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Original Article

Correlations between C-myc expression, BMI-1 expression, and vaginal microecology with HPV-DNA load in patients with different cervical lesions

Yingzhen Zhou[1], Junfei Zhu[1], Hao Zhang[2]

[1]Department of Laboratory, Suzhou Hospital of Integrated Traditional Chinese and Western Medicine, Suzhou 215000, Jiangsu, China; [2]Department of Laboratory, Xukou Town Health Center, Wuzhong District, Suzhou 215000, Jiangsu, China

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Abstract: Objective: To investigate the correlations between the expressions of proto-oncogenes C-myc and B-cell-specific Moloney leukemia virus integration site-1 (BMI-1), vaginal microecology, and human papillomavirus-DNA (HPV-DNA) load in patients with different cervical lesions. Methods: A total of 51 patients with cervix squamous cell carcinoma (CSCC), 72 patients with cervical intraepithelial neoplasia (CIN) and 50 patients with normal cervix (NC) who were diagnosed or admitted between Jan. 1st 2020 and Dec. 31st 2022 at the Suzhou Hospital of Integrated Traditional Chinese and Western Medicine were selected and divided into three groups, i.e., the CSCC group, the CIN group and the NC group, for a retrospective analysis. Hybrid capture 2 (hc2) was used to detect the HPV-DNA load in each group. Immunohistochemistry was performed to detect C-myc and BMI-1 expressions in each group. The indicators of vaginal microecology in patients were compared among groups to analyze the correlations between C-myc, BMI-1 expressions, vaginal microecology and HPV-DNA load. Results: The HPV-DNA load and expression levels of positive C-myc and BMI-1 in the CSCC group were all higher than those of the CIN and NC groups ($P<0.05$). The detection rate of lactobacillus in the CSCC group was lower than that of the CIN and NC groups. The percentages of leukocyte esterase (LE) positivity and pH ≥4.6 were higher in the CSCC group than those in the CIN and NC groups ($P<0.05$). The difference in the detection rate of spores among the three groups was not significant ($P>0.05$). Both C-myc and BMI-1 scores were positively correlated with HPV-DNA load in the 173 samples. Conclusion: The proto-oncogenes C-myc and BMI-1 were highly expressed in the cervical tissues of CIN and CSCC patients, whose vaginal microecology was also altered. Both may play an important role in the progression of cervical lesions.

Keywords: Cervical lesions, proto-oncogene C-myc, B-cell-specific Moloney leukemia virus integration site-1, vaginal microecology, human papillomavirus

Introduction

Cervix squamous cell carcinoma (CSCC) is the most common histologic type of cervical cancer in the reproductive systems of females, particularly married females aged between 35 and 50 years old in China, with a high prevalence worldwide. Common clinical signs and symptoms of CSCC include vaginal bleeding, abnormal vaginal fluid discharge, frequent urination, hematuria, pain, cachexia, and cervical cauliflower-shaped or endophytic infiltrative mass growth. Cervical intraepithelial neoplasia (CIN) is a collective term for a group of precancerous lesions closely related to CSCC, the presence of which reflects the possibility of cervical carcinogenesis and carcinoma development. Therefore, investigating how CIN progresses into CSCC is important to prevent the formation of CSCC in the uterine cervix.

The proto-oncogenes C-myc and B-cell-specific Moloney leukemia virus integration site-1 (BMI-1) are key factors in the malignant proliferation of tumor cells and are associated with the development of many malignancies and poor prognosis of cancer patients [1-4]. Human papillomavirus (HPV) infection is a sexually transmitted disease and an important cause of CIN and CSCC [5, 6]. Previously, C-myc expression

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was found to be upregulated in the cervical tumor tissues of patients with high-risk subtype HPV infection, a hallmark for cervical cancer diagnosis [7]. However, studies on BMI-1 expression in cervical lesions are still very limited, and whether its expression is in association with HPV infection remains unclear. Hence, analysis on correlations between both C-myc and BMI-1 expressions and HPV infection will help promote research advancement on the role of HPV infection in the formation of cervical lesions. In addition, factors such as imbalanced vaginal microecology, reproductive tract infections, premature sexual intercourse, and too many sexual partners increase the risks of CIN and CSCC [8-10]. The local immune microecology in the cervix plays an important role in HPV infection and pathogenicity, as well as in the development and progression of cervical lesions. Studies have showed that a decrease in lactobacilli, or inhibition of their functions in the vagina, leads to changes in the enzymes secreted by the microorganisms, which in turn changes the local vaginal environment [8]. However, whether localized changes in vaginal microecology influence the pathogenicity and progression of HPV infection remains unclear. This study investigated the correlations between the expressions of proto-oncogenes C-myc, BMI-1 and vaginal microecology and HPV-DNA load in both CSCC and CIN patients, aiming to provide references for the guidance on CIN and CSCC treatments and recovery.

Subjects and methods

Subjects

A total of 51 CSCC patients, 72 CIN patients and 50 NC patients who were diagnosed or admitted between Jan. 1st 2020 and Dec. 31st 2022 at the Suzhou Hospital of Integrated Traditional Chinese and Western Medicine were selected for a retrospective analysis. Inclusion criteria: patients were eligible if they met the diagnostic criteria for CSCC and CIN as published in the *Obstetrics and Gynecology* (verison 2013) [11]; they were initially diagnosed with CSCC and CIN at the Suzhou Hospital of Integrated Traditional Chinese and Western Medicine; they were aged between 18 and 70 year old; they had sexual intercourse experience; their menopause ended for about 3-7 days upon diagnosis or admission; they had no concomitant other malignant tumors or serious diseases; they participated in the study voluntarily and offered informed consent in accordance with the ethical norms of the hospital. Exclusion criteria: patients were excluded from the study if they had undergone vaginal douching or administered intravaginal drugs within 3 days; they had received radiotherapy or chemotherapy prior to clinical consultation; they had undergone surgical treatment or hysterectomy prior to clinical consultation; they had sexual intercourse within 3 days prior to clinical consultation; they were pregnant, or undergoing lactation or menstruation; they presented with mental abnormalities, or unable to communicate or cooperate. This study was approved by the Ethics Committee of Suzhou Hospital of Integrated Traditional Chinese and Western Medicine.

Methods

Baseline data collection: Baseline data of patients were collected upon their admission, which included their age, marital status, sexual life, height, weight, etc. Body mass index (BMI) was calculated as follows: BMI = weight/height^2.

Detection of HPV-DNA load in each group with hybrid capture 2 (hc2) technique: After admission, patients were placed in a bladder truncated position, with their cervix being exposed using a speculum. Cervical cell specimens were collected by a special cervical cell collection brush, which was rotated 3 to 5 turns clockwise and counterclockwise. The experiment was operated strictly according to the kit instructions (Digene, USA). Detection of high-risk HPV-DNA load as well as any of the high-risk HPV types (16/18/31/33/35/39/45/51/52/53/56/58/59/66/68) were considered HPV infection. The relative light unit ratio of the tested sample to the standard positivity in the control group was ≥1.0, suggesting HPV positivity.

Detection of C-myc and BMI-1 expressions in each group by immunohistochemistry: Cervical cell specimens were collected using the methods as described in 1.2.2 section from participants after admission. The experiments were operated strictly according to the kit instructions (Shanghai Anyan). The interpretation of the staining results was done independently by

Table 1. Baseline data of patients with different cervical lesions in the CSCC group, CIN group, and NC group

Indicator	CSCC group (n=51)	CIN group (n=72)	NC group (n=50)
Age (years)	48.82±8.11	46.63±7.84	46.82±7.08
BMI (kg/m^2)	22.54±1.88	21.97±1.84	21.92±1.90
Marriage [n (%)]			
Unmarried	3 (5.88)	5 (6.94)	2 (4.00)
Married	42 (82.35)	57 (79.17)	44 (88.00)
Divorced	6 (11.76)	10 (13.89)	4 (8.00)
Smoking [n (%)]	8 (15.69)	12 (16.67)	8 (16.00)
Drinking [n (%)]	13 (25.49)	17 (23.61)	10 (20.00)

Table 2. HPV positive expression rate in patients with different cervical lesions in the CSCC group, CIN group, and NC group

Indicator	CSCC group (n=51)	CIN group (n=72)	NC group (n=50)
HPV [n (%)]	42 (82.35)	21 (29.17)$^{\theta}$	1 (2.00)$^{\theta,\square}$

Note: $^{\theta}P$<0.05 compared to the CSCC group; $^{\square}P$<0.05 compared to the CIN group.

two pathologists. The final staining results were concluded by joint negotiation through the two pathologists. The C-myc protein was observed in the nucleus and the BMI-1 protein in the nucleus or cytoplasm. Positive cells were stained brownish yellow and scored according to the degree of staining, with no staining denoting for 0 points, light yellow for 1 point, standard yellow for 2 points and dark yellow for 3 points, as well as scored in accordance with the number of positive cells, with positive cells <25% standing for 0 points, 25%≤ positive cells <50% for 1 point, 50%≤ positive cells <75% for 2 points and positive cells ≥75% for 3 points. If the two types of score combined together were >1, this was considered positive expression, and <1 was considered negative [12, 13].

Determination of vaginal microecology in each group: Cervical cell specimens were collected using the methods as described in 1.2.2 section from participants after admission. One swab of the specimens was evenly coated on a clean slide. The specimens were subsequently gram-stained and observed under a conventional microscope. The concentrations of lactobacillus, gardnerella, trichomonas and spores were observed. The other swab of specimens were collected for the detection of leukocyte esterase (LE), sialoglucosidase (SNA) and pH using a combined bacterial vaginosis assay kit (dry chemoenzyme method, Zhejiang Lansen).

Statistical methods

Statistical analysis was carried out with the use of SPSS 23.0 software. The quantitative date conforming to a normal distribution were expressed as mean ± standard deviation ($\bar{x}$±s). The *t* test was used for comparison of data between two groups. The *one-way ANOVA* was used for comparison among the three groups, followed by post hoc pairwise Bonferroni test. Qualitative data [n (%)] were compared between groups with χ^2 test or *Fisher's exact test*. Pairwise comparison was carried out using χ^2 partition test. *Pearson correlation* analysis was used to analyze the correlations between C-myc and BMI-1 expressions and HPV-DNA load. The primary outcomes were the expression of C-myc and BMI-1 in each group, while the secondary outcomes were HPV-DNA load and vaginal microecology. P<0.05 was considered a ssignificant difference.

Results

Baseline data of patients with different cervical lesions in the CSCC, CIN, and NC groups

The differences in basic information such as age, BMI, and marital status pf patients in the CSCC, CIN, and NC groups were not significantly different (P>0.05). See **Table 1**.

HPV positive expression rates and HPV-DNA load in patients with different cervical lesions in the CSCC, CIN, and NC groups

The HPV positive expression rates were 82.35% (42/51), 29.17% (21/72), and 2.00% (1/50) in the CSCC, CIN, and NC groups, with HPV-DNA loads of (10.50±1.59), (6.48±1.20), and (2.83±0.55), respectively. The HPV positive expression rate and HPV-DNA load in the CSCC group were higher than those in the CIN and NC groups, with both indexes higher in the CIN group than those in the NC group (P<0.05). See **Table 2** and **Figure 1**.

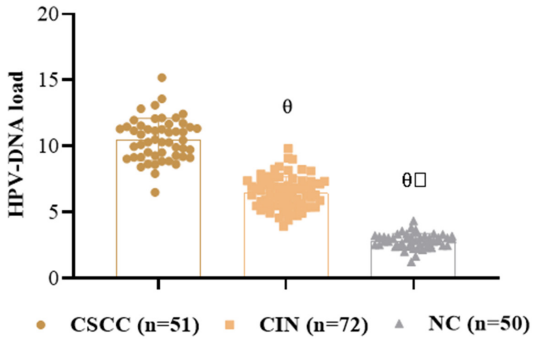

Figure 1. HPV-DNA load in patients with different cervical lesions in the CSCC group, CIN group, and NC group. Note: $^{\theta}P<0.05$ compared to the CSCC group; $^{\square}P<0.05$ compared to the CIN group.

Positive expression rates of C-myc and BMI-1 in patients with different cervical lesions in the CSCC, CIN, and NC groups

The positive C-myc expression rates were 74.51% (38/51), 52.78% (38/72), and 4.00% (2/50) in the CSCC, CIN, and NC groups, respectively. The positive BMI-1 expression rates were 72.55% (37/51), 40.28% (29/72), and 2.00% (1/50) in the three groups, respectively. The positive expression rates of C-myc and BMI-1 in the CSCC group were higher than those of the CIN and NC groups, with the three indexes all higher in the CIN group than those in the NC group ($P<0.05$). See **Table 3**.

Vaginal microecology in patients with different cervical lesions in the CSCC, CIN, and NC groups

The detection rate of lactobacillus in the CSCC group was lower than that of the CIN and NC groups ($P<0.05$). The percentages of LE positivity and pH≥4.6 were higher in the CSCC group than those of the CIN and NC groups ($P<0.05$). The detection rates of gardnerella, SNA positivity and pH≥4.6 in the CIN group were higher than those of the NC group ($P<0.05$). The detection rates of lactobacillus and trichomonas were lower in the CIN group than those of the NC group ($P<0.05$). The differences in the detection rates of spores among the three groups were not significantly different ($P>0.05$). See **Table 4**.

Correlations between C-myc and BMI-1 scores with HPV-DNA load in patients in each group

Pearson correlation analysis showed that both C-myc and BMI-1 scores were positively correlated with HPV-DNA load in the 173 samples ($r=0.828$, $r=0.811$, respectively; both $P<0.001$). Also, the same results were found in the CSCC group, CIN group, and NC group ($P<0.05$). See **Figure 2**.

Table 3. Positive expression rates of C-myc and BMI-1 in patients with different cervical lesions in the CSCC group, CIN group, and NC group

Protein	CSCC group (n=51)	CIN group (n=72)	NC group (n=50)
C-myc [n (%)]	38 (74.51)	38 (52.78)$^{\theta}$	2 (4.00)$^{\theta,\square}$
BMI-1 [n (%)]	37 (72.55)	29 (40.28)$^{\theta}$	1 (2.00)$^{\theta,\square}$

Note: $^{\theta}P<0.05$ compared to the CSCC group; $^{\square}P<0.05$ compared to the CIN group.

Correlations between vaginal microecology and HPV-DNA load in patients in each group

In the 173 samples, the detection rate of lactobacilli in the vagina of patients was lower in the HPV-positive group than that of the HPV-negative group ($P<0.05$). The detection rates of gardnerella, LE-positivity, SNA-positivity, and pH≥4.6 accounted for higher percentages in the HPV-positive group than those in the HPV-negative group ($P<0.05$). No significant differences were found in the comparison of the detection rates of spores and trichomonas between the two groups ($P>0.05$). See **Table 5**.

In subgroups, it was found that the detection rate of lactobacilli in the vagina of CSCC patients was lower in the HPV-positive group than that of the HPV-negative group ($P<0.05$). The detection rate of gardnerella was higher in the vagina of NC patients in the HPV-positive group than that in the HPV-negative group. Meanwhile, LE-positive accounted for a higher percentage in both CSCC and CIN patients in the HPV-positive group than that of the HPV-negative group ($P<0.05$). See **Table 6**.

Discussion

The long-term progression of CIN to cervical squamous cell carcinoma (CSCC) provides an implementable pathway for early clinical interventions. Both the environmental and genetic factors result in the development of CSCC. It is agreed upon that CSCC is a malignant lesion caused by the long-term effects of HPV infection in the lower genital tract of patients with high-risk HPV types (about 15 types) [14]. Some

Table 4. Vaginal microecology in patients with different cervical lesions in the CSCC group, CIN group and NC group

Indicator	CSCC group (n=51)	CIN group (n=72)	NC group (n=50)
Lactobacillus	10 (19.61%)	35 (48.61%)[θ]	30 (60.00%)[θ,□]
Gardnerella	11 (21.57%)	22 (30.56%)	7 (14.00%)[□]
Trichomonas	1 (1.96%)	0 (0.00%)	3 (6.00%)[□]
Spores	0 (0.00%)	3 (4.17%)	1 (2.00%)
LE positivity	34 (66.67%)	33 (45.83%)[θ]	22 (44.00%)[θ]
SNA positivity	9 (17.65%)	19 (26.39%)	6 (12.00%)[□]
pH≥4.6	47 (92.16%)	45 (62.50%)[θ]	21 (42.00%)[θ,□]

Note: [θ]P<0.05 compared to the CSCC group; [□]P<0.05 compared to the CIN group.

surveys have shown that nearly 90% of people will develop transient HPV infection during their lifetime, among whom only 10% are persistent. However, of the 10% patients, whether their HPV can be completely cleared, or whether their HPV infection stays latent in the basal cells for a long time without manifesting any clinical symptoms but becomes active again in response to certain stimuli, eventually developing into various cervical lesions or even cancer, still remains controversial [15]. In this study, the HPV positive expression rate and HPV-DNA load in the CSCC group were higher than those in the CIN and NC groups; and the three indexes were all higher in the CIN group than those in the NC group. This was consistent with previous reports and confirmed that high-risk HPV infection is a key factor for the progression of CIN to CSCC.

The progression from CIN to CSCC involves changes in multiple oncogenes and tumor suppressor genes, driven by multiple factors and typically spanning a prolonged disease course. The proto-oncogene C-myc is a transcription factor closely related to human malignancy and is considered one of the critical oncogenes in tumor development. Results of this study showed that C-myc was highly expressed in patients in the CSCC, CIN, and NC groups. Moreover, its expression was positively correlated with both the severity of patients' disease and HPV-DNA load. The C-myc protein has two major functions. One is to regulate cell proliferation and differentiation, and the other is to promote cell metabolism and apoptosis, which are mainly achieved by regulating cells from the GI phase into the S phase [16]. Existing studies at home and abroad have found a correlation between C-myc and the development of cervical cancer. It was reported that when high-risk HPV types were integrated into host DNA, E6 and E7 mRNA inactivated oncogenes P53 and PRb, resulting in the onset of cervical cancer [17]. Under normal conditions, PRb binds to the cytokine E2F. When stimulated by certain factors, the amount of free E2F increases, which activates the C-myc protein. This activation triggers a large number of proto-oncogene cells to enter the cell cycle from their resting phase, leading to abnormal cell proliferation and cancer development [18]. Kubler et al [19] identified recurring genetic variations in CSCC patients, with frequent amplifications in chromosomal regions 3q and 8q. These regions are largely consistent with the localization of the telomerase Terc gene (3q26.3) and the proto-oncogene C-myc (8q24.2). Consequently, their findings suggested that the upregulation of Terc and C-myc might be a key factor in the progression of cervical precursor lesions to malignant lesions. The proto-oncogene BMI-1 is a chromatin regulator of the polyukaryotic gene family and is involved in various biologic processes such as stem cell self-renewal, differentiation, cell growth and proliferation, as well as embryonic development [20]. DiMauro et al [21] found that BMI-l was regulated at the transcriptional and translational levels through different pathways. It could bind to the downstream INK4a/ARF regulatory genes, thus prolonging the cell proliferation cycle and preventing cell apoptosis. Herzog et al [2] found that the inhibition of BMI-l enabled increased sensitivity of head and neck cancer cells to chemotherapy, the result of which might lead to suppressed cell proliferation. Related studies have confirmed that the expressions of BMI-1 may also participate in tumor progression and lymph node metastasis in lung cancer [22], gastric cancer [23], and ovarian cancer [24]. In the current study, it was found that the expression of BMI-1 was positively correlated with the severity of patients' disease and HPV-DNA load, suggesting that the high expression of BMI-1 might promote the occurrence and development of cervical cancer, conforming to the aforementioned study results. These results all together support the fact that BMI-1

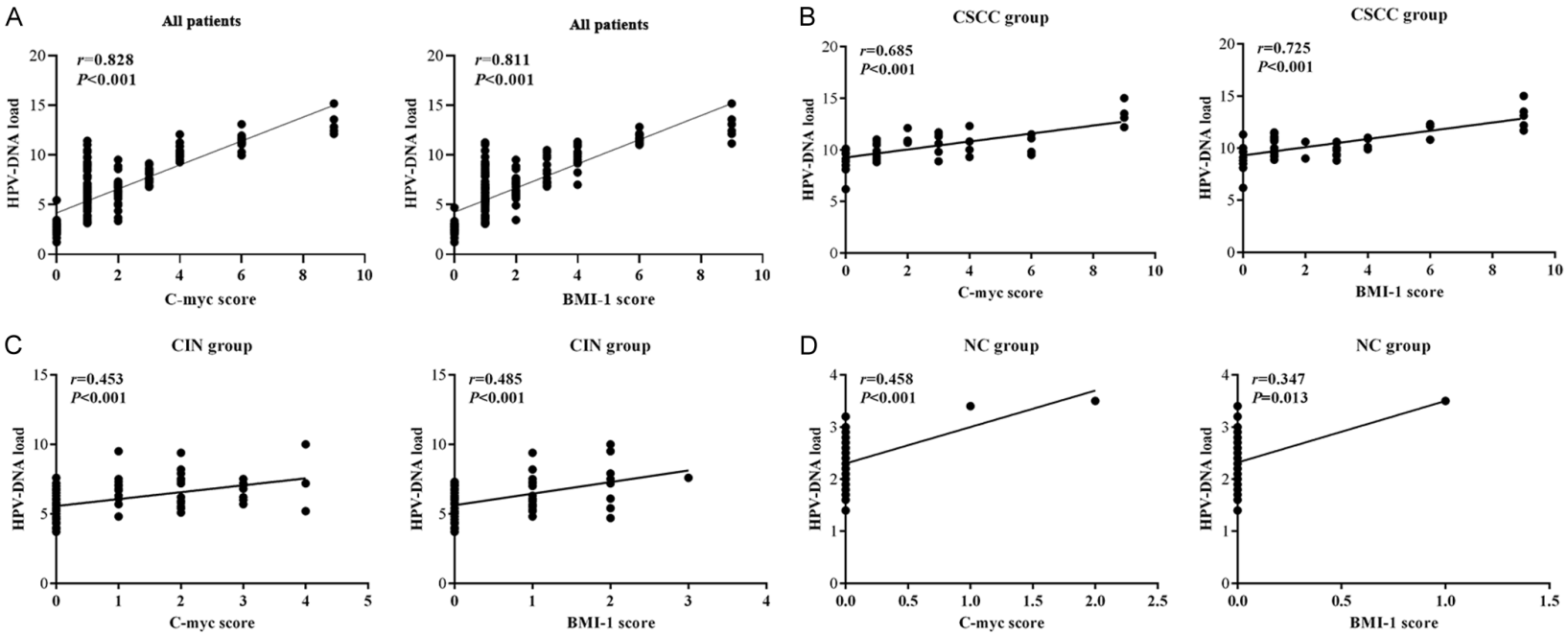

Figure 2. Correlations between C-myc and BMI-1 scores and HPV-DNA load. A: Correlation between C-myc and BMI-1 scores and HPV-DNA load in all patients; B: Correlation between C-myc and BMI-1 scores and HPV-DNA load in the CSSC group; C: Correlation between C-myc and BMI-1 scores and HPV-DNA load in the CIN group; D: Correlation between C-myc and BMI-1 scores and HPV-DNA load in the NC group.

Table 5. Correlations between vaginal microecology and HPV-DNA load in the HPV-positive group and the HPV-negative group

Indicator	HPV-positive group (n=64)	HPV-negative group (n=109)
Lactobacillus	18 (28.13%)	57 (52.29%)$^{\theta}$
Gardnerella	25 (39.06%)	25 (13.76%)$^{\theta}$
Trichomonas	1 (1.56%)	3 (2.75%)
Spores	2 (3.13%)	2 (1.83%)
LE positivity	51 (79.69%)	38 (34.86%)$^{\theta}$
SNA positivity	26 (40.63%)	8 (7.34%)$^{\theta}$
pH≥4.6	54 (84.38%)	59 (54.13%)$^{\theta}$

Note: $^{\theta}P<0.05$ compared to the HPV-positive group.

enables cells to divide and proliferate both indefinitely and malignantly.

Recent studies have found that re-establishing dynamic balance within vaginal microecology is beneficial for reducing the risk of HPV infection [25]. The female vaginal microecology encompasses the anatomical structure, local immunity, microbiota, and endocrine regulation. The vagina of a healthy woman hosts more than 50 microorganisms that colonize the vaginal mucosa epithelium in a hierarchical and sequential manner, leading to the formation of a biofilm. Under normal conditions, microorganisms such as the dominant bacteria, led by lactobacillus, reside in the biofilm, which constantly evolves in response to changes in the physiological state and local environment of patients, keeping a microecological balance within the human body. However, once the vaginal microecology becomes imbalanced due to the presence of abnormal dominant, diverse, dense and inflammatory indicators, or unusual pH of the vaginal flora, which destroys the inherent protective mechanism in the vagina, patients become more susceptible to infections caused by pathogenic microorganisms [26]. Lactobacillus belongs to the group of gram-positive bacilli with the ability to inhibit the growth of pathogenic microorganisms by producing lactic acid and secreting various antimicrobial components such as cytokines, surface active substances and H_2O_2. Meanwhile, lactobacillus can prevent pathogenic microorganisms from adhering to vaginal epithelial cells through a competitive adhesion mechanism, thereby keeping balance in vaginal microecology by stimulating the immune system [27]. Our study revealed that the detection rate of lactobacillus in the CSCC group was lower than that of the CIN and NC groups; the detection rate of lactobacillus in the CIN group was lower than that of the NC group; and the detection rate of vaginal lactobacillus in the HPV-positive group was lower than that of the HPV-negative group. All these results were in line with the findings of Zheng et al [28], suggesting that vaginal lactobacillus gradually decreased and miscellaneous bacteria increased in patients with worsening of their cervical lesions. Therefore, in clinical settings, it is important to appropriately supplement vaginal lactobacillus for patients with cervical lesions to help them eliminate HPV. Detection of gardnerella and positive SNA are two effective approaches for the diagnosis of bacterial vaginitis [29]. In this study, we found that the detection rates of gardnerella and positive SNA were higher in the CIN group than those of the NC group, and the detection rates of gardnerella and positive SNA were higher in the HPV-positive group than those of the HPV-negative group. This suggests that CIN patients were at higher risk for bacterial vaginitis in comparison to healthy subjects. In addition, the application of vaginal treatment with live lactobacilli capsules after loop electrosurgical excision for CIN patients also reduces the positivity of various indicators (LE, SNA, pH≥4.6) for vaginal microecology imbalance, which in turn alleviates vaginal infections and prevents HPV occurrence. LE is one of the important inflammatory indicators of vaginal disease [30]. The rate of LE positivity in the CSCC group was higher than that of both CIN and NC groups in this study, and the rate of LE positivity in the HPV-positive group was higher than that of the HPV-negative group, suggesting that the onset of stronger vaginal inflammatory responses in both CSCC patients and HPV-positive patients than in CIN patients, healthy subjects, and in HPV-negative subjects. pH is also a crucial indicator for vaginal microecology balance, with a pH below 4.5 indicating the breakdown of the defensive system in the vagina, resulting in the occurrence of physical and chemical changes, which further leads to histological alterations in the vaginal mucosa and cervical epithelium [31]. The percentage of pH≥4.6 in specimens was higher in the CSCC group than that of the CIN and NC groups in this study, and the percentage was also higher in the CIN group than that of the NC group, and higher in the HPV-positive group than that of

Table 6. Correlations between vaginal microecology and HPV-DNA load in the CSCC group, CIN group, and NC group

Indicator	CSCC group (n=51)		CIN group (n=72)		NC group (n=50)	
	HPV-positive (n=42)	HPV-negative (n=9)	HPV-positive (n=21)	HPV-negative (n=51)	HPV-positive (n=1)	HPV-negative (n=49)
Lactobacillus	5 (11.90%)	5 (55.56%)$^{\theta}$	13 (61.90%)	22 (43.14%)	0 (0.00%)	30 (61.22%)
Gardnerella	10 (23.81%)	1 (11.11%)	4 (19.05%)	18 (35.29%)	1 (100.00%)	6 (12.24%)$^{\theta}$
Trichomonas	1 (2.38%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (6.12%)
Spores	0 (0.00%)	0 (0.00%)	2 (9.52%)	1 (1.96%)	0 (0.00%)	1 (2.04%)
LE positivity	32 (76.19%)	2 (22.22%)$^{\theta}$	18 (85.71%)	15 (29.41%)$^{\theta}$	1 (100.00%)	21 (42.86%)
SNA positivity	8 (19.05%)	1 (11.11%)	18 (85.71%)	1 (1.96%)$^{\theta}$	0 (0.00%)	6 (12.24%)
pH≥4.6	38 (90.48%)	9 (100.00%)	16 (76.19%)	29 (56.86%)	0 (0.00%)	21 (42.86%)

Note: $^{\theta}$ is $P<0.05$ compared with HPV-positive group.

the HPV-negative group. This demonstrates that as the severity of cervical lesions grows, the function of the acid-based defensive system in the vagina get more impaired. The detection rate of trichomonas in the CIN group was lower than that of the NC group; there was no significant difference in the detection rate of spores among the three groups, as well as in the detection rate of both spores and trichomonas between the HPV-positive group and the HPV-negative group. This suggests that trichomonas and mycotic vaginitis did not show increases in their positive rate as the severity of the cervical lesions grew.

However, this study has some limitations. Firstly, our study focusing on the correlation between C-myc, BMI-1 expressions and vaginal microecology and HPV-DNA load in patients with different cervical lesion is still at the preliminary stage, and more studies are needed to investigate in-depth associations among them. Secondly, the retrospective nature of this analysis did not allow randomization of patients in either group, hence patients in the groups were unsimilar. Thirdly, vaginal microecology is a dynamic environment, whose indicators might be insufficiently or incorrectly interpreted due to incomplete understanding about some exogenous factors, such as contraception, sexual intercourse experiences, and hygiene habits. Thus, in order to further clarify the correlations between the proto-oncogenes, vaginal microecology and HPV infection, a well-designed, randomized, and controlled trial with prospective data and a bigger sample size is are necessary to confirm the findings in our study and to provide new perspectives for preventing and treating HPV infection as well as reducing the incidence of cervical cancer.

Conclusion

The proto-oncogenes C-myc and BMI-1 were highly expressed in the cervical lesions of CIN and CSCC patients. Changes in vaginal microecology were one of the main causes of CIN progressing to CSCC. The interactions between the two may play an important role in long-term HPV infection and the proliferation of cervical cancer cells.

Disclosure of conflict of interest

Authors declare this study was conducted without any circumstances that could be interpreted as a potential conflict of interest.

Address correspondence to: Hao Zhang, Department of Laboratory Medicine, Suzhou Hospital of Integrated Traditional Chinese and Western Medicine, No. 39, Xia Sha Tang, Mudu, Wuzhong District, Suzhou 215000, Jiangsu, China. Tel: +86-13771713414; E-mail: 13771713414@163.com

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