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[Diagnostic Test Accuracy Review]

Human papillomavirus testing versus repeat cytology for triage of minor cytological cervical lesions

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ABSTRACT

Background

Atypical squamous cells of undetermined significance (ASCUS) and low-grade squamous intra-epithelial lesions (LSIL) are minor lesions of the cervical epithelium, detectable by cytological examination of cells collected from the surface of the cervix of a woman.

Usually, women with ASCUS and LSIL do not have cervical (pre-) cancer, however a substantial proportion of them do have underlying high-grade cervical intra-epithelial neoplasia (CIN, grade 2 or 3) and so are at increased risk for developing cervical cancer. Therefore, accurate triage of women with ASCUS or LSIL is required to identify those who need further management.

This review evaluates two ways to triage women with ASCUS or LSIL: repeating the cytological test, and DNA testing for high-risk types of the human papillomavirus (hrHPV) - the main causal factor of cervical cancer.

Objectives

Main objective

To compare the accuracy of hrHPV testing with the Hybrid Capture 2 (HC2) assay against that of repeat cytology for detection of underlying cervical intraepithelial neoplasia of grade 2 or worse (CIN2+) or grade 3 or worse (CIN3+) in women with ASCUS or LSIL. For the HC2 assay, a positive result was defined as proposed by the manufacturer. For repeat cytology, different cut-offs were used to define positivity: Atypical squamous cells of undetermined significance or worse (ASCUS+), low-grade squamous intra-epithelial lesions or worse (LSIL+) or high-grade squamous intra-epithelial lesions or worse (HSIL+).

Secondary objective

To assess the accuracy of the HC2 assay to detect CIN2+ or CIN3+ in women with ASCUS or LSIL in a larger group of reports of studies that applied hrHPV testing and the reference standard (coloscopy and biopsy), irrespective whether or not repeat cytology was done.

Search methods

We made a comprehensive literature search that included the Cochrane Register of Diagnostic Test Accuracy Studies; the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*), MEDLINE (through PubMed), and EMBASE (last search 6 January 2011). Selected journals likely to contain relevant papers were handsearched from 1992 to 2010 (December). We also searched CERVIX, the bibliographic database of the Unit of Cancer Epidemiology at the Scientific Institute of Public Health (Brussels, Belgium) which contains more than 20,000 references on cervical cancer.

More recent searches, up to December 2012, targeted reports on the accuracy of triage of ASCUS or LSIL with other HPV DNA assays, or HPV RNA assays and other molecular markers. These searches will be used for new Cochrane reviews as well as for updates of the current review.

Selection criteria

Studies eligible for inclusion in the review had to include: women presenting with a cervical cytology result of ASCUS or LSIL, who had undergone both HC2 testing and repeat cytology, or HC2 testing alone, and were subsequently subjected to reference standard verification with colposcopy and colposcopy-directed biopsies for histologic verification.

Data collection and analysis

The review authors independently extracted data from the selected studies, and obtained additional data from report authors.

Two groups of meta-analyses were performed: group I concerned triage of women with ASCUS, group II concerned women with LSIL.

The bivariate model (METADAS-macro in SAS) was used to assess the absolute accuracy of the triage tests in both groups as well as the differences in accuracy between the triage tests.

Main results

The pooled sensitivity of HC2 was significantly higher than that of repeat cytology at cut-off ASCUS+ to detect CIN2+ in both triage of ASCUS and LSIL (relative sensitivity of 1.27 (95% CI 1.16 to 1.39; P value < 0.0001) and 1.23 (95% CI 1.06 to 1.4; P value 0.007), respectively. In ASCUS triage, the pooled specificity of the triage methods did not differ significantly from each other (relative specificity: 0.99 (95% CI 0.97 to 1.03; P value 0.98)). However, the specificity of HC2 was substantially, and significantly, lower than that of repeat cytology in the triage of LSIL (relative specificity: 0.66 (95% CI 0.58 to 0.75) P value < 0.0001).

Authors' conclusions

HPV-triage with HC2 can be recommended to triage women with ASCUS because it has higher accuracy (significantly higher sensitivity, and similar specificity) than repeat cytology.

When triaging women with LSIL, an HC2 test yields a significantly higher sensitivity, but a significantly lower specificity, compared to a repeat cytology. Therefore, practice recommendations for management of women with LSIL should be balanced, taking local circumstances into account.