www.ajlifesciences.com / ISSN: 2663-1040 *AJ Life Sci. 2026, 9 (1): 19-27*

Research Article

Abasyn Journal of Life Sciences

Open Access

DOI: 10.5281/zenodo.19364419

Association of Bacterial Vaginosis and HR-HPV Infection with Uterine Cervical Intraepithelial Neoplasia among Saudi women in Al-Madinah Al-Munawarah

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Abstract

Bacterial vaginosis (BV) is an infection of vagina. Millions of women suffer from this prevalent infection. Obstetric and gynecological issues may cause from the infection. Cervical cancer may be related to BV. However, different studies have demonstrated that papillomavirus infections, particularly those related to the high-risk human papillomavirus (HR-HPV) group, are among the most important causes of malignant and premalignant lesions in women's uterine cervixes. There for this study aimed to detect the association of BV and the development of HR-HPV related cervical intraepithelial neoplasia (CIN) among Saudi women in Al-Madinah Al-Munawara. Two hundred and thirty-eight (n=238) samples were processed for cytological examination and PCR targeting HPV as well as BV (only 170). Precancerous epithelial lesions were found to be uncommon among Saudi women (13/238, 5.5%). On the other hand, the incidence of HR-HPV was detected in only six (2.5%) cases, two of them present in patients with epithelial change with prevalence of HPV in relation to epithelial change of 15.4% (2/13) both exhibiting genotype 16, Conversely, the remaining genotypes (HPV 52, 33 and HPV58) were found in patients free for premalignant and malignant cells. Concerning BV, 12.4% (21/170) of the study population were found to be suffering from investigated BV, distributed as follows: *G.vaginalis* and *P. lacrimalis* were detected in 4(2.3%) cases for every pathogen. While *L. iners* was demonstrated n 13(7.6%). Moreover, the two patients exhibiting both HPV 16 positive and abnormal cytological changes appeared to be free from bacterial vaginosis. The study concluded that there is no relation between bacterial vaginosis and the progression of HPV-related cervical cytological changes. Furthermore, low prevalence of HR-HPV among Saudi women with slight correlation with cervical intraepithelial neoplasia (CIN), This might guide the researchers to search for other suspected HPV genotypes rather than investigated types involved in the study.

Key words: Cervical cancer, high-risk human papilloma virus (HR-HPV), low-risk human papilloma virus (LR- HPV), Saudi women, Al-Madinah Al Munawarah, Saudi Arabia, bacterial vaginosis

Article Info:

Received:
February 16, 2026
Received Revised:
March 26, 2026
Accepted:
March 27, 2026
Available online:
April 1, 2026

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INTRODUCTION

Vaginal dysbiosis refers to an imbalance in the vaginal microbiome, which can lead to various health issues, including bacterial vaginosis. Part of the microbiome associated with (BV) is Gardnerella vaginalis. One of the earliest species linked to the BV was a Gram variable facultative anaerobic bacterium. Next, a common component of bacterial microflora associated with the humans, Peptoniphilus lacrimalis gram-positive anaerobic cocci and Lactobacillus is a Gram-positive bacterium that does not generate a spore. For the BV syndrome, it is necessary for at least 3 of 4 Amsel criteria to be positive (Amsel et al.,1983). Although it is commonly believed to be a precise method for identifying patients with BV. Cervicovaginal dominant lactobacilli have been demonstrated to preserve the homeostasis in the normal state by a variety of means, such as the production of antimicrobial compounds (Amabebe EAnumba, 2018; Łaniewski et al., 2020). The symbiotic relationship between the host and microbes may be disrupted by alterations in the cervicovaginal microbiome, which can play an important role in the pathogenesis of many diseases. There are several pathogenic processes linked to the dysbiosis, particularly in the development of human papillomavirus (HPV) infection and associated tumorigenesis processes at high-risk (Audirac-Chalifour et al., 2016; Dong et al., 2022; Kyrgiou MMoscicki, 2022, Łaniewski et al., 2020).

One of the world's most common sexually transmitted infections is HPV (Dunne et al 2007). The majority of HPV infections go away in a few months to the years. (Plummer et al 2007). The fourth most frequent cancer in women worldwide is cervical cancer, which can result from a persistent HPV infection (zur et al 1999; Ferlay et al 2019). Smoking, having several sexual partners, and having a weakened immune system are mostly risk factors for contracting HPV and developing cervical cancer (WHO, et al 2014). HR-HPV infections, particularly HPV-16 and HPV-18, are the main causes of over 90% of cervical cancer cases (Muñoz et al., 2003; Santella et al., 2022). The pathogenic mechanisms of HR-HPV include chronic inflammation (Borges, 2018; Georgescu et al., 2018; Lin et al., 2021), involving cells that release proinflammatory cytokines (Georgescu et al., 2018). As CC develops, the local microbiome is becoming more recognized as a contributing factor. The accumulation of evidence suggests that those who suffer from dysbiosis are more susceptible to persistent HR-HPV infections, which are frequently in conjunction with chronic ineffective cervical inflammation, which eventually progresses to cervical atypical hyperplasia and ultimately leads to cervical cancer (Norenhag et al., 2020; Usyk et al., 2020; Dong et al., 2022; Wang et al., 2022; Rosário et al., 2023; Xu et al., 2023). The microbiota has a significant impact on reducing the immune responses and genital tract inflammation during the cervicovaginal carcinogenesis caused by HR-HPV infection (Nicolò et al., 2021; Dong et al., 2022), having an effect on how oncoproteins are expressed and produced in HR-HPV oncogenes. (Nicolò et al., 2021, Hu et al., 2023), Furthermore, the restoration of microbial homeostasis has emerged as a promising technique to aid in the elimination of HPV infections.

The connection between BV and the development of cervical cancer remains conflicting and unclear. A few studies confirm that the connection between BV and CIN shows the connection of bacterial vaginal infection with cervical cancer (Nam et al., 2009; Gillet et al., 2012), and other research reveals no correlation at all (Peters et al.,1995; Long et al., 2023). There is still a chance that BV plays a role in the formation of CIN by acting as a cofactor for HPV.

Several studies have shown a correlation between microorganisms that are linked to bacterial vaginosis (BV), including the transition from HPV to CIN to CC, Prevotella species, Sneathia amnii, Porphyromonas species, Peptostreptococcus species, Gardnerella vaginalis, and Atopobium vaginae (Oh et al., 2015, Ritu et al., 2019, Usyk et al., 2020, Wu et al., 2021, Dong et al., 2022, López-Filloy et al., 2022, Santella et al., 2022). A significantly increased abundance of Prevotella and Gardnerella has been observed in individuals with persistent HR-HPV infection and HSIL. It is suggested by evidence that microbes associated with BV have the potential to change metabolic features in the microenvironment, which can be seen through the buildup of proinflammatory lipids and 2-hydroxybutyric acid, oxidative stress, and the generation of hydrogen sulfide (Maarsingh et al., 2022). These changes may contribute to localized inflammation and genetic toxicity, thereby clarifying the observed epidemiological association between bacterial vaginosis (BV) and cervical cancer (CC) (Brusselaers et al., 2019; Suehiro et al., 2019).

1. MATERIALS AND METHODS

1.1. Study design, study Population, study area, and collection of samples

Following the informed consent, 238 gynecological samples (n=238) were obtained from women of varying ages and gynecological symptoms who were attending the Maternity and Children Hospital (MCH) in the

Yanbu Poly clinic and Al-Madinah Al Munawarah. This study was cross-sectional. A customized cyto-brush was used to collect each sample, then washed into a labeled vial with 15 ml of PreserveCyt® transport medium.

1.2. Sample preparation and processing

Firstly, samples were prepared for cytological examination using liquid-based cytology (Beckton, Dickson; PrepStain Slide Processor/TriPath Imaging Inc, 2005). Then the residual samples were frozen until used for B.V and HR-HPV genotypes detection.

B.V and HR-HPV genotypes tests are based on three major processes: DNA extraction, multiplex amplification of DNA by using certain HPV and B.V primers, and detection of the amplified products on agarose gel.

2.3. DNA extraction:

Following the manufacturer's instructions, DNA was extracted using a DNA extraction kit (Sacace Biotechnologies - Italy).

2.4. Detection of Human Papillomavirus

By using an HPV kit in accordance with the manufacturer's instructions, HPV was detected (Sacace Biotechnologies) as follows:

2.5. PCR Amplification for HPV

For high-risk (12 genotypes) HPV detection, three sets of PCR premix-1 were used (PCR mix-1 “16-35”, PCR mix-1 “18-59”, and PCR mix-1 “52-66”). Primers targeting four HPV type regions and the B globin gene, which serves as an internal control, are included in each of the PCR-mix-1 tubes. Polymerase chain reaction (PCR) for samples and controls was adopted in 25 µl in a PCR tube as in an amplification protocol (Sacace Biotechnologies), containing 5 µL of PCR-mix-1, 10 µL of 2.5 PCR buffer, 0.5 TaqF polymerase, and 10 µL of (DNA sample for the test, buffer for negative control, internal control "B-globine " for internal control and HPV C+ for positive control). A PCR machine (SYNGENE, UK) was used to amplify the target sequences only when the temperature reached 95°C and started the following program: 42 cycles of amplification by using a PCR processor were conducted after a 15-minute denaturation stage at 95°C. Each cycle included a denaturation step at 95°C for 30 seconds, a primer annealing step at 63°C for 30 seconds, and a chain elongation at 72°C for 40 seconds. To know that the amplified DNA was fully extended, the last elongation step was extended by one minute (the storage was at 10°C).

2.6. Visualization of PCR product, results analysis, and interpretation

The amplified products were resolved by electrophoresis on the 2% agarose gel and stained with ethidium bromide, visualized on an ultraviolet trans-illuminator and photographed. The product was compared with 100 bp ladder DNA; HPV genotype is determined based on the length of a specific amplified DNA fragment, with reference to see Supplementary tables (1 and 2).

2.7. Detection of B.V

One hundred and seventy samples, including HPV positive samples, were subjected to BV detection. Specific primers were used to amplify sequences of the bacterial genes. These primers targeted *G.vaginalis*, *L. iners, and P.lacrimalis*. The Primers were imported from Macrogen, Korea, as shown in Supplementary Table 3. Before beginning the master mix production, 70% ethanol was used to disinfect the bench before each batch was prepared. End-point PCR was used for PCR. The DNA amplification was carried out using TECHNE® Ltd peltier thermal cycler (Germany), and the DNA amplification was done using Maxime PCR Premix kit (iNtRON, Korea). A total volume of 25 µL was used for the PCR assay. After the addition of each component, the contents of the master mix were vortexed. Five microliters of sterile distilled water were added to the negative control. The reaction mixtures were then put in the thermal cycler (TECHNE®ltd Peltier Thermal Cycle) for targeted gene amplification using the standard PCR procedure.

2.8. Visualization of PCR product, results analysis, and interpretation

Amplification products were electrophoresed, visualized on a UV trans illuminator, and compared with a 100 bp ladder. The type of BV is determined based on the length of a specific amplified DNA fragment, with reference to the Supplementary Table 3.

3. RESULTS AND DISCUSSIONS

This study was designed to provide evidence about the association of bacterial vaginosis and the development of HR-HPV related cervical intraepithelial neoplasia in Al- Madinah Al-Munawwarah Region.

Two hundred and thirty-eight (n=238) cervical smears were collected from women with different age groups and gynecological symptoms. The study population ranged in age from 15 to 80 years, with a mean of 39.7 ± 1.1 years.

3.1. Cytological results

According to cytological analysis, the incidence of aberrant epithelial cells is modest, accounting for 5.5% (13/238) of cases, which are split as follows: ASCUS in 4 cases (1.7%), LSIL in 4 cases (1.7%), and HSIL in 5 instances (2.1%).

3.2. PCR Results

3.3. Detection of HPV

HPV was detected in only six (2.5%) cases, particularly among women between 20 and 50 years old. These HPV genotypes include HPV 16, 52, 33 and 58 (Table 3 and figures 1 & 2).

Regarding the distribution of HR-HPV in patients with epithelial changes, only two (2/13, 15.4%) patients were found to be positive for HPV, specifically HPV 16. It is worth mentioning that these patients had HSIL (Table .4).

Table 3. Distribution of age groups among HPV positive cases

Age group	HPV genotype				
	16	33	52	58	Total
Less than 20					
20-30	1			1	2
31-40			2		2
41-50	1				1
51-60		1			1
More than 60					
Total	2	1	2	1	6

Table 5. Distribution of cytological diagnosis among HPV positive cases

HPV genotype	Cytological diagnosis			
	Normal	Inflammation	HSIL	Total
HPV16	0	0	2	2
HPV33	0	1	0	1
HPV52	0	2	0	2
HPV58	1	0	0	1
Total	1	3	2	6

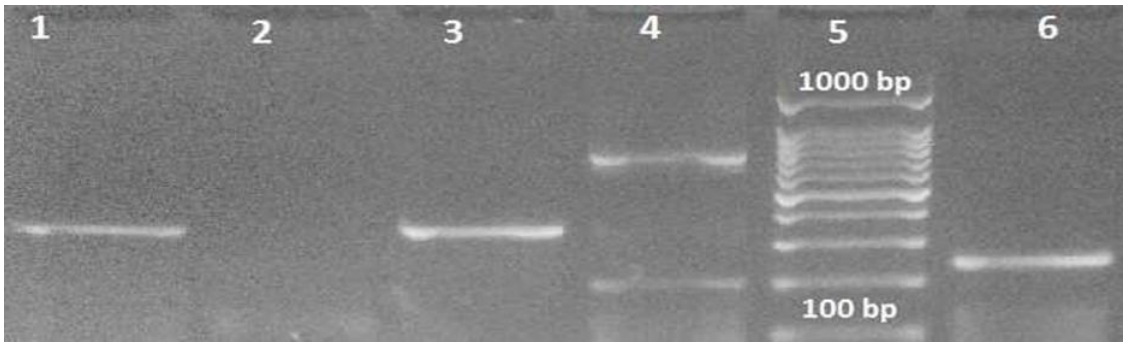

Figure 1. PCR amplicons of HPV from the cervical smears were electrophoresed on a 3% agarose gel. Lanes: 5 = 100 bp ladder; 1 = HPV 52 positive control (360 bp); 2 = negative control; 3 = HPV52 positive sample; 4 = internal control (723 bp); and 6 = HPV58 positive sample (240 bp).

3.4. Detection of Bacterial Agents

The targeted pathogens were detected in 21 (12.4%) patients among the study subjects (n=170). The highest pathogen frequency *was L. iners,* which was detected in 13 out of 170 (7.6%), while similar frequencies were observed in *Gardinella vaginalis and P. lacrimalis,* constituting 2.4%% (4/170) for each, shown in supplementary Table (6) and supplementary figure (3).

Table 6. Distribution of bacterial vaginosis among enrolled subjects (n=170)

	PCR results	Frequency	Percentage
1	*Gardnerella vaginalis*	4	2.4%
2	*Peptoniphilus lacrimalis*	4	2.4%
3	*Lactopacillus iners*	13	7.6%
Total		21	12.4%

3.5. Bacterial vaginosis versus HPV

Two (9.5%) out of twenty-one Bacterial vaginosis infected women were found to be positive for HPV, including HPV 52 and 58 (supplementary Table. **7**).

Table 7. Bacterial vaginosis and HPV genotypes positive cases in relation to epithelial changes.

HPV genotypes	Epithelial change	Bacterial vaginosis
16	2	0
33	0	0
52	0	1
58	0	1
Total	2	2

4. DISCUSSION

Our study showed a low prevalence of HPV among Saudi women (2.5%). This is likely influenced by the cultural and religious context of Saudi Arabia, where sexual activity is largely confined to marriage (Muslim laws) and mostly monogamous, which limits the potential for widespread HPV transmission through sexual contact. Our finding aligns with several studies conducted in Saudi Arabia: (Alshammari *et al.*, 2022), "conducted in Al-Madinah", and Mousa *et al.*, 2019, "in Jeddah", which are 4.7% and 5.9%, respectively. Conversely, a high prevalence 15.1% HPV positivity was reported recently by El-Daly *et al*. (2025. Their study was carried out at the gynecology clinics at King Abdulaziz University Hospital in Jeddah, Saudi Arabia, including 106 females. This discrepancy highlights the need for further investigation into the HPV burden in Saudi Arabia to identify the prevalence of different HPV types and the effectiveness of vaccination programs. Furthermore, assessing awareness and knowledge of HPV and vaccination among different groups within Saudi Arabia is crucial for developing effective public health strategies. Also, El-Daly *et al. (*2025) noted that the most frequent HPV genotype is HPV 16 (43.75%). Worth noting majority of studies proved that the most prevalent HR-HPV genotype in Saudi Arabia linked to cervical cancer is HPV 16, followed by

HPV18(ICO/IARC, 2023; Khalid *et al.,* 2019; Bondagji *et al.,* 2013), as well as globally. Further, several studies in Saudi Arabia suggest that the third common HR-HPV genotype is HPV 45 (AlObaid, 2014; Rola Turki, 2013), which is also not far from a worldwide updated study by (Wei *et al*., 2024) , who reported that about three-quarters of cervical cancer was caused by HPV types 16 and 18 worldwide, followed by HPV types 31, 33, 45, 52, and 58 (15-20), while other HPV types were responsible for approximately 5% of cervical cancer globally with some remarkable regional differences, such as a higher percentage (~4%) of HPV 35 in Africa than in other regions, can be identified. In this study the most frequent HPV is HPV 16 (2/6, 33.3%) and 52 (2/6, 33.3%) followed by 33(1/6, 16.7%) and 58(1/6, 16.7%), which is consistent with the provided study from Saudi Arabia (Alshammari *et al.,* 2022) highlights HPV 16 as the most prevalent genotype, followed by HPV 52, HPV 58, and HPV 33, with respective percentages of 42.9%, 21.4%, 14.3%, and 14.3%.

However, only 2/13 of abnormal cervical smears (HSIL/CIN3) were represented with HPV positive, which is HPV16 in both; meanwhile, these two cases were younger than 50 years old, which emphasizes the highest oncogenicity of HPV16. These results agree with several studies in Saudi Arabia (Faqih *et al*.,2023; El-Daly *et al*., 2025). Whereas the other HPV types were isolated from women that were negative for intraepithelial lesion or malignancy (NILM), this may suggest a recent HPV infection, as the cytological changes can appear many years after the initial infection, so infected women may suffer later from cytological changes if the HPV infection persists. Other suggestions may indicate low oncogenicity of these HPV subtypes. These women require a regularly follow-up.

Notably, 50% (3/6) of HPV positive women were diagnosed with inflammation; two were demonstrated with HPV 52, and the other one exhibited HPV 33. This indicates that HPV infection can induce inflammation. Nevertheless, HPV 58 was isolated from a female with a normal cervical smear. Additionally, the high proportion (11/13, 84.6%) of abnormal cervical cytology presents in women negative for HPV infection may suggest the presence of other HPV subtypes rather than the 12 HR-HPV investigated types. An association between independent squamous cell carcinoma (SCC) and negative HPV status has been documented by many researchers (Faqih *et al*.,2023; Regauer *et al*., 2022).

The primary objective of this study is to investigate whether bacterial vaginosis (BV) is associated with the development of cervical precancerous lesions among HPV-infected women. Different systematic reviews suggest an association between BV and increased risk of HPV infection and CIN development, especially through microbiome disturbance (Mitra A et al., 2020;). Similarly, Studies from 2020–2024 emphasize the role of microbial imbalance (e.g., Gardnerella, Sneathia) in increasing the risk of cervical intraepithelial neoplasia (CIN) [Usyk M *et al*., 2020)

On the other hand, many studies noted that the Elevated vaginal pH (above 4.5) has been associated with higher-grade CIN in women who are also infected with HR-HPV (Norenhag J *et al*., 2020). Moreover, a previously published study noted that a higher rate of BV (33%) was found among women with high-grade SIL (Discacciati *et al*., 2006).

Our findings reflect the low ratio of *G.vaginalis* 2.3% (4/170), *P.lacrimalis* 2.3% (4/170), and high ratio of *L. iners* 7.6% (13/170) among enrolled subjects. Bacterial vaginosis was detected in twenty-one (12.4%) women, with only two of them having HPV, 9.5% (2/21), including HPV52 (31 years) and 58 (28 years), whilst no epithelial change occurred. This may suggest recent infections. Conversely, two HPV-positive cases with epithelial changes showed no BV.

This observation suggests that while BV is often linked to abnormal cervical cells related to HPV, it's not a prerequisite for these changes; some individuals can exhibit them even without BV. Particularly, these two cases that are positive for HPV16, which is known to have high oncogenicity and is the most prevalent HPV type found in cervical cancer, account for approximately half of all cervical cancers, and together with HPV 18, they account for roughly 70% of cervical cancers worldwide.

As our study targeted only three types of BV, infection by other types may occur, taking into consideration that there is an increase in the prevalence of BV globally as well as among Saudi females.

Based on previous studies, we suggest a complex, possibly indirect relationship between BV and HPV/CIN.

5. CONCLUSIONS

The study indicates no correlation between BV and HR-HPV/CIN. On the other hand, a low incidence of HPV among Saudi women was observed with a weak association with cervical intraepithelial neoplasia. Hence, direct the researchers to look for other types of HR-HPV and/or LR-HPV, along with exploring the potential influence of bacterial vaginosis (BV).

Informed Consent Statement: All women enrolled in this study in this study after being given their informed consent.

Acknowledgement

None.

Conflict of Interest

There is no conflict of interest.

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