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Exploration of treatment strategies for normal cytology smears with reactive cellular changes

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ABSTRACT

Objective: To evaluate the use of high-risk humanpapillomavirus (HR-HPV) DNA testing in women who have normal cytology result with reactive cellular changes to identify high risk patients of developing precancerous cervical lesions and cervical cancer.
Study design: Outpatient patients with normal liquid-based cytology (LCT) results showing reactive cellular changes (case group, $n = 1085$) and normal LCT without reactive cellular changes (control group, $n = 1085$) were recruited from cervical clinics at the International Peace Maternity & Child Health Hospital from January 2012 to December 2013. The HPV status and cervical biopsy pathology results were analyzed.
Results: The HR-HPV positive rate of the case group (598/1085) was higher than that of the control group (163/1085) ($P < 0.001$). HR-HPV prevalence among CIN1, CIN2, CIN3 and cervical cancer was 73%, 87%, 100%, and 100% respectively ($P < 0.05$). In patients with positive HR-HPV results, more CIN2+ were found significantly in case group (37/598) than those in control group (3/163), $P = 0.027$. The sensitivity of diagnosis of CIN2+ lesions by HR-HPV testing was 92.5%, the specificity was 36%, the positive predicted value was 8.6%, and the negative predictive value was 98.6%. The incidence of CIN2+ lesions was not different among different age groups ($P > 0.05$).
Conclusion: Reactive cellular changes in normal cervical smears should be further investigated. HR-HPV testing could be used as an effective triage in cases of reactive cellular changes. Colposcopy is recommended for those cases showing reactive cellular changes combined with HR-HPV positivity to reduce the risk of failure to diagnose cervical cancer and precancerous lesions.

Introduction

Cervical cancer is the third most common cancer and the fourth most common cause of cancer deaths among females worldwide, accounting for 9% (529,800) of the total new cancer cases and 8% (275,100) of the total cancer deaths among females in 2008. More than 85% of these cases and deaths occur in developing countries, with approximately 100,000 new cases in China annually accounting for 20% of the total number worldwide [1].

Fortunately, screening of cervical cancer allows early diagnosis and treatment to reduce its morbidity and mortality [2]. Conventional pap smear (CPS) examinations are a simple and economical method of cervical cancer screening that has been used for nearly 50 years; however, in the presence of obscuring blood, inflammation or thick areas of overlapping epithelial cells, the sensitivity of this screening method falls below 50% [3,4]. Advances in liquid-based cytology (LCT) since the late 1980s have yielded significant improvements in the rate of cervical cancer detection compared with CPS [5]. LCT technology is recognized internationally as the first step in the diagnosis and treatment of cervical lesions in clinical practice and prevents an estimated 4500 cervical cancer-related deaths each year in England alone [6]. Multiple studies and meta-analyses have demonstrated that the application of LCT for cervical diseases screening is of significant value when used alone [7,8] although, similar to existing screening methods, this technique is unlikely to achieve 100% screening efficiency. The sensitivity of LCT for this purpose is 85–95% [9], yet LCT contains 12% false negative results, which dangers most those who do not have follow up access [10].

Compared with cervical cytology in relation to primary screening, humanpapillomavirus (HPV) testing has been shown to have a generally higher sensitivity and negative predictive value

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for the detection of clinically relevant preinvasive disease. However, the use of HPV testing as a screening technique is limited by its relatively low specificity and the absence of consensus with regard to a protocol for treating women who are HPV positive but who do not have cytologic abnormalities [11]. Zhao' study showed that the incidence of low grade squamous intraepithelial neoplasia/cervical intraepithelial neoplasia 1 (LSIL/CIN1) was significantly higher in women with at least one positive HPV test result than in women with only negative follow-up HPV test result. This study also indicates the high negative predictive value of HPV testing in addition to the limited specificity of high-risk humanpapillomavirus (HR-HPV) testing in predicting more significant CIN2+ lesions [12].

Most researches have focused on the clinical significance of ASCUS and have developed a standardized mode of hierarchical clinical management [13,14]. According to the limits set by the Clinical Laboratory Improvements Amendments of 1988 (CLIA 88), excessive diagnosis of ASCUS is indicated if the frequency of ASCUS diagnoses exceeds two or three times the rate of squamous intraepithelial lesions (SIL) in the same laboratory [15]. To some extent, this increases with the ratio of normal cytology smears with reactive cellular changes. In the clinic, normal cytology smears with reactive cellular changes are often shown to be high-grade lesions by cervical biopsy. Currently, there is a lack of consensus regarding the appropriate assessment and management of such cases. Therefore, strategies for improving the screening efficiency and reducing the risk of failed diagnosis are urgently required.

In this study, we aimed to explore the processing strategies for normal cytology smear screening. The HR-HPV DNA testing results of 1085 outpatients whose liquid-based cytology (LCT) results showed reactive cellular changes were compared with those of 1085 controls who have normal LCT results without reactive cellular changes. The cervical biopsy pathology results were also analyzed.

Materials and methods

Study population

The retrospective study was designed and initiated after obtaining approval from the ethics committee of the International Peace Maternity & Child Health Hospital. In total we screened 141,256 women in cervical clinics at the International Peace Maternity & Child Health Hospital affiliated to Shanghai Jiao Tong University School of Medicine from January 2012 to December 2013, in which 108,610 women have normal LCT results including 21,696 normal LCT with reactive cellular changes. The case group was composed of all the outpatients (n = 1085) aged from 18 to 85 who had normal LCT results with reactive cellular changes and who have HPV DNA testing results. All the cases were tested for HR-HPV and all cases underwent colposcopy. Areas of suspicion were biopsied by colposcopy (650/1085). The incidence of inflammation and other benign lesions, CIN1, CIN2, CIN3, and cervical cancer was 562, 48, 23, 14, and 3, respectively.

Patients who had normal LCT results without reactive cellular changes and frequency-matched to cases in terms of age (<30 y, 30–49 y, >50 y) were selected from the same clinics from January 2012 to December 2013 as control group (n = 1085). All controls received HR-HPV testing and all HR-HPV positive patients (163/1085) were evaluated by colposcopy. Areas of suspicion were biopsied (17/163). Three CIN2+ lesions were detected.

LCT testing

Samples were taken from the cervical squamous column border areas using an endocervical brush. The cervical canal and cervical os were brushed five times using a circular (clockwise) movement to collect exfoliated cells on the surface of the cervix [16]. The brush head was put into CytoRich Preservative solution (BD Diagnostics – Tripath, Burlington, NC, USA) in a vial, and the pap smear was prepared for automatic Papanicolaou staining with the AutocyteThinPrep detection system (BD Diagnostics – Tripath). Final diagnoses were made by the cell room physicians according to the new terminologies of The Bethesda System (TBS) introduced in 2001[17].

HR-HPV DNA testing

Cervical samples for HR-HPV DNA testing [18,19] were obtained during cytological examinations in which cells were collected from the cervix using an endocervical brush as described previously. The brush head was put into a small tube of CytoRich Preservative solution (BD Diagnostics – Tripath). The Hybrid Capture 2 (HC2) High-Risk HPV DNA kit (Digene, Gaithersburg, MD, USA) was used to detect HPV DNA of 13 high-risk types (HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68). HPV DNA levels ≥1.0 pg/ml were deemed to be positive.

Colposcopy and histology

Colposcopists had access to the patients' cytology results and HPV status. Suspicious areas of the cervix identified in colposcopy were biopsied. Samples were evaluated histologically by pathologists who were not blind to the cytologic or HPV testing results but were reviewed by investigators who were blind to the patient's study group, original diagnosis, and cytologic and HPV testing results [20]. Abnormal biopsy criteria were defined according to TBS classification standard [21]. The study end-point was the presence of histologically confirmed severe CIN2+ lesions [20].

Statistical analysis

Data were checked for completeness and then entered into a Microsoft Excel 2003 spread sheet. Statistical analysis was carried out using SPSS 17.0 software. Comparisons of categorical responses were evaluated using the Chi-square test. A P value < 0.05 was considered to indicate statistical significance.

Results

Basic characteristics of case and control group

Basic characteristics (age of menarche, gravidity, parity, number of sexual partners, and proportion of menopause, etc.) of the cases and controls are shown in Table 1. No statistical difference was found in those variables between the two groups ($\chi^2 = 0.000$, $P > 0.05$).

Comparison of HR-HPV positive ratio between case and control groups

The overall HR-HPV infection rate in normal LCT patients is 35% (761/2170). In the control group, 15% (163/1085) of women were HR-HPV positive, while 55% (598/1085) of women in case group were HR-HPV positive. Thus, the HR-HPV positive ratio of the case group was significantly higher than that of the control group ($\chi^2 = 382.950$, $P = 0.000$).

Comparison of CIN2+ incidences in HR-HPV positive patients in case and control groups

All patients who had HR-HPV positive results in case group and control groups underwent colposcopy and suspicious areas were