Impact of increasing Papanicolaou test sensitivity and compliance: a modeled cost and outcomes analysis

Montz F J, Farber F L, Bristow R E, Cornelison T

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 liquid-based cytology (LBC) to improve the sensitivity of conventional Papanicolaou smear (CPS) screening (with 10% re-screening) for the detection of cervical cancer (CC).

Type of intervention
Screening.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised a hypothetical cohort of 20-year-old women. Sub-groups of white and black women were considered. In addition, a sub-group of elderly women aged older than 50 years was considered.

Setting
The setting was secondary care. The economic study was carried out in the USA.

Dates to which data relate
The effectiveness and some resource use data were derived from studies published between 1986 and 2000. The price year was 1997.

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

Modelling
A published time-varying, longitudinal Markov model was modified and used to examine the clinical and economic impact of using LBC screening, in comparison with usual screening based on CPS, in a hypothetical cohort of 100,000 20-year-old women screened until age 80 years. The cycle length was one year. Each member of the cohort was assigned a variety of possible health outcomes:

- contraction of CC,
- death from CC,
- death from other causes,
CC survivors,
hysterectomy,
true-negative screening,
true-positive screening, that is, all grades of cervical intra-epithelial neoplasia (CIN), carcinoma in situ (CIS), or squamous cell cancer found on colposcopy,
false-negative screening, and
false-positive screening.

Women with a positive screening test received colposcopy and appropriate treatment. After a treated CIN, women had the potential to develop CIN again. Women who were CC survivors, or who had a hysterectomy, were removed from the screening pool.

Outcomes assessed in the review
The outcomes estimated from the literature were:
- the rates of death from all causes,
- data associated with CC (including incidence and death rates),
- the age-specific rates of hysterectomy,
- the false-negative rates for CPS and LBC, and
- compliance rates, divided into three categories according to compliance (never compliant women, partially compliant women, and fully compliant women).

Study designs and other criteria for inclusion in the review
It was unclear whether a systematic review of the literature had been undertaken to identify relevant studies. The design of the primary studies was unclear. Death from all causes and data associated with CC were derived from National Statistics. Three sets of compliance rates were considered:
- self-reported compliance rates, as derived from the Behavioral Risk Factor Surveillance System;
- compliance using Healthy People 2000 goals (5% never compliant, 85% fully compliant, and 10% partially compliant women); and
- Healthy People 2010 goals (3% never compliant, 90% fully compliant, and 7% partially compliant women).

Sources searched to identify primary studies
Not stated.

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
Eleven primary studies provided the clinical evidence.

Methods of combining primary studies
Where the primary estimates were combined, a narrative method appears to have been used.

Investigation of differences between primary studies
Not stated.

Results of the review
The mean age of women with any CIN lesion was 35, with a peak incidence of 3,550 per 100,000 women at age 29.

All CIN lesions regressed at the rate of 65% over 6 years for ages 20 to 34 years, and at the rate of 40% over 6 years for ages 35 plus and over.

Thirty-five per cent of CIS lesions regressed over 6 years. Progression from CIN to CIS occurred in 6 years, whereas progression from CIS to cancer occurred in 10 years.

To account for interval cancers, 10% of all CINs that would ever progress to cancer would do so within 1 year.

The false-negative rate was 49% with CPS and 27% (20% to 40%) with LBC.

Other data were not reported.

Methods used to derive estimates of effectiveness
Some assumptions were made and used in the decision model.

Estimates of effectiveness and key assumptions
Fully compliant women were divided equally between those women screened annually, biannually and triennially. Half of the partially compliant women were screened every 5 years, while the other half was screened once every 10 years. Noncompliant women had incidence rates of CC equal to the rate in an unscreened sub-population.

Measure of benefits used in the economic analysis
The summary benefit measure used was the expected survival associated with the two alternative screening strategies. The main model output was the average incidence of CC over the course of screening. An annual discount rate of 3% was applied to the expected survival.

Direct costs
Discounting was relevant since the costs were incurred during a long timeframe. An annual discount rate of 3% was applied. The unit costs were presented only for some items, and a detailed breakdown of the costs was not provided since some costs were presented as macro-categories. The health services included in the economic evaluation were CPS, LBC, clinic visit, colposcopy, treatment for CIN and CC, and resources associated with terminal care and CC survivors. The costs associated with the reference visits were not considered. The cost/resource boundary of the study appears to have been that of the third-party payer. The costs were estimated on the basis of median charges for indemnity insurers, which were derived from Current Procedural Terminology codes and a published study. The source of the resource use data was less clear but some quantities were derived from the literature. The price year was 1997.
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
Univariate sensitivity analyses were performed to investigate the impact of changing the sensitivity value of both CPS (40% false-negative rate) and LBC (20% to 40% false negative-rates). The ranges of values were derived from authors' assumptions and published evidence.

Estimated benefits used in the economic analysis
Using self-reported compliance rates, the expected average yearly incidence of CC was:
- 12.4 cases in the full cohort (11.8 cases for white women and 15.1 cases for black women) without screening,
- 11.8 cases in the full cohort (10.8 cases for white women and 13.5 cases for black women) with CPS, and
- 8 cases in the full cohort (7.3 cases for white women and 9.1 cases for black women) with LBC.

Using Healthy People 2000 compliance goals, the expected average yearly incidence of CC was:
- 10.5 cases in the full cohort (9.6 cases for white women and 12.6 cases for black women) with CPS, and
- 7 cases in the full cohort (6.4 cases for white women and 8.3 cases for black women) with LBC.

Using Healthy People 2010 compliance goals, the expected average yearly incidence of CC was:
- 9.1 cases in the full cohort (8.4 cases for white women and 11.3 cases for black women) with CPS, and
- 5.9 cases in the full cohort (5.4 cases for white women and 7.2 cases for black women) with LBC.

Therefore, the use of LBC reduced CC incidence in comparison with CPS screening. The results held in the sensitivity analysis when compliance rates were varied for both CPS and LBC. The reductions in the incidence of CC were confirmed also in the cohort of elderly women (aged older than 50 years), but these improvements were even more dramatic, especially among black women.

The estimated survival was not reported.

Cost results
The estimated costs were not reported.

Synthesis of costs and benefits
An incremental cost-effectiveness ratio (ICER; i.e. cost per life-year saved) was calculated to combine the costs and benefits.

The ICER of LBC over CPS was:
$15,296 ($17,967 for white women and $10,335 for black women) using self-reported compliance rates,

$16,796 ($19,466 for white women and $10,244 for black women) using Healthy People 2000 compliance goals, and

$20,424 ($23,503 for white women and $11,346 for black women) using Healthy People 2010 compliance goals.

The sensitivity analysis revealed that the ICER of LBC over CPS remained below the value of $50,000 per life-year saved in all patient populations at all compliance levels. If LBC operated at a 20% false-negative rate, the ICER was less than $20,000 per life-year saved for all populations and was less than $10,000 for black women.

Improvements in compliance from Healthy People 2000 compliance goals to Healthy People 2010 compliance goals did not change substantially the ICER of LBC over CPS for women at current higher compliance rates (i.e. black women), but it did lead to slight increases in the ICER of less compliant groups.

Authors' conclusions
Liquid-based cytology (LBC) used to improve the sensitivity of conventional Papanicolaou smear (CPS) screening for cervical cancer (CC) was a cost-effective strategy in conjunction with increased compliance.

CRD COMMENTARY - Selection of comparators
The selection of the comparator was appropriate since it reflected usual care in the authors' setting. You should decide whether this is a valid comparator in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness evidence came mainly from published evidence. However, it was not stated whether a systematic review of the literature had been undertaken to identify primary studies. Further, no information on the characteristics and patient populations of the primary studies was provided, although most of the evidence came from national statistics. The methods used to extract and then combine the primary estimates were not described. Similarly, no comments on the quality and comparability of the primary sources were made. Experts' opinions were used to derive some clinical estimates. Almost all of the clinical inputs were varied in the sensitivity analysis.

Validity of estimate of measure of benefit
The use of life-years as the summary benefit measure was appropriate because it captured the impact of the screening strategies on the most relevant dimension of health, that is, survival. Survival is comparable with the benefits of other health care interventions. Discounting was applied, as recommended in US guidelines. The impact of the interventions on CC incidence rates was also reported, because it represented a relevant model output.

Validity of estimate of costs
The perspective of the third-party payer was adopted and reimbursement rates were used as a proxy for the costs. Only medical direct costs were included in the analysis. Information on the unit costs and the quantities of resources used was not reported separately for all items. The fact that some costs were presented as macro-categories reduces the possibility of replicating the results of the analysis. The source of the costs was given, but the information pertaining to the source of resource consumption was less clear. The costs were treated deterministically and were specific to the study setting. The price year was reported, which makes reflation exercises in other settings easy.

Other issues
The authors stated that their findings varied markedly from a published study but were similar to the results of another study. The reasons for the potential differences between the conclusions were discussed. The issue of the generalisability of the study results to other settings was not explicitly addressed and only a few sensitivity analyses were performed. This reduces the external validity of the analysis. The authors noted that the use of assumptions not
supported by literature-based evidence, and the fact that some hidden costs were not accounted for in the analysis, represent two important weaknesses of the study.

**Implications of the study**
The study results supported the use of LBC screening for the detection of CC. However, the authors pointed out that increased compliance and LBC should be used in parallel to improve the cost-effectiveness of CC screening in all patient populations.

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