Cost-effectiveness of pap smear screening for vaginal cancer after total hysterectomy for benign disease

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 Papanicolaou (Pap) smear screening for vaginal cancer, following a total hysterectomy for benign disease.

Type of intervention
Screening.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised a hypothetical cohort of women aged 40 or older, with a history of total hysterectomy for benign disease. Women with a history of premalignant or malignant genital disease, maternal exposure to diethylstilbestrol, other risk factors for genital malignancy, or supracervical hysterectomy were excluded from the analysis.

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

Dates to which data relate
The effectiveness data, test characteristics and transition probabilities were obtained from literature published between 1979 and 2001. The year to which the cost data referred (both resources and prices used) was not stated.

Source of effectiveness data
The effectiveness data were derived from a review and synthesis of published studies. The authors used estimates derived from expert opinion in areas where the data were incomplete.

Modelling
Three decision models were used to estimate the total costs and benefits of various clinical approaches to screening after total hysterectomy, which were then compared with "no screening". All of the models incorporated the test characteristics (sensitivity and specificity) of Pap smear screening, the risk of vaginal cancer, and the survival rates of healthy women and women in different stages of cancer. Possible outcomes of the models included disease-free survival, cell abnormalities or cancer that received treatment, and death.

The first model, structured as a decision tree, assumed one-time screening at the age of 50.

The second model was similar, except that it included an additional tree, representing a second screening at the age of
60 for patients who were disease free after the first screening.

In the third model, a Markov model, two different patient cohorts (aged 40 and aged 50) were screened annually until they had three normal smears, after which they were screened every 3 years. This model reflected practice widely recommended in the USA.

Thus, three screening strategies were evaluated for women aged 50, and one for women aged 40, all against "no screening".

Outcomes assessed in the review
The outcomes assessed in the review and used as input parameters in the model were:

- the test characteristics (sensitivity and specificity) of the Pap smear test for the detection of vaginal cancer;
- the prevalence and the progression (death) rates of vaginal cancer; and
- the survival rates of women without vaginal cancer.

Clinical strategies and screening recommendations were extracted from the review in order to construct the models.

Study designs and other criteria for inclusion in the review
All English language studies on hysterectomy and vaginal smears or vaginal smears and vaginal neoplasms were included in the review. No further inclusion or exclusion criteria were stated.

Sources searched to identify primary studies
MEDLINE was searched for the primary studies used in the analysis. Major gynaecologic textbooks were also reviewed for relevant information.

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

Methods used to judge relevance and validity, and for extracting data
Research team clinicians and health services researchers extracted the data from the literature. No further details were reported.

Number of primary studies included
Approximately 5 primary studies were included in the review.

Methods of combining primary studies
According to the authors, parameter estimates were combined using meta-analytic methods, where appropriate. Where possible, the range of estimates was used in the sensitivity analysis.

Investigation of differences between primary studies
Although the authors identified differences in the estimates between individual studies, they did not provide any further analysis or justification for these differences.

Results of the review
The sensitivity of the Pap smear test was 0.80 and the specificity was 0.994.

The life expectancy for patients without cancer was 29.762 years at age 50 and 21.439 years at age 60.

The 5-year survival rate for patients with vaginal cancer was 0.66 at stage I/IIA cancer, 0.298 at stage IIB/III cancer and 0 at stage IV cancer.

The risk of vaginal cancer among women with positive Pap smears could not, apparently, be identified in the review of the literature. The authors therefore made assumptions on the basis of expert opinion (see Estimates of Effectiveness and Key Assumptions).

**Methods used to derive estimates of effectiveness**

Where the required data for the analysis could not be identified in the literature, best estimates were obtained through an expert panel discussion of the particular issue and identification of a best estimate of the clinical parameter in question. The expert panel included members with expertise in obstetrics, pathology, family medicine and health policy. The experts met and discussed potential values for data to be included until reaching consensus. Some further assumptions about the structure and input parameters of the model were also reported, although it was unclear from the paper whether these were also derived on the basis of expert panel consensus, or were made by the authors themselves.

**Estimates of effectiveness and key assumptions**

According to the expert panel, the risk of vaginal cancer among women with a positive Pap smear was 95% for cell abnormality, 1.74% for stage I/IIA cancer, 2.33% for stage IIB/III cancer and 0.93% for stage IV cancer. The panel estimated that 50% of cell abnormalities were treated with 5-fluorouracil and 50% with laser ablation. The assumptions of respective proportions of cancer cases in relation to treatment were not reported.

The review of the literature failed to identify the test characteristics of the Pap smear test for the detection of vaginal cancer. Therefore, the sensitivity and specificity of Pap smear testing for cervical cancer was adopted, as an optimistic estimate of the accuracy of the test for detecting vaginal cancer. In the Markov model, it was assumed that if an abnormality was detected it was treated and the patient then underwent surveillance, defined as a Pap smear every year. Patients under surveillance had no risk of further abnormalities. It was also assumed that the patients had no change in their risk factors for developing vaginal cancer. Finally, patients with abnormalities that were not detected were assumed to be detected with certainty in the next screen. In general, as stated by the authors, all modelling assumptions were biased in favour of screening for vaginal cancer.

**Measure of benefits used in the economic analysis**

The outcome measure used in the economic analysis was the life expectancy of a hypothetical cohort of screened women.

**Direct costs**

The study perspective was not stated, but the analysis included the costs to the third-party payer only. The costs were for the Pap smear test, the diagnostic package after an abnormality was detected (colposcopy, biopsy and clinical examination), and the treatment of abnormalities and vaginal cancer. The costs of the Pap smear test assumed that 90% of the tests were read by a cytotechnologist, whereas a pathologist read 10% of normal and all abnormal tests. The treatment costs included 5-fluorouracil, laser ablation, vaginectomy, exenteration and radiation therapy.

The quantities and the unit costs were not reported separately. The cost estimates were derived using the actual reimbursement rates of third-party payers in the state of Michigan. Medicaid, Medicare and private industry reimbursement rates received by the University of Michigan were used in the analysis. The price year was not reported. Discounting was carried out, which was appropriate as the costs were calculated for more than one year.
Statistical analysis of costs
No statistical analysis of the costs was performed. However, a range of costs was presented for each cost component, possibly obtained by different third-party payers’ reimbursement rates. This range of costs was subjected to a sensitivity analysis.

Indirect Costs
The indirect costs were not included in the analysis.

Currency
US dollars ($).

Sensitivity analysis
One-way sensitivity analyses were conducted to determine the impact of uncertainty in the probability estimates for each of the four screening strategies. The parameters examined were all input data used in the models that were based on weak or conflicting information. A threshold analysis was also carried out to examine the cost and test characteristic values required to make the screening strategy cost-effective. The range of values used in the sensitivity analyses was presented, but was not fully justified.

Estimated benefits used in the economic analysis
The benefits were presented as the life expectancy (in years) resulting from adopting each of the strategies examined. The benefits were discounted at a rate of 3%.

The life expectancy of screening strategies starting at age 50 was:

19.1283 years (27.5585 undiscounted) for no screening;
19.1287 years (27.5594 undiscounted) for one-time screen;
19.1289 years (27.5647 undiscounted) for two-time screen; and
19.1312 years (27.7246 undiscounted) for screen every 3 years after three normal annual screens.

The life expectancy of screening strategies starting at age 40 was:

22.4651 years for no screening; and
22.4652 years for screen every 3 years after three normal annual screens.

The maximum gain in life expectancy between no screening and any screening strategy was approximately 3 weeks.

Cost results
The estimated average costs per woman screened, discounted at 3%, were:

at age 50, $0.93 for no screening, $58.43 for one-time screen, $98.33 for two-time screen, and $1,269.76 for screen every 3 years after three normal annual screens;

at age 40, $0.93 for no screening, and $1,278.74 for screen every 3 years after three normal annual screens.

The incremental costs were not presented in the analysis. The period during which the costs were incurred was not stated. The costs of adverse effects were not relevant.
Synthesis of costs and benefits
The estimated costs and benefits were combined to give an incremental cost-effectiveness ratio (ICER). The ICER expressed the cost per life-year gained (LYG), with both the cost and benefit discounted at a rate of 3%. Each screening strategy was compared with "no screening".

For screening starting at age 50, the ICERs were $143,875/LYG for one-time screen, $162,333/LYG for two-time screen, and $437,527/LYG for screen every 3 years after three normal annual screens.

For screening starting at age 40, the ICER was $12,778,200/LYG for screen every 3 years after three normal annual screens.

The authors stated that none of the sensitivity analyses caused the ICER of any strategy to come to less than $100,000/LYG in comparison with no screening.

Authors' conclusions
Papanicolau (Pap) smear screening for vaginal cancer after total hysterectomy for benign disease is neither clinically effective, nor cost-effective.

CRD COMMENTARY - Selection of comparators
The selection of alternative screening strategies to "no screening" was based on current screening practices adopted in the USA. The "no screening" option allowed the active value of the screening strategies to be evaluated. You should decide whether the specific screening strategies examined reflect current practice in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness data were extracted from a review of the literature. Where the data were inadequate or controversial, assumptions were made on the basis of expert opinion. It was stated that the review was systematic, but details on the methods and conduct of the review (e.g. inclusion and exclusion criteria) were not fully reported. The effectiveness estimates were combined using meta-analytic methods, where appropriate. It was unclear how many primary studies were used, or whether the authors considered the impact of differences in the primary studies when estimating the effectiveness measures. It was not reported which measures of effectiveness were derived from the meta-analysis.

Some estimates were derived from expert panel discussions, after reaching consensus, but the authors did not report the process by which the expert panel was recruited. The authors themselves probably made some assumptions that were used in the models, without explicitly justifying their choice. However, they stated that all of the modelling assumptions were deliberately biased in favour of the screening strategies. All estimates were subjected to a sensitivity analysis, although no justification was provided for the ranges used.

Validity of estimate of measure of benefit
The estimate of benefits was modelled. The decision trees and Markov model used were appropriate for this purpose. They included all possible screening results and treatment options following the diagnosis of vaginal cancer.

Validity of estimate of costs
Although not explicitly stated, the study adopted the perspective of the third-party payer. All the categories of cost relevant to this perspective were included in the analysis. The costs and the quantities were not reported separately. The costs were derived from third-party reimbursement rates. Hence, they might not reflect actual resource use. A range of these costs was used in the sensitivity analysis. The costs were discounted, which was appropriate as they were estimated for more than one year. The specific time period during which the costs were incurred was not specified. The price year was not reported.
Other issues
The authors did not compare their results with those from other studies, as they claimed this was the first study to examine the cost-effectiveness of Pap smear screening after total hysterectomy for benign disease. However, they referred to other studies that questioned the scientific merit of such a strategy. The issue of generalisability to other settings was not addressed. The study results were adequately reported. The incompleteness of the data was considered to be a limitation of the study, although this issue was dealt with by performing sensitivity analyses or using estimates in favour of screening. The results of the sensitivity analysis were not presented, but it was reported that they were not favourable for any screening strategy examined. The study conclusions were clearly reported and reflected the scope of the analysis.

Implications of the study
The authors questioned the routine Pap smear screening of women, without risk factors, who have undergone total hysterectomy for benign disease. However, they admitted that there is a lack of data concerning the value of such screening to women with risk factors for genital malignancy. It was emphasised that research is needed to address the utility of pelvic examinations in women who have undergone total hysterectomy for benign disease. Finally, the authors suggested that the savings arising from withdrawing screening in this population of women should be invested in the testing of women with an intact cervix, who have the greatest need for screening.

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