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Original Article

Characteristics of bacterial vaginosis infection in cervical lesions with high risk human papillomavirus infection

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Abstract: High risk human papillomavirus (HPV) infection is the major cause of cervical cancer. Bacterial vaginosis (BV) is considered as the most prevalent vaginal imbalance affecting women of reproductive age. However, the relationship between HPV and BV infection is unclear. This study aimed to assess the prevalence of human papillomavirus (HPV) infection combined with bacterial vaginosis (BV) infection in Shanghai suburbs and evaluate associations between bacterial vaginosis with HPV infection, cervical intraepithelial neoplasia (CIN) and cervical cancer. Methods: From October 1, 2009 to October 31, 2013, a total number of 3502 women who visited Fengxian Hospital, Southern Medical University were enrolled in this study. All participants gave informed consent and agreed to HPV, BV, chlamydia, mycoplasma and thinprepcytologic test (TCT). In addition, all women took histopathologic examination under colposcopy. Statistical analyses were done using SPSS 17.0 for windows (IBM). In present study the overall BV-positive rate was 9.25%. The top three high risk HPV types were listed as follows (in descending order): HPV16, 52, 58. Moreover, our data showed BV infection tended to occur in the HPV positive women, HPV infection also tended to occur in the BV positive women. Most of the women who present HPV with BV infection were younger than 30 years old. We also found that CIN and cervical cancer occurred mainly in HPV/BV positive and HPV with BV positive group. BV infection and HPV infection may haveconsistency or synergies. HPV with BV infection may increase the incidence of CIN and cervical cancer.

Keywords: Bacterial vaginosis infection, HPV types, cervical lesion

Introduction

Human papillomavirus (HPV) is one of the major causes of cervical tumors [1]. At the meantime, it is one of the most common sexually transmitted infections worldwide [2]. The persistent and repeated high risk HPV types are found to be a main causative agent of cervical cancer and cervical intraepithelial neoplasia (CIN) III [3, 4]. However, only minority turns into CIN or cervical cancer, a majority of high risk HPV infection are cleared. Individual differences in immunological defense may be one explanation [5, 6].

Bacterial vaginosis (BV) is considered the most prevalent vaginal imbalance affecting women of reproductive age [7-9]. The characterizer of this infestation is a concurrent massive overgrowth of anaerobic bacteria. It often performs as a thin homogenous, uniformly adherent, vaginal discharge, a vaginal pH > 4.5, a fishy odour on addition of 10% KOH and presence of clue cells [9, 10]. Risk factors for BV included the minority nationality, women's lower education levels, smoking, usage of an intrauterine device (IUD), higher number of sexual partners and so on [9, 11, 12]. BV has been shown to increase the risk of gynaecologic complications such as postabortion pelvic inflammatory disease, postoperative infection, cervicitis, human immunodeficiency virus (HIV), and possibly cervical intraepithelial neoplasia (CIN) [13]. Moreover, BV has been associated with some sexually transmitted diseases, including infection with

Table 1. Distribution characteristics of HPV infection in 3502 women

	HPV-positive	HPV-negative	*P*-value
Age (years)			
Mean (SD)	38.3 (10.7)	39.76 (9.03)	
Median (Min, Max)	38 (15-80)	40 (18-71)	
≤30	461 (26.5%)	278 (15.8%)	<0.001
30-40	517 (29.7%)	564 (32.1%)	
≥40	760 (43.7%)	916 (52.1%)	
BV infection			
Positive	270 (15.5%)	54 (3.1%)	<0.001
Negative	1468 (84.5%)	1710 (96.9%)	
TCT			
Normal	1354 (78.4%)	1690 (95.8%)	<0.001
Abnormal	374 (21.6%)	74 (4.2%)	
Pathology			
Cervicitis	1375 (79.1%)	1727 (97.9%)	<0.001
CIN	329 (18.9%)	37 (2.1%)	
Cervical cancer	34 (2.0%)	0 (0%)	
Mycoplasma infection	113 (6.5%)	22 (1.2%)	
Chlamydia infection	43 (2.5%)	5 (0.3%)	

Table 2. Distribution characteristics of BV infection in 3502 women

	BV-positive	BV-negative	*P*-value
Age (years)			
Mean (SD)	36.6 (11.8)	39.3 (9.6)	
Median (Min, Max)	35 (15-73)	39 (18-80)	
≤30	136 (42.0%)	603 (19.0%)	<0.001
30-40	52 (16.0%)	1035 (32.6%)	
≥40	136 (42.0%)	1540 (48.4%)	
HPV infection			
Positive	270 (83.3%)	1467 (46.2%)	<0.001
Negative	54 (16.7%)	1711 (53.8%)	
TCT			
Normal	220 (67.9%)	2824 (88.9%)	<0.001
Abnormal	102 (31.5%)	349 (11.0%)	
Pathology			
Cervicitis	193 (59.6%)	2909 (91.5%)	<0.001
CIN	119 (36.7%)	247 (7.8%)	
Cervical cancer	12 (3.7%)	22 (0.7%)	
Mycoplasma infection	39 (12.0%)	96 (3.0%)	
Chlamydia infection	23 (7.1%)	25 (0.8%)	

Chlamydia trachomatis, Neisseria gonorrhoeae [14]. However, the relationship between BV and HPV is not clear.

The purpose of the present study is to assess the prevalence and characteristic of HPV infection combined with BV infection in Shanghai suburbs and investigate the relationship between BV and CIN or cervical cancer.

Materials and methods

This study was reviewed and approved by the Institutional Review Board of Fengxian Hospital, Southern Medical University. A written informed consent form was obtained from all recruited individuals, all procedures were performed in accordance with the Human Investigation Ethical Committee of Fengxian Hospital, Southern Medical University.

Fengxian Hospital, Southern Medical University is located in the central of the Fengxian District, the southern suburb of Shanghai. From October 1, 2009 to October 31, 2013, 3102 cervicitis women, 366 CIN grading (I, II and III) women and 34 cervical cancer women confirmed by biopsy of cervical tissue were enrolled in this study. All participants were recorded complete personal and clinical examination data and agreed to HPV, BV, chlamydia, mycoplasma and thinprepcytologic test (TCT). The specimens were collected before treatment. All individuals had a history of sexual intercourse and no history of uterus resection or/and cervical surgery. Pregnancy at the time of examination was excluded from this study.

We performed the HybriBio HPV GenoArray test (Cat# 110101/101201/110301, HybriBio, Hong Kong) to simultaneously identify 21 HPV types, including 13 high risk types (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68), five low risk types (HPV 6, 11, 42, 43 and 44) and three Chinese common types (HPV 53, 66 and cp8304).

TCT results were categorized according to the Bethesda System [15], and abnormal TCT results were defined as follows: atypical squamous cells of unknown significance (ASC-US), low-grade squamous intraepithelial neoplasia (LSIL), high-grade squamous intraepithelial lesion (HSIL) and atypical glandular cells. The ASC-US, LSIL and HSIL were defined to be abnormal.

All biopsy samples were histopathologically evaluated by two gynecologic pathologists for

Table 3. Distribution characteristics of HPV infection in 324 BV positive women

	HPV-positive	HPV-negative	*P*-value
Age (years)			
Mean (SD)	36.2 (12.2)	39.0 (9.7)	
Min, Max	15-73	22-71	
≤30	127 (47.0%)	9 (16.7%)	<0.001
30-40	31 (11.5%)	21 (38.9%)	
≥40	112 (41.5%)	24 (44.4%)	
TCT			
Normal	176 (65.9%)	44 (81.5%)	0.060
Abnormal	92 (34.1%)	10 (18.5%)	
Pathology			
Cervicitis	147 (54.4%)	46 (85.2%)	<0.001
CIN	111 (41.1%)	8 (14.8%)	
Cervical cancer	12 (4.4%)	0 (0.0%)	

Table 4. Association between BV infection and the cervical lesion in HPV-positive women

	BV-positive n (%)	BV-negative n (%)	*P*-value
Cervicitis	147 (10.69)	1228 (89.31)	<0.001
CIN	111 (33.74)	218 (66.26)	
Cervical cancer	13 (38.24)	21 (61.76)	

multiple punch biopsy under colposcopy. Cervical lesions were defined as follows: cervicitis, CIN grading (I, II and III) and cervical cancer.

Every vaginal infection was defined using standard criteria. Presence of bacterial vaginosis was determined by Nugent scoring of a gram-stained slide. A Nugent score of 7 to 10 defined bacterial vaginosis, whereas a score of 0 to 6 defined normal-intermediate vaginal flora. For visits without a Nugent score (<1%), bacterial vaginosis was defined by modified Amsel's criteria [16]. The chlamydia and mycoplasma test followed the protocols of Polymerase Chain Reaction kit (Cat# 1616-2009, KHB, Shanghai).

The differences in selected variables between the HPV/BV-negative and HPV/BV-positive groups were evaluated by the Pearson's x^2-test. We performed Student's *t* test or ANOVA test to compare continuous variables between two groups, and we used chi-square test or Fisher exact test to analysed categorical data. All statistical analyses were performed with SPSS 17.0 for windows (IBM). All *P* values were two-sided with a significance level of P<0.05.

Results

Overall situation of HPV and BV infection

Among the 3502 women, 1738 women were positive for HPV while 1764 women were negative for HPV, 324 women were positive for BV infection while 3178 women were negative for BV infection. The total rate of BV infection was 9.25%. The rate of BV infection in the HPV positive group was more than the rate in HPV negative group (P=0.0000) (**Table 1**). It prompts that BV infection tends to occur in those women who have a HPV infection. The HPV infection rate in the BV positive group was more than the rate in BV negative group (P=0.0000) (**Table 2**). It showed that HPV infection also tends to occur in women with BV infection. Thus, we speculate that there may be consistency or synergies between HPV infection and BV infection.

HPV/BV infection and age

The mean age of HPV positive group was 38.3±10.7 (range 15-80 years) while the mean age of HPV negative group was 39.76±9.03 (range 18-71 years). The mean age of BV positive women was 36.6±11.8 (range 15-73 years). The mean age of BV negative women was 39.3±9.6 (range 18-80 years). The mean age of women with HPV and BV infection was 36.2±12.2 (range 15-73 years). Among the women younger than 30 years, 26.5% cases were HPV positive and 15.8% cases were HPV negative (P=0.0000) (**Table 1**). 42.0% women were younger than 30 years with BV infection while 19.0% women were younger than 30 years without BV infection (P<0.001) (**Table 2**). Further analysis showed that there was a statistical difference between the rate of women younger than 30 years in BV-positive with HPV infection and without HPV infection (P<0.001) (**Table 3**). All the results above showed HPV/BV infection and BV infection with HPV infection tend to occur in the women whose age younger than 30 years.

HPV/BV infection and cervical histological and cytological examinations

The rate of CIN or cervical cancer with HPV infection was higher than without HPV infection (P<0.001) (**Table 1**). The rate of CIN or cervical cancer with BV infection was higher than without BV infection (P<0.001) (**Table 2**). It suggest-

Table 5. HPV type and BV infection

	BV-negative N (%)	BV-postive N (%)	Total (%)
Single infection			
High risk			
HPV 16	208 (11.98)	55 (3.17)	263 (15.15)
HPV 18	63 (3.63)	13 (0.75)	76 (4.38)
HPV 31	82 (4.72)	15 (0.86)	97 (5.59)
HPV 33	65 (3.74)	12 (0.69)	77 (4.44)
HPV 35	8 (0.46)	0 (0.00)	8 (0.46)
HPV 39	30 (1.73)	9 (0.52)	39 (2.25)
HPV 45	11 (0.63)	2 (0.12)	13 (0.75)
HPV 51	11 (0.63)	0 (0.00)	11 (0.63)
HPV 52	208 (11.98)	34 (1.96)	242 (13.94)
HPV 56	12 (0.69)	1 (0.06)	13 (0.75)
HPV 58	131 (7.55)	22 (1.27)	153 (8.81)
HPV 59	11 (0.63)	4 (0.23)	15 (0.86)
HPV 68	56 (3.23)	5 (0.29)	61 (3.51)
Low-risk			
HPV 6	23 (1.32)	3 (0.17)	26 (1.50)
HPV 11	33 (1.90)	8 (0.46)	41 (2.36)
HPV 42	3 (0.17)	1 (0.06)	4 (0.23)
HPV 43	2 (0.12)	0 (0.00)	2 (0.12)
HPV 44	5 (0.29)	0 (0.00)	5 (0.29)
Common in China			
HPV 66	32 (1.84)	5 (0.29)	37 (2.13)
HPV 53	85 (4.90)	16 (0.92)	101 (5.82)
HPV cp8304	45 (2.59)	3 (0.17)	48 (2.76)
Double infection	273 (15.73)	47 (2.71)	320 (18.43)
Multiple infection	69 (3.97)	15 (0.86)	84 (4.84)

ed that CIN and cervical cancer occurs mainly in HPV/BV positive group. It is noteworthy that more women diagnosed of CIN and cervical cancer with HPV and BV infection compared with HPV/BV infection women (P=0.000) (**Tables 3**, **4**). It indicated that HPV with BV infection may promote CIN and cervical cancer.

In terms of TCT results, there was a significant difference of abnormal results rate between HPV positive group and HPV negative group (P<0.001) (**Table 1**). At the meantime, the difference also existed between BV positive group and BV negative group (P<0.001) (**Table 2**). The HPV/BV positive women tend to have abnormal result of TCT testing.

HPV types and BV infection

For BV negative patients, HPV16 and HPV52 (11.98%) were the first leading high risk type among single infection, which was followed by HPV58 (7.55%), HPV31 (4.72%), HPV 33 (3.74%) and HPV 18 (3.63%). And 273 cases were double HPV infection, 69 cases were multiple infection (**Table 5**). Except HPV6, 59, 35, mostly women with HPV infection were older than 40 years. Furthermore, most cases were also older than 40 years in double and triple infection (**Figure 1A**). The HPV type of 21 women without BV infection diagnosed cervical cancer were HPV16, 59, 52, 18 and multiple infection (**Figure 2A**).

For BV positive patients, HPV16 was the first leading high risk type among single infection (3.17%), which was followed by HPV-52 (1.96%), HPV58 (1.27%), HPV31 (0.86%), HPV18 (0.75%). And 47 cases were double HPV infection, 15 cases were multiple infection (**Table 5**). Mostly, women with HPV68, 58, 33, 18 and 16 were younger than 30, same as the double and multiple infection (**Figure 1B**). The HPV type of 13 women with BV infection diagnosed cervical cancer were HPV16, 66, 59, 58, 18 and multiple infection (**Figure 2B**).

Combined infection of HPV, BV, mycoplasma and chlamydia

The infection rate of chlamydia and mycoplasma was higher in HPV/BV positive women than HPV/BV negative women (P<0.001) (**Table 6**). In single HPV infection group, most of the women were older than 40 years old. Compared with the double infection most of the women were younger than 30 years or older than 40 years in triple infection group (**Table 7**). Our dates also showed that the more types of infection, the more present of abnormal TCT results and CIN (**Table 7**).

Discussion

The persistent and repeated high risks HPV types are found to be a main causative agent of cervical cancer [1]. Certainly it is not the solo pathogenesis. The persistent oncogenic HPV infection itself is not sufficient to immortalize and transform the epithelial host cells to cancer cells [17]. BV is the most prevalent vaginal disorder in adult women characterized by an increased vaginal pH (>4.5), a concurrent massive overgrowth of anaerobic bacteria. BV has shown a relationship with HIV infection [18, 19]. Thereby more and more researchers start to pay attention to the relationship between BV

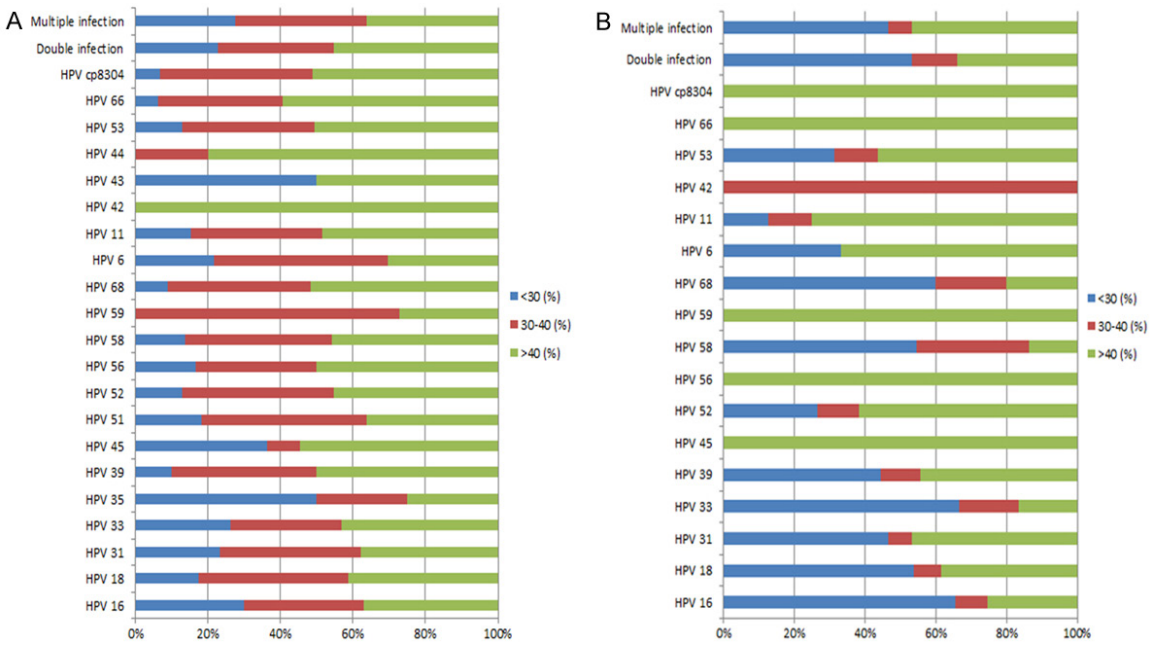

Figure 1. Distributions of HPV types in BV infection. A. Distributions of HPV types with BV negative in different age. B. Distributions of HPV types with BV positive in different age.

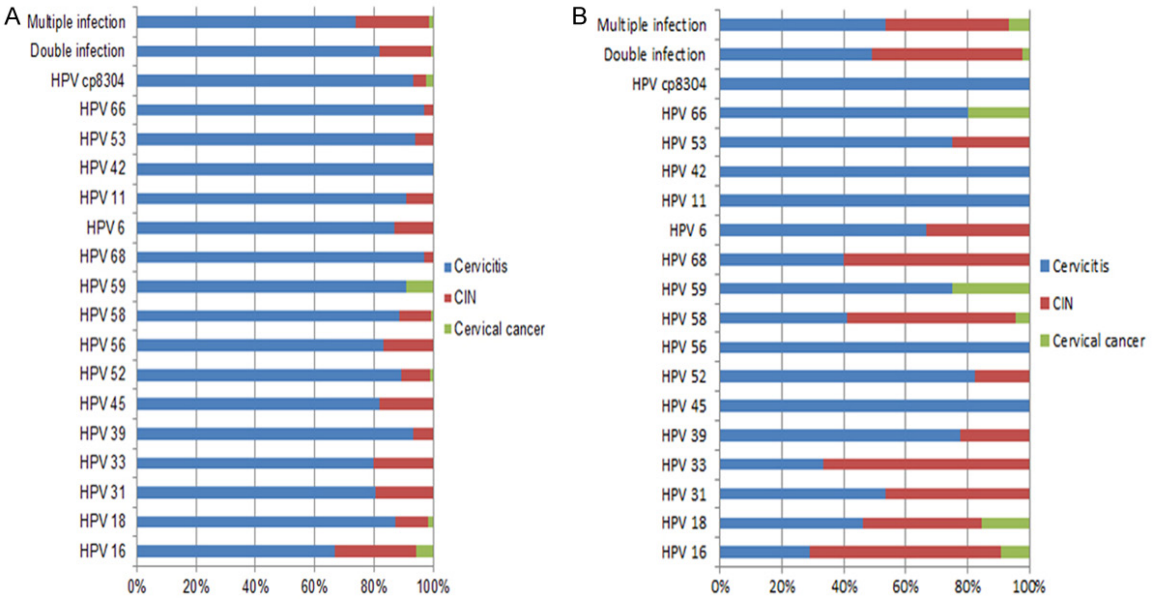

Figure 2. Distributions of HPV types in different cervical lesions. A. Distribution of HPV types with BV negative in different cervical lesions. B. Distributions of HPV types with BV positive in different cervical lesions.

and vaginal cervical infection diseases (such as HPV infection, cervicitis, CIN and cervical cancer, etc).

Our data showed that BV infection tends to occur in HPV positive women, HPV infection also tends to occur in BV infected women. It is possible that BV is a cofactor involved in acquisition or reactivation of HPV infection by affecting immunological balance within the cervical tissue as a result of changes in production of factors, such as cytokines (interleukin-1β, interleukin-10) [20]. Enzymes produced by anaerobic bacteria involved in the pathogenesis of BV can potentially alter immune signals and promote degradation of host factors, rendering women more susceptible of acquiring HPV. However, Mao et al. reported that there is a tem-

Table 6. Association between BV/HPV infection and Mycoplasma infection/Chlamydia infection

	HPV positive	HPV negative	*P*-value	BV positive	BV negative	*P*-value
Mycoplasma positive	113 (6.5%)	22 (1.2%)	<0.001	39 (12.0%)	96 (3.0%)	<0.001
Mycoplasma negative	1625 (93.5%)	1742 (98.8%)		285 (88%)	3082 (97%)	
Chlamydia positive	43 (2.5%)	5 (0.3%)	<0.001	23 (7.1%)	25 (0.8%)	<0.001
Chlamydia negative	1695 (97.5%)	1759 (99.7%)		301 (92.9%)	3153 (99.2%)	

Table 7. Distribution characteristics of combined infection

	Quadruple infection	Triple infection	Double infection	Single infection	*P*-value
Age (years)	2	56	304	1356	
Mean (Std)	27.00 (9.89)	35.91 (11.15)	37.04 (12.61)	38.41 (9.89)	0.029
Min, Max	20, 34	19, 63	15, 75	18, 80	
≤30	1 (50%)	27 (48.2%)	124 (40.7%)	309 (22.8%)	<0.001
30-40	1 (50.0%)	1 (1.8%)	59 (19.3%)	456 (33.6%)	
≥40	0 (0%)	28 (50.0%)	122 (40.0%)	591 (43.6%)	
TCT					
Normal	1 (50.0%)	38 (69.1%)	212 (70.4%)	1090 (80.7%)	0.005
Abnormal	1 (50.0%)	17 (30.9%)	89 (29.5%)	261 (19.3%)	
Pathology					
Cervicitis	1 (50.0%)	30 (53.6%)	190 (62.3%)	1136 (83.7%)	<0.001
CIN	1 (50.0%)	25 (44.6%)	98 (32.1%)	205 (15.1%)	
Cervical cancer	0 (0%)	1 (1.8%)	17 (5.6%)	16 (1.2%)	

poral relationship between HPV and BV, with HPV infection generally preceding BV [21]. It may be changed vaginal environment caused by HPV infection and makes it prone to infection BV. So the question is whether BV and HPV infection are simply related because there is a biologic interaction between them, or because both occur frequently in sexually active women. Therefore, a large number of epidemiological and molecular studies are further needed.

In our previous research, the rate of HPV infection in Shanghai suburbs is 12.6% [22]. In this study, the top type was HPV 16 followed by HPV 52 and HPV 58. This is slightly different from our previous report [22]. The reason for differences relates to difference of data collection time, the collection time was from March 08 to May 30, 2011 in our previous study. The high risk HPV types of women diagnosed cervical cancer were 16, 18, 59 and 52. The high risk HPV types of women diagnosed CIN were 16, 33, 52 and 58. HPV 16 was the major type of cervical cancer and CIN patients infected.

A global systematic review of more than 12,400,000 women from 103 studies indicated that age is a risk factor for cervical cancer and HPV infection [23]. Moreover, the infection rate of a continuous HPV infection was much higher than that of a new HPV infection in women older than 45 years [24], women older than 45 years is a peak in HPV infection rates [25]. Our data showed that 43.7% women with HPV infection were older than 40 years. It is consistent with our previous findings [22]. In our data, most women with HPV infection were in ≤30 years group.

In our study, the total BV positive rate was 9.25%, significantly lower than the other reports. In the evaluation of women aged 14 to 49 years in the 2001-2004 National Health and Nutrition Examination Survey, 29% were positive for BV [26]. The prevalence of BV was 11.99% (6,391/53,286) in a 53,652 married women enrolled study from Anhui Province of China [12]. Furthermore, the prevalence of BV in the female adult population of the Aland Islands has declined between 1993 and 2008 from 15.6% to 8.6% [27]. Maybe the difference of race and sexual style cause the difference of BV infection rate [9]. In our data, most of women with BV positive were younger than 30 years compared with the BV negative group.

Moreover, we found most of the women infected HPV and BV were younger than 30 years,

especially the HPV16 and 58 (**Figure 1B**). The cause of this difference is still unclear. A possible explanation is that the vaginal environment of young women, which younger than 30 years was more susceptible to BV. We should pay more attention to the BV testing in women younger than 30 years.

Our data showed that the rate of double and multiple HPV infection was 18.43% and 4.84% in the HPV positive group. However, when BV infection present's the double HPV infection rate increased (2.71%), second only to the proportion of HPV16 infection (3.17%) (**Table 5**). It is possible that bacterial vaginosis is associated with high levels of anaerobic microorganisms and their byproducts, that can damage vaginal epithelium, degrade cervical mucus [28, 29], which leads to vaginal environment disorder and prone to other pathogen infection.

The research about whether BV infection and cervical cancer related is still less. As for BV infections and CIN association, there are also two different points of view. Denslow et al. reported among 1954 HIV-seropositive South African women, BV was not associated with an increased risk of HSIL or cervical lesion progression [30]. Boyle et al. found that BV is not associated with CIN after testing 379 women with BV testing and cervical smear detection [31]. On the other hand, Gillet et al.'s meta-analysis confirms a positive association between BV and cervical precancerous lesions and emphasizes the potential role of a disturbed vaginal microflora in gynaecologic complications [32].

We analyzed the relationship between cervical lesions and infections such as HPV, BV, Mycoplasma or Chlamydia infection. We found that more than half (52.94%) women diagnosed cervical cancer present the other vaginal infections excluding the HPV infection. The BV positive rate was 35.3% and 32.5% in cervical cancer and CIN women, which is significantly higher than the total rate of BV infection (9.25%, 324/3502 cases). It may suggest that BV promoting the CIN and cervical cancer from the epidemiological point of view.

Infection and chronic inflammation have been recognized as important cofactors for carcinogenic HPV [33]. In our data, CIN and cervical cancer were significantly increased in the women with HPV and BV infections. Once again, it is shown that HPV infection with BV infection may promote the occurrence of CIN and cervical cancer. BV infection may be a cofactor and a risk factor of HPV cause CIN and cervical cancer. However, further studies were needed to improve this view by expanding the CIN and cervical cancer sample.

In conclusion, the rate of BV infection was 9.25% in 3502 women. Most of women infected HPV/BV or BV with HPV were younger than 30 years old. BV infection and HPV infection are cooperative. HPV infection with BV infection may increase the incidence of CIN and cervical cancer. What we need is strengthen and emphasize the combined detection of HPV and BV in a clinic population, particularly the women younger than 30 years, in the meantime treat the BV infection actively.

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Disclosure of conflict of interest

None.

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