Advances in Obstetrics and Gynecology Research, 2024, Volume 2, Issue 1
https://ojs.bbwpublisher.com/index.php/AOGR

Research Progress on the Relationship between Intestinal Microecology and Cervical HPV Infection

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Abstract: In recent studies, researchers have found a close relationship between intestinal microecology and human papillomavirus (HPV) infection. Gut microbiota refers to the microorganisms present in the human intestine, including both beneficial and harmful bacteria. These microorganisms exert a significant impact on human health. Some studies suggest that an imbalance in gut flora may lead to systemic abnormalities and increased susceptibilities to HPV. Consequently, the adjustment of intestinal microbiota to counteract HPV has emerged as a rapidly growing research area. Probiotics, as essential components of intestinal microecology, can effectively modulate it. They increase the population of beneficial bacteria while suppressing the growth of harmful ones, thereby restoring the balance of intestinal flora. This, in turn, contributes to intestinal health, bolstering the body's defenses. This article aims to explore and review the relationship between intestinal microecology and cervical HPV infection.

Keywords: Intestinal microecology; Cervical HPV infection; Relationship; Research progress

Online publication: February 27, 2024

1. Introduction

Cervical cancer stands as one of the prevalent gynecological malignancies. According to the 2023 ICO/IARC China HPV and Related Diseases Report, in 2020, among women aged 15 to 44 in China, cervical cancer ranked third in both incidence and mortality among female tumors, with approximately 110,000 new cases and nearly 60,000 deaths. This poses a significant threat to women's health. On November 17, 2020, the World Health Organization (WHO) officially released the "Global Strategy to Accelerate the Elimination of Cervical Cancer." In 2023, China's National Health Commission, Ministry of Education, Ministry of Civil Affairs, and 7 other departments jointly issued the "Global Strategy to Accelerate the Elimination of Cervical Cancer Action Plan (2022–2030)," aimed at promoting and expediting the elimination of cervical cancer in China to safeguard and enhance women's health [1].

Intestinal flora plays a crucial role in maintaining digestive tract homeostasis, constituting a diverse microbial community [2]. Numerous studies have explored the correlation between intestinal flora microecology

and the onset and progression of gynecological diseases, making it a current research focal point. This article delves into the relationship between intestinal microecology and cervical human papillomavirus (HPV) infection.

2. Research related to cervical HPV infection

HPV infection constitutes a sexually transmitted disease wherein the virus infects cervical epithelial cells, inducing squamous epithelial proliferation. Transmission primarily occurs through sexual contact, indirect contact, mother-to-child transmission, and other means. Cervical HPV infection is highly prevalent, typically manifesting symptoms such as common warts, genital warts, and flat warts, with severe cases potentially leading to cervical cancer [3,4].

Symptoms vary across different stages, including the incubation period, early stage, and late stage. During the incubation period, HPV may remain dormant for 3 weeks to 8 months, with an average of about 3 months, primarily affecting sexually active individuals aged 20–25, often without noticeable symptoms. In the early stage, patients may develop small, light red papules on the vulva, progressively enlarging into bumpy, soft papillary lesions resembling cauliflower. Increased secretions, appearing off-white, dirty gray, or red, characterize these lesions. In the late stage, vulvar surface erosion and exudation may occur, accompanied by itching, potential secondary bacterial infection, purulent discharge, odor, and local pain. Diagnosis involves physical examination, laboratory tests, and imaging tests. Currently, over 200 types of HPV have been identified and categorized into high-risk and low-risk types based on their carcinogenic potential [5]. Common high-risk HPV types include HPV16, HPV18, HPV31, HPV33, HPV35, HPV39, HPV45, HPV51, HPV52, and HPV58, with approximately 98% of cervical cancers in Chinese women attributed to high-risk HPV [6,7].

The introduction of HPV vaccines has transformed cervical cancer into a preventable disease, with eradication on the horizon. In 2023, China's "Comprehensive Cervical Cancer Prevention and Control Guidelines (2nd Edition)" proposed a three-level prevention strategy. Primary prevention involves health education and HPV vaccination, while secondary prevention focuses on efficient cervical cancer screening. Tertiary prevention emphasizes appropriate treatment according to the disease stage. HPV vaccination represents the cornerstone of effective cervical cancer prevention. Women are encouraged to prioritize self-health protection, acquire accurate knowledge about HPV and cervical cancer, undergo timely vaccination, and participate in regular cervical cancer screening.

3. Research on the association between intestinal microecology and cervical HPV infection

Normal intestinal flora plays a pivotal role in maintaining the stability of the human intestinal tract. Imbalances in intestinal flora can lead to a decline in bodily functions. Numerous studies have confirmed a correlation between intestinal flora and the onset and progression of tumors. Tumors such as breast cancer and colorectal cancer have been linked to intestinal flora, primarily through mechanisms involving mucosal damage, chronic inflammation, and the production of harmful substances, all contributing to tumor formation and development [8-10]. Additionally, some studies have indicated a connection between intestinal flora and tumor metastasis and drug resistance. Gastric, cervical, and rectal cancers, among others, have been closely associated with intestinal flora, which is vital in immune defense, digestive metabolism, inflammation, and cell proliferation. Intestinal flora not only interacts with intestinal epithelial cells but also communicates with distant organs and body systems [11-13].

Advances in genome sequencing technology have revealed that intestinal flora imbalance is associated

with various female reproductive system diseases, including endometriosis (EMS), polycystic ovary syndrome (PCOS), perimenopausal syndrome, cervical cancer, and ovarian cancer [14,15]. In healthy women, the gastrointestinal and vaginal microbiota are shielded from the host by a multi-level defense system comprising the mucosal layer, secretion of soluble immune mediators, intact epithelial cell tight junctions, and immune cells. Disruption of this defense system allows pathogenic bacteria to penetrate the gastrointestinal tract and vaginal epithelium, leading to diseases, including cancer. Cervical cancer, the fourth most common malignant tumor in terms of morbidity and mortality, is primarily caused by high-risk HPV infection. Dysbiosis has been identified as a risk factor for HPV infection and cervical cancer development [16]. Expert consensus underscores the significance of maintaining intestinal microecological balance in preventing cervical cancer.

Research has confirmed that HPV is a carcinogenic factor for cervical cancer, with chronic infections, sexually transmitted diseases, and smoking acting as synergistic factors. Persistent infection with high-risk HPV, particularly HPV16 and HPV18 [17,18], accounts for most cases of cervical cancer. HPV infection can be cleared when local resistance is robust. Studies have indicated that HPV-positive women exhibit a more diverse intestinal microecological composition, potentially increasing their susceptibility to multiple HPV types and raising the risk of cervical low-grade squamous intraepithelial lesions. Consequently, intestinal microecology plays a crucial role in HPV infection and clearance, with the composition of intestinal microecology influencing persistent HPV infection and secondary cervical cancer.

Numerous studies exploring the relationship between intestinal flora and cervical cancer, have identified differences in intestinal microorganisms between cervical cancer patients and healthy individuals. A study published in “Food & Function” demonstrated that traditional Chinese medicine *Sanghuang* (*Shanghuangporus* spp.) can promote the proliferation of *Akkermansia* intestinal bacteria, which in turn interferes with tumor glucose uptake and utilization, inducing tumor autophagy and inhibiting the growth of cervical cancer cells. Additionally, research has highlighted the connection between intestinal microorganisms and estrogen metabolism [19], with elevated estrogen levels playing a significant role in endometrial cancer. Imbalances in intestinal flora may contribute to endometrial cancer by influencing the secretion and metabolism of estrogens.

4. Research on the application of adjusting intestinal microecology in the treatment of cervical HPV infection

Research conducted both domestically and internationally has reached a consensus that HPV infection does not inevitably lead to cancer, and nearly all cervical cancer patients are positive for HPV infection. It typically takes 5–10 years from HPV infection to the development of cervical cancer. During this period, the body’s immunity strengthens, leading to the clearance of the virus in approximately 80% of infected individuals, particularly among young women. The risk of disease primarily hinges on the continuous accumulation and intensification of HPV infection, notably the accumulation of specific HPV subtypes, leading to various outcomes.

Imbalances in intestinal flora result in a gradual increase in harmful bacteria and a decrease in beneficial bacteria, thereby disrupting the intestinal environment. Intestinal microecological treatments can effectively increase the number and types of beneficial bacteria while inhibiting the growth of harmful bacteria, thereby restoring ecological health to the intestinal tract. The principle of intestinal microecological preparations involves utilizing normal microorganisms or substances that promote microbial growth beneficial to the host to maintain the host’s microecological balance and improve overall health. These preparations play a crucial role in maintaining intestinal function, inhibiting the growth of intestinal pathogens, forming a protective layer on the intestinal mucosa, producing various enzymes to aid in food digestion and absorption, alleviating symptoms of lactose intolerance, promoting probiotic proliferation, improving intestinal flora, and providing healthcare benefits.

There exists a close connection between intestinal flora microecology and cervical cancer. Maintaining a healthy and stable intestinal flora can aid in the prevention and treatment of cervical cancer. Conversely, an unhealthy intestinal flora may promote cancer development and negatively impact cancer immunity, chemotherapy efficacy, and prognosis [20]. Therefore, it is imperative for women to regularly monitor the status of their intestinal flora. Comprehensive and accurate detection of changes in intestinal flora and metabolite levels can facilitate the early detection and prevention of cervical cancer and other related diseases, providing scientific references and personalized prevention and treatment recommendations.

Studies have demonstrated that chemotherapy can increase intestinal permeability, leading to ectopic colonization of intestinal microorganisms and the induction of systemic immune responses. These responses can result in chronic inflammation, promoting the occurrence of metabolic disorders, malnutrition, and cachexia. Hence, maintaining intestinal barrier function may help alleviate cachexia symptoms in cervical HPV infection. Research has indicated that supplementation with a probiotic complex containing *Bifidobacterium breve*, *Lactobacillus acidophilus*, *Lactobacillus casei*, and *Streptococcus thermophilus* can mitigate 5-fluorouracil-induced intestinal damage, including reduced severity of intestinal tissue scores, increased villus length, crypt depth, and mucus layer, as well as decreased expression of inflammatory cytokines and markers.

5. Conclusion

Gut microbiota can influence tumor susceptibility and progression through various mechanisms, including the regulation of inflammation, induction of DNA damage, and production of metabolites involved in tumorigenesis or tumor suppression. As research in this field continues to deepen, it is becoming increasingly common to screen for cervical cancer using intestinal flora, aiming to detect the disease at an earlier stage or enhance treatment efficacy. This approach offers women a novel direction in the prevention and treatment of cervical cancer.

Maintaining the health and stability of intestinal flora microecology holds significant importance in preventing and treating cervical HPV infection. The judicious use of antibiotics to preserve the health and stability of the body's bacterial flora is crucial for bolstering the immune function against cervical HPV infection. This ensures the effectiveness of antimicrobial drugs in patients with cervical HPV infection, thereby facilitating successful prevention and treatment measures.

Disclosure statement

The author declares no conflict of interest.

References

[1] Pang H, Li K, Han B, et al., 2023, Effects of Postoperative Radiotherapy for Cervical Cancer on the Imbalance of Intestinal Flora Structure in Patients. Chinese Maternal and Child Health Care, 38(12): 2157–2160.

[2] Nguyen CL, Markey KA, Miltiadous O, et al., 2023, High-Resolution Analyses of Associations between Medications, Microbiome, and Mortality in Cancer Patients. Cell, 186(12): 2705–2718.e17. https://doi.org/10.1016/j.cell.2023.05.007

[3] Park JS, Gazzaniga FS, Wu M, et al., 2023, Targeting PD-L2-RGMb Overcomes Microbiome-Related Immunotherapy Resistance. Nature, 617(7960): 377–385. https://doi.org/10.1038/s41586-023-06026-3

[4] Han B, Kong X, 2023, Research Progress on the Relationship between Intestinal Microecology, Endometrial

Microecology, and Endometrial Cancer. Journal of Practical Obstetrics and Gynecology, 39(8): 591–594.

[5] Zhang L, Ping S, Hao Y, et al., 2023, Risk Factors for High-Risk HPV Infection in Infertile Women and Its Impact on T Lymphocyte Subgroup Levels. Chinese Journal of Hospital Infection, 33(18): 2837–2840.

[6] Naghavian R, Wolfgang F, Oldrati P, et al., 2023, Microbial Peptides Activate Tumor-Infiltrating Lymphocytes in Glioblastoma. Nature, 617(7962): 807–817. https://doi.org/10.1038/s41586-023-06081-w

[7] Li Y, Wang N, Zhang Q, et al., 2023, Screening Methods and Applications of High-Risk HPV Infection in Patients with Cervical Lesions. Chinese Journal of Hospital Infectious Diseases, 33(22): 3461–3465.

[8] Shalon D, Culver RN, Grembi JA, et al., 2023, Profiling the Human Intestinal Environment Under Physiological Conditions. Nature, 617(7961): 581–591. https://doi.org/10.1038/s41586-023-05989-7

[9] Sui X, Zhang X, Liao M, et al., 2023, The Relationship between the Degree of Cervical Lesions and the Distribution of Vaginal Flora in High-Risk Human Papillomavirus Infection. Chinese Journal of Hospital Infection, 33(22): 3456–3460.

[10] Jiang L, Ma S, Zhang G, et al., 2023, Analysis of Tobacco Exposures and High-Risk HPV Infection in American Women: National Health and Nutrition Examination Survey. Environ Sci Pollut Res Int, 30(51): 110489–110498. https://doi.org/10.1007/s11356-023-30175-7

[11] Luo C, Liu J, Liu L, et al., 2023, Classification of High-Risk HPV Infection in Patients with Cervical Lesions, Its Influencing Factors and Model Construction. Chinese Journal of Hospital Infection, 33(23): 3630–3634.

[12] Liang Y, Gao K, 2023, Effect of External Irradiation of Cervical Cancer on Intestinal Flora. Journal of Hebei Medical University, 2023(10): 1168–1177.

[13] Wang M, Yuan Y, Song A, et al., 2023, Research Progress on the Regulatory Effect of Microecological Regulators on Intestinal Microbiota Under Heavy-Load Exercise. Life Science, 35(12): 1639–1651.

[14] Mondatore D, Bai F, Augello M, et al., 2022, Persistence of High Percentage of Peripheral Activated $CD8^+$ T-cells Predict Cytologic HPV-Related Dysplasia in cART-Treated, HIV-Positive Subjects. Open Forum Infect Dis, 9(4): ofac046. https://doi.org/10.1093/ofid/ofac046

[15] Sheng X, Zhu R, Li S, 2020, Clinical Study on Intestinal Microecology and Cervical Cancer Combined with Radiation-Induced Intestinal Damage. Parenteral and Enteral Nutrition, 27(2): 78–83.

[16] Du H, Fan J, Fan M, et al., 2022, The Impact of Intestinal Flora on the Progression and Treatment of Malignant Tumors. Medical Information, 35(2): 57–60.

[17] Xie L, Li Y, 2022, Research Progress on the Relationship between Intestinal Flora and Cervical Cancer Immunotherapy. Cancer Progress, 20(19): 1954–1957.

[18] Laurie C, El-Zein M, Tota JE, et al., 2022, Efficacy of a Carrageenan Gel in Preventing Anal Human Papillomavirus (HPV) Infection: Interim Analysis of the Lubricant Investigation in Men to Inhibit Transmission of HPV Infection (LIMIT-HPV) Randomized Controlled Trial. Sex Transm Infect, 98(4): 239–246. https://doi.org/10.1136/sextrans-2021-055009

[19] Yang F, Guo Y, Jiang F, et al., 2023, Research on the Effectiveness of Probiotic-Assisted Radiotherapy in Patients with Cervical Cancer and Analysis of Its Effect in Preventing Radiation Cystitis. Chinese Medical Engineering, 31(1): 33–37.

[20] Carter MM, Olm MR, Merrill BD, et al., 2023, Ultra-Deep Sequencing of Hadza Hunter-Gatherers Recovers Vanishing Gut Microbes. Cell, 186(14): 3111–3124.e13. https://doi.org/10.1016/j.cell.2023.05.046