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HPV testing in cervical screening

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High-risk human papillomavirus (hrHPV) bearing cervical intraepithelial neoplasia (CIN) is considered, as the real precursor lesion of cervical cancer and persistence of an hrHPV infection is necessary for the progression to cervical cancer. This knowledge warrants the use of hrHPV testing as an adjunct to cervical cytology in population-based screening programmes and for monitoring therapy efficacy of high-grade CIN lesions. Replacement of cytology by hrHPV testing altogether is considered, but for this to be (cost-) effective, accurate information about the specificity of the hrHPV test is required. Additional test systems that can be used to stratify women with a positive hrHPV test are HPV genotyping, viral load analysis and hrHPV mRNA analysis. The need for HPV genotyping of cervical smears is illustrated by the increased risk for high-grade cervical lesions associated with HPV types 16 and 18. In particular, for women who have normal but persistently (>1 year) HPV18-positive smears, endocervical curettage is suggested (evidently considering the age and possible future pregnancies of the respective woman) because HPV18 is associated with glandular lesions in the cervix, which are difficult to detect by cytology.

Key words: cervical cancer; cervical intraepithelial neoplasia; cytology; HPV; human papillomavirus; population-based screening.

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High-risk human papillomavirus (hrHPV) bearing cervical intraepithelial neoplasia (CIN) is now considered as the real precursor lesion of cervical cancer and persistence of an hrHPV infection is necessary for the progression to cervical cancer.[1] This well-established knowledge has led to the development of diagnostic applications for hrHPV testing that will be discussed in this chapter. In addition, we will elaborate on more recent findings in hrHPV research and possible improvements of hrHPV diagnostics derived from these.

HRHPV TESTS CURRENTLY IN USE

The most widely used hrHPV testing methods include the commercially available Hybrid Capture 2 (hc2)[2] and polymerase chain reaction (PCR)-based methods. Hc2 detects 13 genital hrHPV types by a mixture of full-length RNA probes. Hybridization of one or more of the probes to hrHPV DNA present in heat-alkaline-denatured clinical samples is detected by peroxidase-labelled antibodies that recognize the RNA/DNA hybrid and are visualized by chemiluminescence. Some cross-reactivity of the hc2 probes with HPV types not represented in the probe mix, including some non-oncogenic HPVs, has been described.[3] When cervical scrapes have been collected in a medium supplied by the hc2 manufacturer, hc2 can be applied directly. Cervical scrapes collected in cytological preservation media require some adaptation before the hc2 test.

PCR-based methods frequently rely on the use of consensus or multiplex primers that amplify a broad spectrum of HPV types. Examples of the former are the MY09/11[4] and GP5+/6+[5] systems, an example of the latter is SPF10.[6] PCR products can be detected with a cocktail of type-specific probes, for example in an enzyme-immunoassay (EIA).[7] HPV typing can be done by, for example, reverse hybridization systems such as reverse line blotting (RLB)[8,4] or line-probe assay (LiPa).[9] In addition, real-time PCR methods have been developed for quantitation of HPV DNA[10,11], but these have a low multiplicity for different hrHPV types and are therefore, not suitable as a high-throughput primary screening tool. PCR methods can be applied to cervical scrapes collected in phosphate-buffered saline[1], in cytological preservation media (generally after extraction of DNA) and even on archival smears.[12]

HRHPV TESTING AS AN ADJUNCT TO CERVICAL CYTOLOGY

The current screening protocols for cervical cancer are based on the ability to cytologically detect precursor lesions of cervical cancer (the 'Pap' test[13]). When identified in good time, these lesions can be treated successfully and with only minor side effects. However, the sensitivity and specificity of cytology are not optimal, resulting, respectively in missed cases of high-grade CIN and over-referral to the gynaecologist with many redundant follow-up smears for low-grade CIN. Given the causal relation between a persistent hrHPV infection and the development of high-grade CIN and cervical cancer, hrHPV testing has been advocated in addition to cytology. hrHPV testing is thought to improve the screening algorithms based on the detection of abnormal cervical cells for cervical cancer[14], the management of women with cytologically equivocal smears[15,16] and the management of women treated for high-grade CIN.[17]