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Chapter 9: Clinical applications of HPV testing: A summary of meta-analyses

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Abstract

Background: More than ever, clinicians need regularly updated reviews given the continuously increasing amount of new information regarding innovative cervical cancer prevention methods.
Material and methods: A summary is given from recently published meta-analyses on three possible clinical applications of human papillomavirus (HPV)-DNA testing: triage of women with equivocal or low-grade cytological abnormalities; prediction of the therapeutic outcome after treatment of cervical intraepithelial neoplasia (CIN) lesions, and last not but not least, primary screening for cervical cancer and pre-cancer.
Results: Consistent evidence is available indicating that HPV-triage with the Hybrid Capture-2 assay (HC2) is more accurate (significantly higher sensitivity, similar specificity) than repeat cytology to triage women with equivocal Pap smear results. When triaging women with low-grade squamous intraepithelial lesions (LSIL), a reflex HC2 test does not show a significantly higher sensitivity, but a significantly lower specificity compared to a repeat Pap smear. After treatment of cervical lesions, HPV testing easily detects (with higher sensitivity and not lower specificity) residual or recurrent CIN than follow-up cytology. Primary screening with HC2 generally detects 23% (95% confidence interval, CI: 13–23%) more CIN-2, CIN-3, or cancer compared to cytology at cut-off atypical squamous cells of undetermined significance (ASCUS) or LSIL, but is 6% (95% CI: 4–8%) less specific. By combined HPV and cytology screening, a further 4% (95% CI: 3–5%) more CIN-3 lesions can be identified but at the expense of a 7% (95% CI: 5–9%) loss in specificity, in comparison with isolated HC2 screening.
Conclusions: Sufficient evidence exists to recommend HPV testing in triage of women with atypical cytology and in surveillance after treatment of CIN lesions. In the United States, recently reviewed knowledge has resulted in the approval of combined cytology and HC2 primary screening in women older than 30 years. However, in Europe, cytology-based screening still remains the standard screening method. The European screening policy will be reviewed based on the longitudinal results of randomised population trials which are currently underway.

Keywords: HPV; Cervical cancer; Screening; Triage; Follow-up after treatment; Meta-analysis

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1. Introduction

The recognition of the strong causal relationship between persistent infection of the genital tract with high-risk HPV types and occurrence of cervical cancer [1] has resulted in the development of a series of HPV-DNA or -RNA detection systems. Detection of high-risk HPV-DNA is considered to be potentially useful in three clinical applications: first as a primary screening test, solely or in combination with a Pap smear to detect cervical cancer precursors; further as a triage test to select women showing minor cytological lesions in their Pap smears needing referral for diagnosis and treatment and, finally, as a follow-up test for women treated for high-grade intraepithelial lesion with local ablative or excisional therapy to predict cure or failure of treatment.

In this chapter, we will summarise and update recently conducted meta-analyses and systematic reviews which synthesise current knowledge on the performance of HPV-DNA testing in each of these three clinical applications.

2. Material and methods

2.1. Triage of cases with minor cytological abnormalities

A first meta-analysis [2,3] addressed the cross-sectional accuracy of HPV-DNA testing to triage women with an index smear showing atypical squamous cells of unspecified significance (ASCUS) or atypical glandular cells of unspecified significance (AGUS) where the purpose is to detect cervical intraepithelial neoplasia of grade II or worse (CIN-2+) confirmed by histology. Studies were included if the HC2 assay (cocktail of probes for 13 high-risk HPV types) was applied to women with a prior ASCUS result and if presence or absence of CIN was verified by colposcopy and subsequent biopsy and/or endocervical curettage when colposcopically indicated. From the ALTS (ASCUS/LSIL Triage Study), we used results from two of the three experimental arms: women randomised to immediate colposcopic verification and women randomised into the HPV-DNA testing arm, where colposcopy was restricted to women showing presence of high-risk HPV-DNA or showing high-grade squamous intraepithelial lesions (HSIL) on the repeat smear [4]. We computed sensitivity and specificity for two outcome thresholds, CIN-2 or worse (CIN2+) and CIN3+, based on the histological result of the biopsy and assuming that a negative colposcopic impression corresponds with absence of high-grade CIN. For studies, where the result of a repeat Pap smear was also documented, we assessed the ratio of the sensitivity and specificity of HPV testing relative to repeat cytology, using three different cytological cut-offs: ASCUS+, LSIL+ and HSIL+. Random effect models were used for meta-analytical pooling [5].

A similar second meta-analysis included studies fulfilling the same criteria but where women with cytological findings of LSIL were enrolled [6].

2.2. Follow-up after treatment of cervical intraepithelial neoplasia

In a third systematic review, we synthesised data on the ability of HPV testing to predict residual or recurrent CIN in women treated for high-grade cervical lesions [6]. Studies were included if the following conditions were fulfilled: (a) women were treated for CIN-2+ using local ablative or surgical procedures, (b) they were subsequently tested for HPV-DNA over varying times after treatment, (c) the histological status of the section margins were described and/or cytological follow-up results were available, and (d) the final eventual outcome, occurrence or absence of residual or recurrent CIN was documented.

2.3. Primary screening

In the final meta-analysis, the cross-sectional accuracy of HPV-DNA screening in asymptomatic women to identify cervical squamous or glandular intraepithelial neoplasia grade II, III or cancer was compared with cytological screening. Two types of study design were considered: concomitant testing with cervical cytology and HPV virology and randomised clinical trials where women were assigned to cytology, HPV testing or combined testing. We considered only studies where viral testing was done using the high-risk probe cocktail of the HC2 assay or a general PCR test system (with consensus primers GP5+/6+, degenerated primers MY09/011 or PGMY09/11 or, pU-1M/pU-2R) followed by identification of at least four oncogenic HPV types.

Often, only women being cytologically or virologically positive were submitted to gold standard verification with colposcopy and colposcopically directed punch biopsies, excision biopsy or endocervical curettage. This design includes a serious risk of verification or work-up bias, yielding an overestimation of the absolute sensitivity and an underestimation of the specificity. In certain studies, a random sample of screen negative women, in addition to screen-positive women, was referred for colposcopy, allowing adjustment for verification bias. In a few studies, all screened women were colposcopied. We assessed absolute sensitivity and specificity for underlying CIN-2+ and CIN-3+, for HC2 and PCR separately from studies with concomitant testing.

We also pooled the relative sensitivity and specificity of HPV testing compared to cytology and of the combination of both cytology and HPV testing compared to each test alone. The evaluation of the relative sensitivity offers the advantage that all types of studies – involving concomitant testing with complete or incomplete verification and randomised trials – can be included.