When to Perform HPV Testing?

Dr. Keith Wing-kit LO

MBBS, MD, FRCOG, FHKCOG, FHKAM(O&G)
Private Gynaecological Oncologist

Introduction

Almost half a million women develop cervical cancer every year; more than half of them die as a result of their conditions. It is the third most common female malignancy ranking after breast and colorectal cancers in the year 2008. After several decades of intensive research, there are now strong evidences to suggest that persistent infection with the oncogenic human papillomavirus (HPV) is a necessary cause of cervical cancer. The oncogenic virus works by triggering alterations in the cervical cells, which can lead to the development of cervical intraepithelial neoplasia (CIN) and subsequent progression to cancer. HPV infection is most common in young, sexually active populations, and more than 50% of all sexually active populations regardless of symptoms are infected at some point during their lives. Although prevalence varies among countries, it reaches a peak of more than 20% among women aged 20-24, with a subsequent decline to approximately 3% among women aged 30 or more. Most HPV infections in young females are transient and have little long-term significance. Up to 90% of the infections are cleared up within 2 years. However, when the infection with oncogenic HPV persists, a minority develops into precancerous lesions, which can progress to invasive cancer. This process usually takes more than 10 years, providing a long window period for detection and treatment of the precancerous lesion. Progression to invasive cervical cancer can almost always be prevented when standard prevention strategies are applied. The prevention programmes generally have relied on cytological testing using cervical smears which resulted in a 75% decline in the death rate. The recognition of the obligatory role of oncogenic HPV in the development of cervical cancer has led to not only the development of HPV vaccines, but also the change in cervical cancer screening strategies with the incorporation of HPV testing. Epidemiological surveys of HPV prevalence, natural history studies of HPV infection and cross-sectional studies of HPV positivity in pathological specimens have led to 3 important conclusions: 1) HPV infection is detected in 99.7% of cervical cancers; 2) Persistent oncogenic HPV infection is necessary for the development of invasive cervical cancer; and 3) The negative predictive value of an HPV testing is high, especially in combination with a normal cervical smear result (>99%). A woman’s oncogenic HPV status have important clinical significance and HPV testing is therefore discussed in the context of triage, primary screening and as a test of cure.

Triage of Women with ASC-US

The first United States Food and Drug Administration (FDA)-approved indication for HPV testing is atypical squamous cells of undetermined significance (ASC-US), the most common abnormality diagnosed on cervical smear. The ASCUS-LSIL Triage Study (ALTS), a large sentinel study supported by the National Cancer Institute, demonstrated that most patients with ASC-US do not have any underlying CIN lesion and only about 15% of patients will have high-grade CIN. The data also confirmed that “reflex” HPV testing was beneficial in triaging these patients. The American Society for Colposcopy and Cervical Pathology (ASCCP) recommends women with ASC-US on smear and a positive HPV testing should be referred directly to colposcopy because these patients are at risk of having high-grade CIN. Women with ASC-US on smear and a negative HPV testing are not at risk for a high-grade CIN lesion and can be managed with repeat smears in 12 months. According to ALTS data, the ASCCP also advises women with ASC-H and LSIL should be directly referred for colposcopy without HPV testing as most of these women were found to be HPV positive and at risk for high-grade CIN. It is now understood that the frequency of HPV is significantly higher in adolescents compared to women 21 years of age or older. The incidence of cervical cancer in younger women is also extremely low. The ASCCP has addressed this issue and recommends that HPV testing should not be performed in women 20 years of age or younger with smear interpreted as ASC-US but rather to repeat the smear at 12 months. The patient should be referred to colposcopy only if the repeated smear shows a more severe finding.

Primary Screening with HPV Testing and Cytology

Since 99.7% of invasive cervical cancers worldwide contain oncogenic HPV, some researchers recommend that HPV testing should be done together with routine cervical screening. It was thought that by using both tests, patients of CIN missed by smear would be detected by HPV testing, thereby providing a more accurate screening result. The ASCCP recommendations suggest using HPV testing as a primary cervical cancer screening in conjunction with traditional smear in women 30 years and older; this is the other FDA-approved indication for the HPV testing. In women 30 years of age or older the prevalence of oncogenic HPV infection is relatively low. With this relatively
low prevalence rate, the use of HPV testing becomes useful to distinguish those who have oncogenic HPV infection from those without and to develop appropriate management strategies. But, given the high prevalence of HPV in women younger than 30 years, routine HPV testing is not recommended as it would cause undue alarm to HPV carriers, more unnecessary follow-up testing, high number of referrals for colposcopy and treatment\textsuperscript{14}. Combined smear and HPV testing has been proven effective in large clinical trials. It increased the sensitivity of detecting high-grade CIN from 60% to 95\%\textsuperscript{14}. Based on these data, the ASCCP consensus recommendation for management of women 30 years of age or older with a negative smear and a positive HPV testing is to return the patient for additional screening and repeat both tests at 12 months. If she shows the same pair of test results after additional screening, she should be referred for colposcopy. When a woman aged 30 or older has a negative smear and a negative HPV testing, she can return for screening in 3 years.

Management of Women with Colposcopically Confirmed Low-grade CIN

ASCCP guidelines do not recommend treating low-grade CIN confirmed by colposcopy and guided biopsy. However, the likelihood of progression to high-grade CIN in a subset of patients with persistent HPV infection increases each year. Therefore, close monitoring of patients with a low-grade CIN lesion is imperative. Suggested strategies include repeat smear every 6 months, with repeat colposcopy if the smear result is positive, and repeat HPV testing in 12 months, with repeat colposcopy if HPV testing is positive.

Post-treatment Follow-up of High-grade CIN

High-grade CIN will recur in about 10\% of patients treated for the disease\textsuperscript{15}. Furthermore, approximately 0.8\% patients treated for high-grade CIN will develop invasive cancer\textsuperscript{16}. Therefore, a close monitoring is mandated for these patients. Multiple large retrospective and prospective randomised studies have proven the association between the presence of oncogenic HPV at follow-up and the increased risk of developing recurrent disease. Thus, HPV testing has been used for follow-up after treatment for high-grade CIN and appears more accurate than smear alone. Persistence or clearance of the oncogenic HPV infection has proven to be a significant early marker, independent from other risk factors, both for failure or cure after treatment\textsuperscript{17,18}. ASCCP guidelines recommend smears every 6 months, either with or without colposcopy, for these patients. Another option is HPV testing at 6 to 12 months with referral to colposcopy if the HPV test results are positive.

Conclusions

A major advance in cervical screening is HPV testing, which makes identification of HPV infections readily available within the clinical setting. Despite the expectation of incorporating this test into several cervical cancer screening algorithms, data from clinical trials demonstrate only two specific instances in which HPV testing is beneficial: 1) Reflex HPV testing in women with ASC-US and 2) as an adjunct to cervical smear in women older than 30 years. These two indications allow triaging of only women at high risk of developing cervical cancer to colposcopy.

References