The application of CYFRA21-1 in cervical lesions screening in high-risk human papillomavirus infected women

Feng Yang-chun, Yang Jia, Liu Cheng-ming, Huang Yan-chun

The Clinical Laboratory Center, Tumor Hospital Affiliated to Xinjiang Medical University, Urumqi, People's Republic of China

ABSTRACT

Objectives: To investigate the role of cytokeratin-19 fragment (CYFRA21-1) in cervical lesions screening in high-risk human papillomavirus (HR-HPV) infected women.

Material and methods: The study was a retrospective study. First, the results of CYFRA21-1, cytology (TCT), and HR-HPV examinations of 1039 outpatients from gynecology department in Tumor Hospital Affiliated to Xinjiang Medical University were collected. Then, the data was analyzed using a series of statistical methods.

Results: There was a correlation between CYFRA21-1 levels and HPV-DNA load in HR-HPV infected women \((r_s = 0.711, p = 0.015)\). CYFRA21-1 levels and positive rate increased along with deepening of cervical cell lesions. In HR-HPV infected women, there was a statistically significant difference \((t = 6.022, p < 0.001)\) in CYFRA21-1 levels between the group with cytological lesions \((4.87 \pm 1.58 \text{ ng/mL})\) and the group with normal cytology \((2.52 \pm 0.96 \text{ ng/mL})\). Positive rates of CYFRA21-1 in the two groups were 62.06% and 7.83%, respectively, and also exhibited statistically significant differences \((\chi^2 = 74.624, p < 0.001)\). When diagnosing cytological lesions via CYFRA21-1 in HR-HPV infected women, sensitivity was 62.07%, specificity was 92.17%, positive predictive value was 88.89%, negative predictive value was 70.67%. Compared to CYFRA21-1 negative women, cytological lesions were detected 19.273 times more often in CYFRA21-1 positive women.

Conclusion: CYFRA21-1 could provide a reference idea for further diagnosis of women who are infected with HR-HPV but whose cytology is normal.

Key words: high-risk, human papillomavirus, CYFRA21-1, cervical lesions

INTRODUCTION

Human papillomavirus (HPV) is a type of virus which tends to parasitize epithelial cells. A HPV infection could lead to hyperplasia in a variety of squamous epithelial tissues, such as cervical squamous epithelial cells, esophageal squamous cells and so on [1–3]. CYFRA21-1 widely exists in layered and squamous epithelial cells and, when a malignant hyperplasia occurs in squamous cells, the levels of serum CYFRA21-1 rise [4]. Cervical malignant lesions or cervical cancer are caused by a persistent infection with high-risk HPV (HR-HPV) which leads to immortalized hyperplasia of cervical epithelial cells [5]. HR-HPV includes hpv16, hpv18, hpv31, hpv33, hpv35, hpv45, hpv51, hpv52, hpv56, hpv58, hpv61 and so on. 90%–95% of cervical cancer is squamous cell carcinoma, so the goal is to research the relationship between the pathological changes in exfoliated cervical cells and CYFRA21-1 in HR-HPV infected women and thus to help to shunt screen HR-HPV infected women in the gynecology clinic.

MATERIAL AND METHODS

The source of the sample

The data was collected from outpatients who visited the gynecology clinic in Tumor Hospital Affiliated to Xinjiang Medical University between July 1st, 2011 and July 31st, 2014. The results of their CYFRA21-1, HR-HPV-DNA and Thinprep Cytology Test (TCT, a liquid-based cytology method)
were obtained through the hospital laboratory information system. The data of those outpatients whose TCT result indicated adenocarcinoma was excluded. Ultimately, data of 1039 outpatients, aged between 18 years old and 71 years old, with a median age of 47 years old, was collected.

Detection methods
HR-HPV test used the Digene HPV Test kit (Digene Corporation, USA) and related instruments (9700 GeneAmp PCR System etc.), and its principle was to generate results using the hybrid capture II method (HCII). The result of HCII was expressed via RLU value, the value of relative light units/cutoff value (threshold). RLU value represented the HR-HPV-DNA load in cervical epithelial cells. A RLU value greater than 1.0 was deemed to indicate positive HR-HPV infection. CYFRA21-1 was detected using Abbott i2000 automatic micro particle chemiluminescence analyzer and original kits. Reference interval for CYFRA21-1 levels was 0~3.3 ng/mL; a value greater than 3.3 ng/mL was considered to be a positive result for CYFRA21-1. TCT results were expressed through terms used in cervical cytopathological diagnosis of TBS classification system, including Within Normal Limits (WNL), Atypical Squamous Cells (ASC), Low-grade Squamous Intraepithelial Lesions (LSIL), High-grade Squamous Intraepithelial Lesion (HSIL) and Squamous Cell Carcinoma (SCC). Positive cytopathological diagnosis included any lesions classified as ASC or above.

Statistical methods
Statistical analyses were performed using the SPSS statistics software version 17.0. Data was presented as \( \bar{x} \pm SD \), median (M) and quarter spacing (Q). Quantitative variables of two independent groups were compared using the parametric Student t-test. Spearman rank correlation analysis was used for assessing the correlation between the two indexes. Quantitative variables of many independent groups were compared using one-way analysis of variance (ANOVA) and if the difference in results was statistically significant, then the Dunnett-T3 method was used to compare every pair of groups. Positive rates between different groups were compared using \( \chi^2 \) test. Significance level was \( \alpha = 0.05 \), \( p < 0.05 \) indicated statistical significance.

RESULTS

General data statistics
Out of 1039 cases which formed the sample, there were 231 cases of women testing positively for HR-HPV infection; the positive rate was 22.91%. In 87 cases CYFRA21-1 tests indicated positive results; the positive rate was 8.37%. In 121 cases TCT results were positive; the positive rate was 12.22%.

Table 1. The comparison of CYFRA21-1 levels and positive rates between different cervical lesion groups

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>CYFRA21-1 levels [ng/mL]</th>
<th>Positive rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative group</td>
<td>912</td>
<td>1.36 ± 0.54</td>
<td>1.64</td>
</tr>
<tr>
<td>Low lesion group</td>
<td>61</td>
<td>2.79 ± 0.79</td>
<td>37.71</td>
</tr>
<tr>
<td>Moderate lesion group</td>
<td>40</td>
<td>5.05 ± 1.38</td>
<td>60.00</td>
</tr>
<tr>
<td>Severe lesion group</td>
<td>26</td>
<td>9.86 ± 0.82</td>
<td>96.15</td>
</tr>
</tbody>
</table>

The correlation between HR-HPV-DNA load and CYFRA21-1

CYFRA21-1 levels (2.79 ± 0.82 ng/mL) in HR-HPV positive cases showed a statistically significant difference (t = 5.014, p < 0.001) compared to HR-HPV negative cases (1.36 ± 0.51 ng/mL). Due to the fact that HPV-DNA quantitative variables showed skewness in distribution in HR-HPV infected cases, they are presented using the median (M) and quarter spacing (Q), which are 5.78 and 42.37, respectively. In Spearman rank correlation analysis, HPV-DNA load showed correlation with CYFRA21-1 (\( r = 0.711, p = 0.015 \)).

The difference in CYFRA21-1 levels and positive rates between different cervical cell lesions groups

Based on TCT results, 1039 cases which formed the sample were divided into four groups: negative group (912 cases) including WNL women, Low lesion group (61 cases) including ASC and LSIL women, Moderate lesion group (40 cases) including HSIL women and Severe lesion group (26 cases) including SCC women. CYFRA21-1 test results for all four groups are shown in Table 1. ANOVA (F = 47.382, p < 0.001) showed statistically significant differences in CYFRA21-1 levels among the four groups; Dunnett-T3 method was subsequently employed and showed that statistical differences existed between any two groups (p < 0.001). CYFRA21-1 positive rates in the four groups also showed statistical significance (\( \chi^2 = 522.300, p < 0.001 \)).

The correlation between cervical lesions and CYFRA21-1 in HR-HPV infected women

Of 231 patients with HR-HPV infection, 115 cases showed no cytopathological pathological changes. CYFRA21-1 was compared between HR-HPV TCT+ cases and HR-HPV TCT- cases. Comparative results are shown in Table 2.

CYFRA21-1 used to diagnose cervical cell lesions in HR-HPV infected cases

When diagnosing cervical cell lesions in HR-HPV infected women as shown in Table 3, sensitivity was 62.07%,
There was certain clinical significance of CYFRA21-1 for
shunting to screen cervical lesions in HR-HPV infected
women. However, the study only encompassed 238 cases
of HR-HPV infected women; the sample number was small.
Also, the positive cutoff value of CYFRA21-1 in the study
was taken from the testing laboratory reference range; a
more
detailed study should be performed to obtain a more significant cutoff value of CYFRA21-1 for shunt screening the HR-HPV infected population.

REFERENCES
3. Feng YC, Yang J, Liu CM, [et al.]. DNA ploidy of cervical epithelial cells should be a cure criterion of high-risk HPV infection in Xinjiang Uygur women. Onco Targets Ther. 2015, 8, 827–833.