Co-testing for detection of high-grade cervical intraepithelial neoplasia and cancer compared with cytology alone: a meta-analysis of randomized controlled trials

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ABSTRACT

Background Human papillomavirus (HPV) DNA testing combined with cytology has been recommended as a primary cervical cancer screening strategy.

Methods PubMed/MEDLINE, Embase, the Cochrane Library and the NIH trial registry were searched for randomized controlled trials comparing co-testing with cytology alone for the detection of high-grade CIN lesions and cancers. Of 1156 articles identified, four met inclusion criteria. The performance of co-testing and cytology alone was compared at baseline screening, second round screening and overall. Cumulative meta-analysis, Begg’s test, Egger’s test and sensitivity analysis were performed.

Results At baseline, co-testing was associated with a significantly higher detection rate of CIN 2þ [risk ratio (RR) = 1.41, 95% confidence interval (CI): 1.12, 1.76] and a non-significantly higher CIN 3þ detection rate (RR = 1.15, 95% CI: 0.99, 1.33). At second round screening, co-testing was associated with significantly lower detection rates of both CIN 2þ and CIN 3þ (RR = 0.77, 95% CI: 0.63, 0.93; RR = 0.68, 95% CI: 0.55, 0.85). The overall detection rate did not differ between co-testing and cytology alone for CIN 2þ (RR: 1.19, 95% CI: 0.99, 1.46) or CIN3þ (RR: 0.99, 95% CI: 0.87, 1.14).

Conclusion Co-testing increases the detection of CIN2þ lesions at baseline and significantly decreases the detection rates of CIN2þ or CIN3þ lesions at subsequent screening compared with cytology alone.

Keywords cancer, gynaecological disorders, screening

Introduction

Infection with human papilloma virus (HPV) is a necessary cause for the development of invasive cervical cancer (ICC) and persistent high-risk type HPV infection plays a key role in the progression of cervical intraepithelial neoplasia (CIN) to ICC.¹

The National Health Service (NHS) in the UK, like many jurisdictions, recommends cervical cytology for women between the ages 25 and 65 every 3–5 years depending on age.² Cervical cytology has been the traditional screening approach and has been successful in decreasing cervical cancer incidence and mortality rates in developed countries.³ However, frequent screening remains necessary due to the
low sensitivity of cervical cytology testing. This limitation has led to the search for alternative screening strategies such as primary high-risk HPV DNA testing.

HPV DNA testing is more sensitive than cytology; however, it is less specific, especially among younger women, and its use in primary screening may lead to potentially unnecessary intervention. Conversely, randomized controlled trials evaluating the role of HPV DNA testing as a primary screening strategy have shown decreased detection of high-grade cervical lesions at subsequent screening compared with cytology alone when participants underwent treatment after positive screening.

In March 2012, new cervical screening recommendations were released in the USA. These updated guidelines include co-testing with a combination of cytology and HPV DNA testing every 5 years in women between the ages of 30 and 65. The evidence is clear that high-risk HPV DNA testing is more sensitive; however, the benefits and overall impact of adding this test to screening programs warrants further consideration. To the extent of our knowledge, there has been no previous meta-analysis specifically comparing co-testing to cytology alone for the detection of high-grade CIN lesions and cancers. This meta-analysis of randomized controlled trials was undertaken to determine whether women between the ages of 21 and 65 receiving screening for cervical cancer with co-testing compared with cytology alone have a lower detection rate of high-risk CIN lesions and ICC at follow-up.

Methods

Search strategy

In accordance with available guidelines and in consultation with a Master of Library and Information Science librarian, we conducted a comprehensive search to identify randomized controlled trials evaluating cytology and HPV DNA testing in cervical cancer screening. PubMed/MEDLINE (NCBI, through 1950–23 March 2012), Embase (Elsevier, 1974–23 March 2012), the Cochrane Library (Wiley, through 28 March 2012) and the online NIH trial registry ClinicalTrials.gov (28 March 2012) were queried broadly (Supplementary Data, Appendix S1). Our search was limited to randomized controlled trials using validated and sensitive study design filters for PubMed and Embase. The Cochrane Library was searched for systematic reviews and the NIH trial registry for completed trials with currently available data. Citations of existing relevant systematic reviews were also examined for inclusion. Our search was not language restricted.

Study selection and data extraction

Article titles and abstracts retrieved were evaluated for inclusion and potentially pertinent articles reviewed by full-text appraisal (Fig. 1). Articles were assessed using pre-specified inclusion criteria and a standardized data extraction form designed a priori was used. Two independent evaluators (G.B.F, L.A.G., K.H., M.M. and D.Z.) extracted data. Disagreements were resolved by review by a third author and consensus discussion. Inclusion was restricted to randomized controlled trials that evaluated screening with HPV DNA testing in combination with cytology compared with cytology alone in women undergoing routine screening and that systematically reported outcomes of either CIN 2 or CIN 3 and greater. Cytologic diagnosis of included studies followed the 2001 Bethesda Reporting System. All included studies required pathologic diagnosis after positive screening. Studies evaluating self-sampled HPV DNA testing or women ≤21 years old were excluded. Positive HPV DNA testing, colposcopy threshold and screening rounds were used as pre-specified in each study. Variables extracted included trial name, extractor initials, publication date, screening time to follow-up, number of individuals in control and intervention arms, number of individuals developing CIN 2+ or CIN 3+ (for baseline, second round and overall detection rate), average age of study population, age range of study population, type of analysis performed (intention-to-screen versus as-screened), HPV DNA test used, type of cytology testing, colposcopy threshold and study quality assessment. The Cochrane Collaboration’s Tool for Assessing Risk of Bias was used for study quality assessment.

Data analysis

Based on intention-to-screen, we determined the effect of co-testing versus cytology alone on the detection of high-grade CIN lesions at baseline screening, second round screening and overall using incidence risk ratios (RR). These were calculated using raw data extracted from the outcome tables and text in each study. The DerSimonian–Laird random effects model was utilized to pool RRs. This method was deemed appropriate over a fixed-effects model to account for inevitable between-study variation and allow for greater generalizability. L’Abbé plots were used to qualitatively assess heterogeneity and to identify which intervention measure of association was most consistent across trials. Forest plots were derived to assess the included RR point estimates and accompanying 95% confidence intervals (CIs) alongside the overall pooled estimates.

Statistical heterogeneity was assessed using the Q-statistic with a threshold of $P = 0.1$. Between-study variability was
also assessed using the $I^2$ statistic. Cumulative meta-analysis was performed to evaluate the trend of cumulative RR estimates over time. Publication bias was evaluated using Begg’s rank correlation test and Egger’s linear regression test. Bias was also evaluated by exclusion sensitivity analysis. All analyses were performed with Stata\textsuperscript{TM} statistical software version 11.

**Results**

**Study characteristics**

Our search strategy yielded 1156 articles (Fig. 1). Screening by title and abstract excluded 1091 studies and full-text appraisal was undertaken on 65 studies. Sixty-one studies were excluded for reasons detailed in Fig. 1. Four randomized controlled trials were included (Table 1).

The average age of women ranged from 35.1 to 41 years and the length of follow-up of the studies ranged from 26 to 92 months. Sample size ranged from 12,527 to 94,370 participants.

**Data selection**

The primary endpoint was defined as the number of women with histologically confirmed high-grade CIN lesions or worse. Studies consistently reported two primary outcomes—CIN 2+ and CIN3+ lesions; therefore, we conducted the data analysis considering these outcomes separately. Meta-analyses were performed for the two screening rounds and for the cumulative incidence.
<table>
<thead>
<tr>
<th>Study characteristic</th>
<th>Naucler et al., 2007&lt;sup&gt;11&lt;/sup&gt;</th>
<th>POBASCAM, 2012&lt;sup&gt;12&lt;/sup&gt;</th>
<th>ARTISTIC, 2009&lt;sup&gt;12&lt;/sup&gt;</th>
<th>NTCC Phase I, 2010&lt;sup&gt;9&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of participants</td>
<td>12 527</td>
<td>44 938</td>
<td>24 510</td>
<td>45 774</td>
</tr>
<tr>
<td>Randomization</td>
<td>1:1 individual randomization</td>
<td>1:1 individual randomization</td>
<td>3:1 individual randomization</td>
<td>1:1 individual randomization</td>
</tr>
<tr>
<td>Follow-up (years)</td>
<td>4.1; mean range (&lt;0.1–7.7)</td>
<td>5 years; median range (29–56)</td>
<td>Between 26 and 54 months</td>
<td>Up to 3.5 years</td>
</tr>
<tr>
<td>Mean age (range)</td>
<td>35.1 (at enrollment) (32–38)</td>
<td>40 at enrollment (interquartile range 34–49)</td>
<td>— (20–64)</td>
<td>41 (25–60)</td>
</tr>
<tr>
<td>HPV DNA test used</td>
<td>(GP5&lt;sup&gt;þ&lt;/sup&gt;/6&lt;sup&gt;þ&lt;/sup&gt;/6&lt;sup&gt;þ&lt;/sup&gt;) PCR enzyme immunoassay&lt;sup&gt;a&lt;/sup&gt;</td>
<td>(GP5&lt;sup&gt;þ&lt;/sup&gt;/6&lt;sup&gt;þ&lt;/sup&gt;/6&lt;sup&gt;þ&lt;/sup&gt;) PCR enzyme immunoassay&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Hybrid Capture 2 Assay&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Hybrid Capture 2 Assay&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cytology</td>
<td>Conventional PAP using cytologic brush</td>
<td>Conventional PAP using Cervex-Brush or cytobrush</td>
<td>Liquid-based PAP using Thin Prep T3000 processor</td>
<td>Liquid-based PAP using Thin Prep T3000 processor (co-testing group). Conventional PAP (control group)</td>
</tr>
<tr>
<td>Colposcopy threshold</td>
<td>ASCUS&lt;sup&gt;+&lt;/sup&gt; or HSIL&lt;sup&gt;+&lt;/sup&gt; (depending on the research site). Based on regional routine practice</td>
<td>HSIL&lt;sup&gt;+&lt;/sup&gt;</td>
<td>HSIL&lt;sup&gt;+&lt;/sup&gt;</td>
<td>ASCUS&lt;sup&gt;+&lt;/sup&gt; or LSIL&lt;sup&gt;+&lt;/sup&gt; (depending on the research site). 2 centers: if ASCUS repeat cytology</td>
</tr>
<tr>
<td>Second round</td>
<td>Cytology and HPV DNA test (included only women who did not have CIN2&lt;sup&gt;+&lt;/sup&gt; or worse and eligible for screening)</td>
<td>Cytology and HPV DNA test</td>
<td>Cytology and HPV DNA test</td>
<td>Cytology alone</td>
</tr>
<tr>
<td>HPV DNA test &lt;sup&gt;+&lt;/sup&gt; with normal cytology</td>
<td>Repeat HPV DNA test and cytology in 12 months. If HPV &lt;sup&gt;+&lt;/sup&gt;ve, referral to colposcopy. Persistent infection with same high-risk HPV type referral to colposcopy</td>
<td>Repeat HPV DNA test and cytology at 6 months. If HPV &lt;sup&gt;+&lt;/sup&gt;ve, referral to colposcopy</td>
<td>Repeat HPV DNA test at 12 months. If positive HPV DNA test, referral to colposcopy or repeat HPV DNA test 12 months later</td>
<td>If aged 35–60 years: referral to colposcopy. If aged 25–34 years: colposcopy only if HPV DNA test positive or ASCUS &lt;sup&gt;+&lt;/sup&gt; after 1 year</td>
</tr>
<tr>
<td>Method of randomization appropriate</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Treatment allocation concealed</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Participants and personnel blinded</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Intention-to-treat analysis</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Complete outcome data</td>
<td>Yes&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Description of losses to follow-up</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Selective outcome reporting</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

<sup>a</sup>Detects high-risk HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68.

<sup>b</sup>Detects high-risk HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68.

<sup>c</sup>Colposcopists had access to the results of the screening tests in both groups.

<sup>d</sup>Censoring was unlikely to induce bias.
Power calculation
A total of 126,749 participants were included in this meta-analysis. Of these, 70,371 participants were screened using HPV DNA testing plus cytology and 56,378 were screened using cytology alone. With the level of significance set to 0.05, this meta-analysis had a power of 86% to identify a 15% difference in the detection of CIN2+ lesions when comparing co-testing with cytology alone.

Pooled analysis
Outcome data were available for all included trials. L’Abbé plots (not included) confirmed that the relative detection rate (RR) was an appropriate association measure to use in these analyses; the observed detection rates in cytology and co-testing groups were consistent with comparable relative detection rates across studies. Figures 2 and 3 illustrate the pooled analysis for CIN 2+ and CIN 3+ detection rates, respectively. At baseline screening, the co-testing screening strategy was associated with a significantly higher detection rate of CIN 2+ lesions (RR = 1.41, 95% CI 1.12, 1.76, P = 0.003) and a non-significant higher detection rate of CIN 3+ lesions (RR = 1.15, 95% CI: 0.99, 1.33, P = 0.064). The pooled analysis for the second screening round (follow-up) showed that co-testing was significantly associated with a lower detection rate of CIN 2+ lesions (RR = 0.77, 95% CI: 0.63, 0.93, P = 0.006) and of CIN 3+ lesions (RR = 0.68, 95% CI: 0.55, 0.85, P = 0.001). The overall detection rate ratio of CIN2+ lesions was higher (RR = 1.19, 95% CI: 0.99, 1.46, P = 0.068) with co-testing versus cytology alone, but this trend was not statistically significant. Co-testing was not significantly associated with a higher detection rate of CIN3+ lesions over two rounds of screening (RR = 0.99, 95% CI: 0.87, 1.14, P = 0.95). Based on the cumulative detection rate difference (i.e. absolute difference between total detection rates of CIN2+ lesions), the number of participants needed to screen with co-testing compared with cytology alone with identify an additional CIN 2+ lesion is 334 (95% CI: 250, 1000).

Evaluation of heterogeneity and sensitivity analyses
In the analysis of cumulative detection rate of CIN2+ lesions, heterogeneity was observed among the four trials \( I^2 = 76.6\% \), \( \chi^2 = 12.87 \) with 3 degrees of freedom (DOF), \( P = 0.0049 \). Sensitivity analysis was performed to evaluate the effect of each individual study by its exclusion from the pooled analysis. The exclusion of the NTCC phase I trial had the largest effect on the pooled point estimate; however, the null effect was maintained (RR = 1.08, 95% CI: 0.98, 1.19). Exclusion of the other studies did not have a significant effect on the estimates. Less heterogeneity was observed in the analysis of the cumulative detection rate of CIN3+ lesions (\( I^2 = 19.5\% \), \( \chi^2 = 3.73 \) with 3 DOF, \( P = 0.292 \)). The exclusion of the ARTISTIC trial had the largest effect on the pooled point estimate, but the null effect was maintained (RR = 1.04, 95% CI: 0.88, 1.23). Exclusion of the other studies did not have a significant effect on the pooled estimate.

In the analysis of the detection rate of CIN2+ lesions at baseline, heterogeneity was observed among the trials (\( I^2 = 76.1\% \), \( \chi^2 = 12.55 \) with 3 DOF, \( P = 0.006 \)). The exclusion of NTCC phase I had the largest effect on the pooled point estimate, but a higher detection rate in the co-testing group was maintained (RR = 1.25, 95% CI: 1.09, 1.43). The exclusion of the other studies did not have a significant effect on the estimates. Less heterogeneity was observed in the analysis of the detection rate of CIN3+ lesions at baseline resulting in a non-significant test of heterogeneity (\( I^2 = 8.7\% \), \( \chi^2 = 3.29 \) with 3 DOF, \( P = 0.349 \)). The exclusion of the ARTISTIC trial had the largest effect on the pooled point estimate and its exclusion resulted in a significantly higher pooled detection rate of CIN3+ at baseline (RR = 1.23, 95% CI: 1.04, 1.45) compared with a null pooled effect before its exclusion. The exclusion of the other studies did not have a significant effect on the pooled estimate.

In the analysis of the detection rate of CIN2+ lesions at the second screening round, less heterogeneity was observed among the four trials (\( I^2 = 11.5\% \), \( \chi^2 = 3.39 \) with 3 DOF, \( P = 0.335 \)). The exclusion of the POBASCAM trial had the largest effect, but a lower detection rate in the co-testing group was maintained (RR = 0.65, 95% CI: 0.49, 0.85). The exclusion of the other studies did not have a significant effect on the estimates. No between-study heterogeneity was observed in the analysis of the detection rate of CIN3+ lesions at second screening (\( I^2 = 0.0\% \), \( \chi^2 = 2.23 \) with 3 DOF, \( P = 0.526 \)).

Publication bias
A funnel plot (Figure 4) with pseudo 95% CIs showed symmetric distribution of individual estimates around our pooled estimate both for CIN2+ and CIN3+ analyses, suggesting that publication bias is not present. Furthermore, both Begg’s test (\( P = 0.734 \) and \( P = 0.308 \) for CIN2+ and CIN3+ analyses, respectively) and Egger’s test (\( P = 0.360 \) and \( P = 0.307 \) for CIN2+ and 3+ analyses, respectively) were not suggestive of publication bias.

Discussion
Main findings of the study
This study reports the meta-analysis of data from four randomized controlled trials that compared HPV DNA testing in combination with cytology to cytology alone as a primary
### Co-testing versus cytology screening strategies — CIN2+ baseline screening

<table>
<thead>
<tr>
<th>Study</th>
<th>RR (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naucler et al.</td>
<td>1.50 (1.13, 2.01)</td>
<td>21.66</td>
</tr>
<tr>
<td>POBASCAM</td>
<td>1.25 (1.04, 1.49)</td>
<td>27.63</td>
</tr>
<tr>
<td>ARTISTIC</td>
<td>1.13 (0.94, 1.37)</td>
<td>26.96</td>
</tr>
<tr>
<td>NTCC Phase I</td>
<td>1.94 (1.51, 2.49)</td>
<td>23.75</td>
</tr>
<tr>
<td>Overall (I-squared = 76.1%, (P = 0.006))</td>
<td>1.41 (1.12, 1.76)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

**NOTE:** Weights are from random effects analysis

### Second screening round

<table>
<thead>
<tr>
<th>Study</th>
<th>RR (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naucler et al.</td>
<td>0.58 (0.36, 0.85)</td>
<td>13.83</td>
</tr>
<tr>
<td>POBASCAM</td>
<td>0.87 (0.71, 1.08)</td>
<td>56.30</td>
</tr>
<tr>
<td>ARTISTIC</td>
<td>0.64 (0.24, 0.96)</td>
<td>18.94</td>
</tr>
<tr>
<td>NTCC Phase I</td>
<td>0.76 (0.43, 1.32)</td>
<td>10.92</td>
</tr>
<tr>
<td>Overall (I-squared = 11.5%, (P = 0.335))</td>
<td>0.77 (0.63, 0.93)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

**NOTE:** Weights are from random effects analysis

### Cumulative

<table>
<thead>
<tr>
<th>Study</th>
<th>RR (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naucler et al.</td>
<td>1.17 (0.92, 1.49)</td>
<td>21.92</td>
</tr>
<tr>
<td>POBASCAM</td>
<td>1.07 (0.94, 1.23)</td>
<td>28.65</td>
</tr>
<tr>
<td>ARTISTIC</td>
<td>1.03 (0.87, 1.23)</td>
<td>26.38</td>
</tr>
<tr>
<td>NTCC Phase I</td>
<td>1.66 (1.33, 2.08)</td>
<td>23.05</td>
</tr>
<tr>
<td>Overall (I-squared = 76.7%, (P = 0.006))</td>
<td>1.20 (0.99, 1.46)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

**NOTE:** Weights are from random effects analysis

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Fig. 2 Pooled CIN 2+ detection rate ratio estimates (with 95% CIs) at baseline, at second screening and over both rounds (cumulative). *Estimates were calculated using random effects model.
Fig. 3 Pooled CIN 3+ detection rate ratio estimates (with 95% CIs) at baseline, at second screening and over both rounds (cumulative). *Estimates were calculated using random effects model.
screening strategy for the detection of high-grade CIN lesions.

A statistically significant 40% increase in the detection of CIN2 lesions or worse was found at baseline in participants screened with co-testing compared with those screened with cytology alone. Grade 2 CIN lesions have traditionally been categorized as precursor lesions to cervical cancer; however, recent literature suggests that CIN2 might represent a mis-classification of Grade 1 or Grade 3 CIN lesions. Currently, the significance of Grade 2 CIN remains uncertain and optimal management of these lesions is controversial. Approximately 40% of CIN2 lesions regress spontaneously over 2 years if left untreated. Conversely, Grade 3 CIN lesions are unquestionably precursor lesions to cervical cancer; they have a high propensity (30%) to progress to cervical cancer if left untreated. Compared with a significant increase in the detection of CIN2+, we found a non-significant 15% increased detection of CIN 3+ with the co-testing strategy compared with cytology alone (P = 0.064) at baseline.

Following increased detection at baseline screening, a statistically significant 23% reduction in the detection of CIN2+ lesions and a 32% reduction in the detection of CIN 3+ lesions was noted at subsequent screening in participants screened with HPV DNA testing plus cytology. These findings suggest that co-testing detected ‘true’ high-grade lesions at baseline, which prompted management according to the pre-specified intervention guidelines in each study and led to reductions in the detection of CIN 2+ and CIN 3+ at subsequent screening.

What is already known on this topic
It is well established in the literature that HPV DNA testing has a higher sensitivity than cytology alone and that co-testing has a higher sensitivity than HPV DNA testing. In a randomized controlled trial, Mayrand et al. reported a sensitivity for HPV DNA testing of 94.6 compared with 55.4% for cytology, whereas the specificity of HPV DNA testing was 94.1 compared with 96.8% with cytology for the detection of Grade 2 or 3 CIN lesions. Thus, the downside of HPV DNA testing is a lower specificity to high-grade CIN lesions, which may potentially lead to over-diagnosis and over-treatment of non-progressive lesions. However, we note that two of the four included studies have enough power individually to demonstrate a significant difference in the number of cervical cancers detected at follow-up, suggesting that earlier detection of persistent Grade 2 CIN or worse is beneficial.

Murphy et al. recently published a systematic review and meta-analysis of HPV DNA testing in primary cervical screening. Their meta-analysis compares HPV DNA testing alone or in combination with cytology to cytology alone and concluded that adoption of HPV DNA testing as primary screening should be considered based on findings of significantly more CIN3+ found at baseline screening and significantly less found at follow-up. Vesco et al. also published a thorough systematic review addressing key topics for cervical cancer screening in order to assist the US Preventative Services Task Force in updating their recommendations; however, a meta-analysis of randomized controlled trials comparing co-testing or HPV alone with cytology alone was not included. The final results of the POBASCAM study, which concluded that further evidence is needed to support primary HPV DNA screening, were not available at the time of publication of either of these analyses.

What this study adds
This is the first meta-analysis specifically evaluating the impact of co-testing with cytology alone. We performed an
intention-to screen analysis yielding results that are generalizable to countries with organized cervical screening programs.

Our analysis refines what is known about the performance of co-testing. It includes the final results of the POBASCAM trial, which were published in Lancet Oncology in January 2012 and not included in previous analyses, and minimizes heterogeneity because it compares co-testing separate from HPV testing alone.

Despite some heterogeneity between studies, which was accounted for in our analysis using DerSimonian–Laird random effects model, our meta-analysis provides a comparison of co-testing with cytology alone. These results are relevant and informative in light of the recently updated American cervical screening guidelines.13

**Limitations of this study**

There are some limitations that should be accounted for when interpreting these results. First, there were a limited number of randomized controlled trials included in the analysis; however, the total number of participants contributing data was relatively large and the meta-analysis had considerable power to discriminate the differences in the detection rates between co-testing and cytology alone.

Secondly, there were variations between the studied populations, length of follow-up and screening protocols of each trial (Table 1). The ARTISTIC trial, NTCC phase 1 and POBASCAM included women between the ages of 20 and 64 years, between 25 and 60 years and between 29 and 56 years, respectively. Conversely, Naucler et al.11 included only women aged 32–38 years. Studies including younger women could have influenced our results away from the null because positive HPV DNA testing has been shown to be prevalent in young women and is limited in its ability to differentiate between transient or persistent HPV infections.22,25,29 Some of the included studies performed subgroup analyses by age group; however, we were unable to account for these in our analysis with the data available. Furthermore, we did not have the data to compare screening protocols used by each study to follow participants with abnormal cytology or HPV DNA test between baseline screen and second round screen.

Finally, our study did not address the potential harms associated with HPV DNA testing. HPV DNA testing is more sensitive than cytology, although less specific, which can potentially lead to unnecessary procedures. Intervention is not without harm and serious reproductive complications have been associated with cervical procedures.30 The included studies provided incomplete data on the number of unnecessary colposcopies, the number and types of interventions performed at or subsequent to colposcopy and the downstream long-term consequences of these cervical procedures.

Therefore, we were unable to provide a summary estimate of potential downsides of co-testing. Moreover, given the varying follow-up algorithms between trials, such summary measures would likely have been too heterogeneous to be clinically generalizable. Modeling studies may be better suited to compare algorithms and point to those that can maximize benefits while keeping unnecessary procedures to a minimum.

The results of this meta-analysis suggest that co-testing is an effective strategy for earlier detection of precancerous lesions, which leads to further intervention and decreased rates of detection of high-grade CIN lesions at subsequent screening. These results favor longer cervical cancer screening intervals when co-testing is used for screening; however, the ideal screening interval remains unclear and further studies are needed to establish optimal screening intervals.

**Supplementary data**

Supplementary data are available at the *Journal of Public Health* online.

**Acknowledgements**

We thank Dr Marie-Hélène Mayrand who assisted in the preparation of our manuscript.

**References**


8 Rijkart DC, Berkhof J, Rozendaal L et al. Human papillomavirus testing for the detection of high-grade cervical intraepithelial


