Clinical and economic implications of adding HPV tests to the routine cytology follow-up and management of patients with histologically defined cervical intraepithelial neoplasia grade 1


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 addition of human papillomavirus (HPV) DNA testing to the commonly applied cytology follow-up and management protocol for women with a histological diagnosis of low-grade cervical intraepithelial neoplasia (CIN1). This approach was compared with cytology alone, to detect patients at high risk of progression to invasive disease. The authors used the Hybrid Capture testing system Types I and II (Digene Corporation, Silver Spring, MD) that had demonstrated a strong correlation between positive high-risk HPV types and the presence of high-grade squamous epithelial lesion (HSIL), that is, CIN2-3, in another published study.

Type of intervention
Screening.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised women with a histological diagnosis of CIN1 that was based on punch biopsies, who had been referred to the Cervical Pathology Unit from several women's health centres in the greater Tel Aviv area. Only women who had completed a 48-month follow-up, and who had cytology, histology and HPV test reports available, were included in the study. The authors did not report any further inclusion or exclusion criteria.

Setting
The setting was secondary care. The economic analysis was carried out in Israel.

Dates to which data relate
The participants had been referred to the Cervical Pathology Unit between March 1997 and March 2000. The follow-up period lasted until April 2001 (mean 29 months). The dates to which the resource use data and prices referred were not reported. All prices were converted to US dollars using the exchange rate of May 2001.

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

Link between effectiveness and cost data
The costing was carried out retrospectively. Although it was not explicitly stated, it appears to have been carried out on the same sample of patients as that used in the effectiveness study.
Study sample
It was not apparent from the study whether the sample size was determined in the planning phase, and no power calculations were performed. The study included a cohort of 356 consecutive patients with a histological diagnosis of CIN1 that was based on punch biopsies. The mean age of the patients was 34 (±3) years (range: 16 - 52). All patients had been referred to the Cervical Pathology Unit from several women's health centres. The analysis included 314 (88.2%) of the 356 referrals who met the inclusion criteria.

Study design
Initially, the authors conducted a prospective study using repeated cytology as the sole parameter for triaging patients with histologic definition of CIN1 for further colposcopic evaluation. The analysis of HPV status of the same 314 participants was conducted retrospectively. The women were referred to the Cervical Pathology Unit from several women's health centres. The mean duration of follow-up was 29 months. The patients were followed up by Pap smears at 6-month intervals. Separate samples for the HPV tests were obtained before the Pap smears, and were taken on the first visit to the authors' institution. The authors mentioned that the clinicians caring for the patients were blinded to the results of the HPV testing until the conclusion of the trial, but the blinding method was not reported in detail. The authors did not report any losses to follow-up.

Analysis of effectiveness
From the initial study population, 42 patients were excluded for not fulfilling the inclusion criteria. The remaining 314 patients were all included in the analysis. The primary outcome was the positive predictive value (PPV) of low-grade squamous intraepithelial lesion (LSIL) to identify cases of CIN1 and of HSIL to identify cases of CIN2-3, for each of the two screening strategies. In the study there were two interventions, cytology and HPV DNA testing. These were each investigated prospectively and retrospectively on the same group of patients.

Effectiveness results
For normal cytology, the PPV of LSIL to CIN1 was 48.9% (22 cases). The PPV of HSIL to CIN2-3 was 95%. The PPV of LSIL for any type of CIN was 62% (28 cases).

For the HPV approach, a positive HPV with normal cytology had a 95.2% PPV for any type of CIN. The PPV of low-risk PHV type for CIN1 and that of high-risk HPV type for CIN2-3 were both 97%.

Of the 314 study participants, 68 (21.6%) were positive for the HPV analysis. Sixty-seven of these (98.5%) had either CIN1 or CIN2-3 on the cone biopsy, with an overall PPV of 95%.

In addition, no patient with a negative HPV had any grade of CIN. Of the 34 cases with high-risk HPV types, 33 had CIN2-3 on the cone biopsy, yielding a PPV of 97%. The PPV of low-risk HPV type for CIN1 was 97%.

Clinical conclusions
The authors concluded that, although the addition of HPV testing to the follow-up of patients with a histologic diagnosis of CIN1 did not have much benefit for patients with a cytological report of HSIL, it reduced the rate of false-negative cases, especially among patients with persistent normal cytology. It also increased the detection rate of patients who were at high risk of progressing to high-grade lesions (CIN2-3), and reduced the number of referrals for colposcopy and unnecessary biopsies without affecting diagnostic accuracy.

Measure of benefits used in the economic analysis
The authors considered cases of high-grade intraepithelial lesion detected as the most appropriate measure to be included in the economic analysis.

Direct costs
The costs were calculated from the provider's point of view. They were extrapolated from the official prices issued by the country's national health care provider, which corresponded to the government estimates for the cost of the procedures, issued to define tariffs in the public health system. The health services included in the economic analysis were visit to the doctor, Pap smear, colposcopy and cervical biopsy, histologic analysis for colposcopy, cone histology, hybrid capture test and cone biopsy. The unit costs were reported. The quantities and resource use were derived from actual data, but only the total intervention costs were reported. The authors only reported the number of cytologies, colposcopies, cone biopsies and HPV tests used. The actual costs included in the economic analysis were not reported in detail. This made it difficult to understand whether visits to the doctor, or any further health services, were incorporated. Discounting was not performed even though the costs were incurred over more than 2 years, making discounting a relevant factor. The costs were only reported in US dollars. The authors used the exchange rate for May 2001, but did not report the date to which the original prices related.

**Statistical analysis of costs**

The costs were treated deterministically.

**Indirect Costs**

The indirect costs were not included.

**Currency**

The costs were reported only in US dollars ($), using the exchange rate for May 2001.

**Sensitivity analysis**

A sensitivity analysis was not performed.

**Estimated benefits used in the economic analysis**

The "conventional approach" (cytology only) detected 26 cases of high-grade intraepithelial lesion, whereas the HPV approach detected 33 cases.

**Cost results**

The total intervention cost was $21,302 for the conventional approach (cytology) and $31,500 for the HPV approach.

**Synthesis of costs and benefits**

The cost per case of high-grade intraepithelial lesion detected was $819 for the conventional approach (cytology only) and $955 for the HPV approach.

An incremental analysis was performed. The incremental cost was $1,457 per additional case detected by the HPV approach. The authors also calculated the theoretical possibility of excluding colposcopy from the HPV approach. In this case, both approaches proved to have almost identical costs for detecting one case of HSIL, namely $820.

**Authors' conclusions**

The range of costs resulting from the economic analysis for detecting high-grade cervical intraepithelial neoplasia (CIN) and preventing potentially invasive cervical carcinoma “should be regarded as worthwhile by any economic evaluation”.

**CRD COMMENTARY - Selection of comparators**

The reason for the choice of the comparators was explicitly stated. Cytology represented standard practice in the
authors' setting. HPV testing was chosen as it had demonstrated a strong correlation between positive high-risk HPV types and the presence of HSIL (i.e. CIN2-3). The authors wanted to test whether the HPV status would help to target those patients who were more likely to progress among women with histologically diagnosed CIN1 lesions. You should decide if this represents a valid comparator in your own setting.

**Validity of estimate of measure of effectiveness**
The authors carried out a prospective study using repeated cytology as the sole parameter for triaging patients with a histologic definition of CIN1 for further colposcopic evaluation. The analysis of HPV status was carried out retrospectively on the same study group. By using this kind of analysis, the authors hoped to assess the potential contributions of adding HPV testing to the commonly applied cytology protocols. The authors did not undertake any statistical analysis to take potential biases and confounding factors into consideration.

**Validity of estimate of measure of benefit**
The measure of benefit used was cases of high-grade intraepithelial lesion detected. This was obtained directly from the effectiveness analysis. There was no yardstick by which to judge the value of this measure of benefit.

**Validity of estimate of costs**
The authors did not explicitly state the perspective adopted in the study. However, it could not have been societal as the indirect costs were not included. The authors reported only the total intervention costs, that is, the costs and the quantities were not reported separately. This made it difficult to determine whether all the categories of costs were included. No sensitivity analysis of the quantities or prices was conducted, which may limit the interpretation of the study findings. Discounting was not performed even though the costs were incurred during more than two years, making discounting a relevant factor. The costs were reported only in US dollars. The authors used the exchange rate for May 2001, but the date to which the actual prices related was not reported.

**Other issues**
The authors made appropriate comparisons of their findings with those from other studies, finding consistency in their results. The issue of generalisability to other settings was not addressed. The authors did not present their results selectively. The study enrolled patients with a histological diagnosis of CIN1 and this was reflected in the authors' conclusions.

**Implications of the study**
The authors did not make any recommendations for policy or practice. They suggested that since their study demonstrated that all patients with CIN2-3 had high-risk HPV types, this would facilitate the analysis of the high-risk types only, thus reducing the costs. They also suggested that the benefits of HPV testing on health, economic and medico legal consequences warrant a cost-utility analysis.

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