High-risk human papillomavirus testing versus cytology in predicting post-treatment disease in women treated for high-grade cervical disease: a systematic review and meta-analysis


CRD summary
This review concluded that the high-risk type human papillomavirus test should be included in post-treatment testing due to its higher sensitivity and similar specificity to cytology. Limitations of the included studies and analysis make the recommendation for the introduction into practice seem a little strong but the overall conclusion regarding relative accuracy seems appropriate.

Authors' objectives
To determine the test performance of testing for high-risk types of the human papillomavirus (hrHPV), cytology and co-testing (combined hrHPV testing and cytology) in predicting high-grade post-treatment disease (Cervical Intraepithelial Neoplasia (CIN) grade 2 or above).

Searching
PubMed, EMBASE, The Cochrane Library and WHO International Clinical Trials Registry were searched without language restrictions between 2003 and April 2011; search terms were reported. Reference lists of retrieved articles and relevant systematic reviews and meta-analyses were searched.

Study selection
Prospective and retrospective studies with at least 12 months follow-up that recruited women diagnosed as CIN grade 2 or 3 were eligible for inclusion. Diagnosis could be by conization (laser or cold-knife) or Large Loop Excision of the Transformation Zone procedure. Post-treatment surveillance had to use hrHPV testing, cytology or a combination of these at six months after treatment. Residual or recurrent high-grade disease (positive result) had to be defined as a histological diagnosis of CIN grade 2 or 3, adenocarcinoma in situ, adenocarcinoma or squamous cell carcinoma CIN grade 2 or over. The negative result had to be defined as either a histological confirmation of CIN grade zero or 1 or a repeat negative cytological test result.

Samples for cytology and hrHPV testing were collected six months after treatment. Participant ages ranged from 19 to 83 years. Prevalence of residual and recurrent CIN grade 2 or over ranged from 4.0% to 11.9%.

Two independent reviewers selected studies for the review; disagreements were resolved by consensus.

Assessment of study quality
Two independent reviewers assessed study quality using a modified 11-point QUADAS tool; blinding of interpreters of the index test and clinical review bias were not assessed and selection bias was added. Disagreements were resolved by consensus.

Data extraction
Two independent reviewers extracted data to construct 2x2 tables of test performance; study authors were contacted if data were not reported in the papers. Sensitivity, specificity and diagnostic odds ratio (DOR) were calculated, with 95% confidence intervals (CI).

Methods of synthesis
Pooled estimates of sensitivity, specificity and diagnostic odds ratio were calculated. Heterogeneity was assessed using the Cochran's $Q$ and $I^2$. Where Cochran's $Q$ was significant, studies were pooled using a random-effects model and otherwise a fixed-effect model was used. The Freeman-Tukey double arcsine transformation was applied. The 0.5 cell correction was used where zero cells were present. A bivariate regression model was used to investigate whether the type of hrHPV test explained between-study variance.

Results of the review
Nine studies met the inclusion criteria and eight provided data for the meta-analysis (1,705 participants, range 63 to 610; 1,513 women treated for CIN grade 2 or 3): seven studies were prospective and one was a case-control study. Most participants were followed-up for between 18 and 24 months (range six to 66 months).

All studies included a representative patient spectrum, used an appropriate reference standard, avoided incorporation bias, mentioned uninterpretable results and defined a positive test result of post-treatment disease as a histological finding of CIN grade 2 or above. A negative test result was verified by colposcopy in five studies and consecutive negative cytological smears in three. Differential verification bias was avoided in four studies. Most interpreters of the reference standard were blinded; two studies referred women for assessment on the basis of the hrHPV test. Half of the studies had no withdrawals to explain and the remaining studies dealt with this item appropriately. Only one study reported avoiding selection bias.

For cytological testing six months after treatment predicting post-treatment CIN lesions, the pooled sensitivity was 79% (95% CI 72% to 85%; I²=0%), specificity was 81% (95% CI 74% to 86%; I²=85.6%) and DOR was 13.81 (95% CI 9.17 to 20.80; I²=2.2%). For hrHPV type test the pooled sensitivity was 92% (95% CI 87% to 96%; I²=0.0%), specificity was 76% (95% CI 67% to 84%; I²=92.3%) and DOR was 34.68 (95% CI 18.87 to 63.73; I²=0%). For co-testing the pooled sensitivity was 95% (95% CI 91% to 98%; I²=0%), specificity was 67% (95% CI 60% to 74%; I²=85.2%) and DOR was 35.86 (95% CI 17.59 to 73.11; I²=0.0%). The type of hrHPV test did not explain between-study variance.

Authors' conclusions
The hrHPV test should be included in post-treatment testing six months after treatment because hrHPV testing had a higher sensitivity than cytology in detecting high-grade post-treatment disease and had a similar specificity.

CRD commentary
The authors addressed a clear research question with reproducible inclusion criteria. Several relevant sources were searched without language restrictions. There was no specific search for unpublished studies. Each stage of the review was conducted in duplicate, which reduced the risk of error and bias. Study quality was assessed using appropriate criteria and the results were reported in full. Pooled estimates of sensitivity and specificity were derived using standard frequentist meta-analytical techniques for seemingly heterogeneous studies. More robust analyses using receiver operating characteristic models are available from which these estimates could have been derived.

The authors acknowledged limitations of the evidence base that included the small number of studies and that the limited follow-up (two years) for which data were available from all studies precluded assessment of longer-term accuracy of the tests. Despite the limitations of the included studies and analysis, the sensitivity of the hrHPV test was consistently higher across the studies. Therefore, although the recommendation for the introduction into practice seems a little strong the overall conclusion regarding the relative accuracy of the two tests seems appropriate.

Implications of the review for practice and research
Practice: The authors stated that the review clearly indicated that post-treatment testing at six months should include hrHPV testing.

Research: The authors stated that more information, especially on long-term recurrence and cost-effectiveness, was needed to recommend a definite follow-up algorithm.

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Bibliographic details

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.