Improved early detection of cervical intraepithelial lesions by combination of conventional Pap smear and speculoscopy


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
Treatment strategies for the detection of cervical intraepithelial lesions were compared, in particular, Pap smear, speculoscopy, and a combination of Pap smear and speculoscopy (PapSure).

Type of intervention
Screening.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised women residing in Keelung, northern Taiwan.

Setting
The tests appear to have been performed in secondary care settings. The economic analysis was carried out in Keelung, Taiwan.

Dates to which data relate
The effectiveness data were collected from March 2001 to November 2001. The dates to which the costs related were not reported. The price year was also not reported.

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

Link between effectiveness and cost data
It appears that the costing has been carried out retrospectively on the same sample of patients as that used for the effectiveness study.

Study sample
The sample size was not determined in the planning phase of the study. In addition, power calculations were not performed retrospectively. Women who had not received a Pap smear in the past 3 years were identified from a nationwide government database of Pap smear registration. Women were excluded if their cervix was in an unusual position and could not be properly examined, if they were using vaginal suppositories, or had had intercourse within 2 days before the study. They were also excluded if they had acute cervicitis or vaginitis, or were menstruating at the time of the study.
Initially, 1,829 women were screened from March 2001 to November 2001. Seventy-one women were excluded from the study as they did not meet the inclusion criteria. Overall, there were 1,717 eligible cases. The mean age was 51.67 (+/- 14.60) years (range: 25 - 89; median 50) and mean parity was 3.39 (+/- 2.02) (range: 0 - 13; median 3). There were 818 postmenopausal cases and 51 cases receiving regular hormonal replacement therapy. All patients received Pap smear and speculoscopy and were referred to a colposcopist for a target biopsy if either the speculoscopy or the Pap smear was abnormal. Overall, 1,082 cases received colposcopy. Of these, 214 were due to positive screenings, while 868 were randomly sampled cases from negative screenings. Five senior colposcopists and gynaecologists performed all of the procedures.

**Study design**
The analysis was based on a multi-centre within-group comparison study. The tests appear to have been performed concurrently. The authors reported that, from the initial sample, 41 women with a positive screening were lost to follow-up, but no reasons for this loss were provided. These patients had already been excluded from the final study sample.

**Analysis of effectiveness**
All the women included in the study appear to have been accounted for in the analysis. The primary outcomes assessed for each of the procedures (i.e. Pap smear, speculoscopy and PapSure) were:

- the detection rate of cervical lesions;
- the sensitivity and specificity;
- the positive and negative likelihood ratio; and
- the positive and negative predictive values (PPV and NPV, respectively) of the screening methods.

The authors do not seem to have investigated the comparability at baseline of those lost to follow-up and those who completed the study.

**Effectiveness results**
The detection rate of cervical lesions was 1.11% with the Pap smear, 1.57% with speculoscopy, 2.27% with PapSure and 2.44% with the gold standard.

When screening for low-grade squamous intraepithelial lesion (LGSIL), the sensitivity was 45.2% (range: 29.2 - 61.3) with the Pap smear, 64.3% (range: 48.0 - 78.4) with speculoscopy and 92.9% (range: 80.5 - 98.4) with PapSure, (p<0.001). The specificity was 99.2% (range: 98.7 - 99.6) with Pap smear, 89.7% (range: 88.2 - 91.1) with speculoscopy and 89.1% (range: 87.6 - 90.6) with PapSure. The PPV was 59.4% for Pap smear, 13.6% for speculoscopy and 17.6% for PapSure. The NPVs were 98.6% (Pap smear), 99.0% (speculoscopy) and 99.8% (PapSure), respectively.

When screening for high-grade squamous intraepithelial lesion (HGSIL), the sensitivity was 87.5% (range: 61.6 - 98.1) with Pap smear, 50% (range: 24.7 - 75.3) with speculoscopy and 100% with PapSure, (p<0.001). However, the specificity was 98.9% (range: 98.3 - 99.4) with Pap smear, 88.8% (range: 87.2 - 90.2) with speculoscopy and 88.0% (range: 86.3 - 89.5) with PapSure. The results demonstrated that the specificity of the PapSure test, when screening either for LGSIL or HGSIL, was lower than that of the Pap smear alone, (p<0.001). The PPV was 43.8% for Pap smear, 4.0% for speculoscopy and 7.2% for PapSure. The NPVs were 99.9% (Pap smear), 99.5% (speculoscopy) and 100% (PapSure), respectively.

The authors reported that false negatives were also present in colposcopy.

**Clinical conclusions**
PapSure achieves much higher sensitivity than either screening test alone (Pap smear or speculoscropy) in screening for cervical cancer, but its specificity is lower than that of the Pap smear.

**Measure of benefits used in the economic analysis**
The measure of benefit used was the number of true-positive squamous intraepithelial lesions (SILs) found. This measure of benefit was fixed at the level at which Pap smear alone and PapSure would find 90.5% of the SILs. It was derived directly from the effectiveness analysis and from some further estimations made by the authors to identify the number of consecutive Pap smear tests that would be required to find 90.5% of SILs (similar to that found in the effectiveness analysis with PapSure when only one Pap smear and one speculoscropy were performed).

**Direct costs**
The direct costs considered in the economic analysis were those of the health service, including those for the examinations (Pap smear, speculoscropy, colposcopy, cervical punch biopsy and histological studies). Moreover, some costs incurred by the patients were also considered (i.e. round-trip city bus transportation and the time spent at the hospital to undergo the tests). The costs were based on actual data and were derived from published sources (Taiwan's Bureau of National Health Insurance). The quantities and the costs were analysed separately. The quantities used were derived from the effectiveness study. The dates to which the costs related and the price year were not reported. Discounting was not carried out, but it seems that the costs have been during less than 2 years, thus making discounting irrelevant. The costs reported were the total costs for the whole population in order to identify 90.5% of all SILs.

**Statistical analysis of costs**
The costs were treated deterministically.

**Indirect Costs**
No indirect costs were reported.

**Currency**
New Taiwan yuan (NT) and US dollars ($). The conversion rate was $1 = NT35.

**Sensitivity analysis**
No sensitivity analysis was carried out.

**Estimated benefits used in the economic analysis**
Thirty-eight true-positive SILs would be found if the tests identified 90.5% of all lesions. For this, four Pap smear tests should be performed per patient if only Pap smear was used, while one Pap smear combined with one speculoscropy would be required if PapSure was undertaken.

**Cost results**
The total cost for the whole population (i.e. 5,600,000 women aged above 30) in order to identify 90.5% of all SILs was NT 1,678,633,400 ($47,960,950) for Pap smear alone and NT 1,076,452,400 for PapSure ($30,755,780).

**Synthesis of costs and benefits**
The estimated health benefits and costs were combined using cost-effectiveness ratios. These calculated the cost per SIL identified when the goal of the screening was set so as to identify 90.5% of all the SILs. The cost-effectiveness ratios were NT 135,442.4 ($3,870) per SIL detected with Pap smear versus NT 86,854.7 ($2,482) per SIL detected.
Authors' conclusions
A single PapSure test (Pap smear plus speculoscopy) can achieve a 90.5% detection rate. This is similar to that of a 4-consecutive Pap smear protocol, therefore enabling patients to receive accurate results in fewer visits, and showing better results in terms of cost-effectiveness.

CRD COMMENTARY - Selection of comparators
Owing to the low accuracy of the Pap smear test and the development of new methods to identify women at risk for cervical cancer, the authors stressed the need to evaluate the efficacy of different screening methods. A justification was given for the evaluation of the PapSure test. It has been approved by the American Food and Drug Administration to screen for cervical cancer and is considered a primary screening method for cervical malignancy. Colposcopy followed by biopsy, on the other hand, was used as the gold standard. You should decide if this is a widely used health technology in your own setting.

Validity of estimate of measure of effectiveness
The study was based on a within-group comparison study, which appears to have been appropriate for the study question. The study sample was very likely to be representative of the study population. The authors do not seem to have investigated the comparability of the baseline characteristics of those lost to follow-up and those who completed the study, and no reasons for losses to follow-up were reported. No appropriate statistical analysis of the effectiveness results was undertaken. Since not all of the patients received all the tests, and many patients with negative results appear not to have undergone colposcopy followed by biopsy, some bias may have been present in the study results.

Validity of estimate of measure of benefit
The summary measure of health benefit was obtained directly from the effectiveness analysis and from some further authors' estimations. The number of cases detected is a common summary measure of health benefit used in screening studies, although it does not permit comparisons across different health care interventions.

Validity of estimate of costs
The authors did not explicitly state the perspective adopted, thus making it difficult to assess whether all the relevant categories of costs were included in the analysis. The resource quantities were derived from the effectiveness study and were identified separately from the direct costs, which would facilitate reflation exercises to other settings. Most of the direct costs were derived from published sources. No statistical or sensitivity analyses of the prices were conducted, which introduced uncertainty into the reliability of the cost results. Moreover, some of the sources of the costs were not clearly identified, and the dates to which the prices related and the price year were not reported. These issues would limit the generalisability of the study findings to other settings.

Other issues
The authors made appropriate comparisons of their findings with those from other studies, reporting that the prevalence of SILs was less than that of other studies. However, this difference was not explicitly justified. In terms of the efficacy of Pap smear compared with colposcopy, the results of the study were consistent with those of other published studies. The issue of the generalisability to other settings was not addressed.

Implications of the study
The authors suggested "physicians should consider it their duty to combine in vitro and in vivo methods of examination as in the PapSure procedure or colposcopy, when dealing with the uterine cervix rather than simply taking a smear". As far as policy implications are concerned, they stressed the need for proper patient education on the nature of the disease and on the necessity for regular follow-ups. The authors did not make any explicit recommendations for
further research.

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**Other publications of related interest**


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