Cost-effectiveness of human papillomavirus DNA testing for cervical cancer screening in women aged 30 years or more

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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
Several strategies for cervical cancer screening were examined:

- conventional cytology (Pap test) for women of all ages (CCall);
- conventional cytology until age 30, with reflex human papillomavirus (HPV) DNA testing and Pap test for women aged 30 years or more (CHPV30);
- liquid-based cytology with HPV DNA testing for women of all ages (LHPVAll); and
- liquid-based cytology until age 30, with HPV DNA testing and Pap test for women aged 30 years or more (LHPV30).

Each screening strategy was performed at different time intervals (1, 2, 3 or 4 years). Thus, 16 strategies were considered.

Type of intervention
Screening.

Economic study type
Cost-utility analysis.

Study population
The study population comprised a hypothetical cohort of women followed from 13 years of age. The target population depended on the screening strategy considered.

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

Dates to which data relate
The effectiveness data were, in part, derived from studies published from 1986 to 2004. The costs and resource use data were estimated from studies published between 1999 and 2004. The price year was 2001.

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

Modelling
A state-transition mathematical model was constructed to simulate the natural history of a hypothetical cohort of
sexually naive women who entered the model at the age of 13 and each month faced an age-dependent risk of acquiring HPV. Women with HPV infection or established cervical lesions could regress to normal, or progress to higher-grade lesions or cervical cancer. Women could die of a cervical cancer-related illness or other causes. The time horizon of the model was the patient's lifetime. Monthly cycles were used. No other details of the model were provided. To validate the model, the results were compared with data from an independent prospective cohort study.

Outcomes assessed in the review
The outcomes estimated from the literature were:

the transition probabilities associated with the natural history of cervical cancer;
the probabilities of cytology results;
the 5-year cancer survival rate;
the annual probabilities of symptom detection; and

test characteristics.

Study designs and other criteria for inclusion in the review
It was not stated whether a systematic review of the literature was undertaken to identify all relevant studies with which to populate the decision model. Limited information on the design of the primary studies was provided.

Sources searched to identify primary studies
Not stated.

Criteria used to ensure the validity of primary studies
The authors did not report any explicit criteria used to ensure the validity of the primary sources. However, it was stated that, whenever possible, data from the largest clinical trials as well as from comprehensive reviews and meta-analyses were used for the estimation of test characteristics.

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

Number of primary studies included
Forty-two primary studies provided clinical inputs for use in the decision model.

Methods of combining primary studies
Not stated.

Investigation of differences between primary studies
Not stated.

Results of the review
The transition probabilities associated with the natural history of cervical cancer were as follows:

from normal to HVP DNA, 0.0007 to 0.0209 (age-specific);
from HPV DNA to cervical intraepithelial neoplasia (CIN 1), 0.0046;
from CIN 1 to CIN 1,2, 0.0011 to 0.0039 (age-specific);
from CIN 2,3 to local invasive cancer, 0.0040;
from local invasive cancer to regional invasive cancer, 0.0200;
from regional invasive cancer to distant invasive cancer, 0.0250;
from HPV DNA to normal, 0.0028 to 0.0397 (age-specific);
from CIN 1 to normal, 0.0068 to 0.0128 (age-specific);
from CIN 2,3 to normal, 0.0029.

The probabilities of cytology results among women with abnormal cytology and CIN 1,2 were as follows:
atypical squamous cells (ASC), 0.380;
ASC of undetermined significance (ASC-US), 0.265;
ASC that cannot exclude a high-grade lesion (ASC-H), 0.115;
low-grade squamous intraepithelial lesion (SIL), 0.450;
high-grade SIL, 0.170.

The 5-year cancer survival rate was 0.86 for local invasive cancer, 0.43 for regional invasive cancer, and 0.11 for distant invasive cancer.

The annual probability of symptom detection was 0.19 for local invasive cancer, 0.60 for regional invasive cancer, and 0.90 for distant invasive cancer.

The test characteristics were as follows:

the sensitivity of ThinPrep cervical cytology was 84% and the specificity was 88%;
the sensitivity of conventional cervical cytology was 69% and the specificity was 97%;
the sensitivity of HPV DNA testing was 88% and the specificity was 95%;
the sensitivity of HPV DNA testing and cytology was 94% and the specificity was 93%.

Methods used to derive estimates of effectiveness
The authors made some assumptions to derive the clinical estimates used in the model.

Estimates of effectiveness and key assumptions
Screening began at an average of 18 years.

Colposcopy was performed for ASC-H or SIL cytology, but treatment was reserved for biopsy-confirmed CIN 2,3.

Women with CIN 1 and previously treated CIN 2,3 were followed with annual cytology.

Women with liquid-based cytology results of ASC-US were managed by using reflex HPV DNA testing.
Women with a conventional cytology result of ASC-US underwent a repeat conventional cytology, and were referred for colposcopy only if the repeat cytology was ASC-US or greater.

In all HPV DNA testing strategies, HPV-positive women were referred for colposcopy.

In all HPV DNA testing strategies, it was assumed that women with CIN 1 and those with treated CIN 2,3 would be followed with annual HPV testing and cytology.

Compliance with primary screening and follow-up was 100%.

**Measure of benefits used in the economic analysis**
The summary benefit measure was life expectancy (LE). Quality-adjusted LE was also estimated by combining survival and utilities derived from the literature. However, no details on the use of quality adjustments were provided. The absolute lifetime cervical cancer risk and the reduction in lifetime cancer risk in comparison with no screening were also reported for each strategy. An annual discount rate of 3% was applied.

**Direct costs**
An annual discount rate of 3% was used as the lifetime costs were estimated. The unit costs were presented for items associated with the screening tests, whereas aggregated costs were given for treatments and cancer care. The economic evaluation considered the costs of the screening procedures, colposcopy and biopsy, and treatment of cancer (depending on disease stage). The costs of screening procedures covered normal Pap, abnormal Pap with physician review, and office visit for cervical cytology; and counselling and co-collection fee with conventional cytology for HPV DNA testing. The cost/resource boundary of the study was that of society. The costs and resource use data were derived from studies and other published sources. All the costs were inflated to 2001 values using the medical care component of the Consumer Price Index.

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

**Indirect Costs**
The indirect costs (i.e. time costs) were included in the economic evaluation. Resource use was based on authors’ assumptions and published evidence. The costs came from the Bureau of Labor Statistics. The unit costs and quantities of resources used were provided. The price year was 2001. The costs were discounted at an annual rate of 3%.

**Currency**
US dollars ($).

**Sensitivity analysis**
Several model inputs were varied in order to address the robustness of the model results. Univariate sensitivity analyses were performed. The ranges of values used were presumably derived from the literature or other sources used to define model inputs.

**Estimated benefits used in the economic analysis**
The estimated LE, quality-adjusted LE, absolute lifetime cervical cancer risk (reduction in lifetime cancer risk in comparison with no screening) were, respectively:

28.6987, 27.5352 and 0.0326 with no screening;
Cost results
The average lifetime costs per woman were:

$210 with no screening;
$1,009 with CCall every 4 years;
$1,163 with LHPVall every 4 years;
$1,196 with CCall every 3 years;
$1,213 with CHPV30 every 4 years;
$1,358 with LHPVall every 3 years;
$1,377 with LHPV30 every 4 years;
$1,453 with CHPV30 every 3 years;
$1,536 with CCall every 2 years;
$1,647 with LHPV30 every 3 years;
$1,707 with LHPVall every 2 years;
$1,899 with CHPV30 every $2 years;
$2,151 with LHPV30 every 2 years;
$2,457 with CCall every 1 year;
$2,653 with LHPVall every 1 year;
$3,135 with CHPV30 every 1 year;
$3,575 with LHPV30 every 1 year.

**Synthesis of costs and benefits**

An incremental cost-effectiveness ratio was calculated to combine the costs and benefits of the alternative diagnostic strategies.

After excluding dominated strategies, the incremental cost per life-year gained (in comparison with the next best non-dominated strategy) was:

- $9,400 with CCall every 4 years (compared with no screening),
- $20,600 with LHPVall every 4 years,
- $95,300 with LHPVall every 3 years,
- $228,700 with LHPV30 every 3 years,
- $257,400 with LHPVall every 2 years,
- $452,600 with LHPV30 every 2 years,
- $2,215,100 with LHPV30 every year.

When quality-adjusted life-years were used, the cost-utility ratios were approximately 20% lower than the previously reported cost-effectiveness ratios.

The sensitivity analysis showed that the rank-ordering of the strategies was not sensitive to variations in the natural history parameters, cost of the diagnostic workup for an abnormal screening test result, and costs associated with CIN 2,3 and cancer.

However, some changes were observed. For example, if the cost of the HPV test was reduced by 25%, lifetime liquid-based cytology alone was dominated by strategies with primary HPV DNA testing in women aged 30 or older at nearly all screening intervals. The relative performance and cost of each test had the greatest impact on the results of the analysis.

When the sensitivity and specificity of liquid-based cytology were above 87% and 90%, respectively, liquid-based cytology was nearly always preferred. However, if these values were below 79% and 86%, respectively, then HPV testing was the preferred option.

**Authors’ conclusions**

Compared with annual conventional cytology, screening at 2- or 3-year intervals with either liquid-based cytology (with HPV DNA testing used only for atypical squamous cells of undetermined significance) or human papillomavirus (HPV) DNA testing combined with cytology in women aged 30 years or more provided increased protection against cervical cancer while reducing the average per-women lifetime costs associated with screening.
CRD COMMENTARY - Selection of comparators
The selection of the comparators was appropriate as several screening strategies for the detection of cervical cancer were considered. Different test intervals were also examined. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness evidence came from a synthesis of published studies. It appears that the primary studies have been identified selectively rather than from a systematic review of the literature. The details of the study characteristics and patient samples were not extensive. However, it appears that the majority of the data have been derived from large clinical trials or meta-analyses, thus ensuring the internal validity of the study. The estimation and calculation of some clinical inputs were extensively described in an appendix. The authors also made some assumptions to derive effectiveness data and to define the decision model. Extensive sensitivity analyses were carried out on clinical inputs in order to assess the robustness of the model results.

Validity of estimate of measure of benefit
The summary benefit measure (life-years) was appropriate because it considers the most relevant aspect of health affected by the interventions. The impact of the interventions on quality of life was also investigated using quality-adjusted life-years, although a less robust analysis was carried out since no information on utility weights was reported. Discounting was applied, as recommended by US guidelines. Other model outputs were also reported.

Validity of estimate of costs
The selection of a societal perspective was appropriate. A detailed breakdown of the cost items was not provided since some costs were presented as macro-categories. Similarly, the unit costs were presented only for a few categories of costs. The source of the data was reported for most items. No statistical analyses of the costs were performed, but key cost estimates were varied in the sensitivity analysis. The price year was given, which enhances the possibility of performing reflation exercises in other time periods.

Other issues
The authors noted that their findings were consistent with those from published studies that had reported that less frequent screening with more sensitive tests was likely to be cost-effective. The issue of the generalisability of the study results to other settings was not explicitly addressed, although it was partially addressed in the sensitivity analysis. The authors noted some limitations of their study. For example, the fact that some unknown factors contributing to population heterogeneity and to an individual's risk of disease progression could not be modelled. Further, there was considerable uncertainty in the longitudinal nature of HPV infections. It was noted that there were no empiric data suitable for inclusion in the decision model, especially for some cost categories and quality of life decrements.

Implications of the study
The study results support the recommendations made by professional societies and organisations. In particular, liquid-based cytology coupled with reflex HPV DNA testing for ASC-US and high-risk HPV DNA testing in conjunction with cytology (either liquid-based or conventional) after women reach the age of 30 years.

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