A cost-effectiveness analysis of four management strategies in the determination and follow-up of atypical squamous cells of undetermined significance

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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
Four strategies for the management of women with atypical squamous cell of undetermined significance (ASC-US) cytological findings on a Papanicolaou (Pap) smear were examined. Strategy 1 was immediate colposcopy, where all women with an ASC-US Pap smear were referred to colposcopy.

Strategy 2 was repeat Pap smear, where women with an initial ASC-US Pap smear returned for a repeat Pap smear within 6 months. Referral to colposcopy occurred only if the second Pap result was ASC-US or greater.

Strategy 3 was conventional Pap smear with reflex human papillomavirus (HPV) testing, where conventional Pap with reflex HPV testing was used for an ASC-US Pap result. Women were only referred to colposcopy if high-risk HPV genotypes were identified.

Strategy 4 was liquid-based cytology with reflex HPV testing. This was identical to the third strategy, with the exception that liquid-based cytology was substituted for the conventional Pap smear.

HPV testing consisted of using the HC II method in which its high-risk probe is able to detect any of 13 high-risk HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68).

The colposcopic examination consisted of all abnormal cervical areas biopsied for all women and the performance of an endocervical brushing of the endocervical canal.

Women diagnosed with cervical intraepithelial neoplasia (CIN) 2 or CIN 3 on colposcopy were referred for ablative therapy using the loop electrosurgical excision procedure (LEEP). Each woman, regardless of the colposcopy result, was asked to return for a repeat smear by either conventional or liquid-based cytology methods, depending on the assigned management strategy, within a 6-month time period.

Type of intervention
Screening.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised a hypothetical cohort of women aged 18 years or older. Three age cohorts were considered in the analysis, 18 - 24 years, 24 - 34 years and >34 years.

Setting
The setting was secondary care. The economic study was carried out in the USA.
Dates to which data relate
The clinical data came from studies published between 1993 and 2003. The resource use data and costs were derived from 2002 sources. The price year was 2002.

Source of effectiveness data
The effectiveness evidence was derived from a synthesis of completed studies and authors' assumptions.

Modelling
A decision model was developed to estimate the costs and benefits of the four screening strategies under investigations. Three hypothetical cohorts of 10,000 women aged 18 - 24 years, 24 - 34 years or >34 years were followed for 1 year. No other details of the model were provided.

Outcomes assessed in the review
The outcomes assessed in the review were:

- the sensitivity and specificity of the conventional Pap smear, liquid-based cytology, HPV test, repeat conventional Pap smear, and colposcopy/biopsy;
- cancer incidence;
- the rate of women lost to follow-up with repeat cytology testing, colposcopy and LEEP;
- the incidence of human immunodeficiency virus (HIV);
- HPV regression;
- the rates of ASC-US;
- the results of colposcopy (negatives or CIN1, CIN 2-3); and
- the rate of persistent ASC-US after conventional Pap smear or after liquid-based cytology.

Study designs and other criteria for inclusion in the review
A systematic review was carried out to identify all relevant studies. The designs of the studies were not described and the inclusion and exclusion criteria were not reported, although only English-language articles were considered.

Sources searched to identify primary studies
MEDLINE was searched from 1990 to July 2003 using the keywords "cost-effectiveness", "Pap smear", "liquid-based cytology", "HPV" and "cervical neoplasia".

Criteria used to ensure the validity of primary studies
Not stated.

Methods used to judge relevance and validity, and for extracting data
Not stated.

Number of primary studies included
Twenty-three primary studies were included in the review.
Methods of combining primary studies
The primary studies appear to have been combined using a narrative method.

Investigation of differences between primary studies
Not stated.

Results of the review
The sensitivity and specificity were, respectively:

0.62 (range: 0.43 - 0.84) and 0.89 (range: 0.70 - 1.00) for conventional Pap smear,
0.81 (range: 0.68 - 0.96) and 0.78 (range: 0.41 - 1.00) for liquid-based cytology,
0.75 (range: 0.33 - 1.00) and 0.73 (range: 0.51 - 0.95) for HPV test,
0.75 (range: 0.60 - 0.93) and 0.62 (range: 0.57 - 0.65) for repeat conventional Pap smear, and
0.94 (range: 0.81 - 1.00) and 0.84 (range: 0.52 - 1.00) for colposcopy/biopsy.

The rate of cancer incidence was 0.11 (range: 0 - 0.25) for women aged 18 - 24 years, 0.97 (range: 0.44 - 1.53) for age 24 - 34 years, and 1.49 (range: 1.31 - 1.68) for age older than 34 years.

The rate of women lost to follow-up was 0.21 (range: 0.11 - 0.32) with repeat cytology testing, 0.10 (range: 0.07 - 0.12) with colposcopy, and 0.04 (range: 0.03 - 0.04) with LEEP.

The HIV incidence was 0.16 (range: 0.04 - 0.30) for women aged 18 - 24 years, 0.09 (range: 0 - 0.28) for age 24 - 34 years, and 0.04 (range: 0 - 0.11) for age older than 34 years.

The annual HPV regression rate was 0.49 (range: 0.31 - 0.71) for women aged 18 - 24 years, 0.27 (range: 0 - 0.49) for age 24 - 34 years, and 0.11 (range: 0 - 0.22) for age older than 34 years.

The rates of ASC-US were 0.08 (range: 0.03 - 0.12) for women aged 18 - 24 years, 0.06 (range: 0.02 - 0.12) for age 24 - 34 years, and 0.05 (range: 0 - 0.11) for age older than 34 years.

The rate of negative or CIN 1 results from colposcopy was 0.92 (range: 0.89 - 0.94).

The rate of CIN 2-3 results from colposcopy was 0.08 (range: 0.06 - 0.10).

The rate of persistent ASC-US was 0.44 (range: 0.23 - 0.59) after conventional Pap smear and 0.49 (range: 0.44 - 0.53) after liquid-based cytology.

Methods used to derive estimates of effectiveness
The authors made some assumptions on screening patterns.

Estimates of effectiveness and key assumptions
It was assumed that women whose cancer was not detected (false-negative result) would not have the abnormality identified before progression of the abnormality. In addition, women lost to follow-up would not be seen at a different facility for additional cytological testing or treatment.

Measure of benefits used in the economic analysis
The summary benefit measure used was the number of true positives. Other outcomes were the numbers of false positives and false negatives and total cancers missed. All benefit measures were obtained from the decision model. No discounting was applied given the short time horizon.

**Direct costs**
Discounting was not relevant since the costs were incurred during a timeframe shorter than two years. The unit costs were presented, whereas information on resource consumption was unclear. The economic evaluation considered the costs of colposcopy and biopsy, LEEP, HPV test, conventional Pap smear, liquid-based cytology, and storage fee for additional HPV specimen. All screening tests included fees for complex office visit and pathology with clinical consult. The cost/resource boundary of the health care system was adopted. The estimation of costs and, presumably, of resources used was based on Medicare reimbursement rates. The price year was 2002.

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

**Indirect Costs**
The indirect costs were not included in the economic evaluation.

**Currency**
US dollars ($).

**Sensitivity analysis**
No sensitivity analyses were carried out.

**Estimated benefits used in the economic analysis**
In the three cohorts of 10,000 women for each age groups (30,000 women in total), the number of true-positive results was 2,337 with immediate colposcopy, 6,566 with repeat Pap test, 1,869 with conventional Pap test with reflex HPV testing, and 2,870 with liquid-based cytology with reflex HPV testing.

The number of false positives was 4,333 with immediate colposcopy, 14,458 with repeat Pap test, 4,585 with conventional Pap test with reflex HPV testing, and 8,735 with liquid-based cytology with reflex HPV testing.

The number of false negatives was 1,007 with immediate colposcopy, 1,703 with repeat Pap test, 926 with conventional Pap test with reflex HPV testing, and 704 with liquid-based cytology with reflex HPV testing.

The total cancers missed were 17.77 with immediate colposcopy, 50.65 with repeat Pap test, 9.49 with conventional Pap test with reflex HPV testing, and 10.00 with liquid-based cytology with reflex HPV testing.

**Cost results**
In the three cohorts of 10,000 women in each age group, the estimated per patient costs (including the cost of false-positive results) were:

$135.58 with immediate colposcopy,

$178.72 with repeat Pap test,

$103.51 with conventional Pap test with reflex HPV testing, and

$114.21 with liquid-based cytology with reflex HPV testing.
Consistently, higher costs were observed for the youngest cohort.

Synthesis of costs and benefits
Average and incremental cost-effectiveness ratios (ACER and ICER, respectively; i.e. the cost per true-positive result) were calculated to combine the costs and benefits of the alternative screening tests.

The ACER was $1,740.47 for immediate colposcopy, $816.58 for repeat Pap smear, $1,661.46 for conventional Pap test with reflex HPV testing, and $1,193.78 with liquid-based cytology with reflex HPV testing. Stratifying by age, the total costs were higher for the 18 - 24 year age group than for women older than 34 years. However, for all management strategies, the ACER was calculated to be lower in the youngest age group.

The ICER was $331.58 for liquid-based cytology versus conventional Pap smear and $306.66 for repeat Pap smear versus immediate colposcopy. The strategy of immediate colposcopy was dominated by liquid-based cytology with reflex HPV testing, which was more effective and less costly. All ICERs were higher with increasing age for all four strategies.

Authors' conclusions
The use of reflex human papillomavirus (HPV) testing in the management of an atypical squamous cell of undetermined significance (ASC-US) Pap smear resulted in lower overall management costs and fewer women with false-positive results being referred to colposcopy. Strategies using repeat cytology led to high costs and fewer clinical benefits, while immediate colposcopy detected fewer actual abnormalities and was more costly. Overall, strategies incorporating reflex HPV testing, particularly with liquid-based cytology, were the most cost-effective.

CRD COMMENTARY - Selection of comparators
The selection of the comparators was appropriate since several screening strategies for cervical cancer were considered. A detailed description of each intervention was provided. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness evidence came from published sources. A review of the literature was undertaken to identify relevant studies. The method and conduct of the review were described. However, there was no information on the designs of the primary studies, or the methods used to ensure the validity of the primary studies and to combine the clinical estimates. Further, uncertainty in the clinical data was not investigated in the sensitivity analysis. Ranges of values were reported, but only average values appear to have been used. Some key assumptions on screening patterns were also made.

Validity of estimate of measure of benefit
The summary benefit measures were specific to the interventions or diseases considered in the study and are not comparable with the benefits of other health care interventions. The impact of the screening strategies on quality of life was not investigated.

Validity of estimate of costs
The perspective adopted in the study was explicitly stated. Only the direct medical costs associated with the screening procedures considered in the study were included in the economic evaluation. The costs associated with cancer care in women who developed the disease were not taken into consideration. Similarly, the inclusion of the indirect costs would have been interesting, although the authors stated that their inclusion would increase the costs associated with repeat Pap test. The unit costs of the screening procedures were reported. However, there was limited information on resource use, which limits the possibility of replicating the analysis in other settings. The cost estimates were treated deterministically and were specific to the study setting. The source of the costs was provided. No adjustment for
geographic variations in the costs was performed. The price year was reported, which aids reflation exercises in other settings.

Other issues
The authors did not make extensive comparisons of their findings with those from other studies, but stated that their findings were consistent with those published in the literature. The issue of the generalisability of the study results to other settings was not addressed and sensitivity analyses were not performed. This reduces the external validity of the study. The authors noted that a strategy of performing immediate colposcopy for all ASC-US smears could be considered as an overly aggressive management approach, because the majority of low-grade lesions will regress without any intervention. Some limitations of the analysis were also highlighted. For example, the women were stratified by age but not by race. In addition, the LEEP was used as a treatment strategy, which could have generated further costs for the management of noninvasive lesions.

Implications of the study
The study results supported the use of screening strategies including reflex HPV testing, particularly with liquid-based cytology, for the detection of cervical cancer.

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None stated.

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Other publications of related interest


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