HPV testing in primary cervical screening: a systematic review and meta-analysis
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CRD summary
The review concluded that evidence from good quality RCTs supported cervical cancer prevention via primary screening with HPV testing starting at age 30 or 35. The review conclusions reflect the evidence and are likely to be reliable.

Authors' objectives
To assess whether the increased sensitivity of human papillomavirus (HPV) testing was a result of over-detection of abnormalities that would regress with time, or whether it represented a lead-time gain.

Searching
MEDLINE, EMBASE and The Cochrane Library were searched for studies in English published between 2005 and November 2010. Two trials registers were searched for trials in any language. Reference lists of primary studies and reviews were consulted for additional studies. Search terms were reported.

Study selection
Randomised controlled trials (RCT) that compared cytology-based testing and HPV-based testing with data for two or more screening rounds in the setting of an organized screening program were eligible. Primary outcomes of interest were relative rates of cervical intraepithelial neoplasia (CIN) 2, CIN2+ and CIN3+, as well as incidence of and mortality due to invasive cervical cancer. Secondary outcomes were the colposcopy rates associated with various intervention strategies and test performance characteristics. Studies were selected for an analysis of test performance if they had submitted all participants or a random sample with negative test results to the same verification test as those who tested positive during initial screening. Any RCT that compared the two interventions of interest was eligible for the comparison of colposcopy rates.

Most trials took place within an organised programme in a Western European country, and most reported using two rounds of screening. HPV-based testing was performed with the Hybrid Capture II test or a polymerase chain reaction-based test, with or without cytology testing. Most control group participants underwent conventional cytology testing. Participant age ranged from 20 to 69 years, with most trials including women 29 or older.

The authors did not state how many reviewers selected studies.

Assessment of study quality
Risk of bias was assessed using the following criteria: randomisation, blinding of outcome assessor, intention-to-treat, withdrawals, funding source, statistical power, length of follow-up and balance of baseline characteristics. Studies evaluating test performance were also assessed using items from the QUADAS tool. The authors did not state how many reviewers assessed the quality of the studies.

Data extraction
CIN 2, 2+ and 3+ rates were extracted to calculate relative detection rates as risk ratios with 95% confidence intervals. Hazard ratios and p-values were extracted for data on cervical cancer incidence and mortality. Data were extracted by one reviewer and checked by a second.

Methods of synthesis
Random effects meta-analysis was used to pool results for both screening rounds, and both screening rounds combined for RCTs that assessed rates of CIN over more than one screening round. Risk ratios higher than 1 indicated a higher detection rate in the intervention group (HPV-based). Heterogeneity was assessed using I² and X². Sensitivity analysis was used to explore the effect of individual studies on heterogeneity and the pooled estimates. One study contributed to substantial heterogeneity and significantly affected the pooled estimates so was excluded from one analysis (CIN3+ in round 1). Results on cervical incidence and mortality, test performance and colposcopy referral rates were reported.
Results of the review

Seven RCTs were included. Follow-up time ranged from over two to eight years. Overall, the quality of the evidence was considered good. Appropriate randomisation and blind assessment of outcome were found in six studies. Where applicable, all performed analyses on an intention-to-treat basis, and all explained reasons for withdrawals. Baseline characteristics appeared balanced in all except one study. One trial was partially funded by industry. The two studies assessed using QUADAS rated highly on this tool.

CIN detection rates: Between 98,517 and 123,027 participants were included in the screening round one analyses, and 112,873 women in the round two analyses.

Significantly more cases of CIN2 (RR 1.64; 95% CI 1.31 to 2.05), CIN2+ (RR 1.52; 95% CI 1.15 to 2.00) and CIN3+ (RR 1.67; 95% CI 1.27 to 2.19) were detected in the first round of screening in the HPV-based testing group. In the second screening round, significantly fewer cases of CIN2+ (RR 0.57; 95% CI 0.45 to 0.71) and CIN3+ (RR 0.49; 95% CI 0.37 to 0.66) were detected in the HPV based testing group. There was a non-statistically significant trend showing lower detection rates for CIN2 in the HPV based testing group in the second screening round (RR 0.73; 95% CI 0.51 to 1.03).

Over both rounds, significantly more CIN2 (RR 1.37; 95% CI 1.12 to 1.68) was detected in the HPV testing group, but there was no difference in the rates of CIN2+ and CIN3+. There was evidence of significant heterogeneity (I²>70%) for several outcomes (CIN2+ in the first screening round, CIN3+ before exclusion of one study and CIN2+ and CIN3+ over both screening rounds).

Cervical cancer incidence and mortality: Two studies assessed cervical cancer incidence. One trial found no cases of invasive cervical cancer in the second round in the HPV group, compared with nine cases in the cytology group (p=0.004). The study found a significantly lower number of cases of invasive cervical cancer in the HPV testing group over both study rounds (p=0.028). Another trial found a lower incidence of stage II+ cervical cancer with HPV testing compared with standard care (HR 0.47; 95% CI 0.32 to 0.69). The incidence for cytology testing was also lower compared to standard care but the difference was not statistically significant (HR 0.75; 95% CI 0.51 to 1.10). This study also found a reduction in mortality from invasive cervical cancer with a single HPV test (HR 0.52; 95% CI 0.33 to 0.83) but no reduction with a single screening with cytology or visual inspection with acetic acid.

Colposcopy referral: Seven RCTs reported on colposcopy referral rates. Colposcopy rates were generally higher with HPV testing at baseline screening and among younger women. Referral rates ranged from 1.1% for women aged 30 to 69 who underwent primary HPV testing (referral threshold of 1pg/mL) with cytology triage of positive results (referral threshold of atypical squamous cells of undetermined significance), to 13% for women aged 25 to 34 who were directly referred to colposcopy after a positive HPV test (referral threshold of 1pg/mL).

Authors’ conclusions
Evidence from good quality RCTs supported cervical cancer prevention via primary screening with HPV testing starting at age 30 or 35.

CRD commentary
The review question and selection criteria were clear. Several bibliographic sources were consulted, but language restrictions were applied to the searches, so some studies may have been missed. Steps were taken to minimise reviewer error and bias during data extraction, but it was unclear if similar measures were taken during study selection and quality assessment.

Quality of the trials was rated as good, and the primary analyses included large trials. However, rates of withdrawals were not reported. Results for CIN detection were generally consistent across trials, showing higher rates in round 1 in the HPV group and round 2 in the cytology group. Fewer trials were found for cervical cancer incidence and mortality, but data supported the authors’ conclusions. The decision to exclude a source of substantial heterogeneity from one of the analyses may not have been appropriate. However, the review conclusions reflected the good quality evidence, and are likely to be reliable.
Implications of the review for practice and research

**Practice:** The authors stated that organised screening programmes in higher resource settings should consider adopting HPV testing as the primary screening test for women 30 or 35 years of age and older.

**Research:** The authors stated that further research was needed to determine what primary screening test was optimal for younger women, and at what age screening should be initiated.

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