Adjunctive human papillomavirus testing in the 2-year follow-up of women with low-grade cervical cytologic abnormalities: a randomized trial and economic evaluation


Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The use of repeated Papanicolaou (Pap) test and oncogenic human papillomavirus (HPV) testing for the detection of cervical intraepithelial neoplasia (CIN) 2 or 3 in women who, on a screening Pap test, showed atypical squamous cells of undetermined significance (ASCUS) or low-grade squamous intraepithelial lesions (LSIL). Two groups were compared. One group received a combined Pap test and Hybrid capture 1 (HC1) oncogenic HPV test, the other received a Pap test only.

Type of intervention
Screening and management.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised women aged between 16 years and 50 years who were members of community-based family practices and who had ASCUS or LSIL on screening cervical cytology. Women were excluded from study enrolment if they had:

- LSIL within the past year;
- more than 1 previous smear with LSIL;
- atypical glandular cells of undetermined significance (AGUS);
- glandular dysplasia;
- high-grade squamous intraepithelial lesion (HSIL);
- previously histologically confirmed CIN or cervical cancer;
- prior destructive cervical treatment;
- prior or current vaginal or vulvar neoplasia; or
- immunosuppression.

Women were also not included if the family physician judged the patient unlikely to comply with follow-up and if they currently were followed with colposcopy, required uterine body or adnexal surgery, or were pregnant.

Setting
The setting was primary care. The economic study was carried out in Canada.

**Dates to which data relate**
The effectiveness and resource use data were collected between May 1995 and April 1998. The costs were estimated at 2001 prices.

**Source of effectiveness data**
The effectiveness data were derived from a single study.

**Link between effectiveness and cost data**
The costing was undertaken prospectively on the same patient sample as that used in the effectiveness analysis.

**Study sample**
The study sample comprised women who were members of community-based family practices and who had ASCUS or LSIL on screening cervical cytology. The authors did not state whether power calculations were performed to derive the sample size. Of the 402 women invited to participate in the study, 145 refused (36%). These women were significantly younger than those who agreed to participate, and more had LSIL on screening Pap test. The authors reported the women's reasons for nonparticipation in the study. Of the remaining 257 participants, 130 were randomised to repeat Pap test plus HPV testing and 127 were randomised to repeat Pap test alone.

**Study design**
The study was a multi-centred randomised controlled trial (RCT), comprising 66 community-based family practices. The participants were stratified according to the screening cytology result (ASCUS or LSIL) then randomised in blocks of 4 using a computer-generated random numbers table. Randomisation was uncontrolled. Follow-up tests were performed every 6 months for up to 2 years. The study end was colposcopic examination performed on all women after 2 years, or earlier if the Pap or HPV tests were positive. A total of 88 participants (34%) were lost to follow-up, 35 (27%) from the combined Pap and HPV tests group and 53 (42%) from the Pap only test group. Women who completed the study were significantly older than those who were lost to follow-up. The authors noted, however, that an adjustment for age made no difference to the results. The women participants, the family physicians, and those assessing the test results, were blinded to the intervention allocation.

**Analysis of effectiveness**
The analysis of effectiveness was conducted on the basis of treatment completers only. The primary health outcome used was the detection of histologically confirmed CIN 2 or 3. The secondary outcome measure was loss to follow-up. At randomisation, the groups were comparable in terms of baseline characteristics. For example, age, ASCUS on screening Pap test, Canadian born, education, ever smoked, ever been pregnant, marital status and employment status. They were also comparable in terms of the median number of sexual partners, history of sexually transmitted infection, and mean age of first sexual intercourse.

**Effectiveness results**
Of the 169 women who completed the study, 21 (12.4%) had histologically confirmed CIN 2 or 3, and 1 (0.6%) had invasive squamous cell carcinoma.

The combined Pap test and HPV test detected 11 of 11 cases (100%), while the Pap test alone detected 7 of 11 cases (63%). Therefore, over 2 years, the sensitivity of the combined Pap and HPV test strategy (100%, 95% confidence interval, CI: 71.5 - 100) was greater than that for the repeat Pap test alone strategy (63.6%, 95% CI: 30.8 - 89.1) for the detection of histologically confirmed CIN 2 or 3. This difference was not statistically significant, (p=0.14).
The specificity of the Pap test alone (71.4%, 95% CI: 58.7 - 82.1) was significantly greater than that of combined testing (46.4%, 95% CI: 35.5 - 57.7), (p=0.005).

The positive and negative predictive values did not differ significantly between the two groups.

Among women presenting with ASCUS on screening and randomised to repeat Pap test alone, sensitivity was 42.9% and specificity was 74.5% for the detection of histologically confirmed CIN 2 or 3. In the combined Pap and HPV test group, sensitivity was 100% and specificity was 56.1%.

Among women presenting with LSIL and assigned to repeat Pap test alone, sensitivity was 100% and specificity was 62.5% for the detection of histologically confirmed CIN 2 or 3. In the combined Pap and HPV test group, sensitivity was 100% and specificity was 25.9%.

A total of 26.8% of the sample defaulted from testing or from colposcopy when referred with an abnormal result.

Clinical conclusions
More than a third of women who received repeat Pap test alone had histologic high-grade CIN that remained undetected. Combined Pap and HPV testing detected all cases of high-grade CIN. However, the results did not reach statistical significance. HPV testing appeared more useful for women presenting with either ASCUS or LSIL.

Measure of benefits used in the economic analysis
The measure of benefit used was the detection of histologically confirmed CIN 2 or 3.

Direct costs
The authors did not state whether the costs had been discounted, although discounting would have been appropriate given that the costs were incurred during 2 years. The quantity/cost boundary adopted was that of the health service. The costs and the quantities were analysed separately. Cost and resource information was collected on test procedures such as the HPV test, repeat Pap test, colposcopy visit, endocervical curettage and biopsies. The costs and quantities were also collected on treatments such as loop electrosurgical excision, laser ablation, cryotherapy, and cone and radiation therapy. The costs of procedures associated with colposcopy were calculated only for women who were designated test positive. The authors did not state from where many of the costs were derived. Physicians’ fees were obtained from the Ontario Health Insurance Plan. The resource quantities were derived using actual data from the trial. The costs were estimated at 2001 prices.

Statistical analysis of costs
The costs were not treated stochastically. No statistical analysis was carried out.

Indirect Costs
The indirect costs were not included in the analysis.

Currency
Canadian dollars (Can$). The conversion rate to US dollars ($) was Can$1.00 = $0.62.

Sensitivity analysis
A limited one-way sensitivity analysis was undertaken, in which the total costs of repeat Pap test alone were varied so as to incorporate the possibility of one or two women with high-grade CIN, which went undetected, developing invasive cancer.
Estimated benefits used in the economic analysis
Over the 2-year period, the combined Pap test and HPV test detected 11 of 11 cases (100%), while the Pap test alone detected 7 of 11 cases (63%). The difference between the two groups was not statistically significant.

Cost results
For the 2-year study period, the total cost of combined repeat Pap test and HPV test to detect 11 cases of high-grade CIN was Can$ 57,916. The total cost of repeat Pap test to detect 7 cases was Can $40,094.

Synthesis of costs and benefits
The cost-effectiveness ratio of combined testing compared with Pap test alone was Can $4,456 per additional case of high-grade CIN. The sensitivity analysis considered the subsequent costs of the four women who had high-grade CIN that was undetected by the Pap test alone. If one of these women developed invasive cancer, and the other three required further intervention, the effectiveness ratio of combined testing compared with Pap testing alone became Can$1,837 per additional case of CIN 2 or 3 detected. If two or more of these women developed invasive cancer, the combined testing strategy became less expensive than repeat Pap test alone.

Authors' conclusions
The combination of repeat Pap and HPV testing was more costly, but it may detect more cases of cervical intraepithelial neoplasia (CIN) 2/3 than the Pap test alone. The authors also stated that poor adherence limits the usefulness of a strategy that requires repeated follow-up.

CRD COMMENTARY - Selection of comparators
Combined repeat Pap and HPV testing was compared with repeat Pap test alone. The latter reflects current practice within the setting of the study. The reader should consider whether this reflects current practice in their own setting.

Validity of estimate of measure of effectiveness
The analysis was based on an RCT, which is the 'gold' standard method for an analysis of effectiveness. Those who agreed to form the study sample were significantly older than those who did not agree to participate, and also comprised fewer women with LSIL on screening Pap test. The authors presented a possible explanation for why fewer women with LSIL on screening were likely to enter the trial, but did not go on to discuss the potential impact of this on the study results. The patient groups were shown to be comparable at analysis. No further statistical tests (to account for potential biases and confounding factors) were undertaken, and the outcomes were analysed for treatment completers only.

Validity of estimate of measure of benefit
The health benefit measure was obtained directly from the effectiveness analysis.

Validity of estimate of costs
The perspective adopted in the economic analysis was that of the health service. Although the authors reported treatment and triage costs, they acknowledged that the additional costs of treatment for those with invasive cancer could have been included, which would have impacted on the cost-effectiveness ratio. The costs and the quantities were reported separately. The resource use statistics were derived from the study, but no statistical analysis on the quantities was performed. The source of the price data was unclear, although some appears to have come from published sources. Discounting was not undertaken, even though the costs were incurred over 2 years. Overall, since the reporting of some elements of the costing data was limited, it was difficult to judge the validity of the results.

Other issues
The authors made a limited comparison of their results with findings from other studies. However, the issue of
generalisability to other settings was not addressed. The authors did not present their results selectively and their conclusions reflected the scope of the analysis.

**Implications of the study**
The authors stated that repeat Pap testing alone is not recommended because it fails to identify CIN 2 or 3 in more than a third of women with ASCUS or LSIL. They also stated that despite the lack of statistical significance, the effectiveness results support further research in this area.

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