META-ANALYSIS

Meta-analysis about correlation between the human Papillomavirus infection and the incidence of cervical intraepithelial Neoplasia

Mingyang Wang, Xiaofeng Zou, Zhiliang Wang*

Abstract

Objective: To determine the correlations between human papillomavirus infection and the incidence of cervical intraepithelial neoplasia.

Method: This study was conducted in the Affiliated Hospital of Zunyi Medical University, Zunyi, China in January 2024. The systematic review and meta-analysis comprised literature search on PubMed, Medline, Embase, Cochrane Library, Web of Science, China Biomedical and Wanfang databases for studies published from January 2010 to December 2020 related to human papillomavirus and cervical intraepithelial neoplasia. The quality of the studies was evaluated using the Newcastle-Ottawa Scale, and meta-analysis was done using RevMan 5.3.

Results: Of the 854 studies identified, 10(1.2%) were included; 7(70%) in English and 3(30%) in Chinese. There was a total of 193,000 patients; 94,298(49%) in the observation group and 98,702(51%) in the control group. Human papillomavirus infection was closely correlated with cervical intraepithelial neoplasia-1, cervical intraepithelial neoplasia-2 and cervical intraepithelial neoplasia-3 in women, with odds ratios of 3.94 (95% confidence interval: 3.53-4.40), 1.03 (95% confidence interval: 1.01-1.06) and 1.13 (95% confidence interval: 1.10-1.16), respectively. Both human papillomavirus single infection and reinfection in cervical intraepithelial neoplasia patients were significantly higher than in normal women, with odds ratios of 0.50 (95% confidence interval: 0.41-0.61) and 0.43 (95% confidence interval: 0.35-0.53), respectively.

Conclusion: The incidence of cervical intraepithelial neoplasia was found to be highly associated with human papillomavirus infection, and the infection increased the risk of cervical diseases.

Keywords: Human papillomavirus, HPV infection, Cervical intraepithelial neoplasia, CIN, Cervical diseases, Meta-analysis.

(JPMA 75: S-158 [Suppl. 02]; 2025) **DOI: https://doi.org/10.47391/JPMA.SRPH-27**

Introduction

Cervical cancer (CC) is a category of malignant tumours that causes death among women worldwide, behind only breast cancer, colorectal cancer and lung cancer.[1] The peak of human papillomavirus (HPV) infection mostly occurs shortly after the start of sexual life. The vast majority of the infections (80%) can be cleared by the body's immune system within months to two years, and only a small minority of the infections persists that may develop into CC. HPV is classified into high-risk and low-risk types, and the persistent infection of HPV is closely related to the occurrence and development of CC.[2] Cervical intra-epithelial neoplasia (CIN) is a precancerous lesion, mostly associated with high-risk HPV infection. A large number of epidemiological data and laboratory evidence has shown that HPV infection is the trigger of CC, with more than 95% of CC being caused by HPV infection, and it takes 5-20 years for HPV infection to develop into dysplasia and, finally, CC.[3] The current systematic review and meta-analysis was planned to investigate the correlation between HPV infection and CIN grades to provide a reference for the early diagnosis and treatment of CC in clinical practice.

Department of Gynecology, Affiliated Hospital of Zunyi Medical University, Zunyi, Guizhou 563000, China.

Correspondence: Zhiliang Wang. e-mail: zlwang0921a@163.com

ORICID: 0000-xxx-xxx-xxxxx

Materials and Methods

This study was conducted in the Affiliated Hospital of Zunyi Medical University, Zunyi, China in January 2024. The systematic review and meta-analysis comprised literature search on PubMed, Medline, Embase, Cochrane Library, Web of Science, China Biomedical and Wanfang databases for studies published from January 2010 to December 2020 related to HPV and CIN grade 1-3.[4] The search terms used were 'human papillomavirus', 'HPV', 'cervical intraepithelial neoplasia', and 'CIN'.

The studies included were those with primary sources published in China in which the diagnosis of HPV infection and cervical diseases met the international unified diagnostic criteria[5] and had at least one control group. The studies excluded were review articles, duplicate studies by the same authors, and those who's raw data was not available.

Two evaluators independently screened the articles, extracted the data, evaluated the literature quality. Subsequently, the two evaluators cross-checked with each other to sort out any difference of opinion. In case the

matter was not resolved, a third evaluator was invited to discuss the evaluation.

The quality of the included articles was evaluated using the Newcastle-Ottawa Scale (NOS).[6] Meta-analysis was performed using RevMan 5.3.[7] The heterogeneity between studies was evaluated by I2 values (I2 represents the percentage of the total variation in the effect size between studies that can be attributed to heterogeneity rather than sampling error) from Q test. I2 <50% indicated homogeneity, and fixed-effect models were sued. I2 ≥50% indicated heterogeneity, and random effect model analysis was used for un-eliminated heterogeneity. P<0.05 was taken as statistically significant.

Results

Of the 854 studies identified, 10(1.2%) were included (Figure 1).[8-17] Of the 10 randomised controlled trials (RCTs), 7(70%) were in English and 3(30%) were in Chinese. There was a total of 193,000 patients; 94,298(49%) in the observation group and 98,702(51%) in the control group (Table). NOS scores for all the 10(100%) RCTs were >8 points, suggesting high quality.

There were 4 (40%) RCTs[14-17] reporting the HPV infection rate in CIN1 patients. Heterogeneity I2 was 100%, (p<0.00001). Significance test Z score was 24.48 (p<0.00001; odds ratios [OR]: 3.94; (95% confidence interval [CI]: 3.53-4.40) (Figure 2), indicating HPV infection was an important factor of CIN1 incidence in women.

All the 10(100%) RCTs[8-17] reported the HPV infection rate in CIN2 patients. Heterogeneity I2 was 99% (p<0.00001). Significance test Z score was 2.45 (p=0.01; OR: 1.03; 95%CI: 1.01-1.06) (Figure 3), indicating HPV infection was an important factor of CIN2 incidence in women.

There were 8 (80%) RCTs[8,10-14,16,17] reporting the HPV infection rate in CIN3 patients. Heterogeneity I2 was 99% (p<0.00001). Significance test Z score was 10.15 (p<0.00001; OR: 1.13; 95CI: 1.10-1.16) (Figure 4), indicating HPV infection was an important factor of CIN3 incidence in

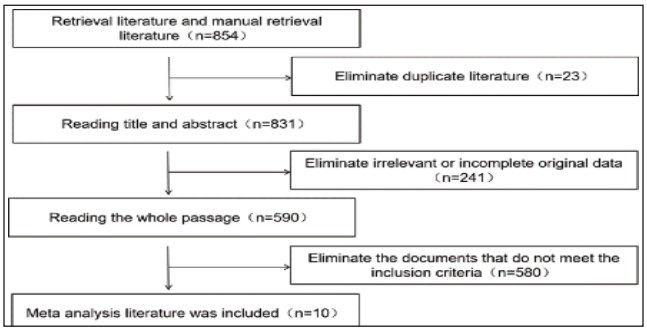

Figure-1: The Study Flowchart.

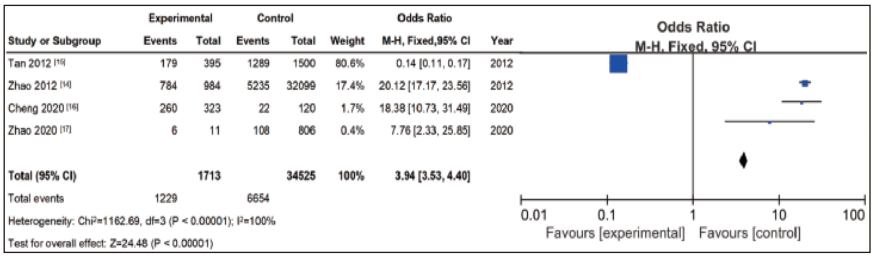

Figure-2: Meta-analysis about the correlation between human papillomavirus (HPV) and cervical intraepithelial neoplasia-1 (CIN1) incidence.

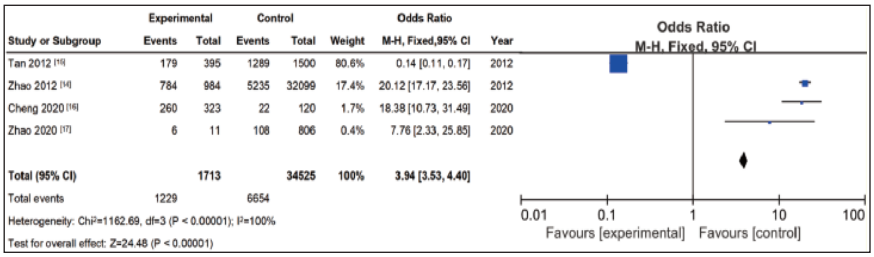

Figure-3: Meta-analysis about the correlation between human papillomavirus (HPV) and cervical intraepithelial neoplasia-2 (CIN2) incidence.

Table: Characteristics of the studies analysed.

Author	year	N		CIN1		CIN2		CIN3		HPV single infection		HPV reinfection	
		Observation	Control	P	N	P	N	P	N	P	N	P	N
Jorge[8]	2012	315	14			78	6	142	7	172	48		
Feng[9]	2017	16422	1160			366	15						
Francesca[10]	2016	672	50			121	19	366	18	357	167	306	218
Ku[11]	2014	446	88			53	88	148	0				
Guglielmo[12]	2010	47369	47001			16706	16658	17724	17747	108	55	98	46
Dorien[13]	2012	22420	22518			106	62	181	62				
Zhao[14]	2012	5,235	26864	784	200	420	21	460	12				
Tan[15]	2012	1289	211	179	216	397	293						
Cheng[16]	2020	22	98	260	63	129	13	271	10				
Zhao[17]	2020	108	698	6	5	2	1	2	3				

HPV: Human papillomavirus, CIN: Cervical intraepithelial neoplasia.

women.

There were 3(30%) RCTs[10,12,13] reporting the HPV single infection in CIN patients. Heterogeneity I2 was 98% (p<0.00001). Significance test Z score was 7.06 (p<0.00001; OR: 0.50; 95%CI: 0.41-0.61) (Figure 5), indicating HPV single infection was an important factor of CIN incidence in women.

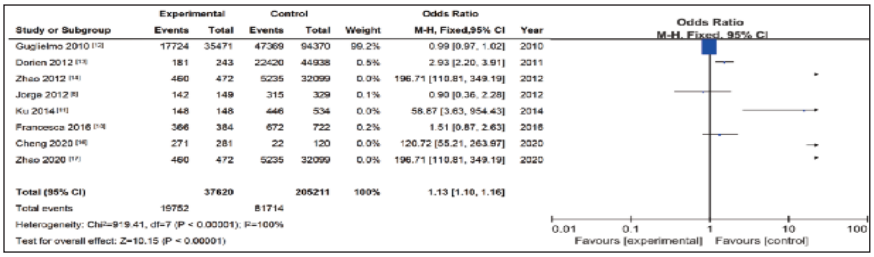

Figure-4: Meta-analysis about correlation between human papillomavirus (HPV) and cervical intraepithelial neoplasia-3 (CIN3) incidence.

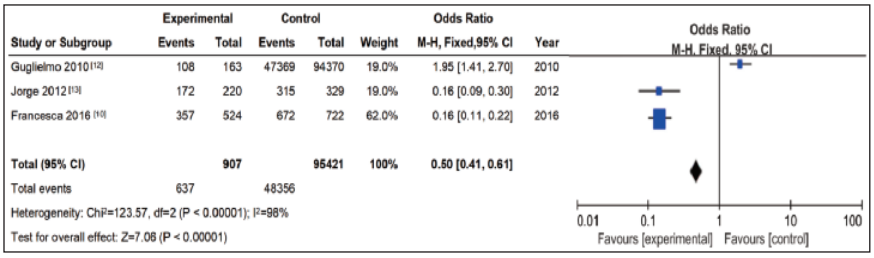

Figure-5: Meta-analysis about correlation between human papillomavirus (HPV) single infection and cervical intraepithelial neoplasia (CIN) incidence.

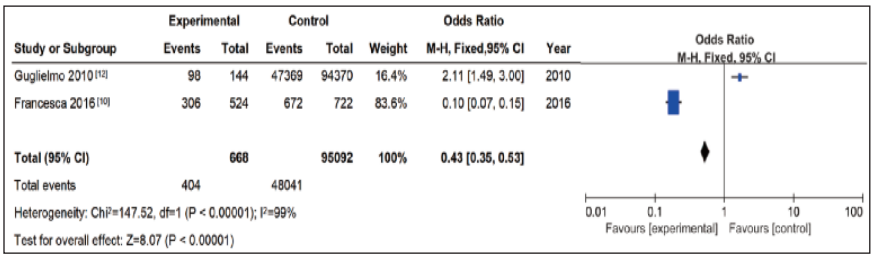

Figure-6: Meta-analysis about correlation between human papillomavirus (HPV) reinfection and cervical intraepithelial neoplasia (CIN) incidence.

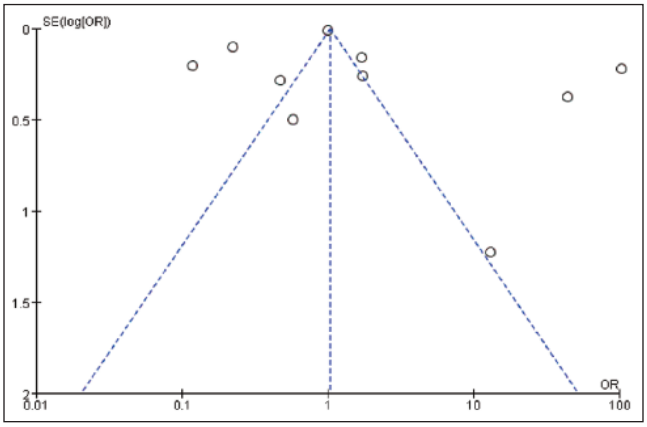

Figure-7: Funnel plot.

There were 2(20%) RCTs[10,12] reporting the HPV reinfection in CIN patients. Heterogeneity I2 was 99% (p<0.00001). Significance test Z score was 8.07 (p<0.00001; OR: 0.43; 95%CI: 0.35, 0.53) (Figure 6), indicating HPV reinfection was an important factor of CIN incidence in women.

Funnel plot had a symmetric distribution, indicating that there was no significant publication bias in the RCTs analysed (Figure 7).

Discussion

Most CC patients have no obvious clinical symptoms in the early stage, but, as disease progresses, the lesion develops into invasive cancer, seriously threatening women's quality of life (QOL), and physical and mental health.[18] Cancer statistics in China for 2015 showed that the incidence trend of CC in China was increasing, with patients mostly aged 30-59 years.[19] Studies have confirmed that HPV is a pathogenic factor in CC.[20] HPV is a genus of papilloma vacuolar virus A belonging to the family lacviridae, and is a spherical deoxyribonucleic acid (DNA) virus that causes squamous epithelial proliferation in human skin mucosa. Most patients infected with HPV have no abnormal manifestations in the early stage, and long-term persistent HPV infection has also become a precursor to CIN incidence. The prevention and control of HPV infection in young women is the main mode of CIN prevention and screening.[21] CIN is a general term for a group of diseases, including cervical dysplasia and cervical carcinoma in situ, and is a pre-CC lesion, often due to persistent HPV infection. CIN is also divided into CIN1, CIN2 and CIN3, reflecting the process of CC evolution, in which HPV plays an important role.[22,23]

The current meta-analysis of 10 RCTs showed that HPV infection was closely related to female CIN1, CIN2 and CIN3 population, indicating that HPV infection had an important influence on the occurrence of CIN lesions in women, and that HPV infection was an important factor in the pathogenesis of cervical disease. With respect to correlation between HPV infection type and CIN incidence, both HPV single infection rates and HPV reinfection rates were significantly higher in CIN patients than in normal women in the current study, indicating that HPV infection was an important factor of CIN development in women.

The current meta-analysis has limitations. The incidence rate of CIN varies around the world, and the feasibility of establishing different CC screening criteria suitable for different regions needed to be further explored. In recent years, large-scale use of blood cell analyser in the clinic has significantly improved the level of blood cell detection in China. Meanwhile, some test indicators that cannot be detected by manual microscopy could be measured by blood cell analyser. However, the detection instrument has certain deficiencies. Therefore, it is necessary to review the results by manual microscopy. Also, the sample size was small, and larger samples are needed to validate the current results. Finally, the meta-analysis was not registered with any international register database.

Conclusion

The female HPV infection was closely associated with precancerous cervical lesion, and was the key risk factor for it.

Disclaimer: None.

Conflict of Interest: None.

Source of Funding: None.

References

1. Buskwofie A, David-West G, Clare CA. A Review of Cervical Cancer: Incidence and Disparities. J Natl Med Assoc 2020;112:229-32. doi: 10.1016/j.jnma.2020.03.002.
2. Palmer TJ, Kavanagh K, Cuschieri K, Cameron R, Graham C, Wilson A, et al. Invasive cervical cancer incidence following bivalent human papillomavirus vaccination: a population-based observational study of age at immunization, dose, and deprivation. J Natl Cancer Inst 2024;116:857-65. doi: 10.1093/jnci/djad263.
3. Sharifian K, Shoja Z, Jalilvand S. The interplay between human papillomavirus and vaginal microbiota in cervical cancer development. Virol J 2023;20:73. doi: 10.1186/s12985-023-02037-8.
4. Loopik DL, Bentley HA, Eijgenraam MN, IntHout J, Bekkers RLM, Bentley JR. The Natural History of Cervical Intraepithelial Neoplasia Grades 1, 2, and 3: A Systematic Review and Meta-analysis. J Low Genit Tract Dis 2021;25:221-31. doi: 10.1097/LGT.0000000000000604.
5. Liu Z, Li P, Zeng X, Yao X, Sun Y, Lin H, et al. Impact of HPV vaccination on HPV infection and cervical related disease burden in real-world settings (HPV-RWS): protocol of a prospective cohort. BMC Public Health 2022;22:2117. doi: 10.1186/s12889-022-14474-1.
6. Bode H, Ivens B, Bschor T, Schwarzer G, Henssler J, Baethge C. Association of Hypothyroidism and Clinical Depression: A Systematic Review and Meta-analysis. JAMA Psychiatry 2021;78:1375-83. doi: 10.1001/jamapsychiatry.2021.2506.
7. Hou L, Li Y, Wang J, Wang Y, Wang J, Hu G, et al. Risk factors for post-extubation dysphagia in ICU: A systematic review and meta-analysis. Medicine (Baltimore) 2023;102:e33153. doi: 10.1097/MD.0000000000033153.
8. Sánchez-Lander J, Cortiñas P, Loureiro CL, Pujol FH, Medina F, Capote-Negrín L, et al. Human papillomavirus in invasive cervical cancer and cervical intraepithelial neoplasia 2 and 3 in Venezuela: a cross-sectional study. Cancer Epidemiol 2012;36:e284-7. doi: 10.1016/j.canep.2012.04.005.
9. Feng RM, Hu SY, Zhao FH, Zhang R, Zhang X, Wallach AI, et al. Role of active and passive smoking in high-risk human papillomavirus infection and cervical intraepithelial neoplasia grade 2 or worse. J Gynecol Oncol 2017;28:e47. doi: 10.3802/jgo.2017.28.e47.
10. Carozzi FM, Tornesello ML, Burroni E, Loquercio G, Carillo G, Angeloni C, et al. Prevalence of human papillomavirus types in high-grade cervical intraepithelial neoplasia and cancer in Italy. Cancer Epidemiol Biomarkers Prev 2016;19:2389-400. doi: 10.1158/1055-9965.EPI-10-0131.
11. Ku CH, Lee SH, Lee SP. Effect of human papillomavirus genotype on severity and prognosis of cervical intraepithelial neoplasia. Obstet Gynecol Sci 2014;57:37-43. doi: 10.5468/ogs.2014.57.1.37.
12. Ronco G, Giorgi-Rossi P, Carozzi F, Confortini M, Dalla Palma P, Del Mistro A, et al. Efficacy of human papillomavirus testing for the detection of invasive cervical cancers and cervical intraepithelial neoplasia: a randomised controlled trial. Lancet Oncol 2010;11:249-57. doi: 10.1016/S1470-2045(09)70360-2.
13. Rijkaart DC, Berkhof J, Rozendaal L, van Kemenade FJ, Bulkmans NW, Heideman DA, et al. Human papillomavirus testing for the detection of high-grade cervical intraepithelial neoplasia and cancer: final results of the POBASCAM randomised controlled trial. Lancet Oncol 2012;13:78-88. doi: 10.1016/S1470-2045(11)70296-0.
14. Zhao FH, Lewkowitz AK, Hu SY, Chen F, Li LY, Zhang QM, et al. Prevalence of human papillomavirus and cervical intraepithelial neoplasia in China: a pooled analysis of 17 population-based studies. Int J Cancer 2012;131:2929-38. doi: 10.1002/ijc.27571.
15. Tan XQ. Relationship of HPV with CIN and cervical cancer. Chin J Mod Med 2012;22:107–9.
16. Cheng Q. Correlation analysis of high-risk human papillomavirus infection and cervical precancerous lesions in Quzhou women. Maternal and Child Health Care of China (MCH) 2020;35:456-8.
17. Zhao LS, Ma GQ, Yang JJ, Mi L, Qiehere G, Yun K, et al. Human papillomavirus infection and its correlation with cervical lesions among women in the Tacheng area. J China Med Univ 2020;49:929–34. doi:10.12007/j.issn.0258-4646.2020.10.013.
18. Ou-Yang X, Cao Y, Leng Q, Wang Y, Yi H, Zhang G. Eliminating cervical cancer in China: Opportunities come and challenges remain. J Med Virol 2024;96:e29480. doi: 10.1002/jmv.29480.
19. Wu S, Jiao J, Yue X, Wang Y. Cervical cancer incidence, mortality, and burden in China: a time-trend analysis and comparison with England and India based on the global burden of disease study 2019. Front Public Health 2024;12:1358433. doi: 10.3389/fpubh.2024.1358433.
20. Yang S, Wu Y, Wang S, Xu P, Deng Y, Wang M, et al. HPV-related methylation-based reclassification and risk stratification of cervical cancer. Mol Oncol 2020;14:2124-41. doi: 10.1002/1878-0261.12709.
21. Piña-Sánchez P. Human Papillomavirus: Challenges and Opportunities for the Control of Cervical Cancer. Arch Med Res 2022;53:753-69. doi: 10.1016/j.arcmed.2022.11.009.
22. Hoyer H, Mehlhorn G, Scheungraber C, Hagemann I, Hirchenhain C, Woelber L, et al. Evaluation of Integrated HPV DNA as Individualized Biomarkers for the Detection of Recurrent CIN2/3 during Post-Treatment Surveillance. Cancers (Basel) 2021;13:3309. doi: 10.3390/cancers13133309.
23. Taku O, Mbulawa ZZA, Phohlo K, Garcia-Jardon M, Businge CB, Williamson A-L. Distribution of Human Papillomavirus (HPV) Genotypes in HIV-Negative and HIV-Positive Women with Cervical Intraepithelial Lesions in the Eastern Cape Province, South Africa. Viruses 2021;13:280. doi:10.3390/v13020280.