HR-HPV was found to be the least common. Similar results were found in other studies. Among the DI cases, the majority were positive with HPV16+non-16/18/45 HR-HPV. This was, in accordance with Ali et al.<sup>(12)</sup> and Liao et al.,<sup>(16)</sup> which reported the highest number of DI cases involving HPV16+non-16/18/45 HR-HPV infection. Opposing the current study and most other

studies where the single infection is more prevalent than DI, Gallegos-Bolaños et al.<sup>(17)</sup> observed DI as more frequent with HPV51+HPV52. The observation that infection with more than one HPV genotype increases the likelihood of developing CC remains controversial. In comparison to SI, double and concurrent HPV infections may be linked to HPV persistence and a higher risk of CC. A biological mechanism by which one HPV genotype leads to the development of another genotype can be considered as one of the reasons for DI.<sup>(12)</sup> The substantial variations in the prevalence of HR-HPV genotypes in different areas worldwide can be attributed to geographical location, sociocultural norms, socioeconomic status, age, and ethnicity of the population.

For the relationship between Pap smear findings and HR-HPV genotypes, the current study found an overall significant correlation ( $P=0.003$ ) with ASC-US, ASC-H, LSIL, and HSIL being significantly associated with HR-HPV genotypes. Of 100 HR-HPV-positive cases, 73% had abnormal Pap smear findings, while 27% had negative smear. Non-16/18/45 HR-HPV (46%) was the most prevalent genotype among the abnormal Pap smear findings, with ASC-US in 38%, LSIL in 6%, and HSIL in 2%. Over-diagnosis of patients with inflammation is one reason ASC-US is the most recurrent abnormal Pap finding. The results of the current study for Pap smear findings agree with other research, which reported the highest number of cases diagnosed with ASC-US and the lowest with SQC.<sup>(8,18,19)</sup> In contrast with our findings, a study by Umakanthan et al. found the HR-HPV detection rate remarkably higher in LSIL, followed by HSIL, ASC-US, and SQC.<sup>(20)</sup>

Concerning the relationship of HR-HPV infection with normal Pap smear results, the current study found that non-16/18/45 HR-HPV was most frequently associated with normal Pap smears, thus complying with one of the research's objectives. The presence of HR-HPV infection in women with normal Pap smear findings could be attributed to the patient's age during the infectious stage, immunity status, as well as the degree of progression due to pathological changes. A similar association was found in a study conducted in Oman, where researchers reported the HPV prevalence in women with normal Pap results to be 17%, which was higher than previous studies conducted in other GCC countries, such as Kuwait and Bahrain, where the prevalence was 2.4% and 9.8% respectively. According to their findings, the higher prevalence could be due to the methodological assays being more sensitive than the techniques used in the prior studies, thus allowing the detection of HPV in samples with a low viral load that would otherwise be considered negative.<sup>(21)</sup>

Besides the HPV-positive cases where one squamous abnormality "progressed" to the other, the current study also observed a "regression" phenomenon in some patients. Four cases in our study with a history of ASC-US (1/4), LSIL (2/4), and HSIL (1/4) showed normal Pap results in the follow-up Pap test, with three of the cases infected with non-16/18/45 HR-HPV genotype. This regression of Pap result could be explained by the patient's age at the time, aiding in self-resolution of the infection and/or early diagnosis and leading to effective treatment. Additionally, one of the patients who

was diagnosed with HSIL was found to have developed DI (HPV16 and non-16/18/45 HR-HPV) one year later, with her Pap result being negative, exhibiting regression even in the presence of HR-HPV infection. This case emphasizes the importance of understanding the potential risk factors for HPV infection persistence in patients with HSIL to optimize the postoperative monitoring program and clinical treatment. Zang and Hu's study reported several pathological and physiological factors such as high viral load, presence of HPV16 infection, age over 50 years, and positive surgical margins were associated with persistent HPV infection in patients with HSIL, but this finding remains controversial.<sup>(22)</sup>

Concerning age, the current study concluded that there is a significant correlation between HR-HPV genotypes and patients' age. A similar correlation was found in a study done in Nigeria.<sup>(23)</sup> On the other hand, other studies, for instance, a study done in Saudi Arabia<sup>(8)</sup> and a study done in China,<sup>(24)</sup> found no significant correlation between HR-HPV genotypes and patients' age. Although new HPV infections may occur at any age, it is difficult to determine at what age a woman acquires the HPV infection that leads to CC. Nonetheless, women's age is one of the significant risk factors for HPV infection. The data from this study revealed that most HR-HPV-positive cases fell in the category of  $\leq 40$  years, with the second most frequently infected age group being 41-50, and  $>50$  years ranked last. Thus, in Bahrain, HPV rates decrease with age. In all age groups, non-16/18/45 HR-HPV prevailed as the most common cause of HPV infection, followed by HPV16/18/45. This coincides with the findings of the Kussaibi et al.<sup>(8)</sup> study, which reported that 66% of the HR-HPV-positive patients were younger than 40 years, with non-16/18/45 HR-HPV being the most frequent genotype. Similar results were seen in a study conducted by Clarke et al.<sup>(26)</sup> On the contrary, a study conducted by Yan et al. found that young women under the age of 20 had the highest infection rates, probably because of their newness to intercourse and the sensitivity of their immune systems to HPV infections. They also found that the age group 61-70 showed a decline in HPV infection rate.<sup>(27)</sup> The cause may be related to the virus's persistence or the potential reactivation of HPV triggered by physiologic and immunological problems during the menopausal transition period. In addition to the results from our data, other recent studies also suggest most of the HR-HPV infections are diagnosed in women between the ages of 30 and 40.<sup>(28)</sup> Henceforth, the WHO recommends screening programs in developed countries beginning at 30.

When comparing the patients' HPV status and Pap findings with their clinical manifestations, genital warts were found to be the most common symptom among HR-HPV-positive women in the current study. Among the women exhibiting genital warts, 23.1% of them were infected with non-16/18/45 HR-HPV, thus revealing the main cause of the symptom. Besides genital warts, other symptoms observed in HR-HPV-infected women include abdominal pain, history of irregular periods, abnormal vaginal discharge, abnormal uterine bleeding, previous HPV infection, and microbial infection. Conversely, a study by Ozaydin-Yavuz et al.<sup>(29)</sup> reported that most genital warts cases were caused by LR-

HPV. In a general sense, most cases of genital warts are caused by LR-HPV, but in recent years, it has been discovered that 20%–50% of patients with genital warts develop HR-HPV infection. There is no sufficient research on the relationship of HPV genotypes with clinical signs and symptoms. Therefore, a definite conclusion regarding the patient's history cannot be formed based on the current studies.

## Conclusion

This study is the first in Bahrain to establish the prevalence of HR-HPV genotypes and analyze the correlation between HR-HPV genotypes and Pap smear findings, age groups, and clinical profiles among women. Results showed that non-16/18/45 HR-HPV infection is becoming more prevalent, with ASC-US being the most common abnormal Pap finding and the highest HPV infection in women aged 40 years or younger. Further investigation is needed to distinguish specific genotypes in the non-16/18/45 HR-HPV pool. Based on our findings, we recommend effective screening and vaccine programs for women aged 40 years and younger, as early detection can lower infection rates and improve recovery. Understanding the patient's clinical history can also help determine the appropriate testing and treatment approach. Future research should focus on the relationship between the Pap smear results, patient progression, regression status, and influential factors.

## Competing Interests

The authors declare that they have no competing interests.

## Acknowledgments

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