Original Article

The diagnostic accuracy of TCT + HPV-DNA for cervical cancer: systematic review and meta-analysis

Tao Li[1,2#], Yi Lai[1,2#], Jialing Yuan[1,2]

[1]Department of Obstetrics and Gynecology, West China Second University Hospital, Sichuan University, Chengdu, China; [2]The Key Laboratory of Birth Defects and Related Diseases of Women and Children (Sichuan University), Ministry of Education, Chengdu, China

Contributions: (I) Conception and design: T Li; (II) Administrative support: J Yuan; (III) Provision of study materials or patients: T Li; (IV) Collection and assembly of data: Y Lai; (V) Data analysis and interpretation: T Li, J Yuan; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work and should be considered as co-first authors.

Correspondence to: Jialing Yuan. Department of Obstetrics and Gynecology, West China Second University Hospital, Sichuan University, No. 20, Section 3, Renmin Nanlu Road, Chengdu 610041, China. Email: cutewing1985@163.com.

Background: This study sought to systematically analyze the clinical diagnostic value of tumor markers combined with ThinPrep cytologic test (TCT) and human papillomavirus (HPV) deoxyribonucleic acid (DNA) detection for cervical cancer and pre-cancerous lesions. However, there is a lot of controversy in the field of TCT + HPV-DNA. Many people have mixed opinions on the accuracy of TCT + HPV-DNA, and there is no unified opinion. Therefore, it is necessary to further confirm the significance of this combined detection method in the early diagnosis of cervical cancer by applying meta method.

Methods: The Cochrane Library, PubMed, Web of Science, Embase, Chinese Biomedical Literature Database (CBM) databases were searched to retrieve studies. To assess the methodological quality of each study and potential risk of bias, QUADAS-2 Guidelines were used to evaluate the quality of all articles that met the inclusion criteria and data extraction of the included articles were performed, and a meta-analysis was performed of the included studies using Review Manager 5.2 software.

Results: A total of 5 studies were included in the study, and a total of 2,778 patients were included in the study, and there was no significant publication bias observed. The meta-analysis showed that there was a statistical difference in terms of the accuracy of the tumor markers combined with TCT in the detection of cervical cancer. The results were as follows: the pooled sensitivity (SEN) was 0.86 (95% CI: 0.75–0.93); the combined specificity (SPE) was 0.79 (95% CI: 0.57–0.92); the diagnostic performance of combined with thin-layer liquid-based cytology and HPV DNA detection in the diagnosis accuracy of cervical cancer by summary receiver operating characteristic (SROC) curve analysis, result showed excellent diagnostic accuracy, with a combined area under the curve (AUC) of 0.90 (95% CI: 0.87–0.92).

Discussion: Tumor markers are important for the early diagnosis of cervical cancer. Combining the tumor markers with TCT and HPV DNA detection effectively improved the detection rate.

Keywords: Tumor marker; thin-layer liquid-based cytology; human papillomavirus (HPV); clinical diagnosis

Submitted Mar 04, 2022. Accepted for publication Jul 08, 2022.

doi: 10.21037/atm-22-1732

View this article at: https://dx.doi.org/10.21037/atm-22-1732

Introduction

Cervical cancer is a gynecological malignant tumor whose incidence is only to that of breast cancer (1). Despite the widespread screening programs, cervical cancer remains the third most common cancer in developing countries (2). The early clinical symptoms of this disease are not typical, and it is easy to be missed and misdiagnosed clinically. In recent years, the incidence of cervical cancer has

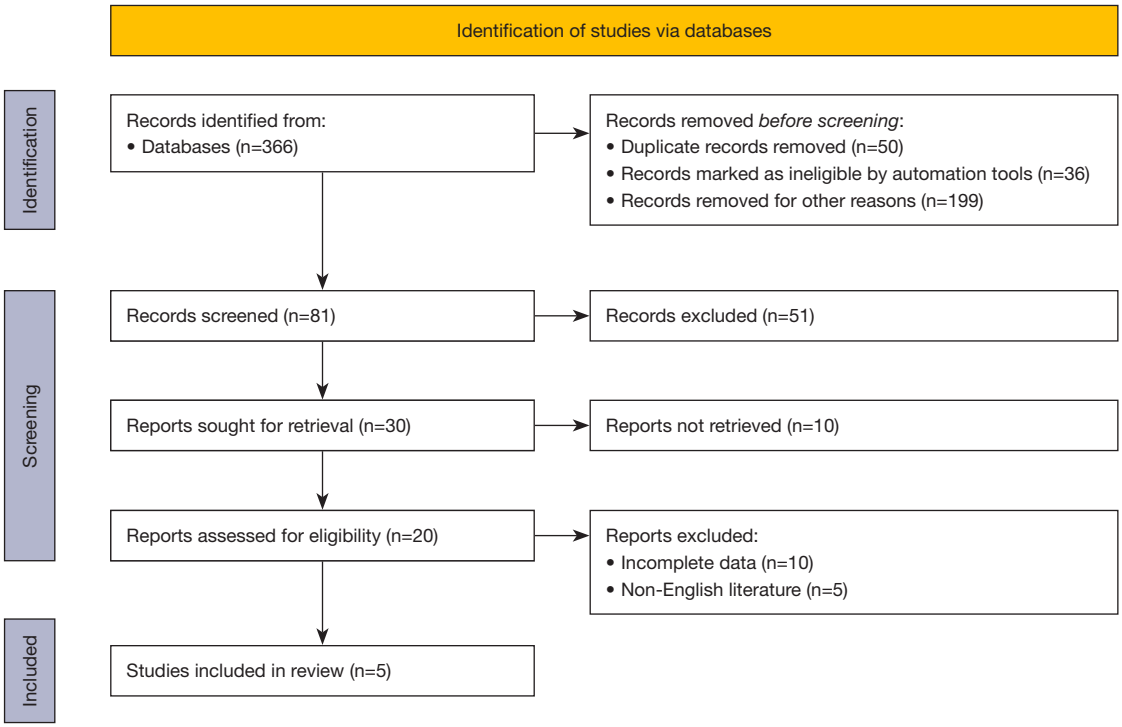

Figure 1 Flow chart of the literature screening process.

continued to increase, and thus it poses a serious threat to the health of patients (3). In recent years, the incidence of cervical cancer has been increasing year by year, as has the incidence among younger women (4). At the beginning of the disease, the patient's clinical symptoms are not obvious, so the diagnostic accuracy is not high. To effectively prevent cervical cancer, it is generally accepted that the early detection of lesions is very important. At present, the application of serum tumor markers in the diagnosis of cervical cancer is increasing, but there is a lack of research on the diagnosis of cervical cancer (5).

At present, many cervical disease screening techniques are widely used in clinical practice, among which human papillomavirus (HPV) examination and ThinPrep cytologic test (TCT) examination have relatively important clinical value. However, there is a lot of controversy in the field of TCT + HPV-DNA. Many people have mixed opinions on the accuracy of TCT + HPV-DNA, and there is no unified opinion (6-10). Therefore, it is necessary to further confirm the significance of this combined detection method in the early diagnosis of cervical cancer by applying meta method. We present the following article in accordance with the PRISMA-DTA reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-1732/rc).

Methods

Search strategy

According to the requirements of the Cochrane Collaboration, a computer search was conducted to retrieve all relevant articles published in The Cochrane Library, PubMed, Web of Science, Embase, Chinese Biomedical Literature Database (CBM) databases. The English search words included cervical carcinoma, cervical lesion, cervical intraepithelial neoplasia, CIN, cervical disease, pre-cancerous cervical cancer, cervical cancer, cervix neoplasms, cervical screening, mass smear, liquid-based, thin-layer liquid-based cytology, Pap smear, Papanicolaou smear, cytology, cyto-diagnosis, cytological techniques, human papillomavirus, HPV, colposcopy, biopsy, and histological diagnosis. All the retrieved articles were manually re-screened (*Figure 1*).

Literature inclusion criteria

To be eligible for inclusion in the meta-analysis, the

Table 1 Basic clinical features of the 5 included studies

Author	Year	Country	Type of cancer	Tumor/control	Stage
Pan	2019	China	Cervical intraepithelial neoplasia	133/168	CINI–III
Liang	2016	China	Cervical intraepithelial neoplasia	110/308	CINI–III
Liu	2017	China	Cervical cancer	199/221	CINI–III
Husaiyin	2021	China	Cervical cancer	477/1,145	CINI–III
Zhang	2020	China	Cervical cancer	95/342	CIN-III

articles had to meet the following inclusion criteria: (I) be an English-language article published; (II) include ≥20 subjects; (III) evaluate the value of the liquid-based cell test, and the HPV test, and the combined value of the 2 methods in cervical disease screening; (IV) be a retrospective cohort study; (V) use a positive criterion for the liquid-based cytology of atypical squamous cells of undetermined significance and above lesions; (VI) use the gold-standard pathological tissue diagnosis, and a positive diagnostic standard for cervical intraepithelial neoplasia I (CIN I) or above lesions; (VII) have complete original data that could be obtained directly or have available data from which the true positive number, false positive number, false negative number, and true negative number of the test could be obtained.

Literature exclusion criteria

Articles were excluded from the meta-analysis if they met any of the following exclusion criteria: (I) comprised a review, conference paper, lecture, or abstract; (II) had incomplete literature data; (III) the main purpose of the study was to examine a HPV vaccine, the *HPV* gene, HIV infection, or another topic; (IV) the cytological examination had been performed using the traditional pap smear method.

Data extraction and quality assessment

Two reviewers independently extracted the data included in the literature, which included the following: We extracted the following data for the diagnostic value of the author name, publication year, country, type of cancer, cancer stage.

Quality assessment of diagnostic accuracy studies (QUADAS) was used for assessing quality of individual studies in this meta-analysis. This method is considered as an evidence-based quality assessment tool developed for use in systematic reviews. The highest score possible is 14.

Statistical method

Diagnostic sensitivity and specificity were calculated using the formulas: sensitivity = true positive/(true positive + false negative); and specificity = true negative/(true negative + false positive). The area under the receiver operating characteristic (ROC) curve was used to evaluate the feasibility of combined with thin-layer liquid-based cytology and HPV DNA detection in the diagnosis accuracy of cervical cancer. Publication bias was evaluated using Deeks' funnel plot. Two-tailed P values of <0.05 were considered statistically significant. All statistical analysis was performed using Stata version 15.0. If I^2>50% and P<0.1 from chi-square analysis showed study heterogeneity, Meta-analysis by random effects models and searched for possible heterogeneity by subgroup analysis source.

Results

Literature retrieval results and included research characteristics

In this study, the PubMed, Cochrane Library, Web of Science, Embase, CBM databases were searched. Repeated publications were excluded based on a reading of the titles and abstracts of the articles, after which 20 articles remained. Next, the full-text of the 20 articles were reviewed, and different reports of the same clinical study and articles inconsistent with the purpose of this study were excluded. Ultimately, a total of 5 studies were included in the study (11-15). All the retrieval and screening processes were completed independently by 2 evaluators, and any differences in opinions were resolved through internal discussion (*Table 1*). Almost all the literatures included in this study are within the effective range of the triangle, so

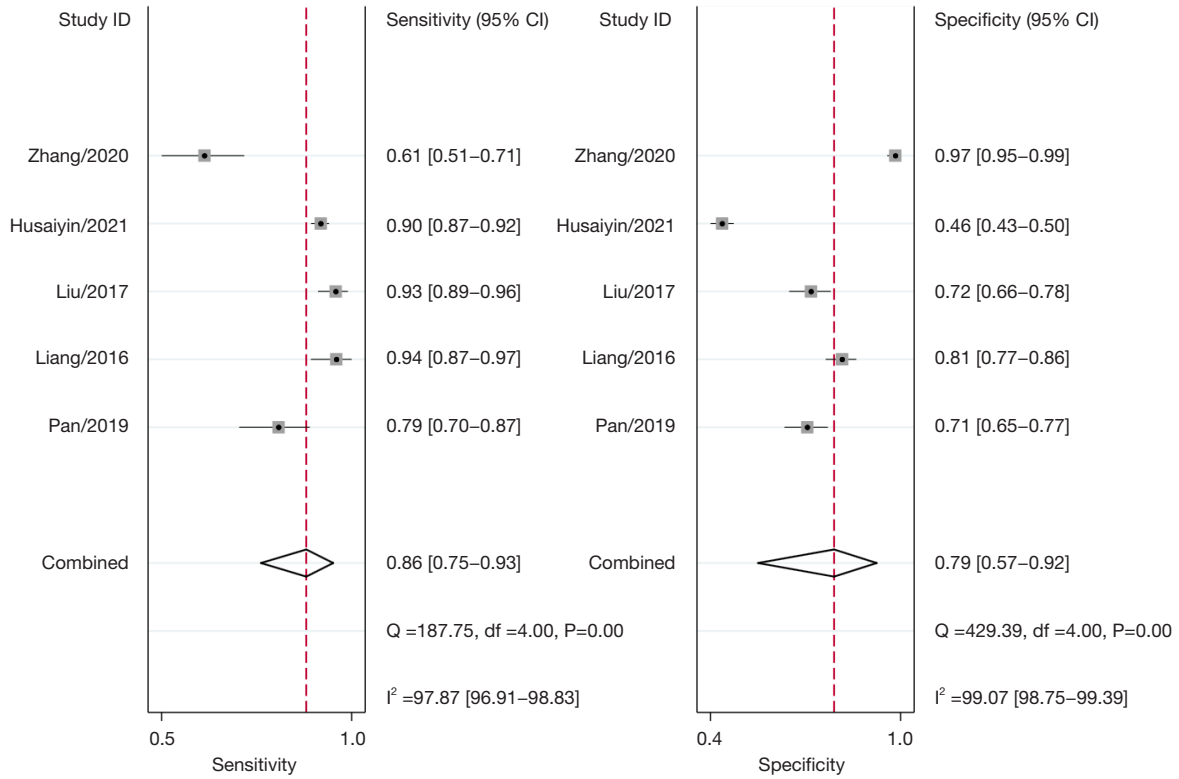

Figure 2 Forest plot of pooled sensitivity and specificity of cervical cancer. Squares specify the effect sizes of individual studies and extended lines denote 95% CIs. Sizes of square imply the weight of studies based on sample size using a random effects analysis. The diamond data indicates pooled prevalence. CI, confidence interval.

there is no obvious risk bias.

Pooled diagnostic sensitivity and specificity

The diagnostic value of combined with thin-layer liquid-based cytology and HPV DNA detection in the diagnosis accuracy of cervical cancer from six studies. The results were as follows: the pooled sensitivity (SEN) was 0.86 (95% CI: 0.75–0.93); the combined specificity (SPE) was 0.79 (95% CI: 0.57–0.92): these results are illustrated by the forest map in *Figure 2*.

Pooled ROC curves

The diagnostic performance of combined with thin-layer liquid-based cytology and HPV DNA detection in the diagnosis accuracy of cervical cancer by summary receiver operating characteristic (SROC) curve analysis, result showed excellent diagnostic accuracy, with a combined area under the curve (AUC) of 0.90 (95% CI: 0.87–0.92) in *Figure 3*.

Publication analysis

The Deeks' Funnel plot shows that there is no publication bias, and *Figure 4* shows that there is no publication bias in diagnostic studies.

Discussion

After breast cancer and colorectal cancer, cervical cancer is the 3rd most common malignant tumor in women worldwide, and the most common malignant tumor of the female reproductive tract (16). In 2021, there were 529,800 new cervical cancer cases and 255,100 deaths, with 85% of the new cases occurring in developing countries (17). Due to advances in cervical cancer screening technology, the incidence and mortality of cervical cancer in developed and developing countries have decreased significantly and become hot (18). The formation of cervical cancer is a

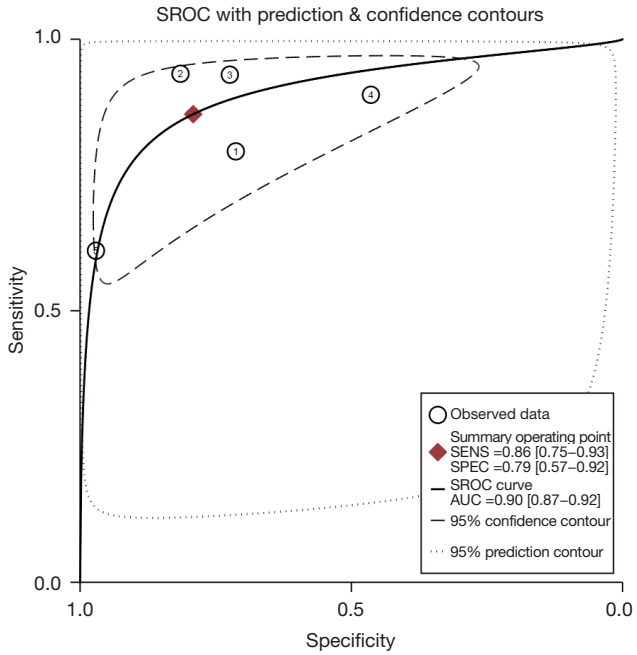

Figure 3 The SROC curves of cervical cancer characteristics. SROC, summary receiver operating characteristic; AUC, area under the curve; SENS, sensitivity; SPEC, specificity.

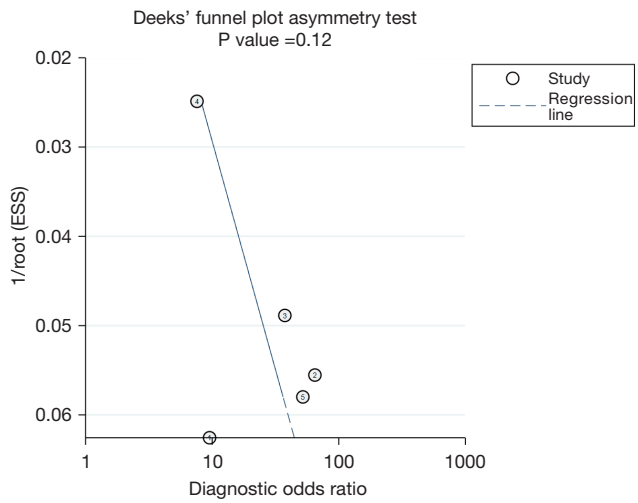

Figure 4 Deeks' funnel plot asymmetry test. ESS, standardized effect sizes.

continuous development process. CIN usually proceeds as follows: CIN I → CIN II → CIN III → carcinoma in situ (CIS) → early invasive carcinoma of the cervix → invasive carcinoma of the cervix. The time from CIN lesions to CIS of the cervix is 3–8 years (19).

Due to the long, reversible pre-cancerous lesion stage in the occurrence and development of cervical cancer, with timely detection and appropriate treatment, the cure rate of early cervical cancer is nearly 100% (20). Thus, more and more attention has been paid to the early screening of cervical diseases in clinical practice, and more effective and reasonable examination methods have been developed to improve the accuracy of cervical disease diagnosis (21). Cervical cancer is the only gynecological cancer that can be diagnosed early and cured, and the early detection of pre-cancerous lesions is the key link in the prevention and treatment of cervical cancer (22-25). Traditional cervical cancer screenings are aimed at the early detection of cervical cancer, while modern cervical cancer screenings are aimed at the early detection of high-grade CIN lesions and the early treatment of obstructive cervical cancer.

Cervical cancer is a popular area of modern medical research. Cervical cancer is an infectious disease caused by HPV infection. The development process for the formation of cervical cancer is continuous. The period from CIM to cervical cancer ranges from 3–8 years (26). Thus, the pre-screening of cervical cancer is particularly important. However, research needs to be conducted to determine which test is the most valuable for cervical disease screening. Extensive research has been conducted on disease screening technology for cervical disease, and based on traditional literature reviews, the research has 2 main characteristics. First, research results is the certain result of the literature more less number of come to the conclusion that generally do not evaluate the literature, also does not consider the quality of the literature. Second, there are 2 main problems; that is, the quality of many similar studies is not the same, and the number of samples in each study differs. Under the equal-weight method, which is used in traditional literature reviews, it is difficult to ensure the authenticity, reliability and scientific nature of research results, especially when the results of multiple studies are inconsistent, and any conclusions drawn may easily lead to misunderstandings or confusion (27). The statistical purpose of a meta-analysis is to merge, analyze, and summarize the results of similar independent research, increase the sample size, increase the efficiency of the inspection, examine inconsistent results, especially when multiple research studies have been conducted or the results are not statistically significant, and reveal the real situation based on a statistical analysis of the results.

The present study had a number of limitations. First, the search of the databases was not sufficiently extensive. The

multi-person, blind-screening method was not adopted in the search and screening of the articles, which may have led to the omission of some articles conforming to the standard. The authors of this study screened the articles according to the inclusion criteria and exclusion criteria, which may be subjective. Second, the unpublished article was not available. Third, only articles published in English were included in the meta-analysis. Due to the influence of language and region, articles in other languages and some unpublished studies were not included in the meta-analysis. The possibility of language bias or publication bias is large. As for some of the published articles, they were not included in the meta-analysis, as the original authors could not be contacted and the complete data were unavailable, which affected the comprehensive quality of the analysis. All the above-mentioned reasons may have led to sampling bias in this study. Future studies need to improve on the above-mentioned aspects to ensure the research results are more comprehensive and reliable and thus can be used to guide clinical applications.

TCT is a thin-layer liquid-based cytology detection system for detecting cervical cells and conducting cytological classification diagnoses. Compared to a traditional pap smear, TCT has a higher detection rate, and thus can provide a pathological basis for the early diagnosis and treatment of cervical cancer, which in turn could reduce the death rate of cervical cancer patients. Pap smears must be performed by experienced and highly skilled laboratory personnel to ensure their accuracy. These methods have been widely used in the clinical screening of cervical cancer, but the detection rate of each method alone needs to be improved. This study examined the diagnostic value of the combined application of various indicators for cervical cancer. The results showed that the diagnostic value of the combined detection methods was far superior to that of a single detection method, and the detection value of HPV deoxyribonucleic acid (DNA) was higher than those of other detection methods. Thus, combined detection represents the best screening choice for individuals with the economic ability to pay for this type of screening.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the PRISMA-DTA reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-1732/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-1732/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Lei J, Ploner A, Elfström KM, et al. HPV Vaccination and the Risk of Invasive Cervical Cancer. N Engl J Med 2020;383:1340-8.
2. Tsikouras P, Zervoudis S, Manav B, et al. Cervical cancer: screening, diagnosis and staging. J BUON 2016;21:320-5.
3. Maver PJ, Poljak M. Primary HPV-based cervical cancer screening in Europe: implementation status, challenges, and future plans. Clin Microbiol Infect 2020;26:579-83.
4. Yang S, Wu Y, Wang S, et al. HPV-related methylation-based reclassification and risk stratification of cervical cancer. Mol Oncol 2020;14:2124-41.
5. Brisson M, Kim JJ, Canfell K, et al. Impact of HPV vaccination and cervical screening on cervical cancer elimination: a comparative modelling analysis in 78 low-income and lower-middle-income countries. Lancet 2020;395:575-90.
6. Sun J, Yue Y, Li R, et al. Detection of HPV E6/E7 mRNA in the diagnosis of cervical cancer and precancerous lesions after kidney transplantation. Am J Transl Res 2021;13:7312-7.
7. Lu WB, Jiang ZN, Chen SM, et al. Clinical research of HPV DNA detection and HPV RNA detection in single time. Zhonghua Shi Yan He Lin Chuang Bing Du Xue Za

Zhi 2009;23:378-80.
8. Buzás GM. History of tumor markers for cancers of the digestive system. Orv Hetil 2013;154:810-9.
9. Zhang T, Hu R, Tang Y, et al. The effect of local photodynamic therapy with 5-aminolevulinic acid in the treatment of vaginal intraepithelial lesions with high-risk HPV infection. Photodiagnosis Photodyn Ther 2022;37:102728.
10. Gao K, Eurasian M, Zhang J, et al. Can Genomic Amplification of Human Telomerase Gene and C-MYC in Liquid-Based Cytological Specimens Be Used as a Method for Opportunistic Cervical Cancer Screening? Gynecol Obstet Invest 2015;80:153-63.
11. Pan D, Zhang CQ, Liang QL, et al. An efficient method that combines the ThinPrep cytologic test with E6/E7 mRNA testing for cervical cancer screening. Cancer Manag Res 2019;11:4773-80.
12. Liang H, Fu M, Zhou J, et al. Evaluation of 3D-CPA, HR-HPV, and TCT joint detection on cervical disease screening. Oncol Lett 2016;12:887-92.
13. Liu Y, Zhang L, Zhao G, et al. The clinical research of Thinprep Cytology Test (TCT) combined with HPV-DNA detection in screening cervical cancer. Cell Mol Biol (Noisy-le-grand) 2017;63:92-5.
14. Husaiyin S, Jiao Z, Yimamu K, et al. ThinPrep cytology combined with HPV detection in the diagnosis of cervical lesions in 1622 patients. PLoS One 2021;16:e0260915.
15. Zhang YY, Xu XQ, Zhang D, et al. Triage human papillomavirus testing for cytology-based cervical screening in women of different ages in primary hospitals: A retrospective clinical study. Medicine (Baltimore) 2020;99:e22320.
16. Silver MI, Kobrin S. Exacerbating disparities?: Cervical cancer screening and HPV vaccination. Prev Med 2020;130:105902.
17. Husseinzadeh N. Status of tumor markers in epithelial ovarian cancer has there been any progress? A review. Gynecol Oncol 2011;120:152-7.
18. Pimple SA, Mishra GA. Optimizing high risk HPV-based primary screening for cervical cancer in low- and middle-income countries: opportunities and challenges. Minerva Ginecol 2019;71:365-71.
19. Miao Z, Shen J, Zhang FQ, et al. The relationship between HPV integration and prognosis of cervical cancer. Zhonghua Zhong Liu Za Zhi 2020;42:1014-9.
20. Balaya V, Guani B, Pache B, et al. Sentinel lymph node in cervical cancer: time to move forward. Chin Clin Oncol. 2021;10:18.
21. Petersen LM, Fenton JM, Kennedy LS, et al. HPV, vaccines, and cervical cancer in a low- and middle-income country. Curr Probl Cancer 2020;44:100605.
22. Leite KRM, Pimenta R, Canavez J, et al. HPV Genotype Prevalence and Success of Vaccination to Prevent Cervical Cancer. Acta Cytol 2020;64:420-4.
23. Kelly-Hanku A, Newland J, Aggleton P, et al. HPV vaccination in Papua New Guinea to prevent cervical cancer in women: Gender, sexual morality, outsiders and the de-feminization of the HPV vaccine. Papillomavirus Res 2019;8:100171.
24. Molina R, Barak V, van Dalen A, et al. Tumor markers in breast cancer- European Group on Tumor Markers recommendations. Tumour Biol 2005;26:281-93.
25. Shao Y, Zhu F, Zhu S, et al. HDAC6 suppresses microRNA-199a transcription and augments HPV-positive cervical cancer progression through Wnt5a upregulation. Int J Biochem Cell Biol 2021;136:106000.
26. Khan AA, A Abuderman A, Ashraf MT, et al. Protein-protein interactions of HPV-Chlamydia trachomatis-human and their potential in cervical cancer. Future Microbiol 2020;15:509-20.
27. Ning YE, Liu Y, Xu XY, et al. Knowledge of Cervical Cancer, Human Papilloma Virus (HPV) and HPV Vaccination Among Women in Northeast China. J Cancer Educ 2020;35:1197-205.

(English Language Editor: L. Huleatt)

Cite this article as: Li T, Lai Y, Yuan J. The diagnostic accuracy of TCT + HPV-DNA for cervical cancer: systematic review and meta-analysis. Ann Transl Med 2022;10(14):761. doi: 10.21037/atm-22-1732

