Detection of human papillomavirus type 16 and 18 by PCR in patients with cervical neoplasia

Choong-Hak Park, M.D.¹, Jae-Kyoung Kim, Ph.D.²

¹Department of Obstetrics and Gynecology, Dankook University College of Medicine; ²Department of Medical Science of Diagnostic Test, Dankook University Hospital, Dankook University College of Medicine, Cheonan, Korea

Objective: The purpose of this study was to evaluate the detection rate of human papillomavirus (HPV) DNA Test (type 16 and 18) and to investigate the clinical significance of HPV DNA test in patients with cervical neoplasia.

Methods: Of the 708 patients aged 21–83 years who had undergone both conventional Papanicolaou cervical cytologic test and HPV DNA test by polymerase chain reaction, 383 cases underwent histologic diagnoses.

Results: Of the 708 cytologic diagnoses, there were 11 positive HPV DNA test diagnoses in squamous cell carcinoma (SCC), 41 in high-grade squamous intraepithelial lesion (HSIL), 20 in low-grade squamous intraepithelial lesion (LSIL), 41 in atypical squamous cells (ASC), and 86 in negative cytology. Of the 383 histologic diagnoses, there were 24 positive HPV DNA test diagnoses in SCC, 42 in cervical intraepithelial neoplasia (CIN) 3, 12 in CIN 2, 12 in CIN 1, 7 in atypical change, and 45 in negative histology. Of the 239 patients with negative HPV DNA test, 28.5% cases showed histologic diagnoses of CIN 1 or worse lesion. Of the 46 patients with negative cytology and positive HPV DNA test, 50.0% cases showed histologic diagnoses of CIN 1 or worse lesion. Pap cytology revealed sensitivity of 72.5%, specificity of 66.4%, and false negative rate of 27.5%, whereas HPV DNA test showed 57.5%, 76.7%, and 42.5%, respectively.

Conclusion: This study confirmed that the primary standard Pap cytology and HPV DNA test were adjunctive. Also this study showed that physicians always should not overrate Pap cytology or HPV DNA test in managing the patient with cervical neoplasia. Combined test was a very effective diagnostic method for detecting cervical neoplasia.

Key Words: Cervical neoplasia, HPV DNA test, Pap cytology, PCR

Cervical cancer is the second most common cancer among women worldwide and is the primary cause of cancer-related deaths in women in developing countries. Of the estimated 500,000 annual incident cases worldwide and the 250,000 deaths attributed to cervical cancer, over 80% occur in low-resource countries.¹² In developing countries, where cervical cancer accounts for 15% of female cancers, with a risk before
age 65 of 1.5%, while in developed countries it accounts for only 3.6% of new cancers, with a cumulative risk (age, 0~64) of 0.8%. The highest incidence rates are observed in sub-Saharan Africa, Melanesia, Latin America and the Caribbean, South-Central Asia, and South East Asia.

Traditional cervical screening methods are conventional Papanicolaou smear cytology and the pelvic examination. Since Dr. George Papanicolaou introduced this test for cervical cancer in 1939, the mortality rate for cervical squamous cell carcinoma in the United States decreased by 70~75% between 1955 and 1992. But unfortunately, this method contains numerous inherent opportunities for error leading to an acceptably high false negative rate. 53~90% of total false negative errors are due to sampling and preparation rather than interpretation errors. In February 1999, a report from the Agency for Health Care Policy and Research in the US admitted that estimates of the sensitivity of conventional Papanicolau (Pap) screening are not as high as previously reported. The report mentioned that, based on the few studies that avoided severe biases, conventional Pap smear cytology showed sensitivity of 51% and specificity of 98%. Furthermore, the report stated that the conventional Pap test is more accurate when a high-grade squamous intraepithelial lesion (HSIL) threshold is used, with the goal of detecting a high-grade lesion, than when lower thresholds, such as a low-grade squamous intraepithelial lesion (LSIL) or atypical squamous cells of undetermined significance (ASCUS), are used, with the goal of detecting low or high-grade dysplasia. Dunton said that the future of the Pap smear may best be summed up by this statement: "The 'new paradigm' of cervical cancer screening could be a combination of the new technology enhancements—liquid-based sampling, computer-assisted screening, and reflex molecular testing."

The major risk factors for developing cervical cancer include early age of marriage or sexual exposure, multiplicity of sexual partners, low socio-economic status, smoking, oral contraceptives and multiparity. Sexual behavior has been linked to cervical neoplasia. Recent epidemiological studies showed that cervical cancer is the result of the process that is initiated by infection of the genital tract with specific types of high risk human papillomaviruses (HR-HPVs). Genital HPV types are divided into those of low and high oncogenic risk. The most representative of these low risk is HPV 6 and 11 and the most representative of the high risk types are HPV 16, 18, 31, and 45. Low risk HPVs cause benign genital warts and have no oncogenic potential. By contrast, high risk HPVs are the causative agents of cervical cancer and its intraepithelial precursors, HPVs 16, 18, 31, 35, 39, 45, 51, 52, 56, 58, 59, and 68 account for about 93% of infections in high grade cervical intraepithelial neoplasias (CINs) and cancer. HPV 16 and HPV 18 are the HPV types most commonly identified in neoplasias.

More than 99% of cervical cancers contain one or more of the approximately 15 HPV genotypes that have been associated with the development of cervical cancer. As approximately 50~60% of these cancers contain HPV 16, and another 10~20% contain HPV 18. Persistent infection with high-risk HPV types, especially 16 and 18, is strongly predictive of cervical neoplasia and cancer.

The purpose of this study was to evaluate the detection rate of HPV DNA Test (type 16 and 18) and to investigate the clinical significance of HPV DNA test in patients with cervical neoplasia.

**Materials and Methods**

1. Study design

This university hospital-based clinical study was performed in the outpatient clinic of the Department of Obstetrics and Gynecology at Dankook University.