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Review Article

Meta-analysis of the correlation between vaginal microenvironment and HPV infection

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Abstract: Purpose: To study the correlation between the vaginal microenvironment and human papillomavirus (HPV) infection by meta-analysis. Methods: Databases including the Chinese Journal Full-text Database, China Science and Technology Journal, Wanfang, PubMed, Embase, Cochrane, and Web of Science were used to comprehensively retrieve published clinical studies on the correlation between the vaginal microenvironment and HPV infection. The retrieval was performed according to the inclusion and exclusion criteria, then qualified clinical studies were included for quality evaluation and data extraction. Revman 5.3 software was used for meta-analysis. The correlation between the vaginal microenvironment and HPV infection was assessed. The statistical results were shown by forest plots. Publication bias was tested by funnel plot. Results: Ten independent studies were included in this study, involving 11,649 patients. The meta-analysis results showed that compared with the HPV-negative group, the HPV-positive group had a significant increase in the aerobic vaginitis (OR = 1.73, 95% CI: 1.19-2.50, P = 0.004), bacterial vaginosis (OR = 2.52, 95% CI: 1.78-3.57, P < 0.001) and trichomonal vaginitis (OR = 1.60, 95% CI: 1.27-2.02, P < 0.001) infection rates, while there was no substantial difference in the vulvovaginal candidiasis infection rate between two groups (OR = 1.48, 95% CI: 0.99-2.23, P = 0.06). Conclusion: The vaginal microenvironment is closely related to HPV infection, especially aerobic vaginitis, bacterial vaginosis and trichomonal vaginitis are high-risk factors for HPV infection.

Keywords: Vaginal microenvironment, HPV infection, vaginitis, vaginopathy, meta-analysis

Introduction

Human papillomavirus (HPV) is a double-stranded circular DNA virus belonging to the papillomaviridae family. It has strong host specificity, and mainly infects the mucosal epithelium of humans [1, 2]. Studies have confirmed that persistent high-risk HPV infection (HPV-HR) is the leading cause of cervical cancer and pre-cancerous lesions in females [3]. Changes in women's vaginal microenvironments are closely linked to the occurrence and development of cervical cancer [4]. The dynamic balance of vaginal microecology depends primarily on four micro-ecosystems, vaginal microbiota, cyclical endocrine changes, vaginal anatomy and local vaginal immune system [5]. The vaginal microenvironment is susceptible to micro-ecological imbalance due to infection by pathogenic bacteria. Because the cervix is directly exposed to the complex vaginal microenvironment, the risk of cervical lesions increases [6, 7]. Aerobic vaginitis (AV), bacterial vaginosis (BV), trichomonal vaginitis (TV) and vulvovaginal candidiasis (VVC) infections are common vaginal diseases caused by vaginal pathogenic microorganisms [8]. Studies [9] have shown that abnormal vaginal flora may increase the risk of HPV infection in women. For a body in a healthy state, the vaginal microbiome maintains a dynamic balance. For a body with HPV infection, part of the pathogenic bacteria can be cleared through autoimmunity, and those pathogenic bacteria that can not be cleared will continue to infect the cervix, eventually leading to cervical lesions [10, 11]. Understanding the relationship between the vaginal microenvironment and HPV infection has practical clinical significance for preventing and treating HPV. In recent years, vaginal microecology has attract-

ed wide attention. Increasing studies have shown that changes in vaginal microecology affect HPV infection, but the conclusions are inconsistent. After an extensive literature search, we found that there are few systematic studies on the relationship between vaginal microecology and HPV infection. Therefore, this paper used a meta-analysis to explore the correlation between the vaginal microenvironment and HPV infection, to provide a reliable direction for clinical treatment.

Materials and methods

Retrieval strategy

With the search strategy based on the Population, Intervention, Comparison, Outcomes and Study (PICOS) framework, literature retrieval was conducted by 2 researchers independently by retrieving related literature in Chinese Journal Full-text Database, China Science and Technology Journal, Wanfang, PubMed, Embase, Cochrane, and Web of Science. The keywords for searching were vaginal microenvironment, vaginal microecology, vaginal microbiome, lower reproductive tract infection, vaginitis, human papillomavirus, HPV, human papillomavirus, microbiome, microbiota, microecology and vaginosis.

Inclusion and exclusion criteria for literature

Criteria for inclusion: (1) Published studies on the relationship between vaginal microenvironment and HPV infection in academic journals. (2) In the studies, participants were divided into case group and control group, with an HR-HPV positive diagnosis in the case group, and HR-HPV negative diagnosis in the control group. (3) The method of HPV detection included at least one of the following methods: polymerase chain reaction, enzyme-linked immunosorbent assay, immunohistochemistry, *in situ* hybridization, hybrid capture II, matrix-assisted laser desorption ionization time-of-flight mass spectrometry, and single base extension. (4) The HR-HPV infection included over 20 HPV subtypes (CP8304, 83, 82, 81, 73, 68, 66, 59, 58, 56, 55, 53, 52, 51, 45, 44, 43, 42, 39, 35, 33, 31, 26, 18, 16, 11 and 6). (5) All data should be complete, including the number of cases in each group as well as data of AV, BV, TV and VVC infections. (6) Diagnostic criteria for changes in vaginal microecology was referred to criteria associated with wet microscopy of vaginal secretions [12]. Diagnosis of AV: diagnostic criteria for wet microscopy (Ponders score 3 points), ß-glucuronidase positive, H_2O_2 positive, and sNa positive. Diagnosis of BV: rapid BV test kit, Gram staining method, and Nugent (score 7 points). Diagnosis of TV: trichomoniasis vaginal can be verified in 0.9% sodium chloride injection under microscopy. Diagnosis of VVC: culture of fungi, pseudohyphae, and spores can be verified by Gram staining method, and 0.9% sodium chloride injection wet mounting [7]. The sample size of the literature needs to meet the study criteria, or the required data is analyzed based on the reported results using reasonable statistical methods. (7) Research methods in all literature were identical. (8) A study with a large sample size was selected if it was conducted repeatedly by the same research institute.

Exclusion criteria: (1) Abstracts from lectures, literature reviews, duplicate literature and unpublished literature. (2) No specific information was obtained. (3) The aggregation approach did not meet the criteria for inclusion in this study.

Data extraction and quality evaluation

Two researchers collaborated to develop a screening strategy and then completed the screening and inclusion of the literature. Then, materials and data were collected. Screening strategy: preliminary screening was done by reading the titles and abstracts of the retrieved literature, then full texts were read for further screening. The literature was screened in strict accordance with the inclusion and exclusion criteria. Two researchers independently evaluated the quality of the included literature using the Newcastle-Ottawa Scale (including three dimensions: selection, comparability and exposure). In the event of any disagreement, the decision was made by discussion or a third researcher. The total score of NOS is 9 points. If the total score is over or equal to 7, the literature is considered to be of high quality.

Statistical analysis

This meta-analysis was performed using RevMan5.3. The Z trial was used to analyze the heterogeneity between the studies, $P > 0.1$ and $I^2 < 50\%$ indicating that there was no heteroge-

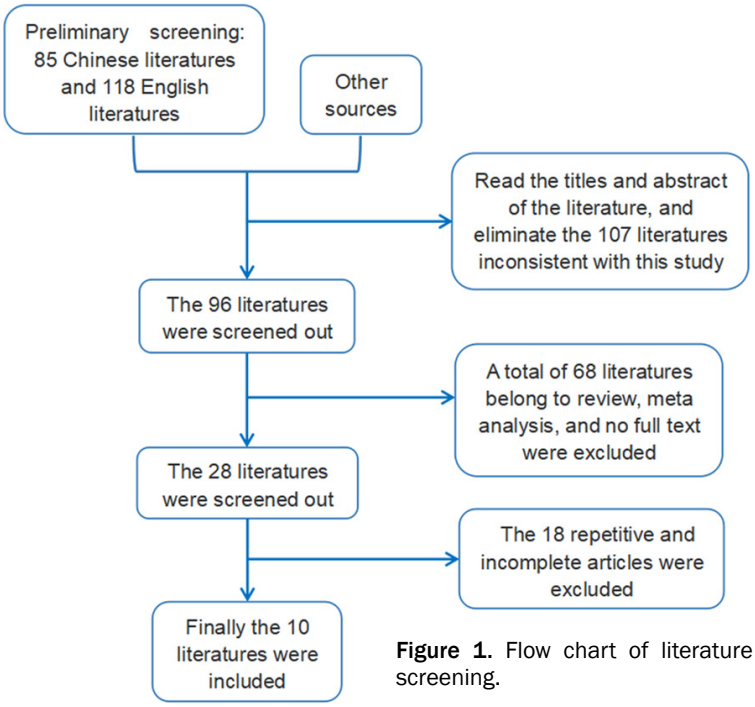

Figure 1. Flow chart of literature screening.

neity between the studies. If so, the study data were analyzed using the Fixed Effects Model (FEM). If there was statistical heterogeneity and the source could not be addressed, the study data were analyzed using the Random Effects Model (REM). Sensitivity was analyzed by removing the studies one by one and recalculating the size of the combined effect. The study data were continuous variables, and the results were expressed as STD mean difference (MDS) and its 95% confidence interval (95% CI).

Results

Results of literature screening

Results of the document analysis: During the screening, 85 Chinese and 9 English publications were obtained. By reading the titles and abstracts to remove some the duplicates, 35 pieces of literature were obtained. Then by reading the full texts of the 35 pieces of literature for further screening, 10 pieces of literature (all in Chinese) were included in this study. These 10 documents included 11,649 gynecological ambulatory patients undergoing HPV and vaginal microecology tests. Among them, 8,626 patients had changes in the vaginal microenvironment, while 2,247 patients had a normal vaginal microenvironment. Of the 8,626 patients whose vaginal microenvironments changed, 3,358 were diagnosed with as positive for HPV and 5,268 were negative. The detailed documentary selection process is set out in **Figure 1**.

Basic characteristics and assessment of the risk of bias of the included literature

The quality assessment scores of all included literature [13-22] were over or equal to 7. The basic characteristics of the literature are shown in **Table 1**.

Study results

According to the coinfection results in 8 included studies, the infection rates of AV, BV, TV, and VVC in the HPV positive group were 16.14%, 21.07%, 3.38% and 12.57%, respectively, and those in the HPV negative group were 9.17%, 12.94%, 3.38% and 8.64%, respectively.

Correlation between vaginal microenvironment and HPV infection

Correlation between AV and HPV infection: Since $P < 0.1$, REM analysis was performed. According to the analysis of the correlation between AV-positive and HPV infection, OR = 1.73, 95% CI: 1.19 to 2.50, the HPV-positive group showed a higher rate of AV positive, with a statistically significant difference ($Z = 2.89$, $P = 0.004$), as displayed in **Figure 2**.

Correlation between BV and HPV infection: Since $P < 0.1$, REM analysis was performed. According to the analysis of the correlation between BV-positive and HPV infection, OR = 2.52, 95% CI: 1.78 to 3.57, the HPV-positive group had a higher rate of BV-positive, with statistically significant difference ($Z = 5.18$, $P < 0.001$), as displayed in **Figure 3**.

Correlation between TV and HPV infection: Since $P > 0.1$, FEM analysis was performed. According to the analysis of the correlation

Table 1. Basic characteristics of literature

First author	Year	Study subjects	Number of cases	AV	BV	TV	VVC	Quality assessment (points)
Chen [13]	2017	HPV$^+$	542	40	149	7	68	8
		HPV$^-$	870	74	155	13	94	
Zhong [14]	2018	HR-HPV$^+$	468	78	184	56	83	8
		HR-HPV$^-$	2477	224	394	169	193	
Wang [15]	2018	HR-HPV$^+$	160	27	83	6	39	9
		HR-HPV$^-$	402	21	52	12	30	
Yuan [16]	2019	HPV$^+$	1614	296	106	21	164	9
		HPV$^-$	1450	97	50	18	122	
Zhang [17]	2019	HPV$^+$	60	3	43	2	8	7
		HPV$^-$	60	0	14	0	10	
Zhang [18]	2020	HR-HPV$^+$	635	129	97	10	14	8
		HR-HPV$^-$	1412	198	154	11	25	
Cheng [19]	2021	HPV$^+$	130	10	72	11	47	8
		HPV$^-$	220	19	64	4	114	
Yang [20]	2021	HPV$^+$	121	19	52	13	46	9
		HPV$^-$	119	10	24	10	18	
Lin [21]	2022	HR-HPV$^+$	138	6	68	0	18	8
		HR-HPV$^-$	310	17	120	4	36	
Rahkola [22]	2009	HR-HPV$^+$	175	-	20	-	-	7
		HR-HPV$^-$	153	-	19	-	-	

Notes: $^+$represents positive; $^-$represents negative; AV = Aerobic Vaginitis; BV = Bacterial Vaginosis; TV = Trichomonal Vaginitis; VVC = Vulvovaginal Candidiasis; HR = High Risk; HPV = Human Papillomavirus.

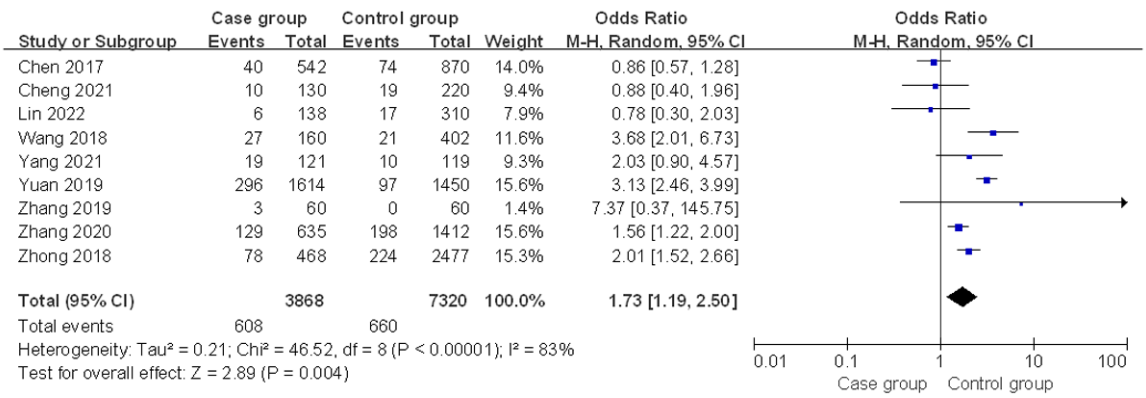

Figure 2. Correlation between AV and HPV infection. AV = Aerobic Vaginitis; HPV = Human Papillomavirus.

between TV-positive and HPV infection, OR = 1.60, 95% CI: 1.27 to 2.02, the HPV-positive group had a higher rate of TV positive, with statistically significant difference (Z = 3.93, P < 0.001), as displayed in **Figure 4**.

Correlation between VVC and HPV infection: Since P < 0.1, REM analysis was performed. According to the analysis of the correlation between VVC-positive and HPV infection, OR = 1.48, 95% CI: 0.99 to 2.23, the HPV-positive group had a higher rate of VVC-positive, but the difference was not statistically significant (Z =1.90, P = 0.06), as displayed in **Figure 5**.

Assessment of risk of bias

The results of funnel plots showed that the funnel plots were symmetrical, indicating that there was no bias in the literature. The results

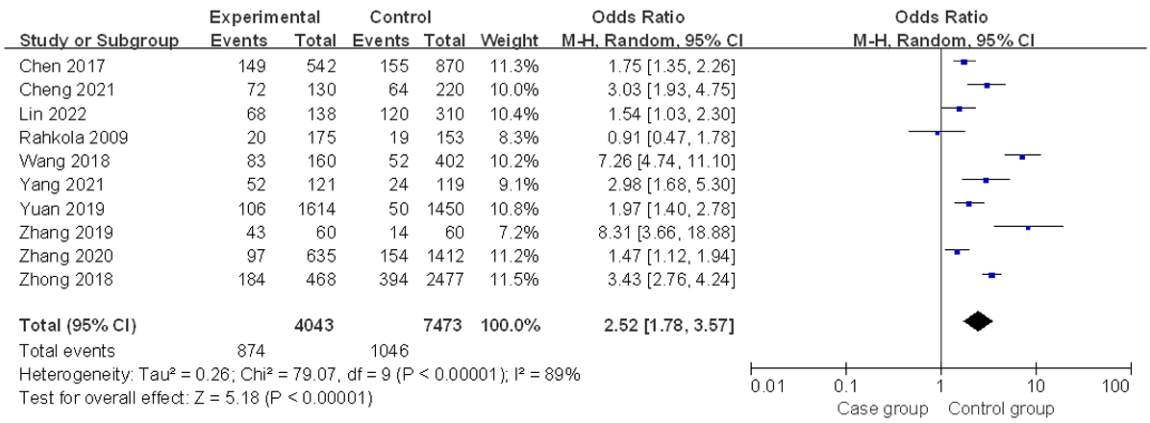

Figure 3. Correlation between BV and HPV infection. BV = Bacterial Vaginosis; HPV = Human Papillomavirus.

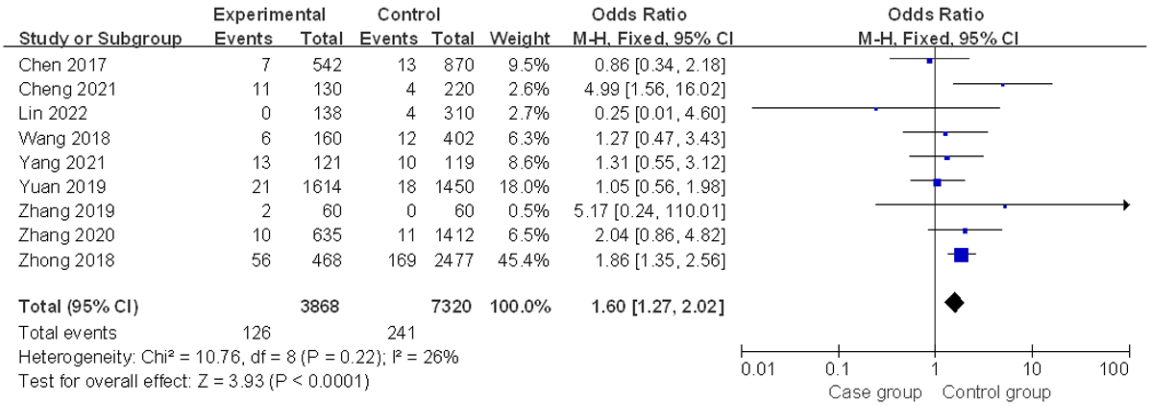

Figure 4. Correlation between TV and HPV infection. TV = Trichomonal Vaginitis; HPV = Human Papillomavirus.

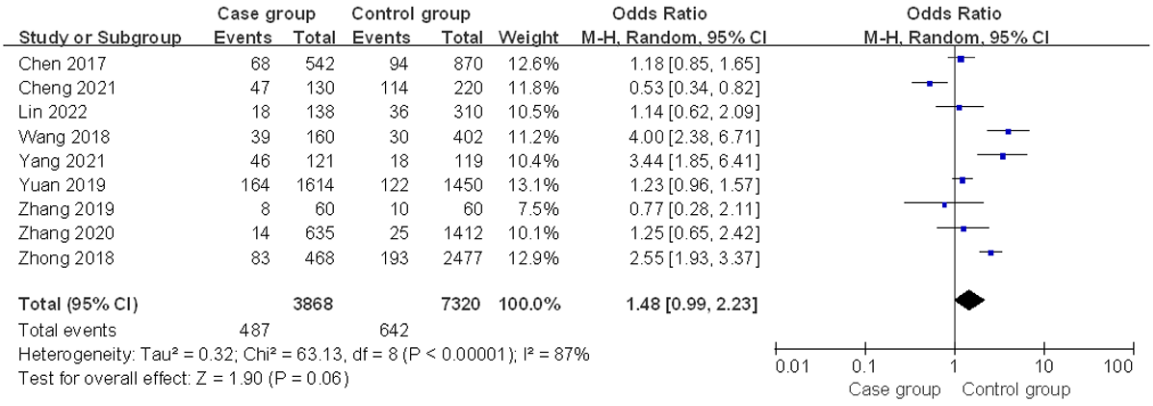

Figure 5. Correlation between VVC and HPV infection. VVC = Vulvovaginal Candidiasis; HPV = Human Papillomavirus.

also indicated that compared with the HPV-negative group, the HPV infection of the HPV-positive group was associated with AV, BV and TV, but was not with VVC (**Figure 6**). In the funnel plots, there were dots placed on or outside the slant, so these studies may have a risk of bias, which may be because the quantity of literature included in this study was small.

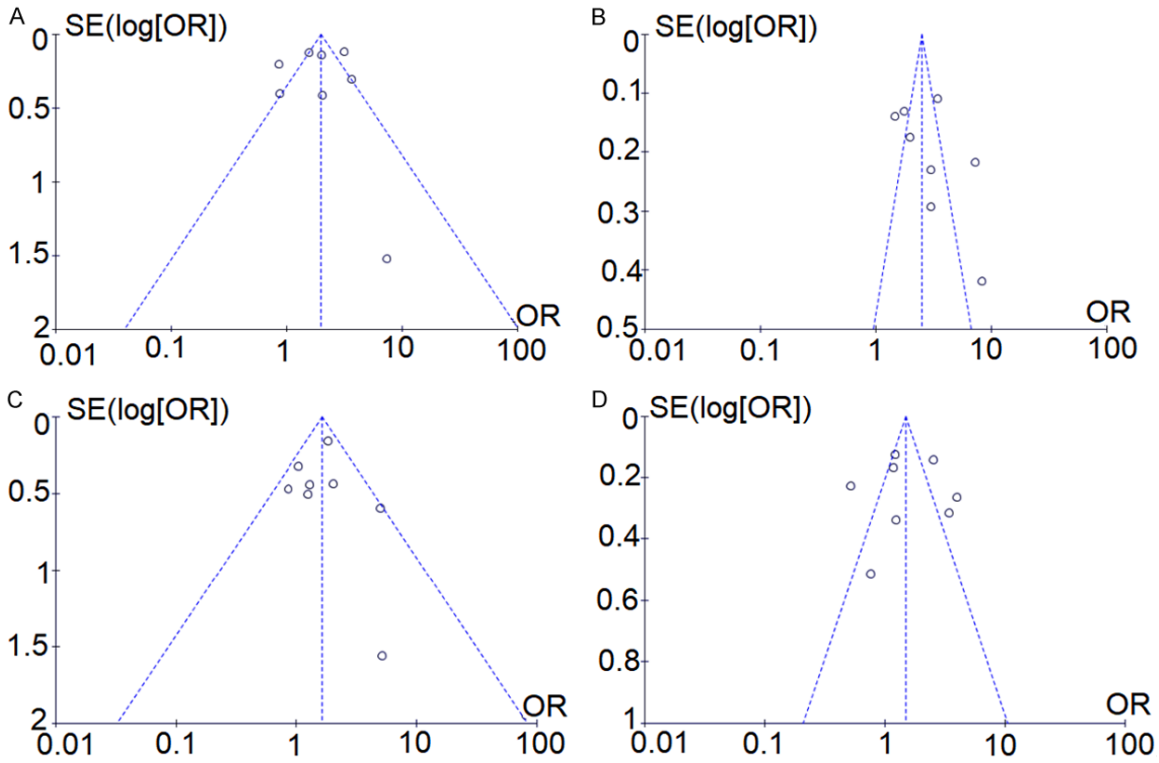

Figure 6. Funnel plots. Note: (A) Funnel plot of correlation between AV and HPV; (B) Funnel plot of correlation between BV and HPV; (C) Funnel plot of correlation between TV and HPV; (D) Funnel plot of correlation between VVC and HPV. AV = Aerobic Vaginitis; BV = Bacterial Vaginosis; TV = Trichomonal Vaginitis; VVC = Vulvovaginal Candidiasis; HPV = Human Papillomavirus.

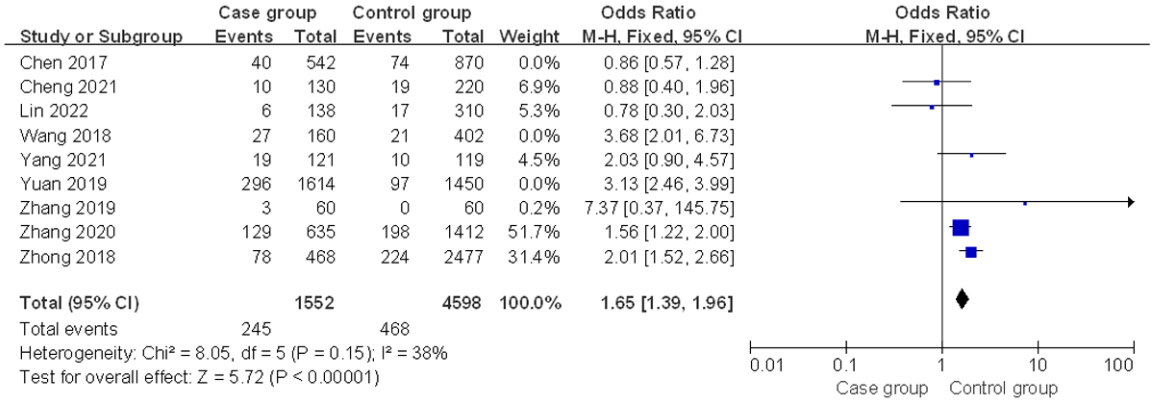

Figure 7. Correlation between AV and HPV infection (after eliminating the lower quality studies). AV = Aerobic Vaginitis; HPV = Human Papillomavirus.

Sensitivity analysis

According to the results of the risk of bias assessment, the studies with a higher risk of bias were excluded, and meta-analysis was performed again. The positive rates of AV, BV and TV in HPV positive group were higher, and the differences were statistically significant (Z = 5.72, 8.22, 3.34). There was no significant difference in the positive rate of VVC between the two groups (Z = 1.95, P = 0.05). This is consistent with the results of the previous analyses (**Figures 7-10**).

Discussion

According to different structures, functions and pathogenesis, HPV is clinically divided into the

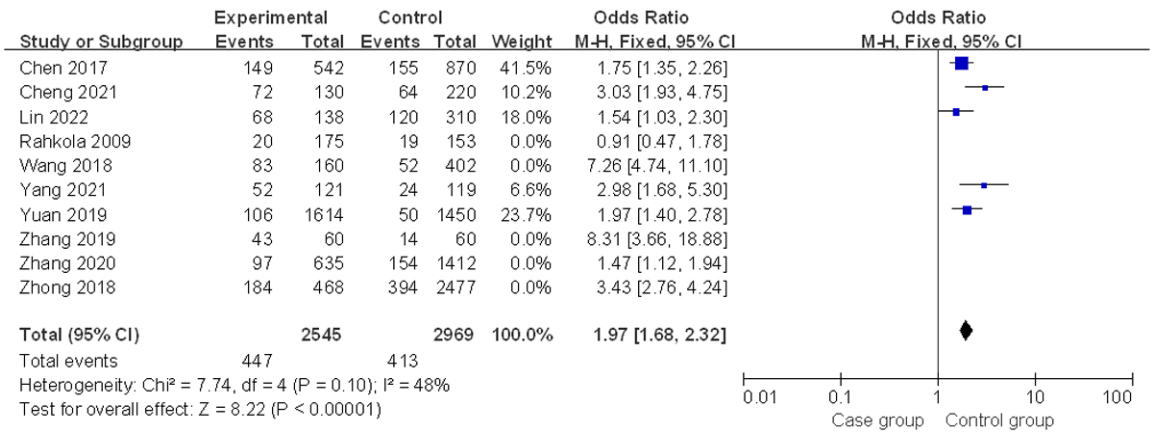

Figure 8. Correlation between BV and HPV infection (after eliminating the lower quality studies). BV = Bacterial Vaginosis; HPV = Human Papillomavirus.

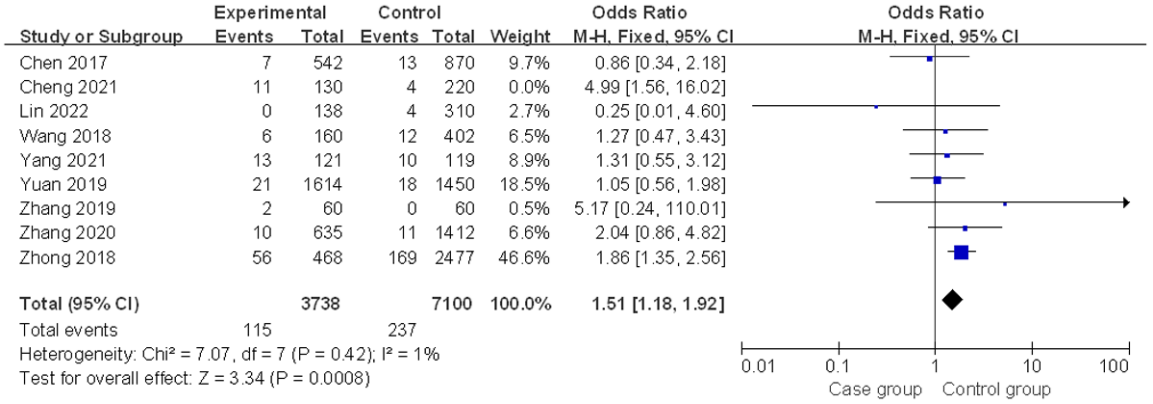

Figure 9. Correlation between TV and HPV infection (after eliminating the lower quality studies). TV = Trichomonal Vaginitis; HPV = Human Papillomavirus.

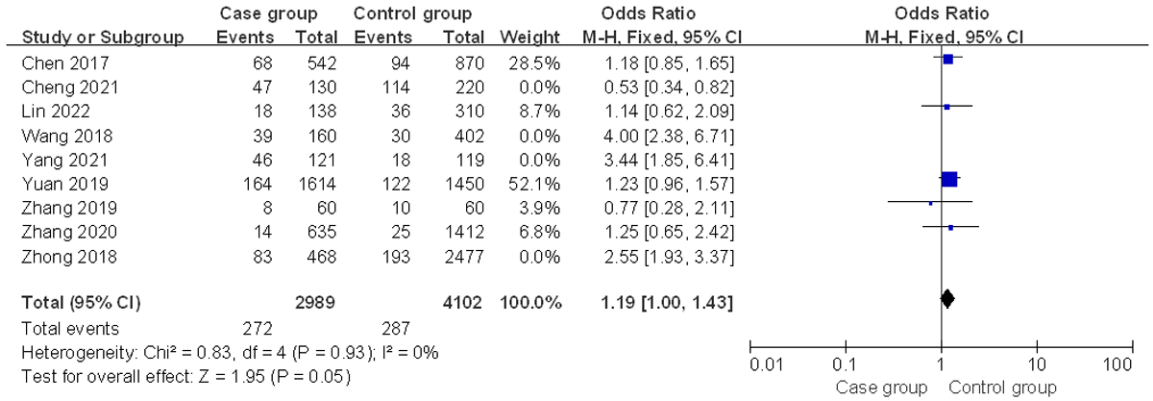

Figure 10. Correlation between VVC and HPV infection (after eliminating the lower quality studies). VVC = Vulvovaginal Candidiasis; HPV = Human Papillomavirus.

high-risk and low-risk types [23]. It mainly invades the immune system of the host [24]. During epithelial differentiation, HPV changes the growth mode of cells and realizes immune

escape by replication and encoding, which specifically interferes with innate and adaptive immunity by hiding itself, causing sustained infection in the host [25]. HPV infection is involved in the development of cervical cancer, while the vaginal microenvironment affects HPV infection and its persistent infection [26, 27]. A growing number of studies suggested that changes in the vaginal microenvironment are strongly associated with HPV infection. The correlation between the vaginal microenvironment and HPV infection was systematically evaluated in this meta-analysis by collecting the results of previous studies and using an evidence-based medical method.

The results of this study showed that AV, BV and TV were the high-risk factors for HPV infection, with OR of 1.73, 2.52 and 1.60 respectively, which were of statistical significance. The risk of publication bias was relatively small, and the conclusions were stable and reliable to some degree. However, the correlation between VVC and HPV infection was not statistically significant, and this conclusion needs to be further verified. The conclusion of this study on BV was consistent with most of the studies published so far, but the conclusions of AV, TV and VVC were inconsistent with the conclusions of some studies, so further research is needed. BV is characterized by excessive growth of dominant bacteria in the vagina, from Lactobacillus to microorganisms dominated by anaerobic bacteria. Studies have shown that BV is associated with HPV infection, particularly HR-HPV infection [28]. Other studies have also shown a substantial statistical association between HPV and BV [29]. Patients with BV are more susceptible to HPV due to the increased pH value in the vagina and missing Lactobacillus [30]. HPV patients often have AV and TV [31], but the results of studies on the correlation of AV and TV with HPV infection were not the same. AV is characterized by changes in the Lactobacillus accompanied by an increase in local inflammation and immune response [32]. Some studies have indicated that AV is strongly associated with HPV infection [33], but some reported no association between them [34]. There are currently few studies about the correlation between AV and HPV infection, and there are differences between the results of different studies. So further studies with larger sample sizes are needed. TV can increase the susceptibility to HPV [35, 36]. The reasons may be that TV can cause damage to the mucosa of reproductive organs, vaginitis and acute inflammatory diseases, thus promoting secondary infections including HPV and HIV [37]. There was also a study showing that TV was not associated with HPV infection [38]. Whether TV can affect HPV infection or not, is still controversial. This needs to be further confirmed by more studies with large sample sizes.

The meta-analysis results of this study showed that VVC was not a high-risk factor for HPV infection, with OR value of 1.48, which was not statistically significant. A previous study reported that VVC was not associated with HPV infection [39]. There are also studies showing that VVC was a high-risk factor for HPV infection. When Lactobacillus is abnormal, the rate of VVC and recurrent VVC infection will increase substantially [40]. Some scholars believe that VVC infection can increase tissue permeability through inflammations, produce invasive enzymes, and destroy reproductive tract epithelial cells, making patients susceptible to HPV. HPV infection contributes to the breakdown of the vagina's defensive barrier through microtrauma, leading to dysbacteriosis, which further aggravates the VVC. In summary, abnormalities in the vaginal microenvironment (especially AV, BV, and TV) are closely associated with HPV infection. Microbial infections of the female genital tract can cause damage to the mucosa of the genital tract, increasing the chance of HPV infection. HPV infection may disrupt the microecological balance by altering the host's immune function, which leads to changes in the structure of the vaginal microbial community, thus predisposing the host to vaginal infection [41].

Advantages and limitations

This study is the first meta-analysis of studies published in the past 10 years about the correlation between the vaginal microenvironment and HPV infection. When screening the literature, the language and nationality of the literature were not limited. So, the conclusions of this study can provide clinical guidance for the prevention, control and treatment of HPV to a certain extent. However, the number of included literature is quite small, so the risk of bias in this study cannot be ignored. Therefore, the

sample size should be increased in future systematic analysis, so as to further enhance the reliability of the conclusions.

Conclusion

In summary, the vaginal microenvironment is closely related to HPV infection, especially AV, BV and TV are high-risk factors for HPV infection.

Disclosure of conflict of interest

None.

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