UDC 616.146-006.52:579.61

INTERRELATIONSHIP BETWEEN HUMAN PAPILLOMAVIRUS (HPV) INFECTION AND DISTURBANCES OF THE CERVICAL MICROBIOCENOSIS

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Abstract: The article analyses evidence published in 2011–2025 on the interrelationship between human papillomavirus (HPV) infection and disturbances of the cervical microbiocenosis. A *Lactobacillus*-depleted anaerobic community state type (CST IV) is associated with HPV persistence and with the severity of cervical intraepithelial neoplasia (CIN): its share rises from 10% in normal cytology to 40% in invasive cancer. *Lactobacillus* dominance is linked to more frequent regression of CIN2 (70.0% vs 42.1%). The expediency of combining HPV screening with assessment of the microbiocenosis is substantiated.

Keywords: human papillomavirus, cervix uteri, microbiocenosis, vaginal dysbiosis, *Lactobacillus*, cervical intraepithelial neoplasia.

Annotatsiya: Maqolada odam papilloma virusi (OPV) infeksiyasi va bachadon bo‘yni mikrobiotsenozi buzilishi o‘rtasidagi bog‘liqlikka oid 2011–2025-yillarda chop etilgan ilmiy ma’lumotlar tahlil qilingan. Laktobatsillalar kamaygan va anaerob flora ustun bo‘lgan mikrob jamoasi (CST IV) OPV persistensiyasi hamda servikal intraepitelial neoplaziya (CIN) og‘irligi bilan bog‘liq: uning ulushi normal sitologiyada 10% bo‘lsa, invaziv saratonda 40% ga yetadi. *Lactobacillus* dominantligida CIN2 regressiyasi ko‘proq kuzatiladi (70,0% va 42,1%). OPV skriningini mikrobiotsenozni baholash bilan birga olib borish maqsadga muvofiqligi asoslandi.

Kalit so‘zlar: odam papilloma virusi, bachadon bo‘yni, mikrobiotsenoz, vaginal disbioz, *Lactobacillus*, servikal intraepitelial neoplaziya.

Аннотация: В статье проанализированы научные данные 2011–2025 гг. о взаимосвязи инфекции, вызванной вирусом папилломы человека (ВПЧ), и нарушений микробиоценоза шейки матки. Микробное сообщество с дефицитом лактобацилл и преобладанием анаэробной флоры (CST IV) ассоциировано с персистенцией ВПЧ и тяжестью цервикальной интраэпителиальной неоплазии (CIN): его доля возрастает с 10% при нормальной цитологии до 40% при инвазивном раке. При доминировании *Lactobacillus* регрессия CIN2 наблюдается чаще (70,0% против 42,1%). Обоснована целесообразность сочетания скрининга ВПЧ с оценкой микробиоценоза.

Ключевые слова: вирус папилломы человека, шейка матки, микробиоценоз, вагинальный дисбиоз, *Lactobacillus*, цервикальная интраэпителиальная неоплазия.

Introduction

Cervical cancer remains one of the most significant problems in women’s oncology: according to GLOBOCAN 2022, about 661,000 new cases and 348,000 deaths were registered worldwide [1]. HPV DNA is detected in 99.7% of invasive cervical carcinomas, and persistent infection with high-risk genotypes is regarded as a necessary cause of the disease [2]. However, most infections are cleared within one to two years, and only a small proportion persists and

FOR CITATION
Abdullayeva M.I. Interrelationship between human papillomavirus (HPV) infection and disturbances of the cervical microbiocenosis // Proceedings of the Republican Scientific and Practical Conference “Status and Development Prospects of Fundamental and Applied Microbiology: The Viewpoint of Young Scientists”. – Tashkent, 2026. – P. 401–404.
DOI: https://doi.org/10.66073/ReFocus-Conf/3010116

progresses through cervical intraepithelial neoplasia (CIN) to cancer. The natural history of the infection is therefore shaped by cofactors, among which the cervicovaginal microbiota attracts growing attention [3].

The healthy microbiocenosis of women of reproductive age is dominated by *Lactobacillus*. J. Ravel et al. described five community state types (CST): four are dominated by *L. crispatus*, *L. gasseri*, *L. iners* or *L. jensenii*, while CST IV contains few lactobacilli and a diverse anaerobic flora [4]. Lactobacilli maintain pH ≤ 4.5 through lactic acid production and compete with pathogens, whereas their replacement by *Gardnerella vaginalis*, *Fannyhessea vaginae*, *Prevotella*, *Sneathia* and other anaerobes corresponds to bacterial vaginosis (BV) and activates mucosal inflammation [3]. For Uzbekistan, where HPV vaccination began in 2019 and HPV testing is entering screening, this question is of practical importance.

The aim of the study was to systematise current evidence on the relationship between HPV infection and disturbances of the cervical microbiocenosis, to assess its dependence on lesion severity and to outline its clinical-laboratory implications.

Materials and methods

A structured literature review was performed following the principles of PRISMA 2020. PubMed/MEDLINE, Scopus, Web of Science and Google Scholar were searched for January 2011 – June 2025 using the terms “human papillomavirus”, “vaginal microbiota” and “cervical intraepithelial neoplasia”. Original studies and meta-analyses were included if the microbiota was characterised by 16S rRNA gene sequencing or Nugent/Amsel criteria and HPV status was determined by molecular methods. Owing to methodological heterogeneity, effect estimates were compared descriptively without pooling.

Results

In the cohort of 396 asymptomatic women studied by Ravel et al., CST III (*L. iners*) was the most frequent (34.1%), followed by CST IV (27.0%) and CST I (*L. crispatus*, 26.2%); thus about a quarter of clinically healthy women carried a *Lactobacillus*-depleted microbiota, with a mean pH of 5.3 versus 4.0 in CST I [4].

In the meta-analysis by Gillet et al. (12 studies, 6,372 women), BV was associated with cervical HPV infection (OR 1.43; 95% CI 1.11–1.84) [6]. Longitudinal studies showed that CST IV is associated with the slowest HPV clearance and with persistent infection [7, 8], and a network meta-analysis confirmed higher odds of HPV and dysplasia in *Lactobacillus*-depleted and, to a lesser degree, *L. iners*-dominated communities [9]. The key studies are summarised in the Table.

Table 1. Key studies of the cervicovaginal microbiota in HPV infection and cervical lesions

Study	Design, n	Main finding
Gillet et al., 2011 [6]	Meta-analysis, 6,372	BV and HPV: OR 1.43 (95% CI 1.11–1.84)
Brotman et al., 2014 [7]	Longitudinal, 32	CST IV-B – slowest HPV clearance
Di Paola et al., 2017 [8]	Cohort, 55	CST IV – persistence of hrHPV
Mitra et al., 2015 [10]	Cross-sectional, 169	CST IV: 10% (normal) → 40% (cancer)
Łaniewski et al., 2018 [11]	Cross-sectional, 100	Loss of lactobacilli, rise of inflammation towards cancer
Mitra et al., 2020 [12]	Cohort, 87	CIN2 regression: 70.0% vs 42.1%

A clear gradient was observed between dysbiosis and lesion severity: the prevalence of CST IV was 10% in normal cytology, 21% in LSIL, 27% in HSIL and 40% in invasive cancer (Figure 1) [10].

DOI: 10.66073/ReFocus-Conf/3010116

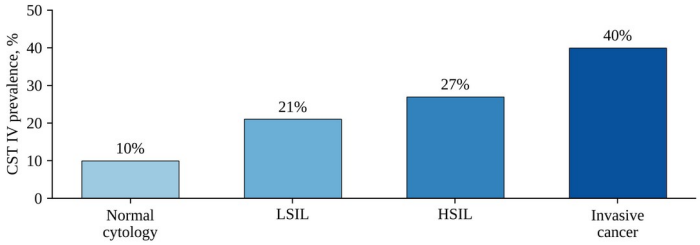


Figure 1. Prevalence of CST IV depending on the severity of cervical lesions, % (based on [10])

The microbiota also affects the outcome of established lesions. Among 87 women with untreated CIN2, regression at 12 months occurred in 70.0% with a *Lactobacillus*-dominant microbiota and in 42.1% with a depleted one (adjusted OR for non-regression 3.56; 95% CI 1.31–9.60) (Figure 2) [12].

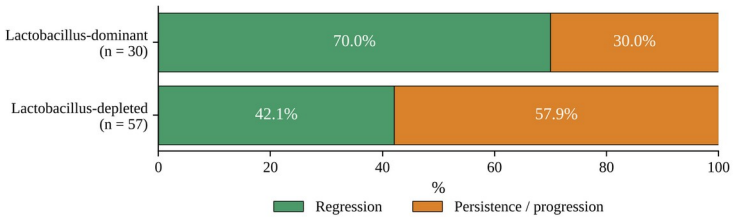


Figure 2. Outcome of untreated CIN2 at 12 months depending on the baseline microbiota, % (based on [12])

Discussion

The association between HPV and cervical dysbiosis concerns not only HPV prevalence but also its persistence and the course of CIN [7, 10, 12]. It is realised through loss of the acidic barrier, damage to mucus and epithelium by bacterial sialidases and cytolysins, chronic inflammation with oxidative DNA damage and genotoxic metabolites [3]. Causality is not proven: most studies are cross-sectional, and the relationship is likely bidirectional, since HPV oncoproteins E6 and E7 suppress local immunity [5]. Ethnic variation of CST IV [4] and the absence of regional data limit the transfer of results to women in Uzbekistan.

In practice, clinical diagnostic laboratories may supplement HPV genotyping with pH measurement, Nugent scoring and quantitative PCR of lactobacilli and anaerobic markers in women with persistent high-risk HPV or CIN. Evidence for probiotic prevention of cervical neoplasia is still insufficient outside clinical trials [13].

Conclusion

1. Depletion of *Lactobacillus* and predominance of anaerobic flora (CST IV) are consistently associated with HPV infection; BV increases the odds of HPV detection (OR 1.43).

2. The share of CST IV rises with lesion severity from 10% to 40%, and *Lactobacillus* dominance is linked to more frequent regression of CIN2 (70.0% vs 42.1%).

3. Assessment of the microbiocenosis may complement HPV screening in women at increased risk; its prognostic value requires prospective studies, including in Uzbekistan.

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 DOI: 10.66073/ReFocus-Conf/3010116