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Review

Evidence Regarding Human Papillomavirus Testing in Secondary Prevention of Cervical Cancer

Marc Arbyn[a,b,*], Guglielmo Ronco[c], Ahti Anttila[d], Chris J.L.M. Meijer[e], Mario Poljak[f], Gina Ogilvie[g], George Koliopoulos[h], Pontus Naucler[i], Rengaswamy Sankaranarayanan[j], Julian Peto[k]

[a] *Unit of Cancer Epidemiology, Scientific Institute of Public Health, Brussels, Belgium*
[b] *European Cancer Network, IARC, Lyon, France*
[c] *Unit of Cancer Epidemiology, Centro per la prevenzione Oncologica, Turin, Italy*
[d] *Mass Screening Registry, Finnish Cancer Registry, Helsinki, Finland*
[e] *Department of Pathology, VU University Medical Centre, Amsterdam, The Netherlands*
[f] *Institute of Microbiology and Immunology, Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia*
[g] *Division of STI/HIV Prevention and Control, BC Centre for Disease Control, Vancouver, Canada*
[h] *Department of Obstetrics and Gynecology, University Hospital of Ioannina, Ioannina, Greece*
[i] *Department of Infectious Diseases; Department of Microbiology, Tumor & Cell Biology, Karolinska University Hospital, Stockholm, Sweden*
[j] *Screening Group, International Agency for Research on Cancer, Lyon, France*
[k] *London School of Hygiene and Tropical Medicine, London, UK*

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ABSTRACT

More than ever, clinicians need regularly updated reviews given the continuously increasing amount of new information regarding innovative cervical cancer prevention methods. A summary is given from recent meta-analyses and systematic reviews on 3 possible clinical applications of human papillomavirus (HPV) testing: triage of women with equivocal or low-grade cytologic 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. Consistent evidence is available indicating that HPV-triage with the Hybrid Capture® 2 assay (Qiagen Gaithersburg, Inc., MD, USA [previously Digene Corp.] (HC2) is more accurate (higher sensitivity, similar specificity) than repeat cytology to triage women with equivocal Pap smear results. Several other tests show at least similar accuracy but mRNA testing with the APTIMA® (Gen-Probe Inc., San Diego, CA, USA) test is similarly sensitive but more specific compared to HC2. In triage of low-grade squamous intraepithelial lesions (LSIL), HC2 is more sensitive but its specificity is substantially lower compared to repeat cytology. The APTIMA® test is more specific than HC2 without showing a loss in sensitivity. Identification of DNA of HPV types 16 and/or 18, or RNA from the five most carcinogenic HPV types allow selecting women at highest risk for CIN3+ but the sensitivity and negative predictive value of these markers are lower than full-range high-risk HPV (hrHPV) testing. After conservative treatment of cervical pre-cancer, HPV testing picks up more quickly, with higher sensitivity and not lower specificity, residual or recurrent high-grade CIN than follow-up cytology. Primary screening for hrHPV generally detects more CIN2, CIN3 or cancer compared to cytology at cut-off atypical squamous cells of undetermined significance (ASC-US) or LSIL, but is less specific. Combined HPV and cytology screening provides a further small gain in sensitivity at the expense of a considerable loss in specificity if positive by either test is referred to colposcopy, in comparison with HPV testing only. Randomised trials and follow-up of cohort studies consistently demonstrate a significantly lower cumulative incidence of CIN3+ and even of cancer, in women aged 30 years or older, who were at enrollment hrHPV DNA negative compared to those who were cytologically negative. The difference in cumulative risk of CIN3+ or cancer for double negative (cytology & HPV) versus only HPV-negative women is small. HC2, GP5+/6+ PCR (polymerase chain reaction), cobas® 4800 PCR (Roche Molecular Systems Inc., Alameda, CA, USA) and Real Time PCR (Abbott Molecular, Des Plaines, IL, USA) can be considered as clinically validated for use in primary screening. The loss in specificity associated with primary HPV-based screening can be compensated by appropriate algorithms involving reflex cytology and/or HPV genotyping for HPV16 or 18. There exists a substantial evidence base to support that HPV testing is advantageous both in triage of women with equivocal abnormal cytology, in surveillance after treatment of CIN lesions and in primary screening of women aged 30 years or older. However, the possible advantages offered by HPV-based screening require a well organised program with good compliance with screening and triage policies.

* Corresponding author. Tel.: +0032 2 6425021; fax: +0032 2 6425410.
E-mail address: marc.arbyn@wiv-isp.be (M. Arbyn).

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1. Introduction

The recognition of the strong causal relationship between persistent cervical infection with high-risk human papillomavirus (HPV) types and occurrence of cervical cancer [1] has led to the development of a series of HPV DNA or RNA tests. Detection of high-risk (hr) HPV DNA is considered to be potentially useful in three clinical applications: (1) as a triage test to select women, whose cytology is equivocal or mildly abnormal, needing referral for diagnosis and treatment; (2) as a follow-up test for women treated for high-grade cervical intraepithelial neoplasia (CIN) with local ablative or excisional therapy to predict cure or failure of treatment; and (3) as a primary screening test, solely or in combination with cervical cytology to detect cervical precancer and to rule it out in the predominantly healthy population.

In this chapter, we will update and extend previously conducted meta-analyses and systematic reviews which synthesize current knowledge on the performance of HPV testing in each of these three clinical applications. In particular, attention is given on the evidence regarding HPV-based primary screening as a new paradigm of cervical cancer prevention and on the identification of HPV assays, which fulfil minimal requirements, allowing use in primary cervical cancer screening.

2. Material and methods

For the purpose of this paper, previous meta-analyses on the absolute and relative performance of HPV- and cytology-based testing of cervical specimens were extended and updated [2]. New HPV-related assays, in addition to the Hybrid Capture® 2 (Qiagen Gaithersburg, Inc., MD, USA [previously Digene Corp.] (HC2), were evaluated as well, including both other HPV DNA assays and E6/E7 mRNA essays. Three major clinical applications were distinguished: (1) triage of women with a cervical cytology of atypical squamous cells of undetermined significance (ASC-US) or low-grade squamous intraepithelial lesions (LSIL); (2) follow-up of women after treatment of a high-grade lesion with the purpose to predict cure or failure; and (3) primary cervical cancer screening. The search strings, consulted bibliographic sources and the last date of literature retrieval are presented in Appendix 1 (web table).

2.1. Triage of women with minor abnormal cytology

The current review evaluated the accuracy of the HC2 assay for underlying CIN2+ and CIN3+ among women with ASC-US or LSIL cervical cytology. In studies where a repeat Pap smear was taken as well, the relative sensitivity and specificity of HC2 versus repeat cytology were evaluated, considering ASC-US or worse as a positive repeat cytology. Reports were included only when verification with a reference standard was available based on colposcopy followed by biopsies for all tested women. The outcome was based on the histology result, when available, accepting negative colposcopy, despite its known less-than-perfect sensitivity, as sufficient ascertainment for absence of the target disease. We also evaluated the accuracy of other HPV tests, as well as their relative accuracy compared to HC2.

2.2. Follow-up after treatment of high-grade CIN

Studies were selected if (1) women were treated for histologically-confirmed CIN2 or CIN3; (2) women had a cytology and HPV DNA test between 3 and 9 months after treatment; (3) there was follow-up during at least 18 months with colposcopy and biopsy for all women or in case of a positive HPV or cytology test. Treatment failure was defined as follow-up histologic diagnosis of CIN2+.

2.3. Primary screening

Criteria for inclusion of reports have been published previously [2,3]. Two types of study design were considered: (1) cross-sectional studies where women were submitted to concomitant testing with cervical cytology (conventional or liquid), a HPV DNA assay and, optionally, other screening tests and (2) randomised clinical trials where women were assigned to cytology, HPV testing or combined testing. In the assessment of absolute sensitivity and specificity, we distinguished three situations: (1) all cases were verified with a reference standard, (2) only screen test positive cases were verified and the assumption was made that none of the women being negative for all tests had underlying CIN2+ and (3) studies in which a random sample of women being negative for all tests was also submitted to verification. For the evaluation of relative sensitivity, we considered the ratio of absolute sensitivities including intra-arm comparisons of randomised trials with combined cytology and HPV testing and the ratio of the detection rates of CIN2+ from the inter-arm comparison of randomised controlled trials. Studies were selected only when the participating women were representative of the general population.

Particular attention was given to the pooling of published aggregated data regarding the baseline and longitudinal outcomes from randomised trials, as well as the cumulative risk for CIN3 and cancer according to the baseline HPV and cytology status observed from non-randomised cohorts.

The review also addressed the question of which high-risk (hrHPV) DNA assays fulfill clinical equivalency criteria recently established to allow claims for use in cervical cancer screening. The candidate test should demonstrate a relative sensitivity and specificity compared to a validated hrHPV DNA test (HC2 or GP5+/6+ polymerase chain reaction [PCR]) of $\geq$0.90 and $\geq$0.98, respectively [4]. A representative set of samples (minimally 60 CIN2+ cases, 800 $\leq$CIN1 cases) derived from a population-based screening cohort should be selected, as specified by Meijer CJLM *et al.* [4]. Moreover, a high reproducibility (lower 95% confidence bound $\geq$87%) should be reached.

3. Results

3.1. Triage of women with minor abnormal cytology

3.1.1. ASC-US

In the 39 retrieved studies (web table liststudies.xls-ASCUStriage), the pooled sensitivity of HC2 was 90.4% (95% confidence interval [CI]: 88.1–92.3%) and 93.7% (95% CI: 90.4–95.9%), whereas the pooled specificity was 58.3% (95% CI: 53.6–62.9%) and 52.3% (95% CI: 45.7–58.7%) for predicting presence or absence of CIN2+ or CIN3+, respectively (Table 1). In 10 of the 39 studies, a repeat smear was also taken. In these 10