Transitioning from HPV 101 to HPV 202

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Although it has taken well over a decade to gain widespread utilization, high-risk HPV (hrHPV) testing is now a major component of cervical cancer screening and management. Originally hrHPV testing was incorporated as a triage test for women with equivocal or atypical squamous cells of uncertain significance cytology based on recommendations from a consensus conference sponsored by the American Society of Colposcopy and Cervical Pathology.[1]

Shortly thereafter, interim guidance on cotesting (cytology and hrHPV testing together) as a screening strategy was introduced and is now preferred and recommended by the US Preventive Services Task Force and numerous professional societies.[2-4] In April 2014, the Food and Drug Administration (FDA) approved a human papillomavirus (HPV) test (with reflex cytology) for primary screening for cervical cancer starting at 25 years of age, and interim guidance was subsequently published to educate providers on this specific strategy.[5]

Current FDA-approved hrHPV testing detects 13 or 14 high-risk types of HPV. Epidemiologically, these types are associated with cervical cancer, but not all types carry the same risk. A seminal paper by Khan et al,[6] from Kaiser Permanente in Portland, OR, demonstrated this clearly: at 10 years of follow-up, the cumulative incidence rates of cervical intraepithelial neoplasia (CIN)-3 in women who were HPV-16 positive and HPV-18 positive at enrollment were 17% and 14%, respectively.

In women who were hrHPV positive but negative for types 16 and 18, the rate was only 3% (and <1% in women who were hrHPV negative).[6] These findings have been subsequently corroborated including a follow-up study from Portland Kaiser, a prospective cohort study from Denmark, and a large FDA registration study conducted in the United States evaluating the Roche Cobas 4800 HPV test.[7-9]

Additionally, not only do specific genotypes put women at greater risk of CIN3+, but persistent infection, particularly with type 16, has been shown to be perhaps one of the most important epidemiological and clinically relevant risk factors.[8,10] Long-term follow-up from the Swedescreen study only further supports this finding.[11] One hundred women, who were cytologically normal yet persistently positive HPV, were followed up for more than 13 years, with repeat cytology, HPV testing, and colposcopy if women were persistently positive for HPV.

The findings from this study are clinically significant and not subtle: all women who were followed up and had HPV persistence developed CIN2+, yet there were no women who developed CIN2+ when they cleared their HPV infection. Most importantly, type 16 conferred the highest risk for CIN2+ and CIN3+ (68% and 56%, respectively) followed by types 18, 31, 33, and 45. The vast majority of these cases occurred within 6 years of follow-up.

The present article is important from several perspectives. Elfgren et al[11] have demonstrated not only the importance of the persistence of HPV in the risk of development of CIN2+ but also have contributed to our knowledge regarding the increased risk with specific types of HPV, specifically type 16 and 18.

The future of screening and management will rely on the identification of patients who have the highest risk for developing CIN 2+ and, when appropriate, aggressively treating those at highest risk. There are many known risk factors for the development of CIN such as HPV status, persistence of HPV, known history of CIN, smoking, and HPV vaccine status, and it has become evident that HPV persistence is perhaps the most important risk factor. The challenge for future cervical cancer prevention will be to clarify the most important combination of risk factors that place a patient at greatest risk and developing tools for clinicians to identify those at highest risk.

Although present treatment guidelines do not specifically stratify treatment and follow-up based on the presence of certain genotypes, it is perhaps time to seriously consider this: it is time to graduate to greater utilization of type-specific testing. As an example, this could involve treating an individual based entirely on HPV persistence despite having normal cytology.

Scientific knowledge regarding the role of HPV has evolved immensely over the last 25 years. This is only the beginning of further refinement of the management of women at risk for cervical cancer. The development of new biomarkers, such as DNA methylation patterns and p16 staining, demonstrate promise in identifying individuals who may be at increased risk for the development of CIN3 and cervical cancer.[12,13] Gage J et al[14] have demonstrated that within 2 large health care systems that the risk for development of cervical precancer based on screening test are consistent: "Reassuringly, screening and treatment algorithms based on cumulative

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risks of precancer or worse can apparently be applied across US settings."

Clinicians who screen women for cervical cancer will have access to a variety of screening tests, including cytology, HPV testing with specific typing, and emerging biomarkers. The ultimate goal of these tests is to improve our ability to risk stratify individuals that require immediate intervention from those who can be monitored with a less costly and less intrusive strategy.

The increased uptake of HPV vaccination will clearly alter the future of screening and management guidelines.

The American Society of Colposcopy and Cervical Pathology has collaborated with numerous national organizations to provide screening and management guidelines that have defined best practice for the last 20 years. Future guidelines will be risk based and more individualized with biomarkers playing an ever-increasing role. Clinicians will need more advanced tools to interpret test results and appropriately assess the risk of an individual patient. Smart phone applications and electronic medical record tools will be essential to the clinician performing cervical cancer screening and management in the near future. Increased precision comes at the price of more complexity, but with the right tools and programs, it is still possible to simplify and streamline decision making. ■

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