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Original Research Report

Clinical utility of HPV–DNA detection: Triage of minor cervical lesions, follow-up of women treated for high-grade CIN: An update of pooled evidence

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Abstract

Objective. Human papilloma virus (HPV) testing and repeat cytology are both proposed as methods to triage women with minor cytological cervical lesions. By triage, those women can be identified who need referral for diagnostic exploration with colposcopy and/or biopsy.

Methods. We conducted meta-analyses of reported studies on the accuracy to detect high-grade cervical intra-epithelial neoplasia or worse disease (CIN2+) in women with ASCUS or LSIL. We also performed meta-analyses to examine the best predictor of recurrence of CIN after treatment for CIN2 or CIN3.

Results. We found that HPV testing using the Hybrid Capture II test is more effective (more sensitive, equally specific) than cytology for the triage of patients with ASCUS Pap smears. Because of the high rate of HPV positivity, this is not the case for patients with LSIL.

Studies concerning post-treatment follow-up were heterogeneous. In general, HPV testing performed better than follow-up cytology to predict success or failure of treatment (significantly higher sensitivity, not significantly lower specificity).

Conclusions. Overall, in comparison with follow-up cytology, HPV DNA testing is more sensitive and equally specific for triage of ASCUS cases and for predicting recurrence of CIN in women treated for high-grade CIN.

Keywords: Cervical cancer; Human papillomavirus; HPV DNA; Triage; ASCUS; LSIL; Follow-up after treatment; Meta-analysis

Introduction

The purpose of this study was to explore emerging directions in the prevention of cervical cancer by comparing efficacy and accuracy of new and conventional methods. The recognition of the strong causal relationship between persistent infection of the genital tract with high-risk human papilloma virus types and the occurrence of cervical cancer [1,2] has resulted in experimental and industrial development of HPV detection systems. Detection of high-risk HPVDNA 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; second as a triage test to select women showing minor cytological lesions in their Pap smears who need referral for diagnosis and treatment; and third as a follow-up test for women who have been treated for high-grade intra-epithelial lesion with local ablative or excisional therapy to predict cure or failure of treatment [3].

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In two recent reviews, we synthesized available knowledge concerning the performance of HPV–DNA testing relative to cytological smears. This was done for the last two indications derived from reports published until 2002 [4–7]. These projects guided our current efforts. Because of the emerging nature of research in this area, it is necessary to constantly update our understanding of current progress. In the present review, we extend the previous meta-analyses by appending new studies reported since the last 2 years.

Materials and methods

A systematic review combines similar studies in one particular area of research. By pooling together all of the studies, researchers can examine a much larger sample of relevant data. In certain conditions, a meta-analysis can produce a numerical figure from the systematic review, which is an estimate of the overall pooled outcome measure.

The first review targeted studies where women showed equivocal or low-grade cytological lesions. Patients in these studies were followed with the high-risk HPV–DNA testing probe of the hybrid capture II assay (HC2), or with repeat cytology. That review was further restricted to reported series where all women were submitted to gold standard verification, consisting of colposcopy and biopsy from colposcopically suspicious areas.

The considered threshold for disease was cervical intraepithelial neoplasia grade 2 or worse (CIN2+). Atypical squamous cells (ASCUS+) and a signal intensity corresponding with 1 pg HPV–DNA /ml were the respective cytological and virological cutoffs defining triage test positivity.

The second review sought to compare the accuracy of HPVDNA testing and follow-up cytology as instruments to predict the outcome of treatment. Occurrence of residual or recurrent CIN was considered treatment failure.

Table 1
Accuracy to detect CIN2 or worse (CIN2+) disease of triage in women with atypical squamous cells of unspecified significance (ASCUS) or low-grade cytological abnormality (LSIL) using the hybrid capture II assay

Study	TP	FN	FP	TN	Se	Sp	PPV	NPV	Test + rate	Prevalence disease
Triage of ASCUS										
Manos, 1999 [8]	58	7	326	582	0.892	0.641	0.151	0.988	0.395	0.067
Bergeron, 2000 [9]	10	2	38	61	0.833	0.616	0.208	0.968	0.432	0.108
Lin, 2000 [10]	27	0	12	35	1.000	0.745	0.692	1.000	0.527	0.365
Lytwyn, 2000 [11]	4	1	19	33	0.800	0.635	0.174	0.971	0.404	0.088
Shlay, 2000 [12]	14	1	47	133	0.933	0.739	0.230	0.993	0.313	0.077
Morin, 2001 [13]	17	2	88	253	0.895	0.742	0.162	0.992	0.292	0.053
Rebello, 2001 [14]	18	3	13	41	0.857	0.759	0.581	0.932	0.413	0.280
Solomon, 2001 [15]	256	11	1050	984	0.959	0.484	0.196	0.989	0.568	0.116
Zielinski, 2001 [16]	11	1	63	138	0.917	0.687	0.149	0.993	0.347	0.056
Kulasingam, 2002 [17]	23	3	115	129	0.885	0.529	0.167	0.977	0.511	0.096
Pambuccian, 2002 [18]	16	0	42	68	1.000	0.618	0.460	0.276	1.000	0.127
Pretorius, 2002 [19]	56	7	250	636	0.889	0.718	0.183	0.989	0.322	0.066
Guyot, 2003 [20]	1	0	11	11	1.000	0.500	0.083	1.000	0.522	0.043
Lonky, 2003 [21]	27	6	35	140	0.818	0.800	0.435	0.959	0.298	0.159
Wensveen, 2003 [22]	9	1	58	80	0.900	0.580	0.134	0.988	0.453	0.068
Dalla Palma, 2005 [23]	32	2	77	45	0.941	0.369	0.294	0.957	0.699	0.218
Pooled	579	47	2244	3369	0.940	0.624	0.223	0.989	0.447	0.103
Triage of LSIL										
Ferris, 1998 [24]	11	1	76	11	0.917	0.126	0.126	0.917	0.879	0.121
Bergeron, 2000 [9]	13	1	142	111	0.929	0.439	0.084	0.991	0.581	0.052
Lin, 2000 [10]	21	0	13	11	1.000	0.458	0.618	1.000	0.756	0.467
Lytwyn, 2000 [11]	3	0	20	7	1.000	0.259	0.130	1.000	0.767	0.100
Rebello, 2001 [14]	48	3	40	26	0.941	0.394	0.545	0.897	0.752	0.436
Zielinski, 2001 [16]	15	0	37	13	1.000	0.260	0.288	1.000	0.800	0.231
Kulasingam, 2002 [17]	20	0	84	21	1.000	0.200	0.192	1.000	0.832	0.160
Pretorius, 2002 [19]	56	3	160	64	0.949	0.286	0.259	0.955	0.763	0.208
Sherman, 2002 [25]	178	4	541	125	0.978	0.188	0.248	0.969	0.848	0.215
Guyot, 2003 [20]	28	1	52	29	0.966	0.358	0.350	0.967	0.727	0.264
Pooled	393	13	1165	418	0.972	0.288	0.273	0.981	0.772	0.199

The sensitivity (Se), specificity (Sp), positive (PPV) and negative predictive value (NPV), test positivity rate and prevalence of disease (CIN2+) are computed from the absolute number of true-positive (TP), false-negative (FN), false-positive (FP) and true-negative (TN) results. The pooled measures at the bottom are derived from random-effect meta-analytical models.