Cellular and Molecular Biology
E-ISSN : 1165-158X / P-ISSN : 0145-5680
www.cellmolbiol.org

Original Research

The clinical research of Thinprep Cytology Test (TCT) combined with HPV-DNA detection in screening cervical cancer

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Received January 9, 2017; **Accepted** February 20, 2017; **Published** February 28, 2017

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Doi: http://dx.doi.org/10.14715/cmb/2017.63.2.14

Abstract: Our objective is to explore the clinical value of thinprep cytologic test (TCT) combined with HPV-DNA detection in screening cervical cancer. 420 cervical cancer patients admitted in our hospital between April, 2011-April, 2014 were selected. All patients received TCT and HPV-DNA detection, and cervical tissue biopsy was used to confirm the diagnosis. TCT screening results showed that there were 175 patients were >ASCUS and the positive rate was 41.7%, histopathological screening showed that there were 199 patients were ≥cervical intraepithelial neoplasia (CIN) I and the positive rate was 47.4%. HPV-DNA detection showed 180 patients were positive which was 42.9%, and the positive rate of HPV-DNA detection was increased as the disease severity increased. The sensitivity of TCT combined with HPV-DNA detection was higher than single TCT or HPV-DNA, however the specificity was relatively low, and the positive predictive value and negative predictive value were higher which were similar to pathological results. TCT combined with HPV-DNA detection has high sensitivity and accuracy in screening cervical cancer, which is worthy of clinical application.

Key words: TCT; HPV-DNA detection; Cervical cancer screening; Clinical value.

Introduction

Cervical cancer is a common malignant cancer in female patients, and the patients are becoming younger in the recent years (1-3). Some clinical researches have shown that cervical cancer is induced by the infection of high risk type human papilloma virus (HPV), and early diagnosis and treatment can decrease the mortality (4-6). In the past, the most common screening method was Pap smear cytologic test. In this method, the operation is simple, the sample is easy to collect, no special equipment is needed, the price is low and it is not easily affected by impurity such as mucus and blood et al (3, 7, 8). At present, the most advanced methods are thinprep cytologic test (TCT) and hybrid capture II which detects the DNA of high risk type HPV (HPV-DNA), which both have advantages and disadvantages (9-13). In this study, 420 cervical cancer patients admitted in our hospital between April, 2011-April, 2014 were selected as objects. All of patients received TCT and HPV-DNA test, and cervical tissue biopsy was compared with them to explore the clinical value of TCT combined with HPV-DNA in screening cervical cancer.

Materials and Methods

General data

420 cervical cancer patients admitted in our hospital between April, 2011-April, 2014 were randomly selected as objects. The age of patients was 20-65 years and the average age was (35.7±9.8) years. All patients had symptoms such as cervical erosion, hyperplasia, hypertrophy and contact bleeding, and had sexual life for more than 1 year. All patients had no uterectomy history or CIN history. The patients with factors that affect the observational results such as pregnancy were excluded.

All patients had histopathological biopsy, and were required not to have sexual life for 2 days and not to have any vaginal medication or washing for 1 week before sampling. The patients at menstrual period were excluded. The patients received TCT screening and HPV-DNA screening. TCT specific sampling brush was used to collect samples, including cast-off cells in cervical canal and at the border of squamous epithelium and columnar epithelium. Specific pelleter was used to prepare thin smears, which received microscopic examination after Pap staining; specific sampling brush purchased from Digene Corporation, Gaithersburg, Maryland, USA was used for HPV-DNA detection to detect 13 high risk subtypes of HPV (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68). HPV-DNA reagent kits were used for detection. Cervical tissue biopsy was completed by colposcope.

Diagnostic criteria

Cervical cytologic diagnosis was referred to the Bethesda System (TBS) classification criteria by Association For International Cancer Research: normal or inflammation; atypical squamous cells of undetermined significance (ASCUS); low squamous intraepithelial

lesion (LSIL): HPV and CIN I; high squamous intraepithelial lesion (HSIL): CIN II-III; squamous-cell carcinoma (SCC); adenocarcinoma (CA). The histological diagnosis of cervical cancer included (15): chronic inflammation; mild atypical hyperplasia (CIN I), moderate atypical hyperplasia (CIN II), severe atypical hyperplasia (CIN III) and SCC; the result >ASCUS, ≥CIN I or HPV-DNA≥1.0pg/mL was defined as positive (14).

Statistical analyses

All data were analyzed by SPSS17.0. The measurement data were analyzed by t test, presenting as ($\bar{x}\pm s$), and the enumeration data were analyzed by X2. $P<0.05$ was considered as statistically significant.

Results

Comparison of TCT and histopatholgical examination

TCT screening results showed that 175 patients were >ASCUS and the positive rate was 41.7%, histopathological screening showed that 199 patients were ≥cervical intraepithelial neoplasia (CIN)I and the positive rate was 47.4%. As shown in Table 1.

Comparison of HPV-DNA screening and histopathological tissue screening

HPV-DNA screening showed that 180 patients were positive which was 42.9%, and the positive rate of HPV-DNA was increased as the disease severity increased. As shown in Table 2.

The result evaluation of TCT combined with HPV-DNA screening

The sensitivity of TCT combined with HPV-DNA detection was higher than TCT or HPV-DNA, however the specificity was relatively low, and the positive predictive value and negative predictive value were higher which were similar to pathological results. As shown in Table 3.

Discussion

Cervical cancer is a common malignant cancer in female patients (16-18). However, effective early diagnosis and treatment can not only avoid missed diagnosis and misdiagnose that bring unnecessary pain, but also decrease the mortality (19-21). The developing stages of cervical cancer often include CIN I, CIN II, CIN III, cervix carcinoma in situ, early stage invasive cervix carcinoma and invasive cervical carcinoma (11, 22, 23). And CIN is closely related to invasive cervical carcinoma, which may reflect the continuous processes of occurrence and development of cervical cancer (24). Some investigtors have shown that there is a long term reversible stage before carcinogenesis, if effective preventive measures are taken in this stage, the curative rate can be up to 100% (22, 25). Colposcopy is considered as the golden standard for diagnosing cervical cancer in clinical, which is an invasive diagnostic method, thus it is not suitable for screening. (26, 27) In the past the most popular screening method was Pap smear cytologic test, and at present the most common methods are TCT and HPV-DNA detection which can avoid interference factors to increase the sensitivity and accuracy of Pap smear test (3, 10, 28). TCT is a popular cytologic diagnostic method, the operation of which is professional and convenient. The samples are processed with corresponding equipment to decrease personal error and increase the accuracy. However the specificity is relatively low. It is easily affected by mutated cells in inflammatory reaction. It is also reported that the diagnosis of ASCUS by TCT is not highly coincidental to histopathological diagnosis, which can cause missed diagnosis, thus the sensitivity to screen early stage cervical cancer is low (29). Some investigators have shown

Table 1. Comparison of TCT and histopathological examination (cases).

Index	Case	Chronic inflammation	CIN I	CIN II	CIN III	SCC
≤ASCUS	245	174	52	19	0	0
LSIL	113	47	41	21	4	0
HSIL	44	0	4	17	21	2
SCC	18	0	0	0	0	18
In total	420	221	97	57	25	20

Table 2. Comparison of HPV-DNA screening and histopathological tissue screening (cases, %).

Index	Case	HPV-DNA positive	Ratio
Chronic inflammation	221	60	27.1
CIN I	97	37	38.1
CIN II	57	41	71.9
CIN III	25	22	88.0
SCC	20	20	100

Table 3. The result evaluation of TCT combined with HPV-DNA screening (%).

Screening methods	Sensitivity	Specificity	positive predictive value	Negative predictive value	Kappa value
TCT	78.3	77.9	73.3	69.2	0.332
HPV-DNA	61.7	69.3	62.5	63.5	0.209
TCT+HPV-DNA	93.5	72.8	75.8	86.7	0.498

that HPV is the main factor that causes CIN and cervical cancer (30, 31). It is reported that there is HPV infection in more than 99% of cervical cancer patients, HPV detection can improve the effectiveness of cervical cytologic screening at present (32). There are many subtypes of HPV, and infection of common 13 high risk subtypes can easily induce cervical cancer (33). At present, the sensitivity of HPV-DNA detection is >88%, which has higher negative predictive value (34, 35). And the repeatability of HPV detection is good, which can avoid the experimental error. However, due to the effect of immune clearance, the false positive rate of HPV detection is high.

In this study, 420 cervical cancer patients admitted in our hospital between April, 2011-April, 2014 were randomly selected as objects, who received TCT, HPV-DNA detection and combined detection. The histopathological results showed that there were 221 patients of chronic inflammation, 97 patients of CIN I, 57 patients of CIN II, 25 patients of CIN III and 20 patients of SCC. And TCT results showed that there were 245 patients ≤ASCUS, 113 patients of LSIL, 44 patients of HSIL, 18 patients of SCC, TCT screening results showed that there were 175 patients >ASCUS and the positive rate was 41.7%. The histopathological results showed that there were 199 patients ≥CIN I and the positive rate was 47.4%. The detection result of TCT was significantly lower than pathological screening. HPV-DNA screening showed 180 positive patients and the positive rate was 42.9%. The HPV-DNA positive rate was increased as the disease severity increased. The detectable rate of SCC was 100%. Single TCT or HPV-DNA screening has advantages and disadvantages. The sensitivity of TCT was 78.3% and the specificity was 77.9%, the positive predictive value and the negative predictive value were 73.3% and 69.2% respectively, and K value was 0.332. HPV-DNA detection results showed that the sensitivity and specificity were 61.7% and 69.3%, which were lower than TCT. This is in accordance with many researches (36, 37). The sensitivity of TCT combined with HPV-DNA detection was up to 93.5%, and the positive predictive rate and negative predictive rate were high. However the specificity was lower than TCT, and the comprehensive detection effect was similar to histopathological examination.

In conclusion, TCT combined with HPV-DNA detection has high sensitivity, which is highly coincidental with histopathological result. It can be used as the preferred method to screen cervical cancer. Especially in the mild patients and susceptible patients, it can increase the accuracy, avoid misdiagnosis and missed diagnosis to diagnose and treat cervical cancer in the early stage, then further improve the curative rate. Thus, it is worthy of clinical application. TCT also has high sensitivity and specificity, which can be used for screening the patients with limited economic condition.

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