Cervical Cancer Screening—Markers of Cervical Carcinogenesis
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It is common when interpreting cervical biopsies to have discrepancies about which lesions are simply viral infections or benign mimickers (eg, atrophy, tangential sectioning, and benign metaplasia) versus those that truly represent neoplastic or precancerous lesions having the potential to go on to invasive carcinoma. It has been proposed that markers specific for real neoplastic disease could be utilized to improve inter-observer variability and accuracy of the final diagnosis as well as to increase the detection sensitivity when screening patients.1

High-risk human papillomavirus (hrHPV) is a common sexually transmitted infection, and, though comparatively rare, a study has shown this infection as an initiating event in the progression to dysplasia (precancer) and invasive carcinomas, particularly with HPV types 16 and 18.2 Therefore, assays for hrHPV are highly sensitive for the detection of high-grade disease. Unfortunately, these tests lack specificity in determining whether the presence of hrHPV represents a common, transient, and benign infection or if it is associated with a true precancer. Current management guidelines use hrHPV status as a method to triage equivocal Pap tests and as primary screening, in some circumstances.3 Once hrHPV has been detected, further clinical interventions may be performed, such as colposcopy or increased surveillance, respectively.

Research has shown that other markers have higher positive predictive values (PPV) for true precancerous lesions, and therefore the use of these markers may be helpful in more accurately defining risk in the hrHPV positive population or acting as potential stand-alone replacements. Although data in initial studies is promising, at present none of these markers have yet achieved FDA approval.

Markers that pathologists may consider using for the above-mentioned applications include those associated with the abnormal cell cycle events that take place when hrHPV-transforming genes $E6$ and $E7$ alter normal p53 and pRb host tumor suppressor gene function, respectively. Marker p16, topoisomerase II-α, minichromosome maintenance proteins (MCM), along with the proliferation marker Ki-67, have been the widely shown to effectively identify cells and histologic lesions of high-grade dysplasia. Benign processes, including transient HPV infections, show different staining patterns than high-grade precancers.

Other molecular events have been associated with high-grade processes and may also be useful for discrimination as well as prognosis. Transformation from a benign to a precancerous lesion is highly associated with activation of the gene for telomerase. This activation is associated with gene amplification of the 3q26 locus, which is detectable by immunohistochemical studies or fluorescence in situ hybridization (FISH).4 Research suggests that if amplifications are not identified, there is little risk of association with, or progression to, cancer.5
The L1 HPV viral capsid protein is present during times of replication and its identification is generally indicative of a proliferative, but benign, lesion. High-grade lesions are most commonly associated with the inability of HPV to replicate. Therefore, L1 detection, especially with the absence of other transformation markers, has significant predictive value in ruling out a precancer.Opposite to L1 protein expression in benign lesions, the transcription of mRNA of the oncogenic components of hrHPV, namely the $E6$ and $E7$ genes, has been shown to indicate a higher risk of cancerous transformation, and it has therefore been touted as another potential marker.

There can be variability in the diagnosis of cervical lesions based on histological and cytological findings. A series of promising markers, linked to our emerging understanding of the cervical carcinogenesis sequence, can help pathologists provide clinicians with higher levels of accuracy in the evaluation of patient specimens and better risk assessments, both of which will ultimately drive better patient management and, hence, better outcomes.

References


